

**Neurofeedback of theta and beta frequencies:
Effects on selective attention and response inhibition**

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Declaration

I declare that the work presented in this thesis is my own.

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Abstract

Despite the widespread employment of electroencephalographic (EEG) neurofeedback (NF) in clinical and cognitive enhancement contexts, its impact on selective attention and response inhibition remains poorly understood. The present research investigated the influence of theta frequency suppression and low-beta frequencies enhancement on these cognitive functions. A first study investigated the differential impact of the sensorimotor rhythm (SMR) and beta1 amplitude enhancement NF on event-related potentials (ERP) and behavioral measures indexing selective attention and response inhibition in the three-stimuli oddball and in the cued-Go/Nogo tasks. The learning curves evinced training-specific amplitude increments in the beta1 but not in the SMR frequency. However, SMR NF was associated with increased Go-P3 amplitude, decreased reaction time mean (RT) and standard-deviation (RT-SD), while control and beta1 NF were associated with increased false alarm rates in the cued-Go/Nogo. A second study attempted to understand whether performance increments in selective attention and response inhibition could be explained by theta suppression NF when compared to beta1 NF in the same task conditions. Within-session theta amplitude was decreased in theta relative to beta1 NF in passive resting state but not during feedback trials. However, for both theta and beta1 NF there was no evidence of training-specific amplitude changes relative to controls. Regarding selective attention, the mean RT was increased following beta1 NF and decreased after theta NF but not in the same task conditions. This study also failed to provide evidence of increased or decreased performance in response inhibition. In conclusion, the present research was not conclusive regarding the NF conditions that might have contributed to improvements in target processing efficiency and cancelation of a previously prepared response in previous studies. Specific proposals to address several methodological limitations that might have hindered the possibility of detecting frequency-specific amplitude changes and cognitive improvements were advanced.

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List of Abbreviations

ADHD – Attention Deficit and Hyperactivity Disorder

ANOVA – Analysis of Variance

BOLD – Blood-oxygen-level dependent

CPT – Continuous Performance Task

d' – d-prime

DAT – Divided attention task

EEG – Electroencephalography

EMG – Electromyography

ERP – Event-Related Potential

ERS – Event-Related Synchronization

fm – Frontal midline

fMRI – Functional Magnetic Resonance Imaging

IAF – Individual Alpha Frequency

Hz – Hertz

ms – milliseconds

NF – Neurofeedback

nVB – Ventrobasal nuclei

PCA – Principal Component Analysis

RF – Random-Frequency

RT – Reaction Time

RT-SD – Reaction Time Standard Deviation

SCP – Slow Cortical Potentials

SMR – Sensorimotor Rhythm

SST – Stop Signal Task

TACS – Transcranial Alternate Current Stimulation

TMS – Transcranial Magnetic Stimulation

TOVA – Test of Variables of Attention

μV – microvolt

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Chapter 1

1. Introduction

The capacities to self-regulate the allocation of attention resources and dominant response tendencies are among the most distinctive features of the human mind. The growing evidence that plasticity across the life span is a fundamental property of the brain (Pascual-Leone, Amedi, Fregni, & Merabet, 2005) has encouraged the search for neurostimulation techniques that might enhance cognitive performance in both healthy and clinical populations. Differently from other forms of neurostimulation, such as the transcranial magnetic stimulation (TMS) and the transcranial electrical stimulation (TES), neurofeedback (NF) presupposes the active engagement of the participant in the modulation of the ongoing brain activity as measured by the electroencephalographic (EEG) and blood-oxygen-level-dependent (BOLD) signals. In this context, EEG NF has received considerable interest for being based on a direct measure of cortical oscillatory activity (i.e., the EEG) that can be related to specific cognitive functions and for its potential in improving cognitive performance through self-regulation. In particular, the NF modulation of EEG amplitude to simultaneously suppress theta and amplify beta frequencies may hold promise for enhancing selective attention and response inhibition in attention deficit hyperactivity disorder (ADHD; for a recent review see Arns, Heinrich, & Strehl, 2014) and in healthy functioning adults (for a recent review see Gruzelier, 2014a, 2014b) as suggested by changes in the amplitude of endogenous event-related potentials (ERPs) and behavioural responses.

However, theta and beta oscillations reflect distinct aspects of neural computation suggesting that they might contribute differently to these cognitive improvements. Moreover, the neural mechanisms by which the NF-related changes in spontaneous oscillatory activity may affect the amplitude and latency of ERPs as well as the speed and accuracy of the behavioural responses remain unclear. Thus, the present thesis aims to explore the

independent effects of EEG NF (henceforth NF) in theta and beta frequencies on ERP and behavioural correlates of selective attention and response inhibition.

1.1. The functional significance of EEG oscillations

The brain oscillatory activity can be defined in terms of its frequency, amplitude and instantaneous phase (Klimesch et al., 2007). The different oscillatory frequencies, traditionally organized into five bands - delta (0-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (>30 Hz) – possibly reflect the size of specific brain networks and the extent of the functional integration of local and distributed neural processing systems (Von Stein & Sarnthein, 2000). Low frequency oscillatory activity has been proposed to reflect the modulation of brain activity over long-range connections and long temporal windows, while high frequencies might influence small spatial regions in short temporal windows (Canolty & Knight, 2010). In support of this view, gamma oscillations have been associated with local visual processing, beta synchronization with modulation of the activity in temporal and parietal neighboring cortical areas during semantic processing, and slow oscillations (e.g., alpha and theta) with the implementation of long range communication between distant fronto-parietal areas during working memory and mental imagery (Von Stein & Sarnthein, 2000).

Even though a direct association between a given cognitive function and a specific frequency band may be difficult and unrealistic to establish, it is widely accepted that different oscillations reflect distinct perceptual sensorimotor and cognitive processes (Buzsáki, 2006; Engel & Fries, 2010; Nunez, 2000; Steriade, 2006). In the resting state, the synchronized activity in high-frequencies is generally taken to be indicative of aroused states, while the synchronization of low-frequencies typically signals a state of cortical deactivation (Steriade, Amzica, & Nunez, 1993).

The amplitude component of oscillations in a certain frequency range reflects the extent to which the underlying neural populations are involved in specific cognitive processes. Variations in amplitude (or power) of the ongoing EEG activity have been shown to reflect cortical activation or deactivation in the sensory and motor system (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998; Grabska-Barwińska & Zygierevicz, 2006; Müller et

al., 2003; Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes da Silva, 1999; Pfurtscheller, Stancák, & Neuper, 1996; Stancák & Pfurtscheller, 1996).

The phase synchronization between pre- and post-synaptic neural populations has been proposed as a mechanism of neural communication by which the activity of distributed neural areas is integrated and gives rise to meaningful cognitive representations (Fries, 2005, 2015; Varela, Lachaux, Rodriguez, & Martinerie, 2001). Inputs that arrive at phases of high postsynaptic excitability benefit from enhanced connectivity relative to those arriving at random phases of excitability. Thus, selective communication is implemented by the reciprocal interaction between neural assemblies in which post-synaptic neural groups communicate preferentially with the coherent pre-synaptic neural groups. Phase coherence provides an estimation of the difference in instantaneous phase angle between two electrodes within the same frequency and an indication of the functional association between neuronal populations.

Local phase coupling in different frequencies (also known as cross-frequency coupling) has been proposed to subserve the synchronization between neuronal networks with different resonance frequency (Canolty et al., 2006; Canolty & Knight, 2010; Holz, Glennon, Prendergast, & Sauseng, 2010; Sauseng, Klimesch, Gruber, & Birbaumer, 2008). In particular, it has been proposed that the phase-amplitude cross-frequency coupling by which a relationship is established between the low-frequency phase and the high-frequency amplitude might provide a mechanism for transient coupling of distinct neuronal populations and functional systems. For instance, theta phase resetting enables the amplitude modulation of theta and gamma oscillations which probably promotes the exchange of top-down (e.g., internal expectancies) and bottom-up (e.g., visual input) information between different networks (Sauseng et al., 2008).

The role of brain oscillations on event-related potentials

Despite evidence that beta/theta NF might contribute to enhance the amplitude of late P3 ERP components subserving the allocation of attention resources and response inhibition (Egner & Gruzelier, 2001; Egner & Gruzelier, 2004; Kropotov et al., 2005; Studer et al., 2014), it is still unclear how the self-regulated changes in the amplitude of theta and beta

frequencies (i.e., in the absence of stimulus modulation) might impact the stimulus related neural responses.

A likely reason for this state of affairs is that the stimulus-evoked neural responses have been traditionally considered to be of an additive nature and inherently independent from the ongoing oscillatory activity. According to this view, the ERP components reflect the neural activity in localized brain regions responsible for processing particular aspects of stimuli and responses. The flow of current resulting from the activation of a sufficient number of dendrites with the same orientation in a certain brain region creates a dipole (i.e., a pair of positive and negative charges), the position and orientation of which defines the distribution of positive and negative voltages recorded at the scalp (Luck, 2014). The temporal sequence of the averaged evoked responses, in which peaks of positive and negative polarity appear in a timely ordered manner, suggests that these brain regions become sequentially activated within certain latencies relative to stimulus onset.

Following this proposal, NF might contribute to increase/decrease the neural activity in the particular brain regions that contribute to the generation of the dipole resulting in amplitude changes of ERP components. In support of this mechanism it has been shown that the NF suppression of alpha activity, generally taken as indicating cortical deactivation, was associated with increase cortical excitability in sensorimotor areas as indicated by increased motor-evoked potentials (MEP) induced by TMS (Ros, Munneke, Ruge, Gruzelier, & Rothwell, 2010). NF might also impact the latency of the evoked neural responses through the modulation of attentional states. For instance, the enhanced top-down control may be associated with reduced transmission times leading to shorter latencies of the ERP components.

An alternative view suggests that ERP components reflect the phase reorganization of ongoing EEG oscillations (Makeig, Debener, Onton, & Delorme, 2004; Sauseng et al., 2007; Sauseng & Klimesch, 2008). Differently from the “evoked model”, in which oscillations are proposed to be noise and ERP components emerge from specific locations, the “phase reorganization model” proposes that oscillations are intimately related to the generation of the ERP components and coordinate the neural processing in distributed neural assemblies (Fries, 2015; Varela et al., 2001).

The fundamental idea of this model is that task-relevant oscillations pre-existing the stimulus presentation (i.e., ongoing) and/or elicited by the stimulus (i.e., evoked) become functionally coordinated in time by transient phase alignment. Phase resetting provides a mechanism by which task-relevant ongoing oscillations reorganize their phase in order to be at the maximal excitability phase when the stimulus is processed. An ERP is produced by averaging a number of trials in which the task-relevant oscillations are phase locked to the stimulus onset (Makeig et al., 2002; Sayers, Beagley, & Henshall, 1974).

This model makes several predictions concerning the contribution of the oscillatory activity to the amplitude and latency of brain evoked response (Klimesch, Sauseng, Hanslmayr, Gruber, & Freunberger, 2007; Sauseng et al., 2007; Sauseng & Klimesch, 2008). Firstly, because the ERP components reflect the timing and frequency of the functional relevant oscillations, an increase or decrease in the average ERP latency may be determined by the inter-trial variability of phase-locking and by changes in oscillatory frequency. A reduction in inter-trial variability would contribute to increase the phase concentration around a certain time point leading either to increased or decreased latency. Moreover, because the interpeak latency is smaller for faster frequencies and larger for slower frequencies, an increase or decrease in oscillatory frequency would determine a shorter or longer ERP latency respectively.

On the other hand, the ongoing oscillatory activity at pre-stimulus might determine the magnitude of the event-related response. Importantly, phase-resetting requires a significant level of ongoing activity in the pre-stimulus period (Shah et al., 2004). As an example, the contribution of the evoked alpha activity to early ERPs amplitude was larger in participants with higher pre-stimulus alpha power (Min et al., 2007). Although there is evidence to suggest that NF might contribute to an increase in post-stimulus evoked theta activity (Enriquez-Geppert, Huster, Figge, & Herrmann, 2014), it is currently unclear whether this increase might be explained by an higher pre-stimulus theta activity induced by NF. Thus, NF might have an effect on the amplitude and latency of the ERP components by increasing or decreasing the ongoing activity of certain oscillatory frequencies relevant for stimulus processing and by decreasing the phase variability between trials.

1.1.1. Electrophysiological and behavioral studies of selective attention

From a neurobiological perspective selective attention comprises voluntary (top-down) and involuntary (bottom-up) attention processes (Corbetta & Shulman, 2002; Escera, Alho, Schröger, & Winkler, 2000; Näätänen, Paavilainen, Rinne, & Alho, 2007; Posner, 1980; Sarter, Givens, & Bruno, 2001; Womelsdorf & Fries, 2007). Voluntary attention concerns the goal-directed processing of stimulus information according to knowledge and expectations as well as the decision process leading to response selection. In contrast, involuntary attention is driven by the properties of the stimulus such as its salience, novelty and potential survival value. Importantly, these attention processes have been related to distinct brain networks and predict distinct patterns of behavior (Corbetta & Shulman, 2002).

1.1.1.1. Electrophysiological indices of selective attention in the oddball task

In both auditory and visual modalities of the three-stimuli oddball task two distinct components could be distinguished in relation to infrequent stimuli: a frontal P3a component with a short peak latency (250-400ms) associated with the distracter task-irrelevant stimulus; and a parietal P3b component, with a longer peak latency (300-600ms), elicited by the target task-relevant stimulus (Courchesne, Hillyard, & Galambos, 1975; Squires, Squires, & Hillyard, 1975). Subsequent studies have suggested that the neural response to infrequent task-relevant targets (P3b) and task-irrelevant nontargets (P3a) may reflect functionally distinct voluntary and involuntary attention processes (Debener, Kranczioch, Herrmann, & Engel, 2002; Debener, Makeig, Delorme, & Engel, 2005; Escera et al., 2000; Escera, 1990; Sawaki & Katayama, 2009).

P3b

The ERP P3b component was first described in response to an unexpected auditory tone in a background of frequent standard stimuli with maximal amplitude in central-parietal sites (Sutton, Braren, Zubin, & John, 1965). The amplitude and latency of the P3b have been found to reflect different processes (for reviews see Polich, 2007, 2012). The P3b amplitude has been found to be sensitive to manipulations task-relevance (Squires, Donchin, Hering, & McCarthy, 1977) and of global and local sequence probability with amplitude increasing as a function of both increased standard/target ratio and target-to-target interval (Polich,

2007, Polich, 2012). In the classical oddball task, the physiological processes underlying the P3b latency appear to be sensitive to the difficulty of target discrimination (Kutas, McCarthy, & Donchin, 1977) but to be independent from those related to response selection and execution as demonstrated by unchanged latencies with varying degrees of target-response incompatibility (Magliero, Bashore, Coles, & Donchin, 1984).

In spite of being one of the most well researched ERP components, there is still some debate regarding the functional significance of the P3b. The context-updating theory suggests that the P3b amplitude reflects the update of a schema upon detection of a conflict between new information and expectations (Kamp, Brumback, & Donchin, 2013). In other words, in the context of high global and local sequence standard stimulus probability, a deviant stimulus will require an endogenous attention-driven comparison process to update the current representation. If no change is detected in the stimulus category the stimulus context is maintained and only sensory processes are involved (Donchin & Coles, 1998).

The P3b amplitude is also believed to provide information on the neural activity underlying allocation of attentional resources and processing capacity (Kok, 2001). Evidence that the P3 is modulated by the amount of attentional resources allocated comes from dual task performance studies showing that the P3 amplitude decreases and its latency gets longer as the difficulty of the primary task increases (Isreal, Chesney, Wickens, & Donchin, 1980; Kramer, Wickens, & Donchin, 1985). In the same way, increased memory load has also been associated with reductions of the P3 amplitude (García-Larrea & Cézanne-Bert, 1998; Kok, 2001). Thus, it has been assumed that the P3b reflects the degree of involvement of voluntary aspects of attention during the task.

Whether this representation update will serve any function in terms of response selection is still a matter of debate. An important proposal of the context-updating theory is that P3b reflects a planning for future responses (i.e., a strategic process) rather than the immediate decision to respond or the generation of a response to a target (i.e., a tactical process). However, other accounts suggest that it also reflects decision processes associated with response selection (Kelly & O'Connell, 2014; Nieuwenhuis, Aston-Jones, & Cohen, 2005; Verleger, Hamann, Asanowicz, & Śmigasiewicz, 2015; Verleger, Metzner, Ouyang, Śmigasiewicz, & Zhou, 2014).

Taken together these findings appear to support the idea that the P3b latency is sensitive to difficulty of stimulus categorization but remains unaffected by factors influencing response selection, whereas the P3b amplitude is sensitive to both factors that influence target discriminability and the strength of association between target and response.

P3a

The P3a designates a family of positive waveforms observed in response to infrequent stimuli without an associated task in the three-stimuli oddball paradigm. Given the absence of an overt response, the P3a necessarily reflects a stimulus-driven process (Polich, 2012). This component presents a variable centro-parietal and fronto-central scalp distribution depending on the type of distracter stimulus and task demands (Polich, 2007, 2012). A frontal-central “novelty P3” has been first described by Courchesne and collaborators (1975) associated with infrequent unexpected novel stimuli (i.e., non-repeated complex visual stimulus) presented in a series of frequent standards and infrequent targets. This component habituates rapidly as demonstrated by decreased amplitude with repeated presentation. Therefore, the novelty P3 has been associated with the orienting response (Courchesne et al., 1975; Friedman, Cycowicz, & Gaeta, 2001; Rushby, Barry, & Doherty, 2005).

On the other hand, a “Nogo-P3” component has been identified in response to deviant typical stimuli (e.g., auditory tones of varying degrees of salience to standard and target stimuli) with variable topography depending on the attentional task demands. In contexts of relatively low attentional task demands (i.e., easy perceptual discrimination between target and standards), the P3 amplitude to deviant nontargets (P3a) elicits a similar centro-parietal topography and has been proposed to have the same functional significance as the P3b (Bennington & Polich, 1999; Jeon & Polich, 2001; Oades, Zerbin, & Dittmann-Balcar, 1995; Wronka, Kaiser, & Coenen, 2008). However, in this context the P3a component has a smaller amplitude and shorter latency relative to the P3b, reflecting the difference in the amount of change required to update the memory representation (Donchin & Coles, 1998; Hagen, Gatherwright, Lopez, & Polich, 2006).

In contexts of difficult target-standard discrimination, the P3a component exhibits a fronto-central distribution as well as an higher amplitude and shorter latency when compared to the P3b (Comerchero & Polich, 1999; Katayama & Polich, 1999; Sawaki & Katayama,

2006, 2008, 2009). The amplitude of the “Nogo-P3a” has been considered to reflect automatic capture and orientation of attention towards a deviant stimulus (Sawaki & Katayama, 2008) involuntary switching of attention (Escera et al., 2000; Escera, Alho, Winkler, & Naatanen, 1998; Näätänen, 1992) and a useful physiological index of distractibility (Berti, Roeber, & Schröger, 2004). In line with the argument that the P3a reflects an automatic process (i.e., independent of the availability of attentional resources), it was found that the P3a amplitude to an auditory stimulus was not significantly modulated by changes in difficulty of a concurrent visual task (Muller-Gass, Macdonald, Schröger, Sculthorpe, & Campbell, 2007). It is currently assumed that the “novelty P3” and the “Nogo-P3” in a difficult target-standard discrimination context are variants of the same ERP component (Polich, 2007), as suggested by the similar frontal-central topography (Polich & Comerchero, 2003) and the failure to distinguish between the two in Principal Component Analysis (PCA) (Simons, Graham, Miles, & Chen, 2001).

An alternative interpretation proposes that the P3a reflects the automatic response inhibition upon detection of deviance. This account assumes that the P3a reflects in part the detection of deviance and a response inhibition process upon proper identification of the stimulus as a nontarget (Azizian, Freitas, Parvaz, & Squires, 2006; Goldstein, Spencer, & Donchin, 2002).

1.1.1.2. Theta and beta oscillatory activity in selective attention

Theta

In healthy adults, theta rhythms are difficult to detect in the fully awake and functional resting state (Klimesch, 1999). Elevations of theta power in the resting state EEG have been attributed to the slowing of alpha activity in pathological cerebral oxygenation and blood flow (Ingvar et al., 1976), poor cognitive performance both in children and cognitively impaired adults (Klimesch, 1999) hypnagogic states (Gruzelier, 2009), transition to sleep (De Gennaro, Ferrara, & Bertini, 2001) and mind wandering states (Braboszcz & Delorme, 2011). Moreover, pre-stimulus theta power increases with decreased alertness, fatigue and drowsiness and has often been associated with increased reaction time (RT) and increased error rates (Gevins & Smith, 1999; Huang, Jung, Delorme, & Makeig, 2008; Makeig & Jung, 1996; Paus et al., 1997; Takahashi et al., 1997; Wascher et al., 2013). Increased occipital

theta power has also been related to vigilance decrements (assessed by omission errors and increased detection latency) during auditory and visual tasks (O'Hanlon & Beatty, 1977; Williams, Granda, Jones, Lubin, & Armington, 1962) which inspired the first investigations in theta suppression NF (Beatty, Greenberg, Deibler, & O'Hanlon, 1974; Williams, Beatty, & O'Hanlon, 1975). The time course of delta and theta power was also found to be increased during prolonged resting state EEG recordings (Brismar, 2007).

At the functional level, frontal midline (fm) theta oscillations have been proposed as a candidate mechanism by which the prefrontal cortex exerts top-down control (Basar-Eroglu & Demiralp, 2001; Besserve et al., 2008; Cavanagh & Frank, 2014; Mitchell, McNaughton, Flanagan, & Kirk, 2008). For instance, increased fronto-parietal synchrony in the lower frequencies was associated with attentional top-down control during visual search tasks (Buschman & Miller, 2007).

Pre- and post-stimulus theta oscillations have been proposed to play an important role in deviant stimulus detection. The pre-stimulus theta and alpha power have been related to stimulus detection. For instance, a low absolute tonic theta power in the pre-stimulus baseline correlated positively with the extent of event-related theta synchronization during target detection in a simple oddball task (Doppelmayr et al., 1998). Consistently, Makeig & Jung (1996) found evidence that pre-stimulus increases in central-parietal theta were predictive of decreased vigilance in a monitoring task, while decreased pre-stimulus theta power was associated with increased detection of targets. Pre-stimulus spectral power in the alpha band was positively correlated with P3 amplitude and negatively correlated with P3 latency (Intriligator & Polich, 1994; Jasiukaitis & Hakerem, 1988).

The oscillatory response to the deviant targets in the oddball paradigm has been characterized by increased theta evoked amplitude and phase-locking relative to the pre-stimulus period. Both evoked theta (Başar-Eroglu, Başar, Demiralp, & Schürmann, 1992; Basar-Eroglu & Demiralp, 2001; Cacace & McFarland, 2003; Choi et al., 2013; Fuentemilla, Marco-Pallarés, Münte, & Grau, 2008; Mazaheri & Picton, 2005; Yordanova & Kolev, 1998; Yordanova, Rosso, & Kolev, 2003) and delta power (Barry et al., 2007; Cacace & McFarland, 2003; Güntekin & Başar, 2010) have been implicated in the generation of the P3 amplitude during auditory information processing.

For instance, a decrease in wavelet entropy reflecting the transient dominance in the theta frequency ERP component over other frequency components was demonstrated for both targets and standards (Yordanova et al., 2002, 2003). The prominence of theta synchronization over other EEG frequencies in the 250-300 ms post-stimulus period was hypothesized to reflect a basic processing stage during which working memory operations are facilitated and interference from other processes is minimized. A more specific involvement of the theta frequency in deviance detection was evinced by the demonstration that the P3a component and frontal-central theta exhibit similar frontal topographies and that theta activity was significantly higher for novel nontargets compared to typical nontargets in the easy and difficult three-stimuli oddball task (Demiralp, Ademoglu, Comerchero, & Polich, 2001). In line with these findings, theta power and phase alignment were found to contribute to the generation of the automatic deviance detection Mismatch Negativity frontal and temporal components (Fuentemilla et al., 2008) and strong phase synchrony in the theta range between frontal and temporal areas was evinced during the automatic detection of deviants (Choi et al., 2013).

Beta

The pioneering work of (Moruzzi & Magoun, 1949) demonstrated that stimulation of reticular formation of the brainstem was associated with the blockage of synchronized slow wave activity and with the appearance of fast low voltage oscillations characteristic of vigilance states. More recently, beta oscillations have been proposed to play a role in top-down-processing.

Computational models provide supportive evidence to the involvement of beta cortical rhythms in attentional signal processing gain by exerting endogenous/top-down control over sensory areas through the activation of ascending synaptic projections (Lee, Whittington, & Kopell, 2013). Similarly, beta oscillations have been proposed to play a role in the maintenance of the current perceptual or cognitive set. The entrainment of neuronal circuits to enhance beta power might result in decreased behavioral flexibility by raising the threshold and slowing down the response to novel and unexpected stimuli while promoting cognitive control in predictable tasks (Engel & Fries, 2010).

More specifically, increased beta power has also been related to increased vigilance. The studies of Wróbel and colleagues in cats and in humans highlighted the role of beta oscillations in controlling the top-down and bottom-up processes in the visual attention system (Bekisz & Wróbel, 1999; Gola, Kamiński, Brzezicka, & Wróbel, 2012; Wróbel, 2000). Their studies proposed that beta activity may induce a background excitation in cortico-thalamic circuits of the visual system (primary visual cortex, higher visual areas and lateral posterior and pulvinar complex). For instance, phase coupling (i.e., the synchronization across different frequencies) between bursts of beta and gamma activity (Bekisz & Wróbel, 1999) suggests that beta activity may function as a carrier of visual attention by allowing for high frequency (i.e., gamma) synchronization during feature binding (Fell, Fernández, Klaver, Elger, & Fries, 2003). Moreover, the increased pre-stimulus fronto-parietal synchrony in both beta and gamma bands was significantly correlated with correct target detection which was interpreted as reflecting a state of increased visual attention with an impact on visual perception (Hanslmayr et al., 2007). In line with the previous results, reduced beta phase synchronization in fronto-parietal areas has been associated with attentional lapses (Gross et al., 2004). More recently, the increased beta activity in the foreperiod of cued-Go/Nogo tasks has been proposed to be involved in the facilitation of cue processing (Kilavik, Zaepffel, Brovelli, MacKay, & Riehle, 2013).

1.1.1.3. Behavioral correlates of selective attention in the oddball task

Low-beta/theta NF has also been associated with improvements in selective attention as indicated by decreased RT and reaction time standard deviation (RT-SD), increased hit rate and overall increased perceptual sensitivity (d') in continuous performance task (CPT), Go/Nogo and divided attention tasks (DAT) (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2001, 2004).

In the context of the oddball task, the same conditions that contribute to the facilitation of the voluntary attention mechanisms indexed by the P3b (e.g, discrimination difficulty, confidence in the detection of the target) have been found to affect the behavioral response. Moreover, the amplitude of the P3b was found to correlate positively with decreased RT (Nieuwenhuis et al., 2005; Pfefferbaum, Ford, Weller, & Kopell, 1985; Verleger, Jaskowski, & Wascher, 2005), decreased RT-SD (Comerchero & Polich, 1999;

Comerchero & Polich, 1998; Ramchurn, de Fockert, Mason, Darling, & Bunce, 2014) increased hit rate and d' and negatively with target omissions and false alarms (Hillyard, Squires, Bauer, & Lindsay, 1971; Wilkinson & Seales, 1978).

Importantly, despite being positively correlated the mean RT and response accuracy reflect different processes from the P3b. The mean RT depends on connectivity between premotor and primary motor areas involved in the selection and preparation of movement (Koch et al., 2006) which are not involved in the generation of the P3b. On the other hand, RT-SD has been recognized in recent years as an index of preserved frontal functioning and top-down control of attention in healthy, neurodevelopmental and brain damaged populations (Karalunas, Geurts, Konrad, Bender, & Nigg, 2014; Stuss, Murphy, Binns, & Alexander, 2003; Vaurio, Simmonds, & Mostofsky, 2009). There is currently evidence that the theta inter-trial phase coherence is related to the variability of RT in ADHD children and typically developing individuals across the life-span (McLoughlin, Palmer, Rijdsdijk, & Makeig, 2014; Papenberg, Hämmerer, Müller, Lindenberger, & Li, 2013). Although it is unclear whether low-beta/theta NF might have an impact of theta phase, an increase in inter-trial theta phase-coherence might explain the decreases in RT-SD observed in previous studies (see table 1.2.).

In sum, the existing evidence suggests any changes in theta and beta oscillatory activity may have been responsible for the electrophysiological and behavioral improvements observed in previous low-beta/theta NF in the context of the oddball task.

1.1.2. Electrophysiological and behavioral studies of response inhibition

Inhibition is a crucial aspect of adaptive behavior in overcoming automatic responses to changing circumstances in the environment. Response inhibition implies the voluntary control or cancelation of a previously prepared motor response. Since successful cancelation of a response is not associated with an overt behavioral response, the ERP technique is especially suited to investigate the chain of cognitive events leading to response inhibition. A standard task designed to investigate response inhibition in cognitive neuroscience is the Go/Nogo paradigm in which participants are required to respond with a button-press to a Go stimulus, while refraining from responding to a lower (or equal) probability Nogo stimulus (Pfefferbaum et al., 1985). The response inhibition demands imposed by the Go/Nogo task

can be defined in terms of action restraint (i.e., the ability to withhold a prepotent response tendency). Other aspects of response inhibition such as action cancelation (i.e., the ability to cancel a response after being initiated) are better described by measures of latency of inhibition (i.e. the stop signal RT) in the Stop Signal Task (SST) (Bari & Robbins, 2013; Schachar et al., 2007).

1.1.2.1. Electrophysiological indices of response inhibition in the Go/Nogo task

The investigation of the neural correlates of response inhibition has been dominated by two major research questions. The first question concerns the functional significance of the ERP components associated with the Nogo stimulus. In comparison to the Go stimulus, the Nogo stimulus elicits a larger fronto-central negative deflection in the time window around 200 and 300 ms after stimulus onset (Nogo-N2), followed by a larger central positive P3 component (Nogo-P3) component with a peak latency around 400-600 ms (Eimer, 1993; Falkenstein, Hoormann, & Hohnsbein, 1999; Pfefferbaum et al., 1985; Sasaki & Gemba, 1986; Simson, Vaughan, & Ratter, 1977).

Recent accounts currently favor the interpretation that the Nogo-N2 and Nogo-P3 components may reflect dissociable processes of response conflict and response inhibition (Bruin, Wijers, & Van Staveren, 2001; Dimoska, Johnstone, & Barry, 2006; Groom & Cragg, 2015; Randall & Smith, 2011). In Go/Nogo tasks in which the probability of the Go stimuli is higher than that of the Nogo stimuli the amplitude of the ERP components may equally reflect response inhibition or increased conflict between response representations (Botvinick, Cohen, & Carter, 2004). Recent findings suggest that the processes of response conflict and response inhibition can be dissociated in cued-Go/Nogo paradigms in which conflict can be elicited in the absence of inhibition by increasing the response activation (Donkers & van Boxtel, 2004; Randall & Smith, 2011). The N2 component was found to be increased to rare unexpected stimuli in situations in which an increase in response activation (GO) rather than response inhibition was required (Donkers & van Boxtel, 2004). The N2 amplitude was more negative when the required response was different from the planned response based on the cue (i.e., Nogo target after Go cue or to Go target after Nogo cue). The Nogo-P3 amplitude was increased when the previously planned response to the Go stimulus (due to a cue, a prepotent Go response or fast responding) had to be inhibited (Bruin et al., 2001; Dimoska et

al., 2006; Randall & Smith, 2011). Furthermore, it has been consistently found that the Nogo-P3 amplitude is increased for fast responders compared to slow responders in cued Go/Nogo (Smith, Johnstone, & Barry, 2006) and in the SST paradigms (Dimoska et al., 2006), possibly reflecting the greater need for inhibitory activation with increase response preparation. Thus, the N2 to Nogo stimulus may reflect the need for a different response – response conflict rather than response inhibition *per se*. The Nogo-P3 is enhanced when a increment in response preparation has to be subsequently inhibited.

Further evidence supporting the differential role of the N2 as a marker response conflict and of the P3 as an index of response inhibition comes from an hybrid Go/Nogo flanker task (Groom & Cragg, 2015) in which the effects of response activation-inhibition and of high-low conflict could be dissociated. The N2 amplitude was enhanced on high response conflict trials (i.e., incongruent) relative to those involving low response conflict (i.e., congruent) but not in those requiring response inhibition. Moreover, P3 amplitude was enhanced in frontal sites on trials requiring response inhibition relative to response activation but not in those involving the resolution of the conflict effect. Thus, the N2 might reflect the need to select between competing responses (which in a situation of prepotent Go response is also present in the Go/Nogo task), while the frontal P3 to Nogo trials might reflect the active suppression of a motor response.

The second question that has been debated in the literature concerns whether the increased evoked responses to the Nogo stimulus reflects cognitive or movement aspects of inhibition. More specifically, some authors (Salisbury, Rutherford, Shenton, & McCarley, 2001; Salisbury, Griggs, Shenton, & McCarley, 2004) have suggested that the increased P3 amplitude in Nogo trials relative to Go trials (Nogo effect), may be related to the presence of negative movement related deflections in Go trials. Smith, Johnstone and Barry (2008) directly tested this prediction by calculating Nogo and Go difference waves in the count and press conditions. A difference between Go press and Go count waveforms, would suggest that the Nogo effect would be associated with movement-related potentials on the Go trials. Contrary to the prediction, there was no difference between Go count and Go press in the P3 amplitude window. Moreover, the Nogo-P3 in the “press” conditions was significantly higher than the in the “count” condition suggesting the Nogo effect was sensitive to response inhibition demands. Moreover, the simultaneous recording of ERP and functional Magnetic

Resonance Imaging (fMRI) confirmed that the increased Nogo-P3 during “press” conditions relative to “count” conditions was associated with a significant deactivation of motor areas related to inhibition such as the inferior frontal gyrus, the precentral gyrus and the supplementary motor area (Smith, Jamadar, Provost, & Michie, 2013).

Taken together these results suggest that the Nogo-P3 amplitude may be considered an electrophysiological index of response inhibition of a prepotent response in the context of the Go/Nogo task.

1.1.2.2. Theta and beta oscillatory activity in response inhibition

Oscillatory activity in the theta and beta range has been associated with response inhibition and executive control.

Theta

Increased fm-theta activity has been associated with both the realization for the need to control and the instantiation of control in several executive tasks (Cavanagh & Frank, 2014; Nigbur, Ivanova, & Stürmer, 2011). Evidence for the differential contribution of pre-stimulus delta and theta oscillations for the amplitude and latency of several ERP components associated with the Go and Nogo responses was obtained in a recent study (De Blasio & Barry, 2013a). High pre-stimulus delta amplitude was found to contribute to enhancements of both early and late components irrespective of the stimulus type. In contrast, the pre-stimulus theta amplitude was significantly modulated by stimulus type. An inverse modulation was observed for the Go stimulus (i.e., low pre-stimulus theta was associated with high Go-P3 and vice versa). However, low pre-stimulus theta activity was associated with increased Nogo-N2 and reduced Nogo-P3. Taking into consideration that the Nogo-P3 appears to be a more direct measure of response inhibition than the Nogo-N2, these results suggest that pre-stimulus theta may be involved in attention (Go-P3) but not response inhibition functions (Nogo-P3).

Other studies have proposed distinct roles for delta and theta oscillations as markers of cognitive control. In one study, the PCA decomposition revealed that post-stimulus delta and theta activity accounted for a significant proportion of the variance of the Nogo minus Go differences scores of N2 and P3 components. However, the moderate correlation between

delta and theta components in Nogo minus Go differences scores suggested that the two components may reflect dissociable process (Harper, Malone, & Bernat, 2014). The specific role of post-stimulus delta and theta synchronization in sustained attention and response inhibition was revealed in another study comparing the equiprobable Go/Nogo and the cued-CPT tasks. In both tasks, the time-frequency decomposition using wavelet transform, revealed that the Nogo condition evoked higher fm-theta coefficients than the Go condition in the early post-stimulus period (corresponding to the N1 and P3 components time windows) probably reflecting response inhibition demands. In the CPT, the theta oscillatory activity was observed to be superimposed in the delta activity suggesting that the delta component in the latency range of the N2 and P3 components may reflect sustained attention demands (Kirmizi-Alsan et al., 2006).

Beta

From a functional point of view, sensorimotor beta oscillations have been related to motor activity. Sensorimotor beta oscillations have been found to desynchronize during self-paced or stimulus-related movement and steady-state muscle contractions (Pfurtscheller & Lopes da Silva, 1999; Stancák & Pfurtscheller, 1996) and to be transiently increased after movement cessation, a phenomenon known as beta rebound (Pfurtscheller, Neuper, Brunner, & Lopes da Silva, 2005; Pfurtscheller & Solis-Escalante, 2009). The beta rebound effect may reflect an active inhibition of the motor system as suggested by a decrease in corticospinal excitability (Chen, Corwell, & Hallett, 1999) and a positive linear correlation between concentration of the inhibitory neurotransmitter γ -Aminobutyric acid (GABA) and beta rebound power (Gaetz, Edgar, Wang, & Roberts, 2011). Alternatively, it may represent a period of recalibration of the motor system after one movement and the preparation for the next (Baker, 2007; Gaetz & Cheyne, 2006). These observations contributed to the conceptualization of beta oscillations as an “idling rhythm” of the sensorimotor areas (Pfurtscheller et al., 1996). However, rather than just reflecting movement execution beta desynchronization may be associated with perceptual and cognitive aspects of motor control (Kilavik et al., 2013; Müller et al., 2003).

More recently, it has been proposed that beta oscillations promote the maintenance of the current sensorimotor state at the expense of new movements (Engel & Fries, 2010;

Jenkinson & Brown, 2011). This view is supported by evidence that increased beta synchrony is associated with the reinforcement of existing movements and posture, and with impaired speed in the execution of new movements (Gilbertson et al., 2005). In consonance with this hypothesis, the enhancement of beta and gamma activities by transcranial alternating current stimulation (TACS) resulted in dissociable behavioral effects. The increase in beta activity was associated with antikinetic and slower movements, while the increase in gamma activity resulted in prokinetic behavior as demonstrated by measures of force in responding to a Go/Nogo task (Joundi, Jenkinson, Brittain, Aziz, & Brown, 2012).

Beta activity has also been associated with enhanced response inhibition in both humans and primates. In Go/Nogo tasks, beta activity is increased when a previously prepared response is followed by the presentation of a Nogo stimulus (Alegre et al., 2004; Kühn et al., 2004; Swann et al., 2009; Zhang, Chen, Bressler, & Ding, 2008). In the monkey, beta desynchronization was initially observed in relation to response preparation to Go and Nogo stimuli, while beta synchronization (beta rebound) was observed exclusively in relation to response inhibition in the Nogo condition and exhibited a similar coherent pattern to that observed during the pre-stimulus condition (Zhang et al., 2008). Moreover, an increase in fronto-central beta synchronization was observed after the decision to withhold a response (Alegre et al., 2004). Recently, a study using transcranial magnetic stimulation and simultaneous EEG recording (Picazio et al., 2014) found enhanced cortical connectivity in the beta frequency between the prefrontal and motor cortex (where the motor plans are inhibited or executed) and increased beta activity in the fronto-central areas following Nogo trials providing direct evidence of the inhibitory influences of the prefrontal cortex on the motor areas.

De Blasio & Barry (2013b) also suggested a differential contribution of pre-stimulus alpha and beta oscillations for the amplitude and latency of several early and late ERP components associated with the Go and Nogo responses. The pre-stimulus alpha amplitude was associated with corresponding modulations of the positive ERP components irrespective of the stimulus type (i.e., high pre-stimulus alpha was associated with increased P1, P2 and P3 amplitude and vice versa). In agreement with the role of beta oscillations in early attentional gain (Iversen, Repp, & Patel, 2009; Lee et al., 2013), the increased pre-stimulus beta amplitude was associated with increased amplitude of the exogenous P1 and N1

component (and decreased latency of the N1 component). However, the pre-stimulus beta amplitude was not predictive of the modulation of the late ERP components associated with the differential responses to the Go and Nogo stimulus.

In sum, the current evidence suggests the involvement of different oscillations in response inhibition. Although in the post-stimulus period both theta and beta synchronization have been associated with response inhibition (Harper et al., 2014; Kirmizi-Alsan et al., 2006; Picazio et al., 2014; Zhang et al., 2008), in the pre-stimulus period other oscillations (delta, alpha) may contribute to the ERP components associated with Go and Nogo stimuli (De Blasio & Barry, 2013a, 2013b).

1.1.2.3. Behavioral correlates of response inhibition in the Go/Nogo task

As shown in table 1.2., low-beta/theta NF has been associated with decreased false alarm rate in Go/Nogo tasks (Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Egner & Gruzelier, 2001; Gruzelier, Foks, Steffert, Chen, & Ros, 2014; Kropotov et al., 2005), which can be related to the ability to withhold a prepotent response tendency, a crucial aspect of response inhibition.

In the Go/Nogo task the difficulty of withholding a prepotent response tendency is determined by the degree of previous response preparation (e.g., whether a warning cue was present or absent) and the Go stimulus probability (Bruin & Wijers, 2002; Eimer, 1993). Inhibition is assumed to be successful when a correct non-response is associated with the Nogo stimulus. Everything being equal and assuming a valid cue, higher demands on response inhibition are expected when a Nogo stimulus is preceded by response priming compared to when it is unexpected. On the other hand, the higher probability of the Go stimulus probably enhances the response preparation to the upcoming trials, therefore increasing the demands on response inhibition to the less probable Nogo stimulus. (Smith, Johnstone, & Barry, 2004). Additionally, response inhibition demands may be affected by individual differences and strategies in response speed. For instance, explicit instructions to increase speed at the expense of accuracy generated more commission errors than speed and accuracy instructions (Band, Ridderinkhof, & van der Molen, 2003).

Behaviorally, the false alarm or commission error rate (i.e., the percentage of incorrect responses to the Nogo stimulus) has been taken as a measure of unsuccessful

response inhibition (Falkenstein et al., 1999). Although variations in Go/Nogo stimulus probability equally affect Nogo-P3 amplitude and the false alarm rate (i.e., both increase as a function of increasing Go/Nogo probability ratio), a functional relation between the two is difficult to establish because these measures are based on different data. In fact, while false alarm rate takes into consideration both correct and incorrect non-responses, the Nogo-P3 represents an average of the correct non-responses after excluding false alarms. Moreover, other ERP components such as the ERN (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) may constitute a more approximated measure of the failure of inhibitory processes.

Additionally, individual differences in RT-SD (but not in mean RT) to Go responses in the context of Go/Nogo tasks have been found to be a strong predictor of successful response inhibition as demonstrated by increased activation of frontal regions in fMRI (Bellgrove, Hester, & Garavan, 2004).

1.2. Neurofeedback of theta and beta frequencies

Despite consistent evidence that improvements in cognitive performance may result from the learned modulation of certain brain signals (Birbaumer, Ruiz, & Sitaram, 2013; Fetz, 1969; Gruzelier, 2014b; Salari, Buchel, & Rose, 2014), the demonstration that the modulation of theta and low-beta amplitudes results from specific experimental manipulations, rather than from unspecific factors affecting the EEG amplitude, has faced considerable conceptual and methodological challenges.

1.2.1. Definition and conceptual aspects of Neurofeedback

A pervasive question in cognitive neurosciences is that the association between changes in brain activity and cognitive performance does not necessarily imply a causal relationship and that the direction of such correlations is often difficult to determine (Seitz, 2013). However, as discussed in sections 1.1.1.2. and 1.1.2.2., there is a substantive body of research demonstrating the functional significance of brain oscillations for attention and inhibition, thus, supporting the assumption that voluntary changes in theta and beta oscillation may affect specific cognitive functions. Although it is commonly accepted that the voluntary induction of certain mental states is associated with the modulation of EEG

oscillations (Buzsáki, 2006; Nunez, 2000), it is still debated whether the direct manipulation of brain oscillations may affect the pattern of synchronization of localized and distributed neural networks that subserve specific cognitive operations.

In NF, additional difficulties in establishing a causal link between voluntary changes in brain activity and behavior result from (1) the complexity of disentangling intended changes in brain activity from epiphenomenal changes related to unspecific cognitive processes and (2) the absence of evidence that the intended changes in brain oscillatory activity are aligned in time with changes in cognitive performance.

Although it is still debated the extent to which NF implicates some form of top-down self-regulation (Bagdasaryan & Quyen, 2013; deCharms, 2008) or is essentially a procedural learning skill dependent on the basal ganglia plasticity (Birbaumer et al., 2013; Ruiz, Buyukturkoglu, Rana, Birbaumer, & Sitaram, 2014; Sherlin et al., 2011), it is currently assumed that, at least in humans, unspecific cognitive processes (such as feedback learning and self-monitoring) probably mediate the learned modulation of any electrophysiological signal (Gruzelier, 2014b).

One question raised here is whether it is possible to disentangle the contribution of top-down from that of bottom-up processes to the resulting changes in brain activity. In fact, the implementation of self-regulatory processes probably recruits low frequencies implicated in cognitive control. This in turn, is likely to constrain the activity of superimposed local high-frequencies governed by cross-frequency phase-amplitude coupling mechanisms. On the other hand, the neurostimulation of the lower levels of the cognitive organization conceivably gives rise to the emergence of higher level conscious experience subserved by low frequencies (Bagdasaryan & Quyen, 2013). Two ubiquitous findings in NF research illustrate this complexity. Firstly, NF appears to have an impact on the activity of the frontal lobes irrespective of the training frequencies and training sites (Angelakis et al., 2007; Egner, Zech, & Gruzelier, 2004; Keizer, Verment, & Hommel, 2010) possibly reflecting the intervention of self-regulatory processes. On the other hand, NF probably implicates complex relations across frequencies as suggested by the amplitude modulation of frequencies that were not targeted by the intervention (Enriquez-Geppert, et al., 2014a; Keizer, Verschoor, Verment, & Hommel, 2010; Nan et al., 2012; Ros et al., 2013).

Thus, considerable difficulties in establishing cause-and-effect relationships stems from the possibility that cognitive changes may constitute a by-product of non-specific self-regulatory processes rather than a primary effect of the modulation of brain activity (Caria, 2016). Here, the comparison of NF with other forms of neurostimulation (such as TACS) that do not implicate self-regulation processes but provide considerable frequency-specificity may help solve this conundrum. Although the two techniques may be difficult to compare in terms of their local specificity and intensity of the stimulation, their differential cognitive impact can be attributed to self-regulatory or other epiphenomenal effects associated with NF.

For the establishment of cause-and-effect relationships between NF modulation and changes in cognitive performance it is also important to demonstrate a temporal association between the two. As will be seen in the next sections, previous reports of NF efficacy have relied on correlational evidence between measures of successful modulation of EEG activity during training and pre- to post-training changes in cognitive tasks which are typically obtained at different times (sometimes with intervals of days). Given the non-stationarity of the EEG signal and the influence of pre-stimulus oscillatory activity on ERPs amplitude and latency (see sections 1.1.1.2. and 1.1.2.2.), these distal NF learning measures might not be a reliable predictor of event-related EEG changes. This might explain the relatively small evidence of positive correlations between NF learning and cognitive outcome obtained in NF applications in optimal cognitive performance (Gruzelier, 2014a).

The establishment of this temporal link would be possible by using EEG-dependent interactive ERP analysis. In this method, the presentation of a stimulus eliciting ERP component is dependent on the spontaneous (Price, 1997; Rahn & Basar, 1993) or TMS induced (Price, 2004) state of the background EEG immediately preceding it. The background activity (e.g., amplitude, instantaneous phase) is then treated as an independent variable and a causal effect on the ERP dependent variable can be argued. In line with this proposal, a recent real-time fMRI neurofeedback study suggests that participants trained to control the level of spontaneous activation of the visual cortex showed a selective increase in stimulus-evoked activity when able to invoke a previously learned up-regulated state at the trained location (Scharnowski, Hutton, Josephs, Weiskopf, & Rees, 2012). Similarly, a causal relationship between NF-induced changes and ERP amplitude and latency could be achieved through the voluntary activation of the desired pattern of EEG background activity trained

during transfer trials (i.e., without feedback) and then used in interactive ERP recordings as an independent variable.

1.2.2. Models of low-beta/theta NF effects on attention and response inhibition

Over the years, several theoretical models have been proposed to explain the alleged influence of NF on attention and response inhibition. These models have been heavily influenced by demonstrations of successful operant conditioning of neuronal spike activity and brain oscillations in animals (Fetz, 1969). Therefore, these models emphasize the implicit nature of brain-regulation and provide only limited understanding of how these processes may be mediated by volitional self-regulation.

The operant conditioning of low-beta frequencies was first demonstrated in the context of the learned suppression of a previously rewarded behavioral response in cats (Roth, Serman, & Clemente, 1967; Serman, Wyrwicka, & Roth, 1969; Wyrwicka & Serman, 1968). The reinforcement of a rhythmic 12-14 Hz EEG activity in the sensorimotor cortex, thereafter labeled Sensorimotor Rhythm (SMR), was associated with a behavioral pattern of quiet alertness, while the reinforcement of higher frequencies and the extinction of SMR activity led to restless and agitated behavior. Serman and colleagues (Harper & Serman, 1972; Howe & Serman, 1972) hypothesized that the SMR originates in the ventrobasal nuclei (nVB) of the thalamus which is associated with conducting the afferent sensorimotor information to the cortex. The behavioral suppression of somatomotor activity and decrease in muscular tone causes the nVB firing pattern to shift from a fast and non-rhythmic to systematic burst discharges that characterize the SMR in intracranial and scalp EEG recordings. Moreover, it was proposed that the SMR was modulated by the brainstem neuromodulatory systems which, during the waking activity, maintain the depolarization of the thalamic structures and prevent the occurrence of the rhythmic activity. Thus, SMR synchronization may reflect an active state of behavioral inhibition characterized by the absence of movement or of intention to move. The SMR activity was also proposed to influence the attentional processes by reducing the interference of sensory and somatomotor information processing in other brain areas (Mann, Serman, & Kaiser, 1996).

With the advent of NF applications to the management of resistant epileptic seizures in humans (for a review and meta-analysis see Serman & Egner, 2006 and Tan et al., 2009), the reinforcement of SMR was complemented by the suppression of theta and high-beta activities justified by the need to signal epileptiform slow and spike activity respectively (Lubar & Bahler, 1976). The goal of enhancing beta relative to theta amplitude was further grounded on the hypothesis that a low-beta/theta ratio may be a physiological marker of cortical arousal responsible for the inattention and impulsivity/hyperactivity symptomatology of ADHD (Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992). Lubar (1997) expanded this conceptualization by proposing that the increase in higher frequencies relative to lower frequencies would facilitate the transition from a hypercoupled to a hypocoupled state (i.e., from a resonate mode characterized by long range communication to more localized and specialized information processing). In support of this theory Lubar, Swartwood, Swartwood, & O'Donnell (1995) reported that ADHD children evinced behavioural improvements in composite measures of attention and response inhibition in the Test of Variables of Attention (TOVA, Greenberg, Kindschi, & Corman, 1996; for a description of the task see section 1.2.4.1.) following an intensive beta1/theta NF regime. Interestingly, these improvements were significantly higher in those participants that showed a higher decrement in theta activity. However, given the composite nature of the cognitive measures the exact implications of theta suppression for the processes of attention and response inhibition remained elusive.

Othmer, Othmer, & Kaiser (1999) later proposed that SMR/theta NF in the right hemisphere and beta1/theta NF in the left hemisphere would have distinct implications for response inhibition and attention processes. This distinction was justified by “a crucial fulcrum point” that “appears to exist in the vicinity of 15 Hz, above which the subjects will be moved toward sympathetic arousal and below which parasympathetic dominance will be promoted” (pp. 282). Based on a model of hemispheric specialization (Tucker & Williamson, 1984), beta1/theta NF in the left hemisphere (C3) was proposed to compensate the underactivation responsible for inattentiveness, while SMR/theta NF in the right hemisphere (C4) would regulate the excessive right hemispheric activity responsible for impulsivity. Although the distinct behavioral and cognitive outcomes of SMR/theta NF and beta1/theta NF have been confirmed in subsequent studies (Doppelmayr & Weber, 2011;

Egner & Gruzelier, 2001, 2004), the assumptions regarding hemispheric specialization and frequency specificity remain to be confirmed.

1.2.3. Learning specificity

The claims that SMR and beta1 NF might be related to specific cognitive outcomes are insufficiently supported by evidence of training- and frequency-specific effects. Following recent proposals (Gruzelier, 2014b; Zoefel, Huster, & Herrmann, 2011) the demonstration of specific learning effects should encompass two aspects: *trainability* or *training-specificity* (i.e., the demonstration that the EEG changes resulted from the training and not from unspecific factors) and *independence* or *frequency specificity* (i.e., the demonstration that the training selectively impacted the EEG parameters targeted by the intervention when other frequencies in the EEG spectrum are taken into consideration). Thus, the disentanglement of specific from unspecific learning effects should be critically dependent on the demonstration of changes in the experimental NF manipulation relative to a comparison or control condition. For example, *training-specificity* was defined as a significant directional change in the frequency of interest (e.g., increments in SMR amplitude) in response to a specific experimental manipulation (e.g., SMR NF) when compared with unspecific comparison or control conditions (e.g., beta1 or control NF).

Table 1.1. presents a summary of the absolute and relative amplitude changes involving theta, SMR, beta1 frequencies in previous studies. As shown in the table, the success of the NF experimental manipulations has been assessed through both changes during active feedback periods and in the passive resting state. In active periods, learning has been defined by both within- and across-sessions changes, while in the passive resting state it has been determined by the across session change in pre-training baseline or by the difference in QEEG power between the beginning and the end of the training.

The within- and across-session distinction evinces the dynamic EEG changes in different time scales. During neurofeedback learning trials, the reinforcement of EEG activity is achieved by rewarding directional changes in the EEG parameter (i.e, amplitude increases or decreases) in relation to a reference period (e.g., pre-training resting state baseline). The repetition of this associative learning process across several training trials in the same training session defines the *within-session learning* process. To the extent that the re-

establishment of the previously learned association is facilitated through repetition over a variable number of sessions a carry-over effect from one session to the next may result, evincing *across-session learning*. A second aspect that must be taken into consideration when determining the specificity of learning concerns the state of the organism during the EEG recording. Given that EEG exhibits distinct patterns of synchronization/desynchronization during the resting state and task performance it is reasonable to assume that the learning process may affect differently the EEG amplitude during *passive resting state* and *active feedback* periods.

1.2.3.1. Within- and across-session changes in active feedback periods

1.2.3.1.1. SMR

Within-session

Despite abundant demonstrations of successful SMR conditioning in single-case and non-randomized controlled studies (Lubar & Bahler, 1976; Lubar & Shouse, 1976; Lubar et al., 1981; Sterman & Friar, 1972; Sterman, Howe, & Macdonald, 1970; Sterman et al., 1974), only recently within-session SMR amplitude increments were demonstrated in controlled studies. In two of these, within-session SMR amplitude increments were evinced by significantly positive slopes from baseline to the last training period in the SMR/theta NF, while the same correlational analysis was not significant in sham NF conditions (Kober et al., 2015; Witte, Kober, Ninaus, Neuper, & Wood, 2013). In two other studies, the cognitive effects of SMR/theta NF were compared with other NF and control conditions (see table 1.2.) but within-session amplitude changes in SMR, theta and SMR/theta ratio were only investigated for the SMR/theta NF (Ros et al., 2009; Vernon et al., 2003). Interestingly, both studies showed SMR/theta ratio amplitude increments but Ros and collaborators. (2009) could not find evidence of SMR amplitude increments. Other studies suggest that despite SMR/theta ratio amplitude increments the SMR amplitude was decreased relative to the initial baseline period in the SMR/theta NF (de Zambotti, Bianchin, Magazzini, Gnesato, & Angrilli, 2012; Gruzelier, Foks, Steffert, Chen, & Ros, 2014).

Table 1.1. Summary of the absolute and relative amplitude changes involving theta, SMR, beta1 frequencies in previous studies. The changes are denoted by the overall trend towards increase (Inc), decrease (Dec) or no change (NC) for each EEG parameter (EEG) during active periods (within- and across-session) and passive periods in pre-training resting state baseline (Baseline) and from pre- to post-training qEEG (qEEG) following different NF protocols including Random Frequency (RF) NF, sham NF. The number of NF sessions (No.) per condition is also indicated.

Study	NF Protocol	No.	EEG	Active		Passive	
				Within	Across	Baseline	qEEG
Vernon et al. (2003)	SMR/(T+B2)	8	SMR/T	Inc	n/a	n/a	n/a
			SMR	Inc	n/a	n/a	n/a
			T	Dec	n/a	n/a	n/a
			SMR/B2	NC	n/a	n/a	n/a
Egner et al. (2004)	SMR/(T+HB)	10	SMR	n/a	n/a	n/a	NC
			Other	n/a	n/a	n/a	NC
	B1/(T+HB)	10	B1	n/a	n/a	n/a	NC
			Other	n/a	n/a	n/a	NC
Hoedlmoser et al. (2008)	SMR	10	Abs. SMR	n/a	NC	NC	NC
			Rel. SMR	n/a	Inc	NC	NC
	RF	10	Abs. SMR	n/a	NC	NC	NC
			Rel. SMR	n/a	NC	NC	NC
Ros et al. (2009)	SMR/(T+HB)	8	SMR/T	Inc	Inc *	n/a	n/a
			SMR	NC	n/a	n/a	n/a
			T	Dec	n/a	n/a	n/a
Doppelmayr & Weber (2011)	SMR/(LT+HB)	30	SMR	n/a	Inc	n/a	n/a
			T	n/a	NC	n/a	n/a
			B1	n/a	NC	n/a	n/a
			B1/T	n/a	NC	n/a	n/a
	B1/T Ratio & RF	30 & 30	SMR	n/a	NC	n/a	n/a
			T	n/a	NC	n/a	n/a
			B1	n/a	NC	n/a	n/a
Weber et al. (2011)	SMR/(LT+HB)	25	SMR	n/a	Inc	n/a	n/a
	SMR/(LT+HB)	25	SMR	n/a	NC**	n/a	n/a
de Zambotti et al. (2012)	SMR/T	16	SMR/T	Inc	Inc	Dec	n/a
			SMR	Dec	Inc	n/a	n/a
			T	Dec	NC	n/a	n/a
Becerra et al. (2012)	T supression	30	Abs. T	n/a	n/a	n/a	Dec
			Abs. A	n/a	n/a	n/a	Inc
	Sham	30	Abs. T	n/a	n/a	n/a	NC
			Abs. A	n/a	n/a	n/a	NC
	T supression	30	Rel. T	n/a	n/a	n/a	Dec
			Rel. A	n/a	n/a	n/a	Inc
	Sham	30	Rel. T	n/a	n/a	n/a	Dec
			Rel. A	n/a	n/a	n/a	Inc

Table 1.1. continued

Study	NF Protocol	No.	EEG	Active		Passive	
				Within	Across	Baseline	qEEG
Kober et al. (2013)	SMR	10	SMR	n/a	Inc	n/a	n/a
			G	n/a	NC	n/a	n/a
	Gamma	10	SMR	n/a	NC	n/a	n/a
			G	n/a	NC	n/a	n/a
Witte et al. (2013)	SMR/(T+HB)	10	SMR	Inc	NC	NC	n/a
	Sham		SMR	NC	NC	NC	n/a
Gruzelier et al. (2014a)	SMR/(T+HB)	10	SMR/T	Inc	NC	n/a	n/a
			SMR	Dec	n/a	n/a	n/a
			T	Dec	n/a	n/a	n/a
			SMR/HB	NC	NC	n/a	n/a
Gruzelier et al. (2014b)	SMR/(T+HB)	10	SMR/T	NC	NC	n/a	n/a
			SMR/HB	Inc	Inc	n/a	n/a
Schabus et al. (2014)	SMR	10	SMR	n/a	Inc	n/a	n/a
			B	n/a	Inc	n/a	n/a
	RF	5	SMR	n/a	NC	n/a	n/a
Kober et al. (2015)	SMR/(T+HB)	10	SMR	Inc	NC	n/a	n/a
			T	NC	NC	n/a	n/a
			HB	Inc	n/a	n/a	n/a
	Sham	10	SMR	NC	NC	n/a	n/a
			T	NC	NC	n/a	n/a
			HB	NC	n/a	n/a	n/a

Low -theta (LT):3-5Hz; Theta (T):4-7Hz; Alpha (A):8-12Hz; SMR:12-15Hz; Beta (B):16-25Hz; B1:15-18Hz; B2:18-22Hz;High-beta (HB):22-30Hz; Gamma (G):40-43Hz; Abs.=absolute amplitude; Rel.= Relative amplitude; * = first half of training; ** = non-learners

Across-session

There is mixed evidence regarding across-session SMR learning following both SMR/theta and SMR (i.e., without theta and high-beta suppression) NF. Doppelmayr and Weber (2011) investigated normalized amplitude changes in SMR, beta1 and theta as function of three NF conditions: SMR/theta, beta1/theta ratio and random-frequency (RF NF). For each of the frequency bands, the mean amplitude was calculated for six blocks of five sessions (each block corresponding to a week of training) and normalized to the mean amplitude in the first block. The SMR amplitude change was significantly higher in the final relative to the initial training block in the SMR/theta NF but not in the beta/theta ratio NF and RF NF suggesting training specific SMR learning.

Another study investigating relative and absolute SMR amplitude changes across ten sessions of SMR NF and RF NF suggests that the demonstration of SMR learning might depend on the method of calculating across-session amplitude changes (Hoedlmoser et al., 2008). In this study, the relative SMR amplitude (calculated by dividing the mean amplitude during active trials for each session by the mean amplitude of the pre-training resting state) was found to increase from early to late training sessions in SMR but not in RF NF. However, the SMR absolute amplitude (calculated by simply averaging the within-session amplitude in active trails) in SMR NF was not reliably increased across-sessions when compared to the RF NF.

In line with these results, Kober and collaborators (2013) revealed linear increases in SMR amplitude across-sessions (as evinced by significant regression slopes in SMR NF), while no increases were observed in a gamma-enhancement NF. Other studies have provide evidence of SMR amplitude increments following SMR/theta NF but the failure to report SMR amplitude changes in comparison conditions (de Zambotti et al., 2012; Ros et al., 2009) or the unequal number of sessions in the control condition (Schabus et al., 2014) prevents further conclusions regarding training-specificity.

In contrast with this body of evidence, recent controlled studies (Kober et al., 2015; Witte et al., 2013) have failed to demonstrate across-session SMR amplitude increments, in spite of evidence of within-session learning. Here, the linear increments in SMR amplitude across ten SMR/theta NF sessions were not significantly different from those obtained by Sham NF conditions. However, given that only within-subjects analysis were reported, these results should be interpreted with caution when considering its implications for the training specificity of across-session SMR increments.

There are several possible explanations for these inconsistent findings. Besides the different methods of defining across-session learning (e.g., relative vs. absolute) mentioned above, the low number of NF sessions might have affected the development and consolidation of an appropriate self-regulatory strategy in some studies (e.g., Kober et al., 2015; Ros et al., 2009). However, other studies with equivalent number of sessions have provided evidence of training-specific SMR increments (e.g., Hoedlmoser et al., 2008; Kober, Witte, & Ninaus, 2013). Additionally, the failure to observe across-session SMR learning may be related to individual differences in learning. One study indicates that a

percentage as high as 50% of the participants may fail to show evidence of across-sessions SMR amplitude increments and that SMR learners can only be reliably discriminated from non-learners after more than ten sessions (Weber et al., 2011). Finally recent studies suggest that individual differences in strategy adoption and consistency of training may play a significant role in across-session learning (Ros et al., 2009; Witte et al., 2013).

1.2.3.1.2. Beta1

Within-session

As shown in table 1.1., no controlled studies to date investigated the within-session amplitude changes in the sensorimotor beta1 frequency.

Across-session

Doppelmayr and Weber (2011) failed to provide supportive evidence of across-session beta1 learning after thirty beta1/theta NF sessions relative to SMR/theta NF and RF NF. However, as noted above, it is unclear whether the absence of significant across-session beta1 amplitude changes may be associated with the method of calculating across-session amplitude changes, individual differences in learning and/or any other factors affecting the development of a consistent self-regulatory strategy. Speculatively, the failure to inhibit high-beta frequencies in the beta1/theta NF could have contributed to a lesser control over states of excessive cortical excitability incompatible with successful sensorimotor beta conditioning (Wyrwicka & Serman, 1968).

1.2.3.1.3. Theta

Within-session

Jackson Beatty and colleagues (Beatty, Greenberg, Deibler, & O'Hanlon, 1974; O'Hanlon & Beatty, 1977; Williams, Beatty, & O'Hanlon, 1975) first demonstrated the possibility of voluntarily modulating relative occipital theta amplitude (i.e., 3-7 Hz/3-30 Hz) during prolonged radar monitoring tasks. In these studies, healthy adult volunteers were able to suppress and enhance theta ratio amplitude relative to a condition where feedback was not provided. These pioneering findings are, however, difficult to integrate with the subsequent literature focusing on functional distinct central and fm-theta rhythms (Enriquez-

Geppert et al., 2014a; Wang & Hsieh, 2013). In fact, posterior theta rhythms often associated with drowsiness and mental effort (Schacter, 1977; Vogel, Broverman, & Klaiber, 1968; Williams, Granda, Jones, Lubin, & Armington, 1962), may be functional distinct from the central-midline theta activity that has been related to executive control. Moreover, because of the lengthier NF sessions those early studies are difficult to compare with subsequent ones in terms of the time course of theta amplitude, i.e., the tendency for theta amplitude to increase over time especially during monotonous and long duration task (Huang, Jung, Delorme, & Makeig, 2008; Maltez, Hyllienmark, Nikulin, & Brismar, 2004; Wascher et al., 2013).

More recently, the investigation of theta-suppression in central electrodes following low-beta/theta NF independent from task performance has provided conflicting evidence. As shown in table 1.1., in several SMR/theta NF studies in healthy adults the within-session increases in SMR/theta ratio amplitude were underpinned by theta decrements (de Zambotti et al., 2012; Gruzelier, Hirst, Holmes, & Leach, 2014; Ros et al., 2009; Vernon et al., 2003). In all of these studies, theta amplitude decreased linearly from the beginning to the end of the training session. However, none of these studies reported within-session theta amplitude changes in comparison or control conditions. Thus, from these studies it remains unclear whether theta amplitude decrements may reflect NF unspecific effects such as time on task, cognitive effort or placebo. Importantly, other SMR/theta NF studies suggest that within-session theta amplitude decrements are not necessarily a by-product of unspecific NF effects. In fact, other studies failed to provide evidence of within-session theta amplitude decrements or changes in the SMR/theta ratio in active or sham NF (Kober et al., 2015; Gruzelier, Foks, Steffert, Chen, & Ros, 2014).

Across-session

As shown in table 1.1., few studies to date examined across-session theta amplitude changes in the context of low-beta/theta NF. However, the available evidence suggests that theta amplitude changes remain constant across sessions (de Zambotti et al., 2012; Doppelmayr & Weber, 2011; Kober et al., 2015), i.e., the extent of theta desynchronization from the beginning to the end of the sessions was not higher as NF training progresses.

1.2.3.2. Across-session changes in passive periods

As previously noted, the impact of theta suppression and low-beta enhancement NF on the resting state theta and beta activity has been assessed exclusively through measures of across session change in pre-training baseline or by the difference in QEEG power between the beginning and the end of the training.

1.2.3.2.1. SMR

Contrary to active periods, Hoedlmoser and collaborators (2008) found no evidence of across-session relative SMR amplitude changes in resting state pre-training baseline. Similarly, subsequent studies either failed to evince SMR amplitude increments or even showed SMR amplitude decrements across pre-training baselines, despite observable increments in active periods (de Zambotti et al., 2012; Witte et al., 2013). Moreover, in line with one previous study (Egner, Zech, & Gruzelier, 2004), Hoedlmoser and collaborators (2008) failed to provide supportive evidence of the impact of SMR NF on the resting state SMR activity as measured by QEEG at the beginning and at the end of training irrespective of whether relative or absolute SMR power was considered. Taken together, these findings support the interpretation that successful SMR amplitude increments might depend on an active self-regulatory mechanism (probably involving the control of voluntary movement) which has little impact on the resting state SMR amplitude.

1.2.3.2.2. Beta1

Similarly to SMR, one previous study failed to provide supportive evidence of beta1 amplitude changes as measures by pre- and post-training resting state QEEG following beta1/theta NF (Egner et al., 2004). Moreover, a recent review of the controlled studies examining the effects of beta1/theta NF on ADHD did not find evidence to support the claims of enduring changes in the theta/beta ratio in QEEG measures (Arns et al., 2014).

1.2.3.2.3. Theta

Regarding theta amplitude changes in passive resting state, only one study provided supportive evidence of successful theta suppression in normal elderly subjects relative to a age-matched control group receiving non-contingent feedback (Becerra et al., 2012). For the theta

suppression NF group the abnormally elevated absolute theta power was identified across the scalp in relation to a normative database and feedback was provided based on the EEG location where the z-score was most deviated from the normal. After thirty sessions of NF, the absolute theta power in frontal and midline electrodes was significantly reduced in the experimental group relative to controls. However, the relative theta power was significantly reduced in both theta suppression (over frontal electrodes) and sham NF (across the scalp). Given the varying locations of these effects and the lack of homogeneity of the training sites care must be taken when extrapolating these findings to central midline theta rhythms.

1.2.3.3. Frequency-specific effects

The self-regulation of EEG activity is a complex cognitive task involving specific mental processes associated with the functional properties of target frequency (e.g., active motor inhibition in SMR conditioning) and unspecific mental processes also present in other forms of feedback learning such as attention and performance monitoring, cognitive control and motivational aspects (Gruzelier, 2014b). Some of these unspecific aspects are known to have a direct effect on the EEG such as post-reinforcement fast wave synchronization during EEG conditioning (Clemente, Serman, & Wyrwicka, 1964) and increases in theta power following negative feedback and in beta power following positive feedback in feedback learning (Cohen & Ranganath, 2007; Luft, Nolte, & Bhattacharya, 2013). Moreover, since any complex mental activity is probably the result of a concertation of multiple oscillatory frequencies (Canolty & Knight, 2010) it comes with no surprise that changes in frequencies other than the ones targeted by the NF interventions has been a prevalent observation in research (Gruzelier, 2014c).

1.2.3.3.1 SMR frequency-specific effects

Besides the already mentioned theta amplitude decrements, SMR/theta NF has been associated with amplitude changes in beta and high-beta frequencies. As shown in table 1.1., previous studies have found conflicting evidence regarding the effects of SMR/theta NF on beta and high beta frequencies. Even despite beta and/or high-beta amplitude suppression instructions, some studies found increments in these frequencies (Kober et al., 2015; Schabus et al., 2014) or could not find evidence that the amplitude in these frequencies became lower

than in SMR as evinced by unchanged SMR/beta and SMR/high-beta ratio amplitudes (Gruzelier, et al., 2014a; Vernon et al., 2003). Furthermore, two of these studies suggest that SMR/theta NF specifically increased the amplitude of higher beta frequencies relative to control conditions (Kober et al., 2015; Schabus et al., 2014). The latter results are surprising in light of the proposed antithetic effects of SMR and higher frequencies conditioning demonstrated in previous non-randomized controlled studies (Lubar & Shouse, 1976; Wyrwicka & Sterman, 1968). The reduced number of NF sessions in some studies may explain this lack of frequency-specificity. In fact, previous non-randomized controlled studies suggest that SMR amplitude increments become independent from increments in adjacent alpha and high beta frequency bands (Lubar & Shouse, 1976; Sterman & Friar, 1972).

In contrast, other studies found no evidence of concomitant changes in beta1 amplitude (Doppelmayr & Weber, 2011) or in gamma frequency (Kober et al., 2013) and found an increase in SMR/high-beta ratio amplitude (Gruzelier et al., 2014b) suggestive of a differentiation between SMR and high beta amplitude after SMR/theta NF.

1.2.3.3.2. Beta1 frequency-specific effects

As shown in table 1.1., fewer studies investigated the specificity of beta1 amplitude increments relative to other frequencies. Doppelmayr and Weber (2011) found no evidence of significant across-session amplitude changes in theta, SMR and beta1 frequencies in beta1/theta NF relative to other NF protocols. Similarly Egner and collaborators (2004) could not find evidence of pre- to post-training QEEG changes in beta1 power or in other frequencies ranging from delta to high-beta. Consequently, these studies were inconclusive regarding the frequency-specificity of beta1 amplitude increments.

1.2.3.3.3. Theta frequency-specific effects

As shown in table 1.1., one previous study found that theta suppression NF was associated with significant absolute and relative alpha amplitude increments (Becerra et al., 2012). However, while the absolute amplitude measures suggest that theta suppression and alpha increments were observed in the theta suppression but not in sham NF, the relative amplitude measures showed that sham NF was also associated with significant theta

decrements and alpha increments. Thus, theta suppression NF may be associated with specific decrements in theta power but also with power changes in other frequencies, namely with an increase in alpha power. However, it is unclear whether unspecific effects of training may explain these changes.

1.2.4. Low-beta/theta NF effects on attention and inhibition

Table 1.2. summarizes the specific effects of SMR/theta and beta1/theta NF on electrophysiological and behavioral measures of selective attention and response inhibition in healthy adults and in ADHD children. To the exception of two studies (Egner & Gruzelier, 2001; Kropotov et al., 2005) only those that could provide evidence of the distinct cognitive effects of the two NF protocols will be discussed. Other studies that provided evidence of cognitive improvements in these domains following mixed protocols combining SMR/theta with beta1/theta NF (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Lévesque, Beauregard, & Mensour, 2006; Rossiter, & Lavaque, 1995), and beta1/theta with slow cortical potentials (SCP) (Gevensleben, Holl, Albrecht, Schlamp, et al., 2009; Gevensleben, Holl, Albrecht, Vogel, et al., 2009; Liechti et al., 2012; Wangler et al., 2011) will not be considered because of difficulties in interpreting the protocol specificity of the results. It is worth noting that, although other NF interventions have been associated with cognitive improvements¹, low-beta/theta NF has received by far the most attention from the literature as an intervention capable of specifically influencing the thalamocortical mechanisms responsible for variations in alertness and behavioral inhibition in both healthy and clinical populations.

1.2.4.1. Mixed low-beta frequencies effects on attention and response inhibition

The impact of low-beta/theta NF on the amplitude of ERP components indexing selective attention (P3b) and response inhibition (Nogo-P3) was demonstrated in both healthy adults and ADHD children.

¹ Cognitive improvements in the young and elderly healthy adults have been associated with frontal-midline theta (Enriquez-Geppert, Huster, Figge, et al., 2014; Wang & Hsieh, 2013) alpha (Angelakis et al., 2007; Escolano, Aguilar, and Minguez, 2011; Hanslmayr et al., 2005; Nan et al., 2012; Zoefel et al., 2011) and gamma enhancement (Keizer, Verment, et al., 2010; Keizer, Verschoor, et al., 2010; Salari and Rose, 2013; Staufienbiel et al., 2014).

Table 1.2. Outcome of studies investigating NF effects on selective attention and response inhibition. The pre- to post-training change was classified as Increased (Inc), Decreased (Dec) or No Change (NC) for the variables Mean Reaction Time (RT), Reaction Time Standard Deviation (RT SD), Accuracy, Hit rate, False Alarm (FA) rate, Go-P3 amplitude and Nogo-P3 amplitude in different cognitive tasks. Information on the type of NF protocol, electrode location and number of NF sessions (No.) is also shown.

Study	NF (electrode)	No.	Task	Pre- to post-training change						
				RT	RTV	Accuracy	Hit rate	FA rate	Go-P3	Nogo-P3
Egner & Gruzelier (2001)*	SMR **	10	TOVA	NC	NC	Inc	NC	Dec	n/a	n/a
			auditory oddball	n/a	n/a	n/a	n/a	n/a	Inc	n/a
	B1 **	10	TOVA	NC	NC	Dec	NC	Inc	n/a	n/a
			auditory oddball	n/a	n/a	n/a	n/a	n/a	Inc	n/a
Vernon et al. (2003)	SMR/B2 (Cz)	8	Digit sequence recognition	n/a	n/a	n/a	Inc	n/a	n/a	n/a
	T/A (Cz)	8		n/a	n/a	n/a	NC	n/a	n/a	n/a
	Wait list	0		n/a	n/a	n/a	NC	n/a	n/a	n/a
Egner & Gruzelier (2004)	SMR/T (Cz)	10	TOVA	NC	Dec (marginal)	Inc	NC	NC	n/a	n/a
			divided attention	Dec	Dec	Inc	Inc	NC	n/a	n/a
			auditory oddball	n/a	n/a	n/a	NC	NC	NC	n/a
	B1/T (Cz)	10	TOVA	Dec	Dec (marginal)	NC	NC	NC	n/a	n/a
			divided attention	Dec	NC	NC	NC	NC	n/a	n/a
			auditory oddball	n/a	n/a	n/a	NC	NC	Inc	n/a
Alexander Technique	10	TOVA	NC	NC	NC	NC	NC	n/a	n/a	
		divided attention	Dec	NC	NC	NC	NC	n/a	n/a	
Kropotov et al. (2005)*	B1(C3-Fz) + SMR (C4-Pz)	15-22	Go/Nogo	Dec	Dec	n/a	Dec	Dec	Inc	Inc
			Go/Nogo***	NC	NC	n/a	Dec	Dec	NC	NC
Ros et al. (2009)	SMR/(T+HB)(Cz)	8	Time on task	Dec	n/a	n/a	n/a	n/a	n/a	n/a
	A/T (Pz)		Time on task	Dec (marginal)	n/a	n/a	n/a	n/a	n/a	n/a
Doppelmayr & Weber (2011)	SMR/(LT+HB) (C3-C4)	30	simple reaction time	Dec	n/a	n/a	n/a	n/a	n/a	n/a
			choice reaction time	Dec	n/a	n/a	n/a	n/a	n/a	n/a
			spatial rotation	n/a	n/a	n/a	Inc	n/a	n/a	n/a
			d2	n/a	n/a	n/a	NC	NC	n/a	n/a
	B1/T Ratio (C3-C4)	30	simple reaction time	NC	n/a	n/a	n/a	n/a	n/a	n/a
			choice reaction time	NC	n/a	n/a	n/a	n/a	n/a	n/a
			spatial rotation	n/a	n/a	n/a	NC	n/a	n/a	n/a
			d2	n/a	n/a	n/a	NC	NC	n/a	n/a
	RF (C3-C4)	30	simple reaction time	Inc	n/a	n/a	n/a	n/a	n/a	n/a
			choice reaction time	Inc	n/a	n/a	n/a	n/a	n/a	n/a
			spatial rotation	n/a	n/a	n/a	NC	n/a	n/a	n/a
			d2	n/a	n/a	n/a	NC	NC	n/a	n/a

Table 1.2. continued

Study	NF (electrode)	No.	Task	Pre- to post-training change						
				RT	RTV	Accuracy	Hit rate	FA rate	Go-P3	Nogo-P3
Bakhshayesh et al. (2011)	Beta1/Theta (CPz-FCz)	30	CPT	Dec	NC	n/a	NC	NC	n/a	n/a
			cancellation	Inc	n/a	Inc	Inc	Dec	n/a	n/a
	EMG-Biofeedback	30	CPT	NC	NC	n/a	NC	NC	n/a	n/a
			cancellation	NC	n/a	NC	NC	NC	n/a	n/a
Gruzelier et al. (2014b)	SMR/(T+HB)(Cz)	10	TOVA	NC	NC	NC	NC	Dec (marginal)	n/a	n/a
	A/T (Pz)	10		NC	NC	NC	NC	Dec	n/a	n/a
	Wait list	0		NC	NC	NC	NC	n/a	n/a	n/a
Kober et al. (2015)	SMR/(T+HB) (Cz)	8	auditory oddball	NC	n/a	Inc	n/a	n/a	n/a	n/a
			Sternberg	n/a	n/a	Inc	n/a	n/a	Inc	n/a
	Sham-NFT (Cz)	8	auditory oddball	Dec	n/a	NC	n/a	n/a	n/a	n/a
			Sternberg	n/a	n/a	Inc	n/a	n/a	NC	n/a

Low-theta (LT):3-5Hz; Theta (T):4-7Hz; Alpha (A):8-12Hz; SMR:12-15Hz; B1:15-18Hz; B2:18-22Hz;High-beta (HB):22-30Hz; * = SMR+beta1/(T+HB) NF; ** = amplitude; *** = non-learners

As shown in table 1.2., to date, just one study investigated the effects of low-beta/theta NF on the Nogo-P3 amplitude (Kropotov et al., 2005). In each session, the ADHD children started by attempting to enhance the right-hemispheric SMR amplitude relative to lower (1-11 Hz) and higher frequencies (19-30 Hz) for 7-10 minutes. In the second half of the sessions the enhancement of beta1 amplitude relative to the same lower and higher frequencies was trained for 20 minutes. For statistical analysis, the participants were divided in two groups (learners and non-learners) according their ability to increase the neurofeedback parameter by 25% in the training periods relative to the resting state baseline in more than 60% of the sessions. At pre- and post-training the participants performed an auditory equiprobable cued-Go/Nogo task. The analyses revealed significant pre- to post-training increases in Go-and Nogo-P3 amplitude only in the learners group. At the behavioural level, separate statistical analysis for learners and non-learners revealed significant decreases in omission and commission errors in both groups. However, just the learners group was associated with decreased RT and RT-SD. Taken together, these results suggest that the successful enhancement of relative beta amplitude (i.e., the learners group)

may be associated with improvements in successful response inhibition (Nogo-P3) but not necessarily with decreasing unsuccessful response inhibition (commission errors). Moreover, increased processing efficiency of task-relevant information (i.e., increased Go-P3, decreased RT and RT-SD) suggest a modification in the responding strategy of learners. A strategic increase in response speed, may have imposed higher demands on response inhibition that could have been reflected in increased Nogo-P3 amplitude (Dimoska et al., 2006; Smith et al., 2006).

Several methodological limitations recommend a careful interpretation of these findings. Firstly, the failure to provide the relevant statistical interactions of time (pre vs. post-training), stimulus (Go vs. Nogo) and group (learners vs. non-learners) precludes the interpretation that the response inhibition effects were specific to the learners group. Another limitation of this study was the variable number of sessions (as shown in table 1.2.). Although the authors provide the criteria for the different moments to terminate the treatment (according to age, ADHD type, learning curves and parent reports), the number of sessions was not taken into account in the statistical analysis comparing learners and non-learners.

In healthy adults, Egnér and Gruzeliér (2001) first provided evidence that SMR and beta1 amplitude increments had significant positive correlations with improvements in response inhibition and selective attention respectively. Here, each thirty-minute session consisted of two equal periods of SMR/theta NF at C4 and beta1/theta NF at C3 in counterbalanced order over the ten training sessions. The P3b amplitude in a divided attention auditory oddball task was taken as a measure of improved selective attention. The oddball task consisted of auditory tones of different pitch and frequency of occurrence presented in two blocks. In the first block participants were instructed to attend to the task-relevant channel (left ear) and to ignore the simultaneous stimulus presentation in the task irrelevant channel (right ear). In the second block the task relevance of the channels was reversed. Stimulus discrimination context was made difficult by the frequency proximity of the pure sinusoidal auditory tones (Standard = 1000 Hz; Target = 1100 Hz). In the absence of a control condition, the pre- to post-training comparisons revealed significant increments in the peak P3 amplitude (averaged across nine electrodes distributed across frontal, central and parietal regions) in the post-stimulus 250-400ms time window.

Moreover, the behavioural performance was investigated in the TOVA. In this choice RT task the target and non-target visual stimuli were presented in two fixed order conditions (infrequent target and frequent target) with a Go/Nogo ratio of 3.5/1 (reversed in infrequent target condition). The results revealed that the mixed low-beta/theta NF was associated with significant reductions in commission errors and increases in perceptual discrimination (d'), while no changes were observed in omission errors, mean RT and RT-SD from pre- to post-training.

As shown in table 1.2., further *post-hoc* exploratory analysis attempted to understand whether enhancements in SMR and beta1 amplitude could differentially predict variations in electrophysiological and behavioural performance. The ratio between successive within-session SMR and beta1 amplitude increments and decrements was taken as an index of SMR and beta1 learning. Partial correlations analysis revealed that both SMR and beta1 enhancements were positively correlated with increased peak P3b amplitude. However, the two learning indices predicted different behavioural outcomes. The SMR learning was positively correlated with reduced commission errors and increased d' when controlling for beta1 learning, whereas beta 1 learning was significantly correlated with increased commission errors and reduced d' when controlling for corresponding enhancements in SMR amplitude. However, the practical significance of these partial correlations may be questioned by the fact that SMR and beta1 enhancement were also positively correlated. These results provided support for the interpretation that SMR and beta1 might be functionally distinct frequencies and motivated a subsequent investigation of this hypothesis in a between subjects design.

1.2.4.2. SMR and beta1 NF differential effects on attention and response inhibition

To date, the specific effects of SMR/theta NF and beta1/theta NF on attention and inhibition were compared in two studies (section 1.2.4.2.1). Other randomized controlled studies investigated these effects separately for SMR/theta NF (section 1.2.4.2.2) and for beta1/theta NF (section 1.2.4.2.3).

1.2.4.2.1. Comparison between SMR/theta NF and beta1/theta NF cognitive outcomes

Based on evidence that SMR and beta1 amplitude increments could predict different patterns of behavioral outcomes (Egner & Gruzelier, 2001), Egner and Gruzelier (2004) compared the effects of SMR/theta NF and beta1/theta NF in a between-subjects design using the same electrophysiological and behavioral measures (see section 1.2.4.1.). Differently from that previous study, the electrode placement was changed to Cz (with left earlobe reference) for both NF protocols and an active control condition was included.

In the auditory oddball task, the P3b amplitude was increased in the beta1/theta NF across the scalp (average of frontal, central and parietal derivations), while no significant changes were observed in the SMR/theta NF. However, because the amplitude of the P3b component was not calculated for other stimulus categories (i.e., standard stimulus in the attended channel, target and standards in the non-attended channel) it is unclear whether the P3 amplitude was selectively increased to the target stimulus relative to other stimulus categories. Moreover, it was not possible to determine whether the P3 amplitude to task-irrelevant (i.e., presented in the unattended channel) frequent or infrequent stimulus (P3a) was changed as a function of any of the NF protocols. Thus, from these results it was not possible to determine whether voluntary or involuntary selective attention processes were influenced.

The changes in behavioral performance were investigated in two attention tasks: the TOVA and the DAT. In the TOVA, the mean RT was significantly modulated by the type of NF, with the *post-hoc* comparisons revealing a significant decrease in beta1 NF. However, because only global mean RT scores were reported (i.e., average of frequent and infrequent target conditions) it was unclear whether this effect could have been modulated by different target frequency contexts. The RT-SD was significantly decreased from pre- to post-training across all groups. In the DAT the participants were instructed to respond to left ear channel high pitch tones and right ear channel low pitch tones with left or right button presses respectively while ignoring the other stimulus category in the relevant channel. Importantly, targets and nontargets were presented with equal probability in each channel and were difficult to discriminate (given the physical proximity of the tones 1000 Hz and 1100 Hz). Differently from the TOVA, in the DAT the analysis failed to provide evidence of a significant modulation of mean RT by the type of NF. Also differently from the TOVA, the

RT-SD was significantly decreased following SMR/theta NF relative to the other training conditions. Taking into consideration the increased P3b amplitude and the decreased mean RT in the beta1/theta NF, these results were interpreted as indicating an increased cortical excitability/arousal state due to enhanced beta activity and improved modulation of the locus coeruleus-norepinephrine system (Nieuwenhuis et al., 2005).

The changes in performance accuracy were assessed by d' , omission and commission errors in the TOVA and in the DAT. Both tasks revealed significant d' increases following the SMR/theta NF. Moreover, this group was associated with a significant decrease in omission errors in the DAT suggesting that the physiological regulation of sensorimotor activity might contribute to reduce processing interference and subsequently increase the resources available for higher order attentional processing. However, these effects were not protected by significant omnibus effects. Moreover, this study did not corroborate the hypotheses advanced by the previous study (Egner & Gruzelier, 2001) that the SMR/theta NF would be associated with improvements in response inhibition due to the reduced cortical excitability in sensorimotor areas (Serman, 1996) and that the beta1/theta NF would contribute to an increase in commission errors. However, it is unclear whether the failure to observe differential effects on response inhibition might have been related to the low response inhibition demands of the tasks for the healthy adults.

Overall, these results suggested that the SMR/theta NF and the beta1/theta NF were associated with a facilitation of different parameters of target information processing efficiency under different tasks conditions. However, it was unclear whether the differential behavioral performance could be explained by the different attention mechanisms, the stimulus modality, the difficulty of target-nontarget discrimination or the target probability imposed by the tasks. Importantly, the failure to provide evidence of training- and frequency-specific effects of SMR/theta NF and beta1/theta NF in the QEEG assessments reported in Egner and collaborators (2004), recommends a cautious interpretation of these findings.

In another study, Doppelmayr and Weber (2011) provided further evidence of differential effects of SMR/theta NF and beta1/theta NF in the attentional domain. In comparison with a RF NF condition, only the SMR/theta NF was associated with decreased RT in a simple target visual detection task (button-press to targets presented with a variable inter-stimulus interval), decreased RT in a choice RT visual oddball task (button-press to

targets and no response to non-targets; target/non-target = 1/5.34) and increased accuracy in a spatial rotation task. However, none of the NF protocols was associated with significant differences in omission and commission errors in a standardized sustained visual attention task (d2,Brickenkamp & Zillmer, 1988). Thus, this study suggests that SMR/theta NF was specifically associated with increased processing speed in sustained and selective attention tasks without affecting performance accuracy. These results are in disagreement with those obtained by Egner and Gruzelier (2004). Since that study suggested that the SMR/theta NF may be implicated in increased performance accuracy but not necessarily with increased processing speed. Regarding beta1/theta NF, Doppelmayr and Weber (2011) could not replicate the protocol-specific increments in processing speed observed in the TOVA (Egner & Gruzelier, 2004).

The different conclusions of the two studies might be explained by methodological differences and limitations. As discussed in section 1.2.3.1.2., a major limitation of this study was the failure to demonstrate successful beta1/theta learning, therefore, critically affecting the possibility of comparing the differential effects of the two low-beta NF protocols. Differently from Egner and Gruzelier (2004), in which separate absolute amplitude signals were delivered for each frequency band (i.e., beta1, theta and high-beta), in Doppelmayr and Weber's (2011) study a single feedback signal was based on the beta1/theta ratio amplitude. Also differently from that previous study, there were more SMR/theta NF sessions (thirty vs. ten) and the theta frequency was suppressed between 3 and 5 Hz rather than between 4 and 8 Hz. However, it is unclear which of these factors might have contributed to the differences in processing speed between the two studies. The two studies also differed in the type of control condition. While in Egner and Gruzelier (2004) the control condition did not involve NF training, in Doppelmayr and Weber's (2011) study the RF involved the suppression of low theta (3-5 Hz) and high-beta (variable frequency band) as well as the counterbalanced enhancement and suppression of target 1 Hz frequency (randomly selected from the 6-35 Hz frequency range) in each half of the training session. Thus, besides the different control for NF placebo effects, the two control conditions might have involved different levels of cognitive effort. Moreover, the cognitive effects associated with the suppression of low-theta and high-beta activity in RF NF could have masked cognitive improvements in the beta1/theta ratio NF.

1.2.4.2.2. Outcome specificity of SMR/theta NF

Several studies have provided supportive evidence of facilitated processing of task-relevant information following SMR/theta NF relative to control or comparison conditions (Gruzelier et al., 2014b.; Kober et al., 2015; Ros et al., 2009; Vernon et al., 2003). Vernon and collaborators (2003) investigated the effects of SMR/theta NF complemented by beta2 inhibition (18-22 Hz), theta enhancement with concomitant suppression of delta and alpha amplitude and wait-list controls in a two-digit sequence detection task. After eight NF sessions, only the SMR/theta NF demonstrated a significant increase in the percentage of correct detections. However, in the absence of a significant omnibus time x group effect, these results must be cautiously interpreted.

In line with these results, Kober and collaborators (2015) recently provided supportive evidence of the contribution of SMR/theta NF to increased accuracy. SMR/theta NF was associated with decreased error rates but not with decreased RT in a two-stimuli auditory oddball task. Notably, sham NF was associated with decreased RT but not with increased accuracy, suggesting that SMR/theta NF might promote accuracy at the cost of speed. In the same study, there was evidence that the N1 and P3 amplitudes elicited by the encoding phase of the Sternberg recognition task were significantly increased in SMR/theta NF but not in sham NF. In this task, the participants memorized a set of four or six digits for 1000ms (encoding phase) and were subsequently probed to indicate by button-press whether a single digit was part of the memory set (recognition phase). Despite the absence of improvements in performance accuracy relative to sham NF, the increased amplitude of the N1 and P3 components in the encoding phase was interpreted as indicating increased strength and availability of processing resources to allocate attention during encoding. Moreover, the P3 amplitude increments at encoding were positively correlated with training-specific within-session increments in SMR amplitude.

Additionally, the authors attempted to test the hypothesis that SMR/theta NF would positively impact cognitive performance by increasing the availability of attentional resources and reducing processing interference (Serman, 1996). Unlike controls, SMR/theta NF was associated with reduced SMR resting state functional connectivity between the motor and visual areas, which was taken as an indication of reduced sensorimotor interference. However, the relation between the reduced connectivity between motor and visual areas and

improved cognitive performance was not entirely clear because the SMR/theta NF seemed to benefit performance accuracy in auditory tasks (e.g., oddball task) but not in visual tasks (e.g., Sternberg task).

SMR/theta NF was associated with enhanced visuo-motor processing speed during surgical procedures as judged by expert independent raters relative to alpha/theta NF (Ros et al., 2009). Importantly, the successful within-session SMR/theta learning was driven by within-session theta amplitude decrements rather than by SMR increments (see section 1.2.3.1.1.). However, school children treated with SMR/theta NF did not outperform those that undergone alpha/theta NF or no-treatment controls in attention and response inhibition scores measured by the TOVA (Gruzelier et al., 2014b). On the contrary, commission errors were significantly decreased in the alpha/theta NF and marginally decreased in SMR/theta NF. Here, the failure to increase the SMR/theta amplitude ratio may partly explain the absence of significant cognitive improvements.

In conclusion, there is conflicting evidence of SMR/theta NF contribution to increased efficiency of target detection. In fact, there is no current evidence that SMR/theta NF may be associated with improved processing of targets as indexed by the P3 amplitude in different cognitive paradigms (Egner & Gruzelier, 2004; Kober et al., 2015). At the behavioural level, some studies provided evidence of increased processing speed (Doppelmayr & Weber, 2011; Ros et al., 2009) and decreased RT-SD (Egner & Gruzelier, 2004) to target stimulus, while other studies failed to corroborate this evidence (Egner & Gruzelier, 2001, 2004; Kober et al., 2015). These inconsistencies were observed under similar task conditions. For instance, in the oddball tasks, decreased RT was observed in one study (Doppelmayr & Weber, 2011) but not in another (Kober et al., 2015). Given that both studies provided evidence of SMR learning and equivalent training contingencies, the higher number of sessions in the former might explain the different outcomes. On the other hand, there is some consensus regarding the SMR/theta NF contribution to increased performance accuracy (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2001, 2004; Kober et al., 2015; Vernon et al., 2003). However, the absence of significant omnibus effects in some studies suggest that increased target detection may not correspond to specific SMR/theta NF outcome (Egner & Gruzelier, 2004; Vernon et al., 2003). The available evidence does not

support a specific SMR/theta NF contribution to decreased false alarm rate (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2004; Gruzelier et al., 2014b).

1.2.4.2.3. Outcome specificity of beta1/theta NF

There is increasing evidence to support the specificity of beta1/theta NF in managing inattentiveness and impulsivity/hyperactivity symptoms in paediatric ADHD in comparison with pharmacological interventions according to parent reports and that the treatment effects may be maintained at a 6-month follow-up according to parents and teachers ratings (Duric, Assmus, Gundersen, & Elgen, 2012; Meisel, Servera, Garcia-Banda, Cardo, & Moreno, 2013; Monastra, Monastra, & George, 2002; for a meta-analysis Arns, de Ridder, Strehl, Breteler, & Coenen, 2009).

However, the impact of the beta1/theta NF on objective measures of attention and response inhibition is less clear. Monastra and collaborators (2002) revealed, that compared to pharmacological intervention, the combination of NF and medication had superior effects in maintaining the reductions in the theta/beta ratio and the improvements in the TOVA indices of attention and response inhibition after a one-week medication washout. However, because the group assignment was non-randomized and the children in the NF intervention group had more contact with a therapist these results could equally be explained by a placebo effect.

Bakhshayesh and collaborators (2011) showed that ADHD children increased the response speed to infrequent targets in a visual cue-CPT task (Knye et al., 2004) following thirty sessions of beta1/theta NF in central scalp locations (FCz/CPz), but not following electromyographic (EMG)-biofeedback targeted at reducing EMG artifacts. In disagreement with the interpretation of a facilitated processing of targets, there was no evidence of increased hit rate or decreased RT-SD in the cued-CPT and the number of hits per time was reduced in a paper-and-pencil cancellation task suggesting an increase in RT. There was also conflicting evidence regarding the effects of beta1/theta NF on response inhibition. In comparison with the control group, there was evidence of decreased commission errors in the paper-and-pencil cancellation task, but not in the cued-CPT. However, the weak correlation of the cued-CPT with response inhibition (Maoz, Aviram, Nitzan, Segev, & Bloch, 2015) warrants caution in the interpretation of these findings.

In sum, beta1/theta NF resulted in unchanged or decreased commission errors effects depending on whether healthy adults (Egner & Gruzelier, 2004) or ADHD children (Monastra et al., 2002) were assessed in the TOVA. This conflicting evidence may be related to differences in sensitivity of the measures to detect improvements in response inhibition in the two populations. In these relatively non-demanding task, healthy adults have typically produced a negligible percentage of false alarm errors resulting in “floor effects” (e.g., Egner & Gruzelier, 2004), while ADHD children are expected to commit significantly more errors than controls (Greenberg, Kindschi, & Corman, 1996). Notwithstanding, there was no evidence of decreased commission errors when healthy adults were tested in more demanding tasks like the DAT (Egner & Gruzelier, 2004).

Moreover, several studies suggest that beta1/theta NF might be associated with decreased RT across different task conditions in ADHD (Bakhshayesh et al., 2011; Monastra et al., 2002) and healthy adults (Egner & Gruzelier, 2004). However, other studies failed to corroborate these findings possibly due to unsuccessful beta1/theta NF learning (Doppelmayr & Weber, 2011). The beta1/theta NF was associated with increased P3b amplitude suggesting increased efficiency in processing task-relevant information in a low Go-stimulus probability context (Egner & Gruzelier, 2004). Moreover, there is mixed evidence of the effects of beta1/theta NF on target detection and on response inhibition (Bakhshayesh et al., 2011; Egner & Gruzelier, 2004).

1.2.4.3. Theta suppression effects on attention and response inhibition

Previous studies suggest that decreases in theta and theta/SMR amplitude may play an important role in improving selective attention (Vernon et al., 2003), motor control and response inhibition (Gruzelier et al., 2014b; Ros et al., 2009). Additionally, higher pre-training theta activity and larger decreases in theta activity from pre to post-training predicted the positive impact of mixed beta/theta and SCP NF on inattention and hyperactivity (Gevensleben et al., 2009a). However, from these studies it remains unclear whether theta amplitude decrements were training-specific because no comparison with controls was provided. In one recent study, Becerra and collaborators (2012) found that theta suppression was associated with improved general cognitive functioning in healthy elderly (as measured by the WAIS-III and the NEUROPSI). However, these improvements were indistinguishable

from those obtained by sham NF control group. Moreover, because theta amplitude was suppressed in individualized scalp locations (corresponding to the maximal theta amplitude in QEEG topographical maps) these findings provide only limited evidence of the possible role of central midline theta suppression to cognitive improvement.

Other studies went further in establishing a causal relationship between the voluntary modulation of relative theta amplitude and improvements in cognitive performance. In the classical investigations of Beatty and colleagues the suppression of occipital theta (3-7 Hz) amplitude relative to other EEG frequencies (3-30 Hz) was associated with increased performance in radar monitoring tasks (Beatty et al., 1974; O'Halon, Royal, & Beatty, 1977; Williams et al., 1975). On the other hand, in line with demonstrations of increased occipital theta and vigilance decrement (O'Hanlon & Beatty, 1977), the reversing of the above NF conditions resulted in performance deterioration as measured by increased error rates. However, it remains unclear whether the improved performance may reflect the facilitation of specific mechanisms involved in the modulation of visual attention (Yamagishi et al., 2003) or increased cognitive control more generally (Cavanagh & Frank, 2014). In line with the latter, recent studies suggest that frontal-midline theta enhancement NF may have a significant impact on executive functioning in healthy adults (Enriquez-Geppert et al., 2014a.,2014b; Wang & Hsieh, 2013). However, only tasks involving proactive cognitive control (such as Task-Switching) but not those involving reactive inhibitory control (such as the SST) were associated with increased post-stimulus theta power and behavioral performance (Enriquez-Geppert et al., 2014b) possibly reflecting the active instructions to develop self-regulatory and metacognitive strategies. Taken together these studies suggest that both theta enhancement (in frontal midline) and suppression (in posterior electrodes) has been implicated in improved cognitive control. However, the specific functional role of central midline theta suppression remains unclear.

1.3. Research questions and goals

Having reviewed the theoretical background and empirical investigations that suggest improvements in selective attention and response inhibition following neurofeedback of low-beta amplitude enhancement and theta amplitude suppression two main research questions

emerge. The first question concerns the specific contribution of these frequencies for the pattern of cognitive improvements observed following NF. The second question is related to the specific nature of the processes of selective attention and response inhibition that may be influenced by low-beta and theta frequencies.

What are the specific contributions of low-beta (SMR and beta1) enhancement and theta suppression for the improvements in selective attention and response inhibition?

As was apparent in the literature review of section 1.2., there are a number of caveats with respect to the distinct cognitive effects of SMR/theta and beta1/theta NF protocols in healthy adults. In fact, the attempts to disentangle the cognitive effects of the two protocols have produced contradictory evidence (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2004) and did not take into consideration possible hemispheric specificities as proposed by Othmer and colleagues (1999). In fact, increases in attention have been associated with both SMR/theta NF (Doppelmayr & Weber, 2011) or beta1/theta NF (Egner & Gruzelier, 2004). Regarding response inhibition, the improvements associated with SMR amplitude increments and deterioration associated beta1 amplitude increments (Egner & Gruzelier, 2001) were not replicated in subsequent studies. Moreover, the failure to provide evidence of learning-specificity for both NF protocols in one study (Egner & Gruzelier, 2004) and for beta1/theta ratio NF in the other (Doppelmayr & Weber, 2011) limits the conclusions that can be drawn from these studies.

Additionally, the examination of the several indices of learning suggested that the cognitive enhancements associated with the low-beta/theta NF protocol could be explained by significant theta suppression as much as by low-beta enhancements (de Zambotti et al., 2012; Gevensleben et al., 2009; Gruzelier, Foks, Steffert, Chen, & Ros, 2014; Lubar et al., 1995; Ros et al., 2009). Although the independent suppression of theta activity may be associated with increased vigilance (Beatty et al., 1974; Becerra et al., 2012; Williams et al., 1975) the existing evidence could not be related to the central-midline theta activity that is usually suppressed in the low-beta/theta NF protocol. Taking into consideration that both low pre-stimulus (or tonic) and high post-stimulus (or phasic) fronto-central theta amplitude were associated with improved selective attention and response inhibition (see sections 1.1.1.2. and 1.1.2.2.), the present thesis will attempt to clarify whether a NF intervention

aimed at suppressing theta amplitude might explain the performance enhancement in these cognitive domains.

What are the specific mechanisms of selective attention and response inhibition associated with the self-regulated modulation of theta and low-beta frequencies?

As seen in previous sections, the extent to which the selective attention and response inhibition improvements may be revealed in Go/Nogo paradigm critically depends on the cognitive demands imposed by the Go stimulus probability of the task. The selective attention demands are increased when the Go stimulus probability is low and an occasional distracter stimulus captures attention (e.g., in the oddball task). In contrast, response inhibition is required when an habitual response to a frequent Go stimulus has to be withheld (Go/Nogo task).

However, previous studies reported commission and omission errors in the TOVA irrespective of the Go stimulus probability (Egner & Gruzelier, 2001, 2004; Gruzelier, Foks, Steffert, Chen, & Ros, 2014; Fuchs et al., 2003; Rossiter and Lavaque, 1995) or in equiprobable Go/Nogo tasks (Kropotov et al., 2005) in which the specific selective attention and response inhibition demands are difficult to ascertain. Moreover, the relatively low response inhibition demands imposed by the TOVA in healthy adults might have determined “ceiling and floor effects” in the behavioral measures of selective attention and response inhibition (Egner & Gruzelier, 2001, 2004). Thus, it is currently unclear whether the contradictory evidence within and between studies regarding the cognitive implications of SMR and beta1 NF might have been related to methodological limitations concerning the specificity and sensitivity of the tasks.

Additionally, the examination of ERP components reflecting selective attention and response inhibition was not conclusive regarding the impact of the low-beta/theta NF in these processes. The study of single electrophysiological measures of selective attention in the context of the classical oddball (i.e., P3b) did not allow for a distinction between voluntary or involuntary mechanisms of selective attention indexed by the P3b and P3a respectively. Moreover, the specificity of the P3b increments relative to other task conditions (i.e., standard tones) could not be established (Egner & Gruzelier, 2001, 2004). Also, the P3 amplitude increments to both Go and Nogo stimuli in ADHD (Kropotov et al., 2005) could be interpreted as reflecting practice effects rather than improved response inhibition.

Moreover, given that a mixed low-beta/theta NF protocol was used these effects could not be related to theta suppression and/or SMR- and beta1 enhancement. Finally, the differential effects of theta suppression and low-beta enhancement on successful response inhibition remain to be explored in a healthy adult population.

Aims of the thesis

The present thesis attempted to further investigate the differential selective attention and response inhibition effects of theta- suppression and SMR- and beta1-enhancement NF inhibition in healthy adults. A primary concern of the thesis was to support the assertions regarding the specific cognitive effects on evidence of training- and frequency-specific effects. In order to achieve this goal, the feasibility of inducing specific EEG amplitude change in the different frequencies was investigated in within- and across-session learning indices and in active and passive restive state. This also implied that the relative contribution of theta suppression was disentangled from that of SMR and beta1 enhancement in different experimental conditions. This was implemented in two studies. In the first study (see Chapter 2), the effects of SMR and beta1 NF in the cognitive processes of interest were compared with a RF NF control condition. In the second study (see Chapter 7), the effects of theta-inhibition NF protocol (theta NF) and beta1 NF in the selective attention and response inhibition were compared with a RF NF control condition.

The other main goal of the thesis was to better understand the differential impact of these NF protocols on specific mechanisms of selective attention and response inhibition. The selective attention and response inhibition demands were experimentally manipulated by varying the Go response probability of two Go/Nogo tasks. The differential effects of the NF protocols on voluntary and involuntary selective attention mechanisms were investigated in the three-stimuli oddball task, while the same effects on the cancelation of a previously prepared and prepotent Go response were examined in the cued Go/Nogo task.

Chapter 2

Study 1: The effects of SMR NF and beta1 NF on selective attention and response inhibition

2.1. Introduction

The proposal that SMR enhancement would improve the regulation of inhibitory functions, whereas beta1 enhancement would increase alertness and attention to the external environment was previously investigated in two studies (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2004). These studies confirmed distinct cognitive outcomes in the two low-beta frequencies, but provided incompatible results in terms of the facilitation of selective attention and were inconclusive regarding the improvements in response inhibition. Moreover, the ability to differentiate between treatment effects was confounded by the failure to provide evidence of training-specific effects in beta1/theta NF (Doppelmayr & Weber, 2011) or in both NF protocols (Egner et al., 2004; Egner & Gruzelier, 2004). Following Othmer and collaborators (1999) the current study attempted to clarify whether the SMR in the right hemisphere and beta1 NF in the left hemisphere would be associated with (1) training- and frequency-specific SMR and beta1 amplitude increments (2) and with specific improvements in selective attention and response inhibition.

2.1.1. SMR NF effects on selective attention and response inhibition

SMR learning

The present study attempted to replicate previous within-session (Vernon et al., 2003; Ros et al., 2009; Kober et al., 2015) and across-session (e.g., Doppelmayr & Weber, 2011; Hoedlmoser et al., 2008; Kober et al., 2013) SMR amplitude increments during active feedback trials. Although previous studies failed to provide evidence of across-session training-specific SMR amplitude increments in passive periods (Arns et al., 2012; Egner et

al., 2004; Hoeldmoser et al., 2008) , the present study investigated within- and across-session SMR amplitude changes in passive periods.

Finally, differently from previous studies (e.g., Kober et al., 2015; Schabus et al., 2014) the frequency-specificity of SMR amplitude changes was examined in a large spectrum of frequencies and not only in the frequencies targeted by the NF intervention.

Cognitive effects of SMR NF

The present study attempted to replicate previous evidence of the association of SMR/theta NF with decreased mean RT (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2004), decreased RT-SD (Egner & Gruzelier, 2004), increased perceptual sensitivity and hit rate (Egner & Gruzelier, 2004; Kober et al., 2015; Ros et al., 2009; Vernon et al., 2003), and decreased false alarm rate (Egner & Gruzelier, 2001; Gruzelier et al., 2014a). Moreover, these effects were investigated in two Go/Nogo tasks imposing different demands on selective attention and response inhibition.

2.1.2. Beta1 NF effects on selective attention and response inhibition

Beta1 learning

The present study attempted to provide novel evidence of beta1 learning. In fact, previous studies either did not investigate within-session beta1 amplitude changes or failed to provide evidence of across-session learning during active feedback (Doppelmayr & Weber, 2011) or passive periods (Egner et al., 2004) following beta1/theta NF.

Cognitive effects of beta1 NF

The present study attempted to replicate previous evidence that beta1/theta NF associated with increased P3b amplitude in the oddball task (Egner & Gruzelier, 2004), decreased mean RT (Egner & Gruzelier, 2004), decreased perceptual sensitivity (Egner & Gruzelier, 2001) and increased hit rate (Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011). Moreover, the current study attempted to clarify whether beta1/theta NF might contribute to increased (Egner & Gruzelier, 2001) or decreased false alarm rate (Bakhshayesh et al., 2011). In sum, it was investigated whether beta1 NF may promote a fast but not

necessarily accurate response mode (Egner & Gruzelier, 2004) in Go/Nogo tasks imposing different selective attention and response inhibition demands.

2.2. Outline of Study 1

Experiment 1 sought to determine whether the amplitude changes in the SMR and beta1 frequencies were training-specific (i.e., could be attributed to the experimental manipulation and rather than to unspecific factors). Given that the adoption of single learning measure may result in the failure to apprehend non-overlapping learning phenomena occurring in the different time scales and in different EEG parameters, this implied an exploratory investigation of different methods (within- and across-session) and types of periods (active feedback periods and passive resting state periods). The combination of these resulted in four learning-indices: (1) within-session amplitude changes in active periods, (2) across-session amplitude changes in active periods, (3) within-session amplitude changes in passive periods, and (4) across-session amplitude changes in passive-periods. Moreover, the frequency-specificity of amplitude changes (i.e., the extent to which the experimental manipulation selectively affects the frequency of interest) was investigated by exploring the effects of SMR NF and beta1 NF in other EEG frequencies. Frequency-specificity was investigated for active and passive periods based on the average within-session amplitude change.

Experiment 2 examined the relative contribution of SMR and beta1 NF to selective attention in three-stimuli oddball task. Increments in P3b amplitude were taken as suggestive of improvement in endogenous /voluntary attention (Donchin & Coles, 1998), while increments in P3a amplitude were assumed to reflect an increase in involuntary attention (e.g., Courchesne, Hillyard, & Galambos, 1975; Sawaki & Katayama, 2009) and response-inhibition (e.g., Goldstein, Spencer, & Donchin, 2002).

Experiment 3 examined the relative contribution of SMR and beta1 NF to response inhibition in a cued-Go/Nogo task. An increment in the Nogo-P3 amplitude was assumed to reflect a more efficient decision to withhold the previously prepared response. Additionally, the false alarm rate was taken as a measure of unsuccessful inhibition of a previously prepared response. Because unsuccessful inhibition is not reflected in the Nogo-P3 amplitude

(which consists of averaged correct non-responses) and changes in efficiency of successful inhibition cannot be measured by a null behavioral response, the electrophysiological and behavioral measures are believed to provide complementary information regarding the successfulness of the inhibitory process.

Increases in performance accuracy were described in terms of increased hit rate, decreased false alarm rate and increased perceptual sensitivity or d' (e.g., Katayama, & Polich, 1996; Hillyard et al., 1971). Increases in response speed have been proposed to reflect the difficulty of target discrimination and response selection imposed by the task. The mean RT was expected to decrease as a function of a faster categorization of the stimulus and closure of the decision process associated with the response (Comerchero & Polich, 1998; Comerchero & Polich, 1999). Finally, decreases in RT-SD to Go responses were regarded as reflecting a higher moment-to-moment consistency in behavioral responses subserved by improvements in top-down and inhibitory control (Bellgrove, Hester, & Garavan, 2004).

Chapter 3

Experiment 1: SMR and beta1 learning

3.1. Hypotheses

Hypothesis 1: Training-specificity of within-session SMR and beta1 amplitude changes in active periods.

It was hypothesized that:

- (1) SMR amplitude would be increased within-sessions in active periods in SMR NF relative to beta1 NF and control NF.
- (2) Beta1 amplitude would be increased within-sessions in active periods in beta1 NF relative to SMR NF and control NF.

Hypothesis 2: Training-specificity of across-session SMR and beta1 amplitude changes in active periods.

It was hypothesized that:

- (1) SMR amplitude would be increased across-sessions in active periods in SMR NF relative to beta1 NF and control NF.
- (2) Beta1 amplitude would be increased across-sessions in active periods in beta1 NF relative to SMR NF and control NF.

Hypothesis 3: Training-specificity of within-session SMR and beta1 amplitude changes in passive periods.

It was hypothesized that:

- (1) SMR amplitude would be increased within-sessions in passive periods in SMR NF relative to beta1 NF and control NF.
- (2) Beta1 amplitude would be increased within-sessions in passive periods in beta1 NF relative to SMR NF and control NF.

Hypothesis 4: Training-specificity of across-session SMR and beta1 amplitude changes in passive periods.

It was hypothesized that:

- (1) SMR amplitude would be increased across-sessions in passive periods in SMR NF relative to beta1 NF and control NF.
- (2) Beta1 amplitude would be increased across-sessions in passive periods in beta1 NF relative to SMR NF and control NF.

Hypothesis 5: Frequency-specificity of SMR and beta1 amplitude changes in active periods.

It was hypothesized that:

- (1) SMR NF would be associated with increased mean SMR amplitude but not with significant amplitude changes in other frequencies relative to beta1 NF and control NF on the average of active periods within-sessions.
- (2) Beta1 NF would be associated with increased mean beta1 amplitude but not with significant amplitude changes in other frequencies relative to SMR NF and control NF on the average of active periods within-sessions.

Hypothesis 6: Frequency-specificity of SMR and beta1 amplitude changes in passive periods.

It was hypothesized that:

- (1) SMR NF would be associated with increased mean SMR amplitude but not with significant amplitude changes in other frequencies relative to beta1 NF and control NF on the average of passive periods within-sessions.
- (2) Beta1 NF would be associated with increased mean beta1 amplitude but not with significant amplitude changes in other frequencies relative to SMR NF and control NF on the average of passive periods within-sessions.

3.2. Methods and materials

3.2.1. Participants

Thirty-one adult students from Goldsmiths, University of London volunteered to take part in the experiment. Twenty-five participants were first-year psychology undergraduate students recruited through a Research Participation Scheme in return of course credit. Six participants were postgraduate students recruited through advertisement in the Campus and received monetary compensation of £10 at completion. All participants were right-handed and had normal or corrected-to-normal vision. None of the participants had previous experience with NF. Prior to the pre-assessment general information regarding the goals of the study and about EEG and NF procedures was given. Participants remained blind to the details of the experimental design and to the frequency-bands of interest. Participants gave written informed consent for participation in the study. The experimental procedures were approved by the Department of Psychology Ethics Commission. Participants were screened for neuropsychiatric disorders and psychoactive substances use (see Appendix A). Participants were randomly allocated to one of three experimental conditions resulting in a control group consisting of 10 participants (6 female, mean age=21.30 years; standard-deviation (SD)=1.64 years), an SMR group consisting of 10 participants (5 female, mean age=23.0 years; SD=5.57 years) and a beta1 group consisting of 11 participants (5 female, mean age=21.91 years; SD=4.16 years). A one-way ANOVA confirmed that the mean age did not differ between the NF protocols ($F(2,28)=0.41$, $p=0.66$, $\eta_p^2=0.03$).

3.2.2. General procedure

As shown in figure 3.1., for each participant the experiment consisted of 8 sessions (1 pre-assessment session, 6 NF training sessions and 1 post-assessment session) taken on different days. The sessions were arranged according to the participants' availability and distributed over a period no longer than four weeks. The final assessment session had to be arranged within one to three days after the last training session. Before the pre-assessment session, the participants were contacted via email with general information about the experiment and returned the completed neuropsychiatric screening questionnaire. Pre- and post-assessment sessions consisted of two resting state (eyes closed and eyes open) 3-minutes

EEG recordings and two cognitive tasks with simultaneous EEG recording (3-stimuli auditory oddball task and cued-Go/Nogo task) performed in counterbalanced order between participants. For each participant, the order of the tasks was kept unchanged on the second assessment.

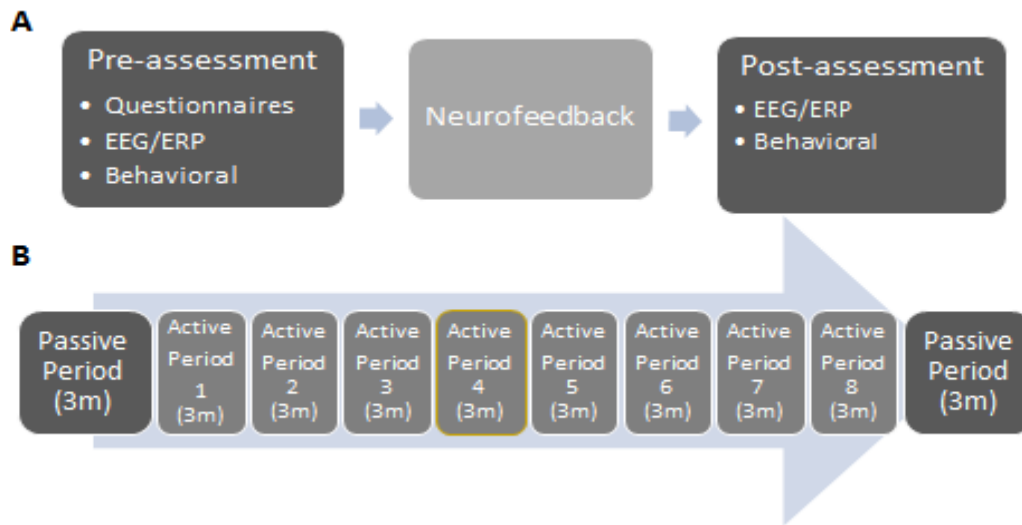


Figure 3.1. General NF procedure. **(A)** For each participant the experiment consisted of three blocks: one pre-assessment session, followed by 6 NF sessions, and finally one post-assessment session. **(B)** NF sessions consisted of ten equivalent periods of 3 minutes: a passive resting state period, followed by eight active feedback periods, and finally by a second passive resting state period.

3.2.3. Neurofeedback Procedure

Participants received six sessions of either SMR NF, beta1 NF or control NF distributed over two to three weeks. Participants, but not the experimenter, were kept blind to the specific frequencies targeted by the NF. To minimize the influence of circadian rhythms variation in the EEG, effort was taken to ensure the sessions were taken at the same time of the day (with an acceptable variation of 1 to 2-hours). As shown in Fig. 3.1, each of the NF training sessions consisted of an initial pre-training passive resting state period, followed by eight active feedback training periods and a post-training passive resting state period. To ensure comparability between resting state and feedback conditions all EEG recordings had an equal length of three minutes (160 seconds) and were performed with eyes open. Each

period consisted of 150 seconds of EEG recording and a resting and blink pause of 10 seconds. Participants were allowed to rest for longer periods if needed.

3.2.4. Neurofeedback training

EEG recording. NF was conducted using a Biograph ProComp Infiniti (Thought technology, Ltd.; Montreal, Canada) differential amplifier. Signal was acquired at a 256 Hz sampling rate, A/D converted, band-pass filtered (IIR Butterworth Filter) and peak-to-peak amplitudes were calculated to continuously extract theta (4-7Hz), low alpha (8-10Hz), high alpha (10-12Hz), SMR (12-15Hz), beta1 (15-18Hz), beta2 (19-22Hz), beta3 (23-26Hz), beta4 (27-30Hz) and electromyographic activity (EMG) (52-58Hz) components. Amplitude measures in the filter-bands were transformed online into visual representations and fed back to the participants via a Hannspree 18.5in LCD (16:9 - 5 ms) monitor positioned at a distance of ~1.5 m. The scalp electrodes were placed at C3 for beta1 NF, at C4 for SMR NF (with reference electrode placed on the contralateral and ground electrode place in the ipsilateral earlobe) and at Cz for control NF (with reference electrode placed on the left and ground electrode place in the right earlobe) according to the 10-20 electrode placement system. Impedance was kept below 5 K Ω .

Neurofeedback task. After the electrodes were attached the participants were instructed in the neurofeedback task. Participants were asked to sit comfortably and instructed to relax, minimize movement and blinking to prevent artifacts. The three groups received similar instructions regarding training goals and procedures (see Appendix B). Feedback consisted of visual representations of peak-to-peak amplitude variations (see *Feedback screens* above). Participants were asked to try to learn from the visual representations by letting themselves be guided by the feedback screen while trying to maximize the positive feedback. A brief explanation of the meaning of the visual signal was provided at the beginning of the first session (see Appendix B).

Feedback screens. In order to keep the participants motivated during NF session two feedback screens were used. During the first four training periods of each session visual feedback consisted of a video game that would respond to the variations in peak-to-peak amplitude by either moving or stopping according to the reward contingencies (see Reward

contingencies section below), while in the last four training periods visual feedback consisted of a circle that enlarged or shrunk according to the absolute amplitude of the target frequency (examples of feedback screens are presented in the Appendix C). The displays used for the passive resting state recordings were similar to the ones used in the first half of the training.

Feedback instructions and groups. In the first screen the participants were instructed to keep the video game moving for as long as possible while trying to keep EMG activity within range. In the circle feedback display participants were asked try to keep the circle as large as possible and above a visible threshold, while also trying to keep EMG activity within range. The SMR and beta1 NF groups aimed to increase the amplitude of the target frequency. In control NF group a bidirectional training strategy was used within the same training session. In each session the participants started by attempting to decrease (initial four active periods) and then to increase (last four active periods) the amplitude of a different EEG frequency. Since during the initial active inhibition period no explicit indication was provided regarding amplitude variations (video game screen), the participants were not aware that the training conditions were reversed in the second part of the session (circle screen). Six different EEG frequencies other than SMR and beta1 frequencies (theta, alpha1, alpha2, beta2, beta3, beta4) were selected from the range of 4 to 30Hz. The order of the training frequencies in the control group was kept constant between participants. In order to reduce the chances of transferring practice effects in a particular frequency range from one session to the next the training sequence of low and high frequencies was counterbalanced as follows: theta, beta2, alpha1, beta3, alpha2, beta4. The purpose of varying target frequency bands in each session was to minimize the chances of inducing systematic neurofeedback-related changes yet providing participants with real feedback.

Reward contingencies. Operant contingencies were such that reward was gained whenever the participants' EEG activity changed in the requested direction relative to the 150-seconds pre-feedback baseline measure. In the SMR and beta1 NF rewards were contingent on increasing the amplitude in the respective frequency, while in control NF they were either contingent on increasing or decreasing the amplitude of the frequency selected for any given session. After extracting the average amplitude of the target frequency during the first passive period (baseline) of each session, the reward threshold for the training periods was

calculated. This was set was set at 0.7 times the baseline average amplitude for enhancement frequencies and at 1.3 times the baseline average amplitude for inhibition frequencies. EMG threshold was kept below 3.5 μV during resting state periods and at 1.2 times the baseline amplitude during the training periods. In accordance with previous studies (e.g., Ros et al., 2009), threshold settings remained adjustable by the experimenter in steps of 0.05 throughout the training sessions, in order to ensure that the reward obtained would neither frustrate nor satiate the participants. From the first training period onwards the threshold adjustment decisions were made based on the absolute change of target-frequency compared to the previous training period.

3.2.5. EEG-Neurofeedback Data Processing

Data preparation. Analysis of the single channel EEG data from NF-training sessions was performed using custom software, programmed using MATLAB (v8.0, The MathWorks Inc., Natick, MA, 2012b). The batch-processing MATLAB script mimicked the NF-training software, using the same band-pass filter and similar peak-to-peak amplitude computation. Single channel peak-to-peak amplitude data of 150 seconds length was segmented in 1 second epochs (i.e., 150 epochs per recording).

Artifact detection and rejection. Three types of artefacts per epoch were identified. Firstly, electro-ocular activity (EOG) was computed as the range of the Z-transformed signal in an epoch after a Butterworth filter (1-15 Hz, 5th order) was applied. After visually inspecting four randomly selected sessions for each participant an individual threshold (ranging from 5 to 8) was set. Epochs were rejected if the Z-score surpassed the individually set threshold. Secondly, electromuscular activity (EMG) was computed by Z-transforming the filtered signal used for the EOG but with band limits set to 52-58 Hz. An epoch was rejected on the basis of EMG if it contained a Z-score larger than 4. Thirdly, epochs with amplitude perturbations larger than 60 μV were rejected if they were still present after the application of a finite impulse response filter (600th order, 1-45 Hz) to the signal. The resulting epoch-rejection rate per participant ranged from 1.5% to 11.5% (Mean=6.5%, SD=2.5%). The percentage of rejected trials did not differ between groups as demonstrated by one-way ANOVA ($F(2,28)=0.27, p=0.76, \eta_p^2=0.02$).

Peak-to-peak amplitude calculation. Peak-to-peak amplitude per frequency band was calculated per epoch after applying a 4th order Butterworth filter. For each recording an average frequency-band amplitude was calculated by averaging all non-rejected epochs.

3.2.6. Statistical Analysis

Statistical analyses were performed with SPSS (Version 22.0. Armonk, NY: IBM Corp., 2013). Statistical significance was assumed at the 0.05 alpha level (two-tailed). Effect sizes were estimated by partial eta square (η_p^2) for the mixed-design Analysis of Variance (ANOVA). All reported ANOVAs used Greenhouse-Geisser degrees of freedom correction for violations of the sphericity assumption (as indicated by significant Mauchly's test of sphericity) and Bonferroni corrected probability values (p -values) for multiple comparisons.

Data reduction and analysis. Normalized measures of within-session amplitude change in any given frequency band were calculated by dividing the EEG amplitude of the active and passive periods by the EEG amplitude of the first active or passive period of each session. The average within-session amplitude change of each session was used as a measure of across-session changes.

3.3. Results

3.3.1. Training-specific learning

The amplitude changes in SMR and beta1 frequencies of the three NF groups were examined in separate analyses for within-session and across-session amplitude changes and for active and passive trials. The normalized within-session amplitude change in active periods was calculated for 8 periods. For passive periods there was only a single measure of normalized within-session change. Thus, four different analyses were performed (1) two-way 8 PERIOD x 3 PROTOCOL for within-session active periods, (2) one-way 3 PROTOCOL for within-session passive periods, (3) two-way 6 SESSION x 3 PROTOCOL for across-

session active periods, and (4) two-way 6 SESSION x 3 PROTOCOL for across-session passive periods.

Hypothesis 1: Training-specificity of within-session SMR and beta1 amplitude changes in active periods.

Active changes within-session in each of the NF protocols were investigated for both SMR and beta1 frequencies in separate two-way 8 PERIOD x 3 PROTOCOL ANOVAs with the amplitude change of each period relative to the first training period collapsed across sessions as the dependent measure.

Figures 3.2A and 3.2B show the within-session amplitude in the SMR and beta1 frequencies for the three NF protocols. These were investigated in separate two-way 8 PERIOD x 3 PROTOCOL ANOVAs for SMR and beta1 frequencies. The analyses indicated a main effect of PROTOCOL for beta1 ($F(2,28)=4.79$, $p=0.02$, $\eta_p^2=0.26$) but not for SMR ($F(2,28)=1.08$, $p=0.36$, $\eta_p^2=0.07$). As hypothesized (Hypothesis 1), pairwise comparisons by independent *t*-tests revealed training-specific enhancements of mean beta1 amplitude in beta1 NF when compared to control NF ($t(19)=3.11$, $p=0.01$). However, contrary to hypothesis the mean increments in beta1 amplitude were not significantly higher in beta1 NF when compared to SMR NF ($t(20)=1.50$, $p=0.45$).

As shown in figures 3.2A and 3.2B, the analyses revealed significant PERIOD x PROTOCOL interaction effects in the beta1 ($F(5.54,77.50)=2.67$, $p=0.02$, $\eta_p^2=0.16$) but not in the SMR frequency ($F(4.95,69.27)=1.55$, $p=0.17$, $\eta_p^2=0.10$). Descriptive statistics of SMR and beta1 amplitude change and statistical results of between-subjects multiple comparisons for each period are presented in table 3.1. As shown in the table, the comparisons between beta1 and control NF groups indicated that beta1 amplitude change was significantly increase in periods 4 and 6 through 8 and a marginally increased in the remaining periods. Moreover, in period 4 beta1 amplitude change was marginally increased in the beta1 relative to SMR NF. In beta1 NF within-subject pairwise comparison failed to provide significant beta1 amplitude changes between periods (all $ps>0.16$). These were also non-significant in the control ($ps>0.45$) and SMR NF ($ps>0.28$). Finally, the main effects of PERIOD were not significant in any of the frequencies (SMR: $F(2.47,69.27)=0.40$, $p=0.71$, $\eta_p^2=0.01$; beta1: $F(2.77,77.50)=0.58$, $p=0.62$, $\eta_p^2=0.02$).

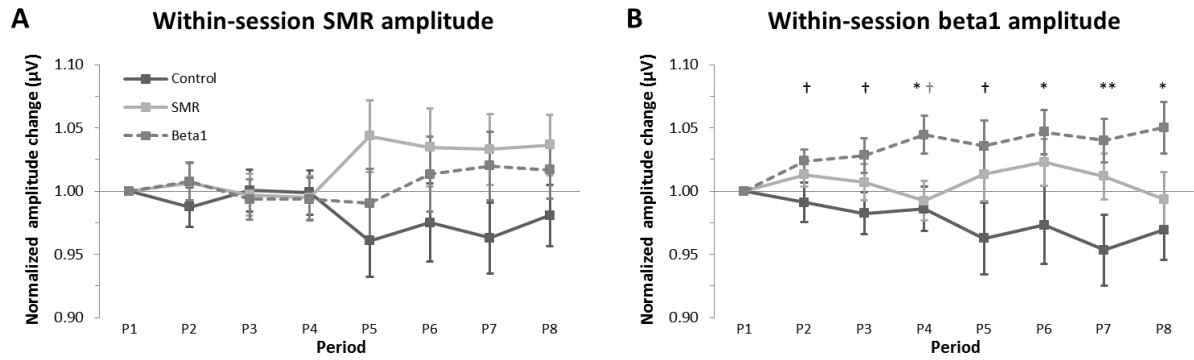


Figure 3.2. Within-session SMR and beta1 amplitude change in active periods for control NF, SMR NF and beta1 NF. The graphs represent the mean amplitude change in eight active periods (from P1 to P8) collapsed across six training sessions relative to the first active period of each session for SMR(A) and beta1 frequencies (B). Error bars depict standard error of the mean. Statistical significance level is represented by asterisks (†= $p < 0.10$, *= $p < 0.05$, **= $p < 0.01$).

Table 3.1. Mean (and SD) of SMR and beta1 amplitude change (µV) for each period (normalized to period 1 of each session) for control NF, SMR NF and beta1 NF; independent *t*-tests (Bonferroni corrected *p*-values) between control NF, SMR NF and beta1 NF.

Frequency	Period	Protocol						Independent <i>t</i> -test		
		Control		SMR		Beta1		Control vs. SMR	Control vs. Beta1	SMR vs. Beta1
		M	SD	M	SD	M	SD			
SMR	1	1.00	0.00	1.00	0.00	1.00	0.00	—	—	—
	2	0.99	0.05	1.01	0.04	1.01	0.05	0.87	0.94	0.06
	3	1.00	0.05	1.00	0.04	0.99	0.06	0.15	0.31	0.16
	4	1.00	0.05	0.99	0.05	0.99	0.06	0.17	0.21	0.04
	5	0.96	0.08	1.04	0.11	0.99	0.07	2.07	0.76	1.35
	6	0.98	0.09	1.03	0.10	1.01	0.10	1.37	0.90	0.50
	7	0.96	0.08	1.03	0.11	1.02	0.07	1.76	1.46	0.34
	8	0.98	0.06	1.04	0.09	1.02	0.07	1.64	1.09	0.59
Beta1	1	1.00	0.00	1.00	0.00	1.00	0.00	—	—	—
	2	0.99	0.03	1.01	0.03	1.02	0.03	1.62	2.47 †	0.82
	3	0.98	0.03	1.01	0.06	1.03	0.04	1.20	2.27 †	1.05
	4	0.99	0.03	0.99	0.04	1.04	0.06	0.29	2.73 *	2.42 †
	5	0.96	0.06	1.01	0.07	1.04	0.08	1.67	2.46 †	0.75
	6	0.97	0.06	1.02	0.06	1.05	0.06	1.89	2.84 *	0.93
	7	0.95	0.06	1.01	0.05	1.04	0.06	2.27	3.46 **	1.12
	8	0.97	0.08	0.99	0.06	1.05	0.07	0.79	2.72 *	1.91

†= $p < 0.10$, * = $p < 0.05$, ** = $p < 0.01$

Hypothesis 2: Training-specificity of across-session SMR and beta1 amplitude changes in active periods.

Figures 3.3A and 3.3B show the SMR and beta1 amplitude changes in active periods across-sessions in the three NF protocols. Across-session SMR and beta1 amplitude changes as a function the type of NF protocol were investigated in separate 6 SESSION x 3 PROTOCOL mixed ANOVAs. Contrary to the hypothesis, the SESSION x PROTOCOL interactions were non-significant for both frequencies (SMR: $F(10,140)=1.07$, $p=0.39$, $\eta_p^2=0.07$; beta1: $F(10,140)=0.59$, $p=0.82$, $\eta_p^2=0.04$).

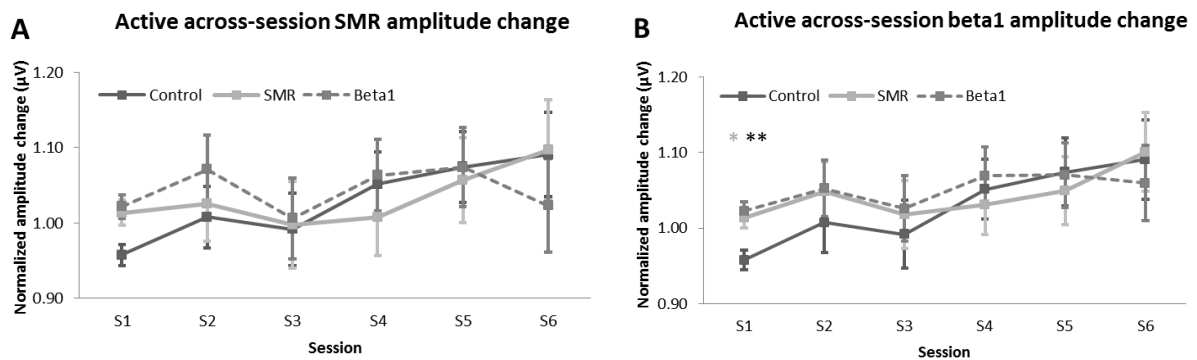


Figure 3.3. Across-session SMR and beta1 amplitude change for control NF, SMR NF and beta1 NF in active periods. The graphs represent the amplitude change in six training sessions (from S 1 to S 6) for SMR (A) and beta1 frequencies (B). Amplitude change was normalized relative to the first active period of the first session. Error bars depict standard error of the mean. Statistical significance level is represented by a cross and an asterisk ($\dagger=p<0.10$; $*=p<0.05$, $**=p<0.01$).

Means (and SD) of SMR and beta1 amplitude change in active periods for each session are presented in table 3.2. As can be observed, between-subject pairwise comparisons (Bonferroni corrected p-values) revealed that in the first session the beta1 amplitude was significantly increased in beta1 relative to control NF ($t(19)=3.56$, $p=0.004$) and in SMR relative to control NF ($t(18)=3.00$, $p=0.02$). In the subsequent sessions beta1 amplitude changes were non-significantly different between NF groups (all $p_s>0.05$). In the SMR frequency none of the between-subjects pairwise comparisons were significant (all $p_s>0.05$).

Table 3.2. Mean (and SD) of normalized SMR and beta1 amplitude change (μV) in active and passive periods for each session and for control NF, SMR NF and beta1 NF; independent t -tests (Bonferroni corrected p -values) between control NF, SMR NF and beta1 NF.

Frequency	Session	Protocol						Independent t -test		
		Control		SMR		Beta1		Control vs. SMR	Control vs. Beta1	SMR vs. Beta1
		M	SD	M	SD	M	SD			
SMR (active)	1	0.99	0.05	1.06	0.09	1.07	0.11	1.63	1.91	0.24
	2	1.05	0.14	1.05	0.14	1.06	0.13	0.01	0.18	0.17
	3	1.06	0.21	0.99	0.13	1.10	0.10	1.08	0.67	1.78
	4	1.11	0.17	1.02	0.15	1.13	0.13	1.39	0.21	1.62
	5	1.10	0.21	1.03	0.11	1.12	0.11	1.02	0.35	1.39
	6	1.13	0.21	1.08	0.16	1.15	0.11	0.69	0.31	1.02
Beta1 (active)	1	0.96	0.03	1.01	0.05	1.02	0.04	3.00 *	3.56 **	0.50
	2	1.01	0.14	1.05	0.10	1.05	0.13	0.72	0.82	0.09
	3	0.99	0.18	1.02	0.11	1.03	0.13	0.41	0.55	0.13
	4	1.05	0.15	1.03	0.14	1.07	0.08	0.36	0.32	0.69
	5	1.07	0.20	1.05	0.09	1.07	0.12	0.39	0.06	0.34
	6	1.09	0.21	1.10	0.10	1.06	0.17	0.13	0.43	0.57
SMR (passive)	1	1.02	0.06	1.01	0.09	1.01	0.05	0.36	0.50	0.14
	2	1.05	0.10	1.03	0.17	1.08	0.19	0.17	0.48	0.66
	3	1.10	0.23	0.96	0.17	1.13	0.16	1.67	0.33	2.04
	4	1.10	0.08	1.00	0.21	1.13	0.15	1.51	0.39	1.93
	5	1.11	0.13	0.98	0.15	1.07	0.13	2.10	0.67	1.47
	6	1.15	0.16	1.04	0.16	1.14	0.15	1.54	0.08	1.50
Beta1 (passive)	1	0.98	0.05	1.01	0.04	1.02	0.06	1.38	1.84	0.44
	2	1.02	0.13	1.03	0.12	1.03	0.12	0.14	0.23	0.08
	3	1.03	0.22	0.99	0.11	1.00	0.10	0.61	0.45	0.18
	4	1.05	0.11	1.03	0.15	1.05	0.09	0.45	0.05	0.41
	5	1.08	0.16	1.01	0.11	0.99	0.18	0.89	1.21	0.30
	6	1.07	0.19	1.08	0.15	1.01	0.16	0.17	0.84	1.01

†= $p < 0.10$, *= $p < 0.05$, **= $p < 0.01$

The apparent linear increase in SMR and beta1 amplitude change across sessions in control NF (see figures 3.3A and 3.3B) was not supported by linear SESSION x PROTOCOL interactions for both frequencies (SMR: $F(2,28)=1.62$, $p=0.22$, $\eta_p^2=0.10$; beta1: $F(2,28)=1.14$, $p=0.33$, $\eta_p^2=0.08$). The analysis also revealed a significant main effect of SESSION for both frequencies (SMR: $F(5,140)=3.13$, $p=0.01$, $\eta_p^2=0.10$; beta1: $F(5,140)=3.77$, $p<0.01$, $\eta_p^2=0.12$). Additionally, polynomial contrasts revealed a linear effect of SESSION for both SMR and beta1 frequencies (SMR: $F(1,28)=9.36$, $p<0.01$, $\eta_p^2=0.25$; beta1: $F(1,28)=9.55$, $p<0.01$, $\eta_p^2=0.25$) indicating a linear increase in amplitude change irrespective of the NF group. Bonferroni corrected post-hoc comparisons revealed marginally

significant increases in SMR amplitude change from session 2 to 6 ($t(30)=3.13, p=0.05$) and in beta1 amplitude change from session 1 to 6 ($t(30)=2.97, p=0.09$) and from session 3 to 6 ($t(30)=3.00, p=0.09$). Both main effects of PROTOCOL were non-significant (SMR: $F(2,28)=1.02, p=0.37, \eta_p^2=0.07$; beta1: $F(2,28)=0.12, p=0.88, \eta_p^2<0.01$).

Hypothesis 3: Training-specificity within-session SMR and beta1 amplitude changes in passive periods.

Within-session SMR and beta1 amplitude changes in passive periods were investigated in one-way between-subjects ANOVA. Data and statistical results are presented in table 3.3. Contrary to hypothesis, the main effect of PROTOCOL was not significant for both SMR and beta1 frequencies (SMR: $F(2,28)=0.12, p=0.89, \eta_p^2<0.01$; beta1: $F(2,28)=2.34, p=0.12, \eta_p^2=0.14$). As shown in figure 3.5B, the mean within-session beta1 amplitude change in passive periods in beta1 NF relative to control NF. However, the post-hoc pairwise comparisons (Bonferroni corrected p-values) did not show significant differences between the groups ($ps>0.12$).

Hypothesis 4: Training-specificity of across-session SMR and beta1 amplitude changes in passive periods.

Figures 3.4A and 3.4B show the SMR and beta1 amplitude changes in passive periods across-sessions in the three protocols. Across-session SMR and beta1 amplitude changes in passive periods was investigated in separate two-way 6 SESSION x 3 PROTOCOL mixed-ANOVAs. Table 3.2. presents means (and SD) of average within-session SMR and beta1 amplitude change in passive periods for each session.

In the SMR frequency, the analysis failed to reveal significant changes across sessions as a function of the type of NF (SESSION x PROTOCOL: $F(10,140)=1.30, p=0.24, \eta_p^2=0.09$). However, there was a significant main effect of SESSION ($F(5,140)=2.75, p=0.02, \eta_p^2=0.09$). Polynomial contrasts evinced a significant linear increment in SMR amplitude change across sessions irrespective of protocol ($F(1,28)=10.43, p<0.01, \eta_p^2=0.27$). Bonferroni corrected pairwise comparisons further revealed a reliable SMR amplitude increment between sessions 1 and 6 ($t(30)=3.37, p=0.04$). The remaining pairwise comparisons were non-significant (all $ps>0.14$).

Table 3.3. Means (and SD) of the mean within-session amplitude change (μV) in active and passive periods for each frequency; statistical values of the between-subjects one-way ANOVAs and multiple comparisons by independent t -tests (Bonferroni corrected p -values) between control NF, SMR NF and beta1 NF.

Source	Frequency	Protocol						ANOVA F	Independent t -test		
		Control		SMR		Beta1			Control vs. SMR	Control vs. Beta1	SMR vs. Beta1
		M	SD	M	SD	M	SD				
Active	Theta	0.975	0.07	0.950	0.06	0.993	0.04	1.52	1.00	0.72	1.74
	Alpha1	0.954	0.07	0.982	0.04	1.000	0.03	2.28	1.28	2.13	0.82
	Alpha2	0.989	0.06	1.026	0.07	1.027	0.05	1.34	1.39	1.45	0.03
	SMR	0.983	0.05	1.018	0.06	1.004	0.05	1.08	1.46	0.90	0.59
	Beta1	0.977	0.04	1.007	0.04	1.034	0.05	4.79 *	1.58	3.07 *	1.48
	Beta2	0.986	0.04	1.003	0.04	1.017	0.04	1.63	0.92	1.80	0.87
	Beta3	0.984	0.05	0.995	0.05	1.008	0.04	0.65	0.49	1.14	0.63
	Beta4	0.979	0.06	0.982	0.05	1.001	0.02	0.74	0.14	1.11	0.97
Passive	Theta	0.971	0.11	0.966	0.08	1.008	0.15	0.40	0.08	0.73	0.81
	Alpha1	0.987	0.11	0.967	0.04	0.999	0.07	0.41	0.55	0.34	0.90
	Alpha2	1.019	0.11	0.971	0.06	1.003	0.10	0.69	1.16	0.40	0.78
	SMR	0.990	0.08	0.973	0.08	0.984	0.09	0.12	0.48	0.19	0.30
	Beta1	0.967	0.08	0.992	0.04	1.032	0.08	2.34	0.81	2.14	1.31
	Beta2	0.975	0.07	0.975	0.04	0.990	0.05	0.26	0.01	0.62	0.61
	Beta3	0.958	0.09	0.955	0.05	0.959	0.06	0.01	0.09	0.03	0.13
	Beta4	0.947	0.10	0.944	0.05	0.976	0.06	0.63	0.08	0.92	1.01

† = $p < 0.10$; * = $p < 0.05$; ** = $p < 0.01$

In the beta1 frequency the main effect of SESSION ($F(5,140)=1.09$, $p=0.36$, $\eta_p^2=0.04$) and the interaction effect of SESSION x PROTOCOL ($F(10,140)=0.87$, $p=0.57$, $\eta_p^2=0.06$) were not reliable.

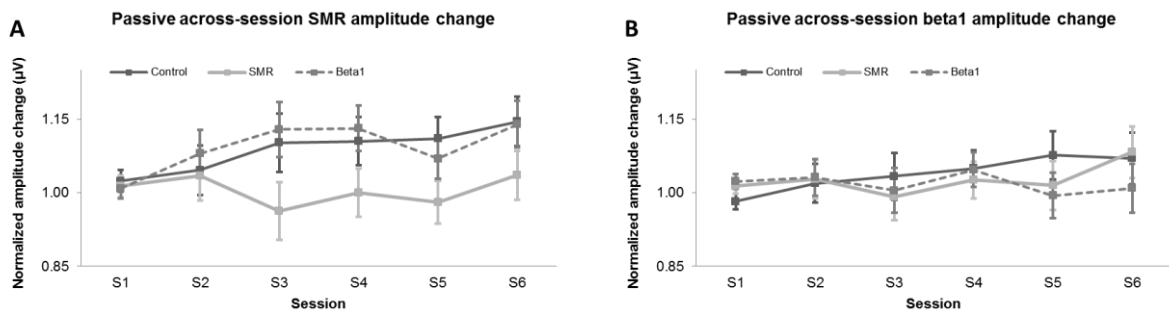


Figure 3.4. Across-session SMR and beta1 amplitude change for control NF, SMR NF and beta1 NF in passive periods. The graphs represent the amplitude change in six training sessions (from S 1 to S 6) for SMR (A) and beta1 frequencies (B). Amplitude change was normalized relative to the first passive period of the first session. Error bars depict standard error of the mean.

3.3.1. Frequency-specific learning

In order to investigate frequency-specific effects, the mean within-session amplitude change for eight frequencies ranging from theta to beta4 was calculated for each NF protocol. Means (and SD) of within-session amplitude changes in the eight frequencies in active feedback and passive resting state periods are presented in table 3.3. Frequency-specific effects were analyzed with two-way 8 FREQUENCY x 3 PROTOCOL mixed-ANOVAs for active and passive periods.

Hypothesis 5: Frequency-specificity of SMR and beta1 amplitude changes in active periods.

For active feedback periods the analysis revealed a significant main effect of FREQUENCY ($F(7,196)=5.01$, $p<0.001$, $\eta_p^2=0.15$). The pairwise comparisons revealed overall significant within-session amplitude decreases in both theta ($M=0.973$; $SD=0.06$) and alpha1 ($M=0.979$; $SD=0.05$) relative to alpha2 ($M=1.014$; $SD=0.06$) (theta vs. alpha2: $t(30)=3.72$, $p=0.03$; alpha1 vs. alpha2: $t(30)=3.89$, $p<0.01$). The interaction effect of FREQUENCY x PROTOCOL was non-significant ($F(14,196)=1.24$, $p=0.25$, $\eta_p^2=0.08$). However, the effects of the three protocols on each of the eight frequencies were explored by one-way ANOVAs and t -tests. As shown in figure 3.5A, beta1 NF appears to be associated with increased within-session amplitudes in alpha1 and beta1 relative to control NF and in theta relative to SMR NF. However, as can be seen in table 3.3., apart from the previously discussed main effects of PROTOCOL in the beta1 frequency (section 3.1.1.), no significant differences between NF groups were observed in the other frequency bands (all $ps>0.13$). The analysis also indicated that the main effect of PROTOCOL was not reliable ($F(2,28)=1.96$, $p=0.16$, $\eta_p^2=0.12$).

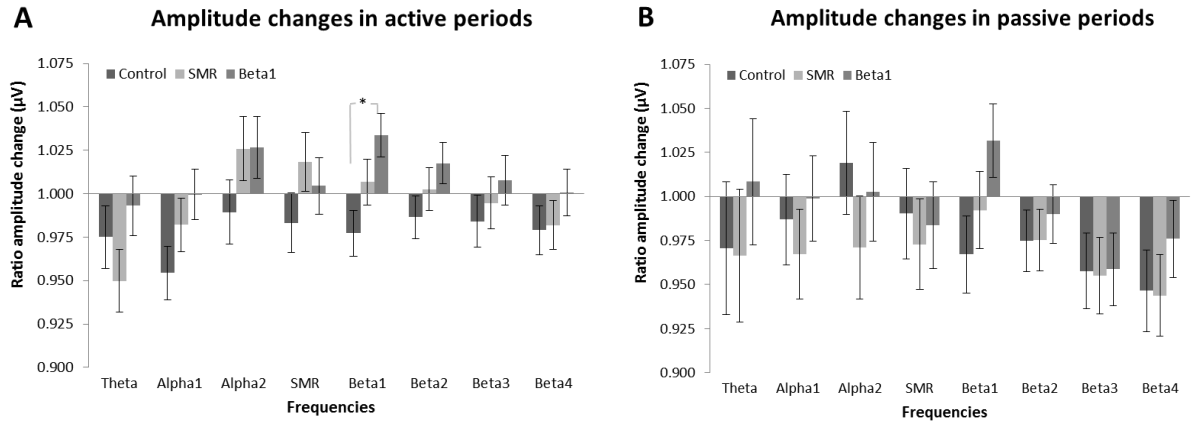


Figure 3.5. Within-session amplitude change in different frequency bands for control NF, SMR NF and beta1 NF protocols. The graphs indicate the mean within-session amplitude change from theta to beta4 frequencies for active periods (normalized to the first active period of each sessions) (A) and passive periods (normalized to the first passive period of each session) (B). Error bars depict standard error of the mean. Statistical significance level is represented by asterisks (* $p < 0.05$ and ** $p < 0.01$).

Hypothesis 6: Frequency-specificity of SMR and beta1 amplitude changes in passive periods.

The mean amplitude changes in passive periods for the frequencies ranging from theta to beta4 for each of NF protocols are shown in figure 3.5B. As shown in the figure, beta1 NF appears to be associated with frequency-specific increments in beta1 amplitude relative to control NF. However, the 8 FREQUENCY x 3 PROTOCOL mixed ANOVA indicated that the interaction effect of FREQUENCY x PROTOCOL was not reliable ($F(14,196)=0.65, p=0.68, \eta_p^2=0.04$). The analysis further revealed a significant main effect of FREQUENCY ($F(7,196)=2.19, p=0.04, \eta_p^2=0.07$). Post-hoc analysis revealed significant within-session amplitude decreases in beta3 ($M=0.957; SD=0.07$) and beta4 ($M=0.956; SD=0.07$) relative to alpha2 ($M=0.998; SD=0.09$; alpha2 vs. beta3: $t(30)=3.63, p=0.02$; alpha2 vs. beta4: $t(30)=3.50, p=0.04$) and relative to beta1 ($M=0.998; SD=0.07$; beta1 vs. beta3: $t(30)=4.00, p=0.02$; beta1 vs. beta4: $t(30)=3.81, p=0.02$). The analysis further indicated a non-significant main effect of PROTOCOL ($F(2,28)=0.50, p=0.61, \eta_p^2=0.04$).

3.4. Discussion

3.4.1. Training- and frequency-specificity in active periods

3.4.1.1. Training-specific within-session amplitude changes

Beta1

The present study provided supportive evidence of the feasibility of using the EEG NF technique to increase the beta1 amplitude, but failed to replicate its effect in enhancing the SMR amplitude (Hypothesis 1). The results present novel evidence that, during active feedback periods, beta1 amplitude was significantly increased in the course of 20-minute-long beta1 NF sessions relative to a RF NF control condition. This finding suggests that the increase in sensorimotor beta1 activity was related to the training rather than to unspecific effects such as time on task, placebo, sensorimotor stimulation and feedback learning.

However, as suggested by figures 3.2B and 3.5A and additionally confirmed by post-hoc comparisons, these beta1 amplitude increases were not significantly larger than those obtained in SMR NF. These latter findings question the training-specificity of the beta1 amplitude increments. In fact, it is conceivable that the differences in the beta1 amplitude might be explained by some common aspect that was present in the SMR and beta1 NF but not in control NF condition. For instance, the experimental manipulation of RF NF might have made it more difficult to develop and maintain a consistent self-regulatory strategy both within and across the training sessions because a new frequency was trained in every session and the training contingencies were reversed halfway through the session. The more stable conditions of the SMR and beta1 NF would be more likely to contribute to the maintenance of the current postural and cognitive set (Engel & Fries, 2010) and the development of top-down mechanisms of attentional control (Wróbel, 2000; Buschman & Miller, 2007; Lee et al., 2013) that correlate with increased beta activity. Further, this explanation appears to be consistent with the absence of beta amplitude increments in sham NF conditions (Witte et al., 2013; Kober et al., 2015) in which the unpredictability of feedback may prevent the development of self-regulatory strategies. Although similar RF NF conditions have been used in previous studies (Hoedlmoser et al., 2008; Doppelmayr & Weber, 2011; Schabus et al., 2014) little is known regarding their comparability with experimental and other control

conditions (e.g., sham NF) in terms of demands imposed on self-regulation, cognitive effort and other unspecific variables with impact on beta and other EEG frequencies. Further work is needed to better understand whether experimental and control conditions impose different self-regulatory and cognitive demands and to prevent such differences by ensuring their consistency within- and across-sessions.

SMR

The present results failed to replicate within-session SMR amplitude increments following SMR/theta (Witte et al., 2013; Kober et al., 2015). Although this is line with other studies (e.g., Ros et al., 2009), several methodological limitations may explain the lack of significant within-session SMR amplitude increments. Firstly, the different visual and kinesthetic properties of the screens used to display feedback information could have interfered specifically with the ability to increase the SMR amplitude. Because the SMR frequency is suppressed with actual or imagined voluntary motor execution (Stancák & Pfurtscheller, 1996; Gilbertson et al., 2005; Pfurtscheller et al., 2005; Kilavik et al., 2013), the movement sensation induced by the first screen (periods 1-4) might have caused difficulties to the synchronization of SMR activity when compared to the more static properties of the second screen (periods 5-8). However, this apparent difficulty (see figure 3.2A) was not confirmed by within-subject comparisons, which failed to show significant differences in SMR amplitude change between periods in SMR NF. Secondly, the shorter duration of the active feedback periods (150 seconds) relative to those previous studies (180 seconds) might also explain the differences in success of within-session SMR learning. While this limits the comparisons between studies, it must be noticed that the duration of the feedback periods was not an impediment to observe training-specific within-session beta1 amplitude increases in the present study. This suggests that the extent to which the duration of the feedback period affects the learning ability might significantly differ from one frequency to the other. The question of whether the duration of feedback trials differentially affects the reactivity, and therefore, the learning success in different EEG frequencies is certainly an important aspect of NF learning to be explored in future studies.

An alternative explanation for the discordant results is that SMR NF did not include explicit instructions to suppress theta and high-beta amplitude. This interpretation is in line

with the proposal that theta and high-beta suppression might play a coadjuvant role in successful SMR amplitude increments by ensuring the necessary conditions of attentional focus and behavioral stability (Serman and Shouse, 1980; Othmer et al., 1999). In light of the present evidence one cannot rule out the hypothesis that the modulation of slow or fast wave activity may play a mechanistic role in within-session SMR amplitude increments as observed in previous studies. A possible candidate mechanism is the ability of the lower frequencies to modulate the amplitude of higher frequencies by phase-amplitude or amplitude-amplitude cross-frequency coupling (Canolty & Knight, 2010). However, in the absence of empirical studies that compare SMR NF with and without suppression of lower and higher frequencies the relative contribution of these frequencies to successful within-session SMR amplitude increments remains unclear.

3.4.1.2. Frequency-specific within-session active amplitude changes

Another goal of the present study was to investigate whether the NF protocols could selectively increase the activity in the target frequencies. Importantly, the non-significant FREQUENCY x PROTOCOL interaction did not allow the interpretation that beta1 NF was related to within-session amplitude increments in beta1 frequency but not in other frequencies (Hypothesis 5). As shown in fig. 3.5A, beta1 NF was also associated with (non-reliable) amplitude increments in other frequencies when compared to the other NF groups. However, the non-reliable main effect of PROTOCOL did not support the hypothesis of an overall within-session amplitude increment irrespective of frequency following beta1 NF either. Instead, there was a significant main effect of FREQUENCY indicating reliable within-session amplitude increases in alpha2 relative to theta and low-alpha irrespective of the NF protocol which may correspond to unspecific effects of NF.

Importantly, the present findings failed to corroborate previous evidence of frequency-specific SMR and beta1 amplitude increments relative to theta and high-beta (Vernon et al., 2003; Ros et al., 2009; Gruzelier et al., 2014a, 2014b). However, as shown in table 1.1, (1) there was conflicting evidence between studies of frequency-specificity relative to theta (e.g., Ros et al., 2009; Kober et al., 2015) and high-beta (Gruzelier et al., 2014a, 2014b), (2) frequency-specificity relative to both frequencies was never observed in the same study (e.g., Vernon et al., 2003; Kober et al., 2015) and, (3) contrary to the present study,

when more than one statistical test was used the p -values were not adjusted to the number of multiple comparisons.

3.4.1.3. Across-session active amplitude changes

Also contrary to hypothesis, the present study failed to provide supportive evidence of training-specific across-session amplitude increments in active feedback periods (Hypothesis 2). In fact, both SMR and beta1 amplitudes were linearly increased irrespective of the NF protocol. These results are in line with previous studies suggesting that, despite linear increments in SMR amplitude at the session level, the absolute SMR amplitude was not superiorly increased across sessions in SMR/theta relative to sham NF (Witte et al., 2013; Kober et al., 2015). They are also consistent with previous failures to demonstrate across-session beta1 learning following beta1/theta when compared to other NF protocols (Doppelmayr & Weber, 2011). However, these results are in disagreement with previous findings of increased SMR amplitude from the beginning to the end of the training following SMR and SMR/theta relative to RF NF control conditions (Doppelmayr & Weber, 2011; Hoedlmoser et al., 2008; Schabus et al., 2014).

In the current experiment, the across-session SMR and beta1 amplitude increments observed in the control NF could have masked the training-specific effects of SMR and beta1 NF. Because similar increments in the RF NF were not observed in previous studies (e.g., Doppelmayr & Weber, 2011; Hoedlmoser et al., 2008), a possible explanation for this divergent findings may rely on the greater difficulty of the present control condition. In fact, the change from down- to up-regulation midway through the session might have imposed higher demands on maintenance of a cognitive and postural set than a single up-regulation strategy (as in the SMR and beta1 NF). These higher demands might have resulted in initial lower levels of beta synchronization relative to later sessions, that despite the absence of a significant SESSION x PROTOCOL interactions, were especially evident in RF NF (as shown in figures 3.3A and 3.3B).

An alternative explanation for the failure to observed across-session SMR and beta1 amplitude increments may rely on the relatively reduced number of sessions in the present study. However, whether across-session learning might be related to the number of sessions *per se* remains elusive. In fact, while some studies suggest across-session SMR amplitude

increments after ten or more sessions (Doppelmayr & Weber, 2011; Hoedlmoser et al., 2008; Kober et al., 2013; Schabus et al., 2014) with SMR/theta ratio reaching a plateau after the initial four sessions (Ros et al., 2009), others failed to yield any evidence of across-session learning after ten NF sessions (Witte et al., 2013; Kober et al., 2015).

3.4.2. Training- and frequency-specificity in passive periods

The results failed to provide supportive evidence of training-specific within-session SMR and beta1 amplitude changes between pre- and post-training passive resting state periods (Hypothesis 3). Thus, it can be concluded that, despite the within-session beta1 amplitude increments in the beta1 relative to control NF observed in the active periods, the same increments in the passive periods did not reach statistical significance (as shown in fig. 3.5B). These results are in agreement with the previous suggestion that the increased beta synchronization during the active feedback state may not necessarily culminate in increased resting state beta activity (Egner et al., 2004).

As also shown in the figure 3.5B, SMR amplitude was globally decreased from pre-to post-training. However, from the present findings it remains unclear whether the failure to observe significant within-session SMR amplitude changes in passive periods may be related to the unsuccessful SMR self-regulation during the active feedback periods. Also contrary to prediction, the results failed to provide supportive evidence of across-session amplitude SMR amplitude increments in passive periods as a function of the specific training conditions (Hypothesis 4). These results are in accordance with the failure to observe training-specific resting state SMR amplitude change across sessions, even when training-specific increments were observed during active feedback conditions (Hoedlmoser et al., 2008; Witte et al., 2013). However, there was a linear across-session increments in post-training SMR amplitude irrespective of the NF. Similarly to the active periods, it is unclear whether control NF could have masked training-specific effects or whether this increments correspond to unspecific effects of NF such as an increase in motor inhibition associated with an increasing compliance with general NF instructions of remaining still to prevent EMG artifacts.

Similarly to active periods, the analysis failed to provide support to the hypothesis of frequency-specific SMR and beta1 amplitude increments in passive periods (Hypothesis 6). The analysis revealed a main effect of FREQUENCY suggesting within-session amplitude

increments in the alpha2 and beta1 frequencies relative to the beta3 and beta4 frequencies regardless of the NF protocol. This amplitude increment in lower relative to higher frequencies may reflect an increased cortical inhibition effect of the NF sessions specific to passive periods. Speculatively, the observation of the opposite pattern of amplitude changes in the active periods (i.e., decrements in lower relative to higher frequencies) provides support to the notion that NF may have a distinct impact on the brain dynamics during task involvement (i.e., increased activation) and resting state (i.e., increased inhibition).

Additionally, the amplitude increments in beta1 relative to beta3 and beta4 suggest that unspecific factors associated with NF may have a differential impact on functionally distinct sensorimotor beta rhythms (Hari & Salmelin, 1997; Neuper & Pfurtscheller, 2001; Cheyne, 2013). However, the nature of the unspecific factors that may have contributed to these patterns of reactivity in the beta band is not entirely clear. An investigation of the possible association of this pattern with dissociable somatosensory processing and movement execution aspects of task performance (Hari & Salmelin, 1997) would contribute to a better understanding of the NF impact on low- and high-beta frequencies.

3.4.3. Summary

The current study provides empirical evidence that the validation of SMR and beta1 NF may benefit from taking into consideration different learning indices and supporting assertions of learning specificity in comparisons with control conditions in a broad range of frequencies. Our results provide novel evidence of the feasibility of enhancing the beta1 amplitude by NF. However, whether such increments may be related to specific or unspecific effects remains unclear. Beta1 amplitude increments may be related to the possibility of maintaining a consistent self-regulatory strategy throughout the session. Also in line with the interpretation that the beta1 amplitude increments in beta1 NF might have been epiphenomenal, we failed to provide evidence that those increments were larger than in other frequency bands. Our findings are consistent with previous studies that failed to demonstrate a net increase in within-session SMR amplitude. However, it is still unclear whether the differences in training-specificity of SMR and beta1 NF might be associated with methodological limitations (e.g., changes in the visual and kinesthetic properties of the screens) or reflect different patterns of reactivity to self-regulatory strategies.

Chapter 4

Experiment 2: The effects of SMR and beta1 NF on selective attention

4.1. Hypotheses

Hypothesis 1: Increased P3a and P3b amplitude as a function of SMR and beta1 NF

It was hypothesized that:

- (1) P3b amplitude would be increased in the beta1 NF relative to SMR NF and control NF conditions and in the SMR NF relative to control NF condition (beta1 > SMR > control).
- (2) P3a amplitude would be increased in the SMR NF relative to beta1 and control NF and in the beta1 NF relative to control NF condition (SMR > beta1 > control).

Hypothesis 2: Decreased RT and RT-SD as a function of SMR and beta1 NF

It was hypothesized that:

- (1) RT would be decreased in the beta1 NF relative to SMR NF and control NF and in the control NF relative to the SMR NF (beta1 < control < SMR).
- (2) RT-SD would be decreased in the beta1 NF relative to SMR NF and control NF and in the SMR NF relative to the control NF (beta1 < SMR < control).

Hypothesis 3: Increased perceptual sensitivity and performance rates as a function of SMR and beta1 NF

It was hypothesized that:

- (1) Target-standard d' and target-nontarget d' would be increased in SMR NF relative to beta1 NF and control NF and increased in beta1 NF relative to control NF (SMR > beta1 > control).
- (2) Hit rate would be increased in the beta1 NF relative to SMR NF and control NF and increased in SMR NF relative to control NF (beta1 > SMR > control).

- (3) Standard false alarm rate and nontarget false alarm rate would be decreased in the SMR NF relative to control NF and beta1 NF and in the control NF relative to the beta1 NF (SMR<control<beta1).

4.2. Methods

4.2.1. Participants

The same thirty-one participants of Experiment 1 took part in the present study. After excluding trials with artifacts and averaging the ERP waveforms four participants (two from the control NF and two from the beta1 NF) were excluded from the analysis for having less than thirty correct trials in at least one of the stimulus conditions at either pre- or post-training. Table 4.1. presents demographic data the remaining twenty-seven participants (12 males, 15 females). The mean age did not differ between NF protocols as confirmed by a one-way ANOVA ($F(2,24)=0.31, p=0.73, \eta_p^2=0.03$).

Table 4.1.

Descriptive statistics of age (mean and standard deviation) and gender (frequency) by NF protocol after excluding four participants with insufficient number of correct trials per stimulus condition.

NF	Age		Gender		
	M	SD	Male	Female	Total
Control	21.38	1.77	4	4	8
SMR	23.00	5.58	5	5	10
Beta	21.89	4.371	3	6	9
Total	22.15	4.38	12	15	27

4.2.2. Stimulus and procedure

The three-stimuli oddball task was presented to the subjects before and after the NF sessions (Experiment 1) in counterbalanced order with the cued Go/Nogo task (Experiment 3). The order of presentation had no effect in either the P3 amplitude for target, nontarget and standard stimuli or the behavioral measures of RT and accuracy.

Stimuli were presented electronically using the E-Prime 1.1 software (Psychology Software Tools, Pittsburgh, PA). Auditory tones were pure sinusoidal tones presented

binaurally in a random series at 75 dB SPL through speakers every 1.75 seconds with a 200ms plateau and 10ms rise/fall times. EEG activity was recorded during 5 blocks, each of which consisted of 100 stimulus presentations. Each block lasted approximately 3 minutes. The stimuli differed in pitch and probability of occurrence and were defined as target (low pitch=500 Hz; probability of occurrence=0.10), standard (medium pitch=1000 Hz; probability of occurrence=0.80) and non-target (high pitch=2000 Hz; probability of occurrence=0.10). Participants were instructed to respond as quickly and accurately as possible to the target stimulus by pressing a button with their right thumb. Response time and accuracy were recorded within the response interval (0 to 1750ms after stimulus presentation). Each participant was given a practice trial block consisting of 20 stimuli with the same probability rates as described above.

4.2.3. EEG recording and analysis

EEG recording.

For EEG acquisition at pre- and post-training a Biosemi Active Two A/D box ADC-9 (Biosemi, Netherlands) digital amplifier was used. EEG data was obtained from 64 electrodes mounted in an elastic cap in accordance with the international 10-20 system. Two additional electrodes, Common Mode Sense (CMS) and Driven Right Leg (DRL), were used as a “ground”. (<http://www.biosemi.com/faq/cmsanddrl.htm>). The EEG was Direct Current-recorded with a low-pass filter of 100 Hz, a high-pass filter of 0.16 and a sampling rate of 512 Hz. Horizontal and vertical electro-oculograms were measured bipolarly from a pair of electrodes placed at the outer canthi of the eyes and a pair of electrodes placed above and below the right eye.

EEG data analysis.

EEG analysis was performed in Brain Vision Analyzer EEG analysis 1.05 software (Brain Products, Munich, Germany). After data acquisition, the EEG was digitally re-referenced to the average of the left and right earlobes and band-pass filtered (high-pass 0.5 Hz, low-pass 40 Hz). EEG continuous recordings were visually inspected to remove extreme EEG artifacts and segmented in reference to the stimuli in intervals of 1000ms (-200ms pre-stimulus to 800ms post-stimulus). Only correct trials (correct response to target and correct

non-response to standard and non-target on the 0 to 1000ms interval post-stimulus onset) were analyzed. The data was then submitted to baseline correction (-200ms to 0ms relative to stimulus onset) and artefact rejection was performed for ocular movements and EEG fluctuations exceeding $\pm 80 \mu\text{V}$. A minimum of 30 trials per condition were used. Subsets of four electrodes were pooled to define three regions of interest: frontal (F1, Fz, F2, FCz), central (C1, Cz, C2, CPz), parietal (P1, Pz, P2, POz). The data was then averaged per region of interest.

In order to isolate the P3a and P3b components the mean amplitudes of *target-standard difference waveform* and *nontarget-standard difference waveform* were calculated by linear subtraction. The deviant-standard difference waveform was obtained by averaging target-standard and nontarget-standard difference waveforms and then subtracting the standard amplitude from it.

Percent of correct ERP trials.

Descriptive statistics of percent of correct trials in the oddball task are presented in table 4.2 Separate two-way ANOVAs on the percentage of correct trials as a function of TIME (Pre- vs. Post-Training) and PROTOCOL (control NF vs. SMR NF vs. beta1 NF) were performed for each type of STIMULUS (target, standard and nontarget). As can be seen in table the three 2 TIME x 3 PROTOCOL ANOVAs yielded no significant main effects or interactions (all $p > 0.12$) suggesting that the artifact rejection on the correct trials did not introduce systematic differences in the analysis in terms of the number of trials per condition.

4.2.4. Behavioral data analysis

Reaction time data preparation

Behavioral responses were collected using E-Prime 1.0 software (Psychology Software Tools, Pittsburgh, PA). Data preparation for RT and RT-SD analysis was as follows. In order to remove outliers from both ends of the RT distribution correct trials (i.e., responses to the target stimulus) which response latencies fell below 100 ms and above 1000ms were excluded from the analysis (rejection rate = 0.07% of the trials). Only participants with a minimum of 30 correct trials were included in the analysis.

***d'* data preparation**

In order to guarantee comparability between RT and ERP data sets, only correct responses (button press) to targets within the 100-1000ms interval were considered “hits” while responses to standard or non-target stimulus within the same interval were considered “false alarms”. The hit and false alarm rates were subjected to a z-score transformation so that the distributions had similar variances and therefore d' was calculated by [$d' = z(\text{hit rate}) - z(\text{false alarm rate})$] where the function $z(p)$ was the inverse of the cumulative Gaussian distribution. This was calculated in MATLAB using the `norminv` function [$d' = \text{norminv}(\text{hit rate}) - \text{norminv}(\text{false alarm rate})$]. To prevent infinity as a consequence of the Z transformation of perfect scores (i.e., hit rates of 1 and false alarm rates of 0) the rates were subjected to a standard correction according to the procedure proposed by Macmillan and Creelman (2005) as follows. When misses were higher than zero the hit rate (H) was calculated by [$H = \text{number of hits} / (\text{number of hits} + \text{number of misses})$]. When misses were zero a standard correction was performed so the hit rate was then given by [$H = (\text{number of hits} - 0.5) / (\text{number of hits} + \text{number of misses})$]. When false alarms were higher than zero false alarm rate (FA) was calculated by [$FA = \text{Number of false alarms} / (\text{Number of false alarms} + \text{Number of correct rejections})$]. When false alarms were zero, an analog standard correction was performed and FA was calculated by [$FA = (\text{Number of false alarms} + 0.5) / (\text{Number of false alarms} + \text{Number of correct rejections})$].

The signal detection accuracy in the 3-stimuli oddball may be described, as in signal detection classification experiments, by the increase in perceptual sensitivity to task-relevant stimuli (targets) in relation to both frequent (standard) and infrequent task-irrelevant stimuli (nontargets). Thus, in the present experiment two d' measures were used: the target-standard d' and the target-nontarget d' . Given that the sensitivity measures are based on standardized scores, stimuli within the same pitch tone dimension can be conveniently compared regardless of different probabilities of occurrence (Macmillan & Creelman, 2005).

4.2.5. Statistical analysis

Specifications of statistical packages and criteria were provided in section 3.2.6.

4.3. Results

4.3.1. Hypothesis 1: Increased P3a and P3b amplitude as a function of SMR and beta1 NF

The differences between the three NF protocols in the P3 amplitude of target-standard and nontarget-standard difference waveforms were investigated at pre-training (4.3.1.1.) and from pre- to post-training (section 4.3.1.2).

4.3.1.1. Pre-training differences between NF protocols

Figure 4.1. shows the grand average of the stimulus-locked ERP elicited by the target-standard and nontarget-standard difference waves in frontal, central and parietal regions at pre-training irrespective of NF protocol. In parietal electrodes a large positive deflection starting around 250ms after stimulus onset with maximal peak amplitude around 300ms – the P3 component - could be identified for both nontarget (P3a) and target stimulus (P3b).

The three-way 2 STIMULUS (target-standard vs. nontarget-standard) x 3 REGION (frontal vs. central vs. parietal) x 3 PROTOCOL (control NF, SMR NF and beta1 NF) ANOVA for the mean P3 amplitude at pre-training yielded significant main effects of STIMULUS ($F(1,24)=23.09, p<0.01, \eta_p^2=0.49$) and REGION ($F(1.37,33.00)=29.35, p<0.01, \eta_p^2=0.55$) as well as a significant interaction of STIMULUS x REGION ($F(1.24,29.86)=10.44, p<0.01, \eta_p^2=0.30$). The main effect of PROTOCOL ($F(2,24)=0.57, p=0.57, \eta_p^2=0.05$) and the interactions involving the between-subject variable were non-significant (STIMULUS x PROTOCOL: $F(2,24)=1.19, p=0.32, \eta_p^2=0.09$; REGION x PROTOCOL: $F(2.75,33.00)=0.65, p=0.57, \eta_p^2=0.05$; STIMULUS x REGION x PROTOCOL: $F(2.49,29.86)=0.57, p=0.69, \eta_p^2=0.05$).

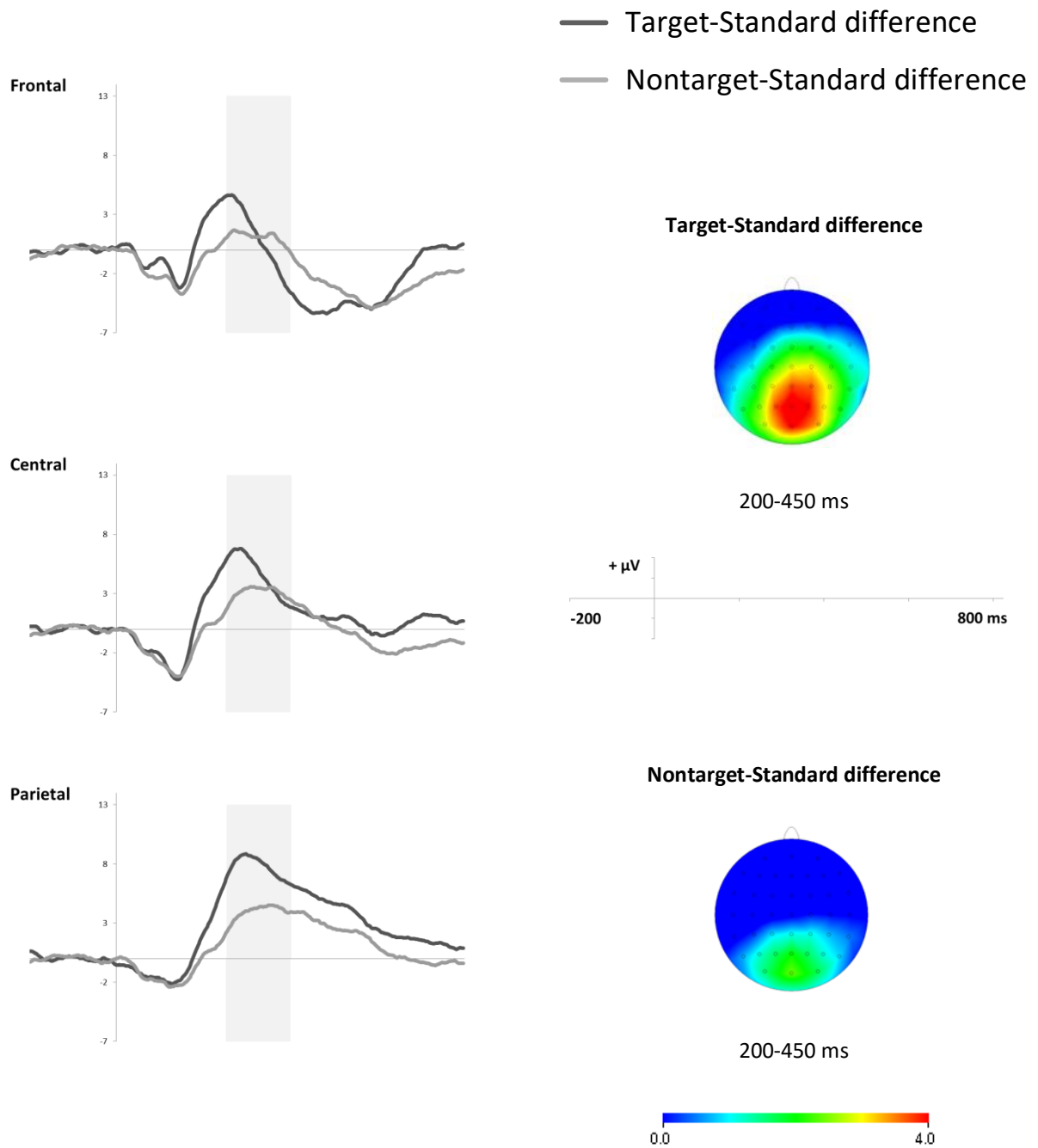


Fig. 4.1. *Left.* Grand average of the stimulus-locked ERP of target-standard and nontarget-standard difference waves in midline frontal, central and parietal regions at pre-training irrespective of the NF protocol. The shaded area represents the 250-400ms measurement window. Positive amplitude is displayed upwards. *Right.* Distribution of the target target-standard and nontarget-standard difference waves.

As shown in fig. 4.2., the post-hoc comparisons (Bonferroni corrected p -values) for the target-standard difference waves revealed a significantly higher P3 amplitude in the parietal region ($M=6.97$, $SD=3.72$) relative to central ($M=4.43$, $SD=3.72$; $t(26)=5.12$, $p<0.001$) and frontal regions ($M=2.32$, $SD=3.14$; $t(26)=5.88$, $p<0.001$) and in the central region relative to the frontal region ($t(26)=4.16$, $p<0.01$). Similarly, the nontarget-standard difference waves P3 amplitude was higher in the parietal region ($M=3.24$, $SD=2.08$) relative to central ($M=2.40$, $SD=2.66$; $t(26)=2.61$, $p<0.05$) and frontal regions ($M=0.97$, $SD=3.21$; $t(26)=4.06$, $p<0.01$) and in the central region relative to the frontal region ($t(26)=4.32$, $p<0.01$). Moreover, the post-hoc comparisons revealed that the P3 amplitude was significantly higher for the target-standard difference waves relative to the nontarget-standard difference waves in three regions (Frontal: $t(26)=2.10$, $p<0.05$; Central: $t(26)=3.41$, $p<0.01$; Parietal: $t(26)=7.44$, $p<0.001$).

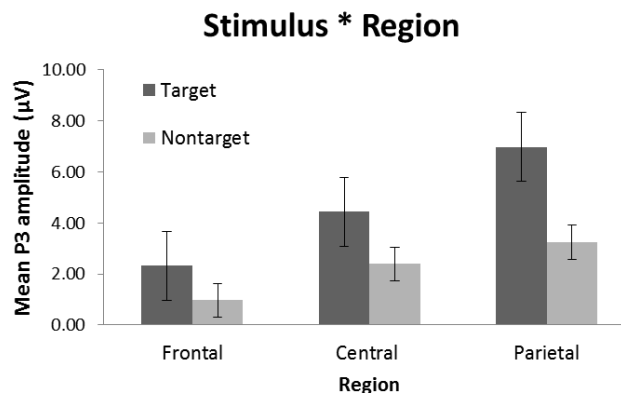


Figure 4.2. Two-way interaction of Stimulus and Region in mean P3 amplitude at pre-training. The graphs shows the mean P3 amplitude (μV) for Target-Standard and Nontarget-Standard stimulus in three Regions (Frontal, Central and Parietal) irrespective of NF protocol at pre-training. For both types of stimuli the P3 amplitude was larger at Parietal electrodes. Error bars depict standard error of the mean.

These results replicated the maximal parietal distribution of the P3a and P3b components and smaller amplitude of the P3a relative to the P3b in the easy target-standard discrimination context (Katayama, & Polich, 1999). Additionally, the analysis did not indicate significant initial differences between the NF protocols in the P3a and P3b amplitude.

4.3.1.2. Pre- to post-training differences between NF protocols

Taking into consideration the above, the effects of the three NF protocols on the P3a and P3b amplitudes were analyzed in the parietal region where these components reached the maximal amplitude. The means (and standard deviations) of the P3 amplitude of target-standard and nontarget-standard differences waves for the three NF protocols at pre- and post-training are shown in table 4.2. These effects were investigated in a two-way mixed-ANOVA with 2 TIME (pre- vs. post-training) x 3 PROTOCOL (control NF vs. SMR NF vs. beta1 NF) for target-standard and nontarget-standard difference waves.

Figures 4.3. and 4.4. present the target-standard and nontarget-standard difference waveforms and the mean P3 amplitude for each of the three NF protocols at pre- and post-training. As suggested by the figures, the statistical analysis did not support the hypothesis of a differential impact of the three NF protocols on the neural processing of targets (TIME x PROTOCOL: $F(2,24)=0.64$, $p=0.17$, $\eta_p^2=0.01$). As shown in the table 4.2., the main effects of TIME and PROTOCOL were also not reliable ($ps>0.66$). The post-hoc comparisons failed to provide evidence of pre- to post-training target-standard P3 amplitude changes in any of the three NF protocols (all $ps>0.50$).

Similarly, the type of NF did not significantly modulate the nontarget-standard P3 amplitude from pre- to post-training (TIME x PROTOCOL: $F(2,24)=1.82$, $p=0.36$, $\eta_p^2=0.08$). Again the main effects of TIME and PROTOCOL were not reliable for the nontarget-standard difference waves ($ps>0.36$). The post-hoc comparisons failed to provide evidence of pre- to post-training nontarget-standard P3 amplitude changes in any of the three NF protocols (all $ps>0.26$).

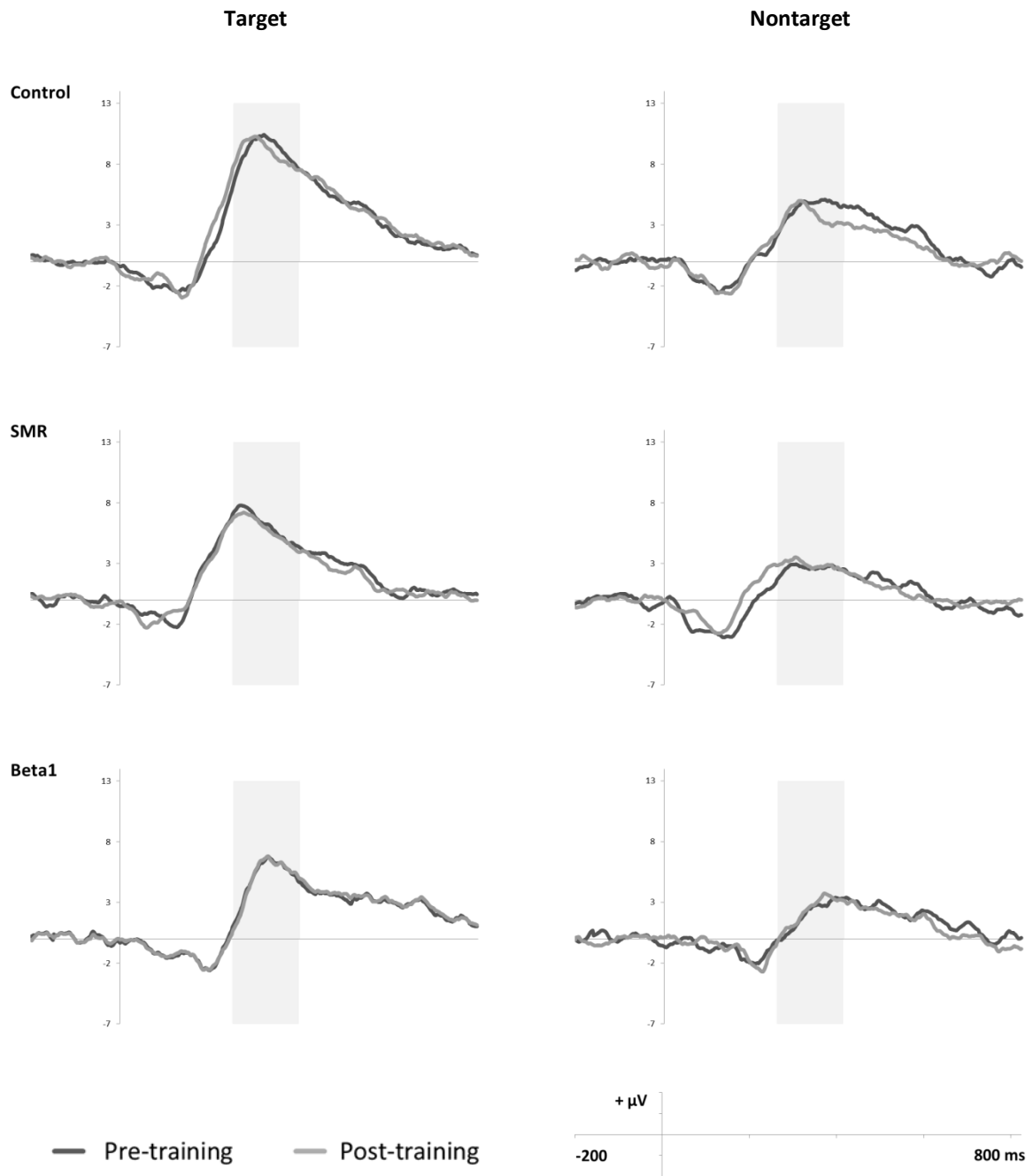


Fig. 4.3. Grand-average of the target-standard and nontarget-standard difference ERP waveforms in the parietal region for Control, SMR and beta1 NF at pre- and post-training. The shaded area represents the 250-400ms measurement window. Positive amplitude is displayed upwards.

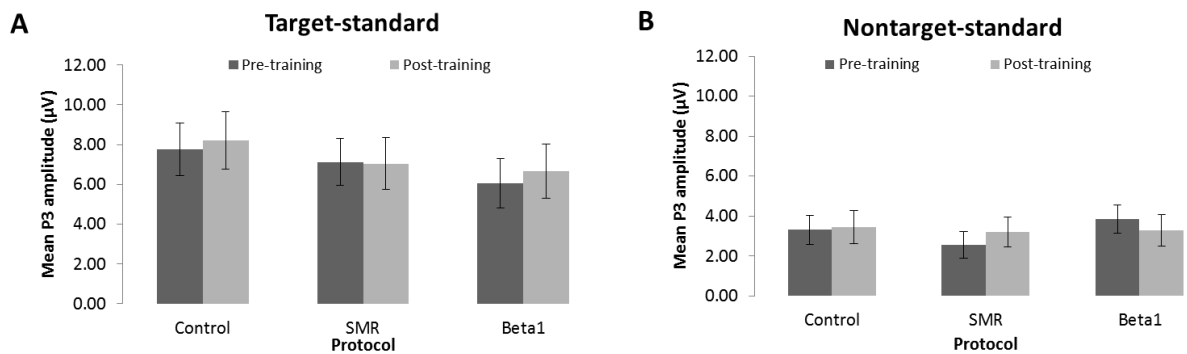


Figure 4.4. Mean P3 amplitude of the target-standard and nontarget-standard difference waveforms for Control, SMR and beta1 NF at pre- and post-training. Both target-standard **(A)** and nontarget-standard P3 amplitudes **(B)** were not significantly modulated by the type NF protocol. Error bars depict standard error of the mean.

4.3.2. Hypothesis 2: Decreased RT and RT-SD as a function of SMR and beta1 NF

Table 4.2. summarizes the data and statistical results for RT and RT-SD at pre- and post-training for the three NF protocols. As can be observed in table, two one-way ANOVAs revealed that there were no initial differences between NF protocols in mean RT and RT-SD (all $p_s > 0.69$). The differential impact of the three NF protocols in mean RT and RT-SD were analyzed in two-way 2 TIME x 3 PROTOCOL mixed-ANOVAs.

4.3.2.1. Mean reaction time

As shown in fig. 4.5A, the three NF protocols were associated with decreased mean RT. The statistical analysis revealed a significant main effect of TIME ($F(1,24)=10.91$, $p < 0.01$, $\eta_p^2=0.25$) indicating that the RT was significantly lower at post-training ($M=385.19$; $SD=113.18$) relative to pre-training ($M=425.89$; $SD=137.56$). This effect was driven by significant decreases in mean RT in control ($t(7)=2.43$, $p=0.02$) but not in the SMR and beta1 NF (all $p_s > 0.22$). However, these decrements were not reliably different as a function of the NF protocol as evinced by a non-significant interaction effect of TIME x PROTOCOL ($F(2,24)=0.62$, $p=0.54$, $\eta_p^2=0.05$). Finally, the main effect of PROTOCOL ($F(2,24)=0.27$, $p=0.76$, $\eta_p^2=0.02$) was not significant.

4.3.2.2. Reaction time standard deviation

Figure 4.5B shows the effects of the three NF protocols on RT-SD. As shown in the figure, the RT-SD decreased from pre- to post-training for both control and SMR NF and increased for the beta1 NF. However, the statistical analysis did not reveal significant main effects (TIME: $F(1,24)=0.08$, $p=0.79$, $\eta_p^2<0.01$; PROTOCOL: $F(2,24)=0.89$, $p=0.42$, $\eta_p^2=0.07$) or interactions (TIME x PROTOCOL: $F(2,24)=1.32$, $p=0.28$, $\eta_p^2=0.10$). The post-hoc comparisons failed to provide evidence of pre- to post-training RT-SD changes in any of the three NF protocols (all $p>0.25$).

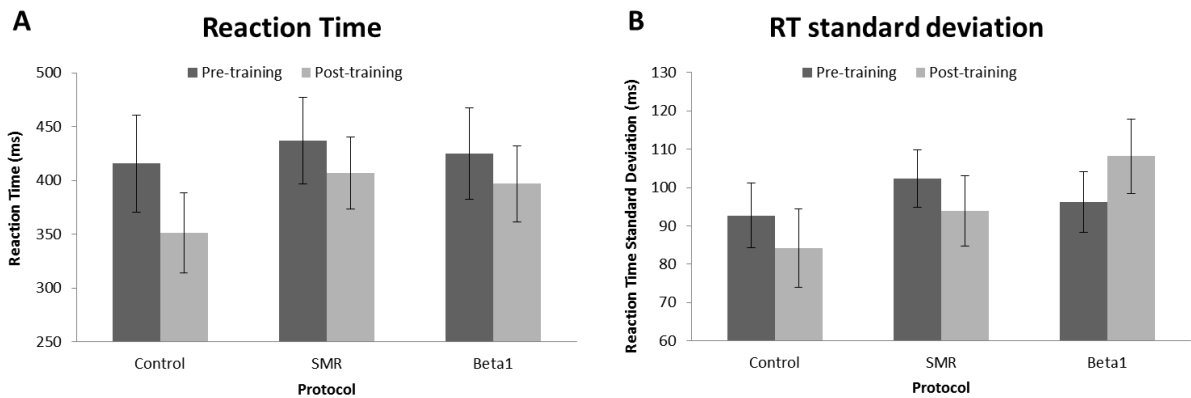


Figure 4.5. Two-way interaction of 2 Time x 3 Protocol for reaction time. The graphs show the effects at pre- and post-training of the three NF protocols on mean RT and RT-SD. **(A)** A significant main effect of Time was observed for RT. **(B)** Both the Control NF and the SMR NF protocols showed a decrease in RT-SD, while the beta1 NF protocol showed an increase in RT-SD. However, the Time x Protocol interaction was non-significant. Error bars depict standard error of the mean.

Table 4.2.

Means (standard deviations) and statistical results of the pre-training one-way ANOVAs and the pre- to post-training two-way ANOVAs on Mean P3 amplitude to Target-Standard (T-S) and Nontarget-Standard (N-S), Hit Rate (H), False Alarm Rate (FA) to Standards (S) and Nontargets (N), d-prime (d') to Target-Standard (T-S) and Nontarget-Standard (N-S), Reaction Time (RT) Mean and Standard Deviation (RT-SD), percentage of Correct Trials (CT) to Targets (T), Standards (S), and Nontargets (N) included in ERP analyses after artifact rejection. Significant differences ($p < 0.05$) are highlighted in bold.

Source							One-way ANOVA			Two-way ANOVA									
	Pre-training			Post-training			Protocol			Time			Time x Protocol			Protocol			
	Control	SMR	Betal	Control	SMR	Betal	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2	
<i>Mean P3</i>																			
T-S	7.76 (3.98)	7.12 (3.40)	6.04 (3.79)	8.21 (4.72)	7.04 (4.26)	6.67 (3.20)	-	-	-	0.39	0.54	0.02	0.17	0.84	0.01	0.42	0.66	0.03	
N-S	3.31 (2.54)	2.56 (2.16)	3.86 (1.54)	3.45 (2.86)	3.22 (2.40)	3.29 (1.80)	-	-	-	0.05	0.83	0.00	1.06	0.36	0.08	0.29	0.75	0.02	
H (%)	97.70 (3.43)	98.22 (0.97)	97.67 (3.16)	98.50 (0.97)	96.44 (7.67)	97.93 (4.43)	0.30	0.74	0.02	0.09	0.76	0.00	1.17	0.33	0.09	0.17	0.84	0.01	
<i>FA (%)</i>																			
S	0.23 (0.31)	0.13 (0.00)	0.13 (0.00)	0.13 (0.00)	0.13 (0.00)	0.22 (0.29)	1.21	0.32	0.09	0.01	0.93	0.00	1.61	0.22	0.12	0.60	0.56	0.05	
N	2.75 (2.71)	2.10 (2.81)	2.33 (2.35)	2.50 (1.69)	1.50 (0.97)	1.67 (1.00)	0.14	0.87	0.01	0.88	0.36	0.04	0.05	0.95	0.01	0.70	0.51	0.06	
<i>d'</i>																			
T-S	5.00 (0.66)	5.18 (0.36)	5.16 (0.20)	5.32 (0.10)	5.24 (0.20)	5.09 (0.77)	0.42	0.66	0.03	0.80	0.38	0.03	0.97	0.39	0.08	0.13	0.88	0.01	
T-N	4.11 (0.53)	4.32 (0.45)	4.24 (0.45)	4.31 (0.27)	4.43 (0.23)	4.32 (0.62)	0.43	0.65	0.04	2.33	0.14	0.09	0.19	0.83	0.02	0.40	0.68	0.03	
<i>RT (ms)</i>																			
Mean	415.74 (131.32)	437.08 (160.94)	424.84 (69.38)	351.58 (123.48)	407.11 (119.72)	396.87 (61.09)	0.06	0.94	0.01	7.94	0.01	0.25	0.62	0.54	0.05	0.27	0.76	0.02	
RT-SD	92.72 (22.46)	102.35 (29.10)	96.18 (17.65)	84.20 (28.26)	93.97 (26.39)	108.17 (32.31)	0.38	0.69	0.03	0.08	0.79	0.00	1.32	0.28	0.10	0.89	0.42	0.07	
<i>CT (%)</i>																			
T	92.25 (6.18)	88.60 (7.95)	84.22 (14.68)	87.75 (10.61)	91.00 (8.39)	85.33 (16.97)	1.29	0.29	0.10	0.01	0.91	0.00	0.50	0.62	0.04	1.08	0.36	0.08	
S	86.13 (7.48)	79.03 (9.63)	75.89 (15.88)	78.41 (13.30)	82.65 (8.71)	79.44 (13.96)	1.71	0.20	0.13	0.006	0.94	0.00	2.32	0.12	0.16	0.47	0.63	0.04	
N	91.25 (7.70)	81.00 (10.42)	79.56 (17.80)	81.50 (9.90)	83.60 (14.32)	79.78 (16.35)	2.09	0.15	0.15	0.57	0.46	0.02	1.47	0.25	0.11	0.83	0.45	0.06	

4.3.3. Hypothesis 3: Increased performance rates and perceptual sensitivity as a function of SMR and beta1 NF

Table 4.2. summarizes the data and statistical results for target-standard d' , target-nontarget d' , target hit rate, standard false alarm and nontarget false alarm at pre- and post-training for the three NF protocols. As can be observed in the table, the one-way ANOVAs failed to reveal pre-training differences between NF protocols in any of these variables (all $ps>0.32$). The differential impact of the three NF protocols in these variables were analyzed in two-way 2 TIME x 3 PROTOCOL mixed-ANOVAs.

4.3.3.1. Target-standard d'

As can be observed in figure 4.6A the target-standard d' increased from pre- to post-training in the control NF and in the SMR NF and showed the opposite tendency in beta1 NF. As shown in table 4.5, the statistical analysis did not yield any significant main effects or interactions (TIME: $F(1,24)=0.80$, $p=0.38$, $\eta_p^2=0.03$; PROTOCOL: $F(2,24)=0.13$, $p=0.88$, $\eta_p^2=0.01$; TIME x PROTOCOL: $F(2,24)=0.97$, $p=0.39$, $\eta_p^2=0.08$). The post-hoc comparisons failed to provide evidence of pre- to post-training target-standard d' changes in any of the three NF protocols (all $ps>0.14$).

4.3.3.2. Target-nontarget d'

As shown in figure 4.6B the target-nontarget d' was slightly increased from pre- to post-training in the three NF protocols. However, the two-way ANOVA on the target-nontarget d' did not reveal significant main effects or interactions (TIME: $F(1,24)=2.33$, $p=0.14$, $\eta_p^2=0.09$; PROTOCOL: $F(2,24)=0.40$, $p=0.68$, $\eta_p^2=0.03$; TIME x PROTOCOL: $F(2,24)=0.19$, $p=0.83$, $\eta_p^2=0.02$). The post-hoc comparisons failed to provide evidence of pre- to post-training target-nontarget d' changes in any of the three NF protocols (all $ps>0.38$).

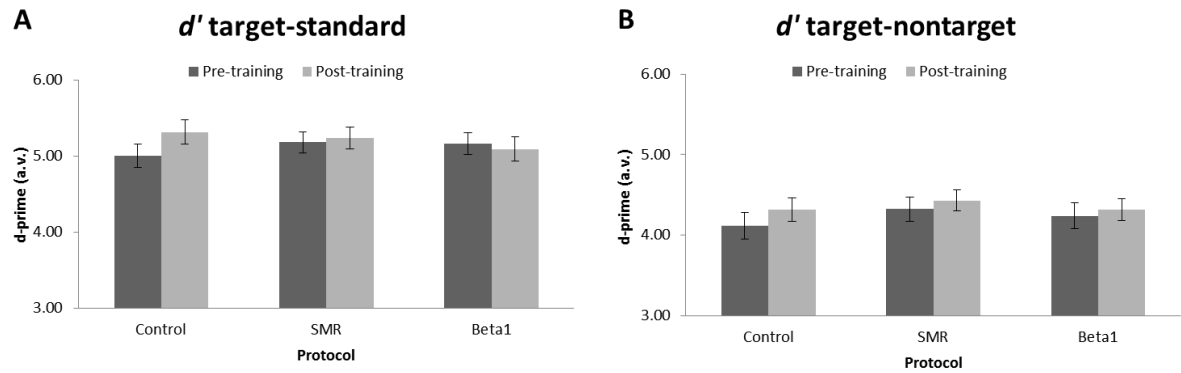


Figure 4.6. Two-way interaction of 2 Time x 3 Protocol for *d*-prime. The graphs show the effects at pre- and post-training of the three NF protocols on *d'* target-standard and *d'* target-nontarget. **(A)** *d'* target-standard *d*-prime was increased from pre- to post-training in the Control NF and the SMR NF, but decreased in the beta1 NF. However, the Time x Protocol interaction was non-significant. **(B)** *d'* target-standard standard *d*-prime was increased from pre- to post-training in the three NF protocols. However, the main effect of Time was non-significant. Error bars depict standard error of the mean.

4.3.3.3. Target hit rate

As shown in figure 4.7A, the mean hit rate increased as function of both control NF and SMR NF and decreased in the beta1 NF. However, the 2 TIME x 3 PROTOCOL mixed-ANOVA revealed no reliable main effects or interactions ($F(1,24)=0.09$, $p=0.76$, $\eta_p^2<0.01$; PROTOCOL: $F(2,24)=0.17$, $p=0.84$, $\eta_p^2=0.01$; TIME x PROTOCOL: $F(2,24)=1.17$, $p=0.33$, $\eta_p^2=0.09$). The post-hoc comparisons failed to provide evidence of pre- to post-training hit rate changes in any of the three NF protocols (all $ps>0.30$).

4.3.3.4. False alarm rate for standards

As shown in figure 4.7B from pre-to post-training the false alarm rate to standard stimulus was decreased in the control NF, changed in the SMR NF and increased in the beta1 NF. However, the two-way TIME x PROTOCOL mixed ANOVA revealed no significant main effects or interactions (TIME: $F(1,24)=0.01$, $p=0.93$, $\eta_p^2<0.01$; PROTOCOL: $F(2,24)=0.60$, $p=0.56$, $\eta_p^2=0.05$; TIME x PROTOCOL: $F(2,24)=1.61$, $p=0.22$, $\eta_p^2=0.12$). The post-hoc comparisons failed to provide evidence of pre- to post-training false alarm rate to standard stimulus changes in any of the three NF protocols (all $ps>0.20$).

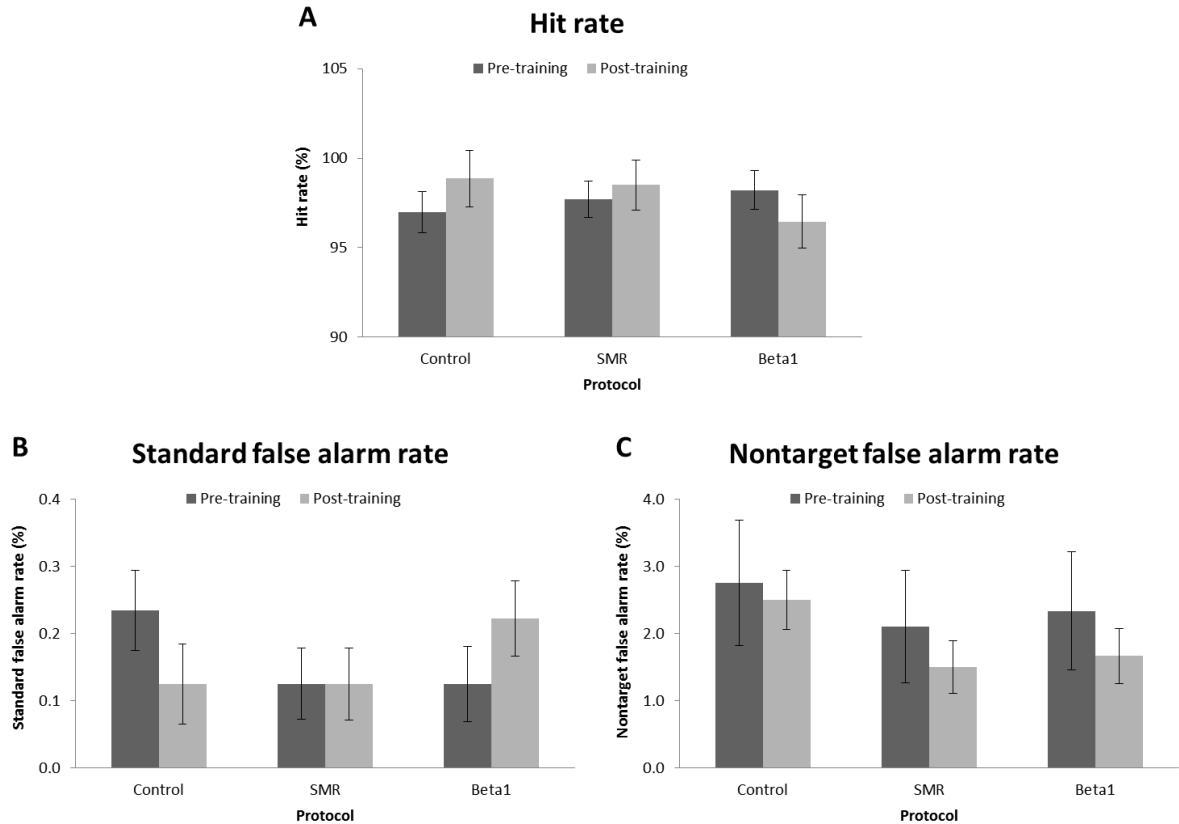


Figure 4.7. Two-way interaction of 2 Time x 3 Protocol for performance rates. The graphs show the effects at pre- and post-training of the three NF protocols on hit rate **(A)**, standard false alarm rate **(B)**, and nontarget false alarm rate. **(A)** Hit rate was increased in the Control NF and SMR NF but decreased in the beta1NF. However, the Time x Protocol interaction was non-significant. **(B)** Standard false alarm rate was decreased in the Control NF, unchanged in the SMR NF and increased in beta1 NF. Again, the Time x Protocol interaction was non-significant. **(C)** Nontarget false alarm rate was decreased in the three NF protocols but the main effect of Time was non-significant.

4.3.3.5. False alarm rate for nontargets

As shown in figure 4.7C a decrease in the false alarm rate for non-targets was observed irrespective of the NF protocol. However, the two-way TIME x PROTOCOL mixed-ANOVA did not reveal a significant main effect of TIME ($F(1,24)=0.88$, $p=0.36$, $\eta_p^2=0.04$). As suggested by the figure, the analysis did not reveal other main effects or interactions (TIME x PROTOCOL: $F(2,24)=0.05$, $p=0.95$, $\eta_p^2=0.01$; PROTOCOL: $F(2,24)=0.70$, $p=0.51$, $\eta_p^2=0.06$). The post-hoc comparisons failed to provide evidence of pre- to post-training false alarm rate to nontarget stimulus changes in any of the three NF protocols (all $ps>0.50$).

4.4. Discussion

The ERP analysis did not support the hypotheses that the SMR NF and beta1 NF would be associated with differential neural response to infrequent nontarget (P3a) and target (P3b) stimuli (Hypothesis 1.1 and 1.2) which would reflect the enhancement of involuntary and voluntary aspects of selective attention respectively (Escera et al., 2000; Sawaki & Katayama, 2009).

Also contrary to hypothesized, the behavioral analyses failed to provide supportive evidence of the differential contribution of SMR and beta1 NF to improve selective attention and response inhibition. In fact, the two NF protocols did not have a distinct effect of behavioral indices of selective attention such as RT (Hypothesis 2.1), RT-SD (Hypothesis 2.2), target-standard d' and target-nontarget d' (Hypothesis 3.1) and hit rate (Hypothesis 3.2). Similarly, there were no significant differences in indices of response inhibition such as standard and nontarget false alarm rate (Hypothesis 3.3).

The next sections will examine several methodological differences relative to previous studies that might have been related to the failure replicate differential electrophysiological and behavioral effects of SMR NF and beta1 NF on selective attention and response inhibition in the context of a three-stimuli auditory oddball (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2001, 2004).

4.4.1. Electrophysiological and behavioral effects of beta1 NF

ERP components

Several methodological differences may account for the failure to replicate the P3b amplitude increments associated with beta1/theta NF in one previous study (Egner & Gruzelier, 2004). Firstly, the two studies differed in the type of auditory attention mechanisms involved in the oddball task. Contrary to the current study, that previous one used a divided attention auditory oddball task in which the participants were instructed to focus the attention on the attended channel, while ignoring the stimuli presented at the unattended channel. This might have resulted in performance advantages associated with top-down biasing mechanisms (Desimone & Duncan, 1995) such as an increase in P3b amplitude. Moreover, in the current experiment the participants had to discriminate

between three types of auditory stimuli, while in the oddball task of the previous study just two stimuli were presented. However, it is unlikely that the introduction of a third stimulus might have affected the P3b amplitude effect. In fact, previous studies suggest that the amplitude of the P3a and P3b components is affected by the probability of the nontarget and targets respectively but not by the probability of the other class of stimulus (Katayama, & Polich, 1996).

Additionally, the physical properties of the stimuli determined that the discrimination between deviant (target and nontarget) and standard stimuli was easier in the current experiment (as demonstrated by the absence of a frontal P3a component) than in that previous one. The higher discrimination difficulty may explain a superior engagement of top-down mechanisms suggested by P3b amplitude increments in frontal and central regions reported by Egner & Gruzelier (2004). Thus, the current experimental situation might have prevented the observation of potential effects of the increased beta1 activity on top-down regulation. On the contrary, the higher demands on top-down regulation imposed by the oddball paradigm used by Egner and Gruzelier (2004) might have facilitated the observation of a P3 amplitude increment effect following beta1/theta NF.

Additionally, the failure to replicate previous findings of increased P3b amplitude might be explained by the different methods of ERP analysis. As seen in section 1.2.4.2.1., it was unclear whether the P3 amplitude increments observed by Egner and Gruzelier (2004) could be interpreted as a selective facilitation of task-relevant stimulus processing because the analysis focused exclusively on the neural response to the target stimuli. On the contrary, the present study isolated the neural response to targets from that associated with standard stimuli in difference waveforms. This allowed the cancellation of the possible contribution of earlier ERP components to the modulation of the P3 and a more clear interpretation of the NF effects on the differential neural response to targets in the P3 time window.

Another aspect that might have contributed to the conflicting results between the two studies was related to the different methods of statistical analysis. In fact, while the current analysis was focused on the regions where the P3 amplitude effect was larger, Egner and Gruzelier (2004) investigated the P3 amplitude in multiple single electrode sites.

The latter method increased the risk of finding a spurious significant effect. Moreover, the failure to adjust the statistical significance level to the number of multiple comparisons might have been responsible for the detection of otherwise insignificant P3 amplitude increments. Finally, because Egner and Gruzelier (2004) did not report electrophysiological results in the control condition it was unclear whether the P3b amplitude increments reflected unspecific effects of NF (e.g., placebo) or practice effects with the oddball task.

Behavioral responses

Also contrary to hypothesis, the beta1 NF was not associated with decreased RT and RT-SD (Hypothesis 2.1 and 2.2.) or increased performance accuracy (Hypotheses 3.1 and 3.2.) relative to SMR NF and control conditions. These findings are in disagreement with one study that showed decreased RT and increased performance accuracy in the cue-CPT following successful beta1/theta NF in ADHD children (Bakhshayesh et al., 2011). A possible explanation to these divergent findings may be that the beta1 NF may contribute to increased target detection efficiency in contexts in which the target is preceded by a cue but not in contexts in which the target is unpredictable. This explanation would be consistent with the role of beta oscillations in response preparation in the foreperiod between cued and target presentation (Kilavik et al., 2013). On the other hand, in situations in which the target stimulus is unpredictable the enhanced attentional control promoted by the beta activity may not represent an advantage. In fact, situations in which the low probability and absence of warning cues determine a higher degree of unpredictability of the target stimulus the facilitation of top-down mechanism may paradoxically induce an increase in RT (Boulinguez, Ballanger, Granjon, & Benraiss, 2009). However, another study suggest that the beta1/theta NF was associated with decreased RT in Go/Nogo tasks in which the stimulus presentation was not preceded by a warning cue (Egner & Gruzelier, 2004).

The failure to demonstrate increased response speed in the context of the oddball task following the beta1 NF is consistent with the hypothesis that the enhancement of beta activity might contribute to the maintenance of the current postural set at the expenses of new movements (Engel & Fries, 2010). In the context of low target probability, the enhancement of beta activity might promote the maintenance of the motor inhibition which would be consistent with the failure to observe a decrease in RT. This explanation is in line

with one previous study in which the beta1/theta NF was not associated with decreased RT in simple and choiceRT tasks with a low target probability (Doppelmayr & Weber, 2011).

The failure to demonstrate an increase in performance accuracy following the beta1 NF is in line with one previous study in which SMR/theta but not beta1/theta NF was associated with increased d' and increased hit rate (Egner & Gruzelier, 2004). However, in the context of the present experiment, the failure to observe increased response accuracy may be related to “ceiling effects” in the percentage of hit rate. As shown in table 4.4., in the present experiment there was a negligible percentage of omission errors (<5%) in all groups at both pre- and post-training possibly reflecting the good cognitive performance of the sample.

The present results also failed to support the hypothesis that the beta1 NF might have a detrimental effect on response inhibition which was proposed to reflect excessive arousal (Egner & Gruzelier, 2004). In fact, despite a slight and negligible (<0.1%) increase in false alarm rate to standards no significant differences between NF were observed in the context of the three-stimuli oddball task. Confirming this idea, the false alarm rate to nontargets showed a slight decrease in beta1 NF comparable to the other experimental conditions.

Taken together, the electrophysiological and behavioral evidence suggests that the the enhancement of beta1 does not necessarily contribute to the facilitation of context updating indexed by the P3 amplitude or to increased response efficiency, consistency and accuracy in situations of an unpredictable target stimulus as would be predicted by an increased involvement of top-down mechanisms of selective attention.

4.4.2. Electrophysiological and behavioral effects of SMR NF

ERP components

In disagreement with the proposal that SMR amplitude enhancement would be associated with increased response inhibition, the present experiment failed to provide evidence of increased P3a amplitude following the SMR NF. However, as seen in section 1.1.1.1., because the extent to which the anterior P3a amplitude reflects response inhibition is still debated (Debener, Makeig, Delorme, & Engel, 2005; Dien, Spencer, & Donchin,

2004; Goldstein, Spencer, & Donchin, 2002) these results must be cautiously interpreted. Moreover, in the easy target-standard discrimination context of the present experiment, the parietal topography of the P3a may reflect the updating of the stimulus representation context rather than the processes of involuntary attention capture and/or response inhibition. Specific recommendations to address this limitation in future studies will be discussed in section 12.3.2.

Also contrary to hypothesis (Hypothesis 1.1.), there was no evidence of increased P3b amplitude in the SMR NF relative to controls. This is in contrast with previous evidence of increased P3b amplitude in a two-stimuli oddball task following SMR/theta NF (Arns et al., 2012). However, differently from the current experiment that study did not control for unspecific effects of NF and used a non-randomized sample of ADHD patients. The present results are, however, in agreement with previous studies that failed to show evidence of significant increments in oddball P3b amplitude following SMR/theta NF in healthy adults (Egner & Gruzelier, 2004).

Behavioral responses

The failure to show an the association of the SMR NF with decreased RT is disagreement with previous findings that indicated a more efficient target detection in simple and choice RT relative to RF NF condition (Doppelmayr & Weber, 2011). In fact, in the present experiment there was a decrease in mean RT from pre- to post-training irrespective of the NF protocol possibly reflecting the increased familiarity with the task at post-training. A reason for these conflicting results might be the difference between studies in the number of NF sessions. Noticeably, the decreased mean RT was observed following thirty daily SMR/theta NF sessions (Doppelmayr & Weber, 2011), while the current and previous studies (e.g., Kober et al., 2015) that failed to replicate that result did not exceed ten NF session. Furthermore, the different behavior of RF NF may also explain the discrepant results. While in Doppelmayr and Weber's (2011) study RF NF was associated with an increased mean RT, in the current one it was associated with a (non-significant) decrease.

The proposed functional association of the SMR with behavioral inhibition additionally suggested a positive impact in reducing the percentage of commission errors.

However, in line with previous studies, the present experiment failed to provide evidence of a specific contribution of the SMR NF to decrease commission errors relative to other NF conditions (Egner & Gruzelier, 2004; Gruzelier et al., 2014). Arguably, a “floor effect” in the false alarm rates imposed by the low response inhibition demands of the task in conjunction with the expected good inhibitory functioning of the sample might have prevented an adequate investigation of this hypothesis. As shown in table 4.4., the false detections of standard and nontarget stimuli taken together did not exceed 3% of the trials.

The present study failed to replicate previous observations of decreased RT-SD following the SMR/theta NF in the specific conditions of an equiprobable target-nontarget DAT (Egner & Gruzelier, 2004). Given that the RT-SD has been found to be modulated by task demands (Hultsch, MacDonald, & Dixon, 2002), a possible explanation for these divergent results may be that the particular cognitive demands imposed by the oddball task were not sensitive enough to the changes in performance consistency induced by the NF manipulation. These differences might be more evident in task contexts that impose demands on response inhibition (Vaurio, Simmonds, & Mostofsky, 2009).

In contrast with previous studies the SMR NF was not associated with increased performance accuracy (Egner & Gruzelier, 2001, 2004; Kober et al., 2015; Vernon et al., 2003). Curiously, Egner and Gruzelier (2004) found that the SMR/theta NF was associated with increased d' and hit rate in the context of higher Go stimulus probability and higher perceptual discrimination demands of the DAT (see section 1.2.5.2.1.), suggesting that tasks that impose higher discrimination and response inhibition demands may be more sensitive to changes in performance accuracy promoted by the SMR NF.

All in all, the present findings did not support the proposal that the SMR NF would be specifically associated with a facilitation of response inhibition. A possible explanation for not observing this effect may be the relatively low response inhibition demands of the three-stimuli oddball task.

4.4.3. Summary

The current results failed to support a functional differentiation between the SMR NF and beta1 NF protocols. In fact, contrary to previous SMR/theta and beta1/theta NF

studies, the electrophysiological and behavioral measures failed to provide evidence of specific impact of any of the NF under investigation on selective attention and response inhibition mechanisms. The current results suggest that SMR and beta1 NF had no effect on the P3 amplitude when controlling for differential neural effects of targets and nontargets relative to standard stimulus and unspecific effects of NF.

Chapter 5

Experiment 3: The effects of SMR and beta1 NF on response inhibition

5.1. Hypotheses

Hypothesis 1: Increased Go and Nogo-P3 amplitude as a function of SMR and beta1 NF

It was hypothesized that:

- (1) Nogo-P3 amplitude would be increased in SMR NF relative to beta1 and control NF and in beta1 NF relative to control NF ($SMR > beta1 > control$).
- (2) Go-P3 amplitude would be increased in beta1 NF relative to SMR and control NF conditions and in SMR NF relative to control NF condition ($beta1 > SMR > control$).

Hypothesis 2: Decreased RT and RT-SD as a function of SMR and beta1 NF

It was hypothesized that:

- (1) RT would be decreased in beta1 NF relative to the SMR and control NF and in SMR NF relative to control NF ($beta1 < SMR < control$).
- (2) RT-SD would be decreased in SMR NF relative to control and beta1 NF and in beta1 NF relative to control NF ($SMR < beta1 < control$).

Hypothesis 3: Increased performance rates and perceptual sensitivity as a function of SMR and beta1 NF

It was hypothesized that:

- (1) d' would be increased in SMR NF relative to control and beta1 NF and in control NF relative to beta1 NF ($SMR > control > beta1$).
- (2) Hit rate would be increased in beta1 NF relative to the SMR and control NF and in SMR NF relative to control NF ($beta1 > SMR > control$).

- (3) False alarm rate would be decreased in SMR NF relative to control and beta1 NF and in control NF relative to beta1 NF (SMR < control < beta1).

5.2. Methods

5.2.1. Participants

The same thirty-one participants of Experiment 1 took part in the present study. As for Experiment 2, after excluding trials with artifacts and averaging the ERP waveforms four other participants (two from control NF and two from beta1 NF) were excluded from the analysis for having less than twenty correct trials in at least one of the four stimulus conditions (Left-cue Go, Left-cue Nogo, Right-cue Go, Right-cue Nogo) at either pre- or post-training. The same participants were included in Experiments 2 and 3 (see table 4.1.).

5.2.2. Stimulus and procedure

The cued Go/Nogo task was presented to the subjects before and after the NF sessions in counterbalanced order with the three-stimuli oddball task (Experiment 2). The order of presentation had no effect on the P3 amplitude for Go and Nogo stimuli or on the behavioral measures of RT and accuracy.

Stimuli were presented electronically using the E-Prime 1.1 software (Psychology Software Tools, Pittsburgh, PA). Stimuli were cues consisting of arrows pointing either left or right and auditory “Go” and “Stop” instructions (Go and Nogo stimuli) presented through speakers. The arrows were constructed as < (Left) and > (Right) signals with an edge length of 35mm presented at the center of a PC-CRT screen in white color against a black background. Go trials (probability=0.67) occurred twice as often as Nogo trials (probability=0.33). The left and right cues were presented for 100 ms with equal probability prior to the Go or Stop auditory instruction. For each participant a total of 160 Go and 80 Nogo trials (summed over left-hand and right-hand responses) were presented which were equally preceded by a left or right cue (80 Right-cue Go; 80 Left-cue Go; 40 Right-cue Nogo; 40 Left-cue Nogo). Participants were instructed to prepare to respond to the direction of the arrows by pressing a button with their right or left thumbs after hearing the Go

instruction and to withhold the prepared response after the Nogo instruction. Auditory “Go” or “Stop” instructions were presented at a fixed interval of 1100 ms after cue onset. The participants were instructed to fixate a white cross in the centre of a black screen in the 1000ms interval after the visual cue and prior to the auditory instruction and in the 1500ms interval after hearing the auditory Go or Nogo instruction and the next visual cue. Response time and accuracy were recorded within the response interval (0 to 1500ms after auditory stimulus presentation). Each trial had the duration of 2600ms. The stimuli were presented in 4 blocks of 60 trials lasting approximately 3 minutes each with short blink-pauses between blocks. Each participant was given a practice trial block consisting of a 20 stimuli presentation with the same probability rate as described above.

5.2.3. EEG recording and analysis

EEG recording.

EEG recording specifications were identical to Experiment 2 (see section 4.2.3).

EEG data analysis.

EEG analysis was performed in Brain Vision Analyzer EEG analysis 1.05 software (Brain Products, Munich, Germany). After data acquisition, the EEG was digitally re-referenced to the average of the left and right earlobes and band-pass filtered (high-pass 0.5 Hz, low-pass 40 Hz). EEG continuous recordings were visually inspected to remove extreme EEG artifacts and segmented in reference to the stimuli in intervals of 1000ms (-200 ms pre-stimulus to 800ms post-stimulus). Only correct trials (correct response to Go stimulus and correct non-response to Nogo stimulus in the 0 to 1200ms interval post-stimulus onset) were analyzed. The data was then submitted to baseline correction (-200ms to 0ms relative to stimulus onset) and artefact rejection was performed for ocular movements and EEG fluctuations exceeding $\pm 80 \mu\text{V}$. A minimum of 20 trials per condition were used. Subsets of four electrodes were pooled to define three regions of interest, similarly do described in section 4.2.3.

In order to visualize the brain’s differential response to Go and Nogo stimuli at pre- and post-training *Nogo-Go difference waveforms* were calculated by linear subtraction.

Percent of correct ERP trials.

Descriptive statistics of percent of rejected trials in the Go/Nogo task are presented in table 5.1. A preliminary analysis revealed that the percentage of correct Go and Nogo responses did not vary as a function of the responding hand (Go: $F(1,26)=0.31$, $p=0.58$, $\eta_p^2=0.01$; Nogo: $F(1,26)=0.07$, $p=0.79$, $\eta_p^2<0.01$) at pre-training.

As shown in the table 5.1., the one-way ANOVAs failed to provide evidence of initial differences between the NF protocols in the percentage of correct Go and Nogo trials (all $ps>0.19$). However, as shown in the table the two TIME (Pre- and Post-Training) x 3 PROTOCOL (control NF, SMR NF and beta1 NF) mixed ANOVAs revealed significant TIME x PROTOCOL interactions for both the percentage of Go ($F(1,24)=4.00$, $p=0.03$, $\eta_p^2=0.25$) and Nogo trials ($F(1,24)=8.63$, $p<0.01$, $\eta_p^2=0.42$). For the Go stimuli, the post-hoc comparisons revealed an decrease in the percentage of correct trials from pre- to post-training in control NF ($t(7)=2.44$, $p=0.02$), while the same difference was not significant in the SMR ($t(9)=1.49$, $p=0.15$) and beta1 NF ($t(8)=0.68$, $p=0.50$). Similarly, for the Nogo stimuli, there was a significant decrease in the percentage of correct trials in control NF ($t(7)=4.17$, $p<0.001$), but not in the SMR ($t(9)=1.55$, $p=0.13$) and beta1 NF ($t(8)=0.82$, $p=0.42$).

5.2.4. Behavioral data recording and analysis

Reaction time data preparation

Behavioral responses were collected using E-Prime 1.0 software (Psychology Software Tools, Pittsburgh, PA). Data preparation for mean RT and RT-SD analysis was as follows. In order to remove outliers from both ends of the RT distribution, correct trials (i.e., responses to the target stimulus) with response latencies below 100 ms or above 1200ms were excluded from the analysis (rejection rate=0.03% of the trials).

d-prime data preparation

In order to guarantee the comparability between RT and ERP data sets only correct responses (button press) to the Go within the 100-1200ms interval were considered “hits” while responses Nogo stimuli within the same interval were considered “false alarms”. The d' calculation was identical to Experiment 2 described in section 4.2.4.

5.2.5. Statistical analysis

Specifications of statistical packages and criteria were provided in section 3.2.6.

5.3. Results

5.3.1. Hypothesis 1: Increased Go- and Nogo-P3 amplitude as a function of SMR and beta1 NF

After investigating initial differences between the NF protocols at pre-training (section 5.3.1.1), the effects of the three NF protocols from pre- to post-training in the Go-P3 and Nogo-P3 amplitude were examined (section 5.3.1.2).

5.3.1.1. Pre-training differences between NF protocols

Figure 5.1. shows the grand average of the stimulus-locked ERP components elicited by the frequent Go and infrequent Nogo stimuli in midline frontal, central and parietal regions at pre-training irrespective of NF protocol. The ERP waveforms (*Left panel*) and the topographical representations (*Right panel*) show that the Nogo-P3 component was especially enlarged in the central location, while the Go-P3 amplitude reached its maximal amplitude in the parietal region.

In order to investigate initial differences in P3 amplitude between Go and Nogo stimulus as a function of the scalp region in the three NF protocols, a three-way 2 STIMULUS (Go vs. Nogo) x 3 REGION (frontal vs. central vs. parietal) x 3 PROTOCOL (control NF vs. SMR NF vs. beta1 NF) ANOVA was performed.

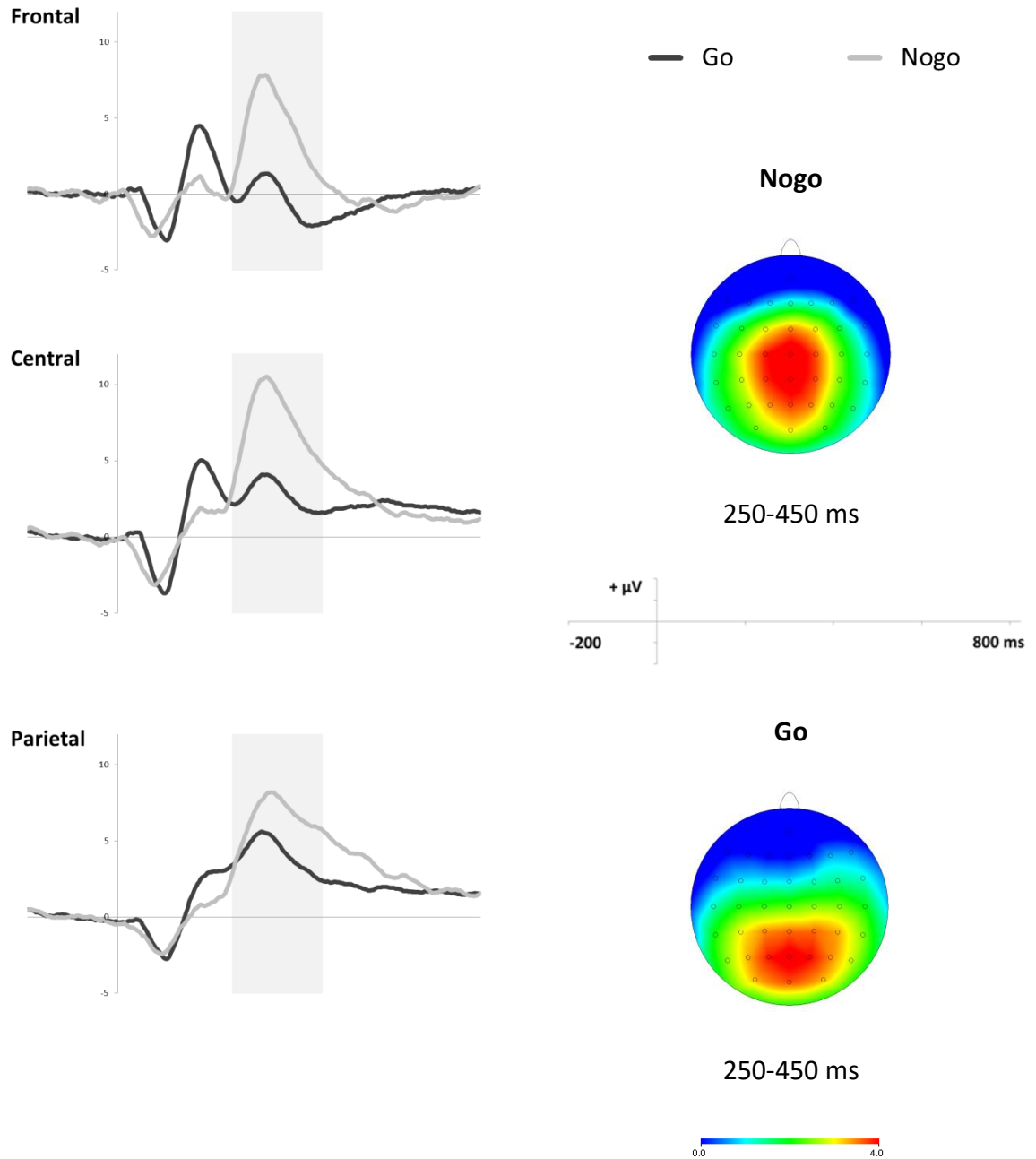


Figure 5.1. *Left.* Grand average of the stimulus-locked ERP original waveforms elicited by the Go and Nogo stimuli in midline frontal, central and parietal regions at pre-training irrespective of the NF protocol. *Right.* Distribution of the P3 amplitude for the Go and Nogo stimuli. Positive amplitude is displayed upwards.

This analysis yielded significant main effects of STIMULUS ($F(1,24)=79.31$, $p<0.01$, $\eta_p^2=0.77$) and REGION ($F(1.50,36.17)=72.93$, $p<0.01$, $\eta_p^2=0.75$) as well as a significant interaction of STIMULUS x REGION ($F(1.43,34.26)=18.19$, $p<0.01$, $\eta_p^2=0.43$). The main effect of PROTOCOL ($F(2,24)=0.76$, $p=0.48$, $\eta_p^2=0.06$) and the interactions involving the between-subject variable were non-significant (STIMULUS x PROTOCOL: $F(2,24)=0.20$, $p=0.81$, $\eta_p^2=0.02$; REGION x PROTOCOL: $F(3.04,36.17)=0.86$, $p=0.44$, $\eta_p^2=0.07$; STIMULUS x REGION x PROTOCOL: $F(2.86,34.26)=0.95$, $p=0.43$, $\eta_p^2=0.07$).

As shown in figure 5.2., the post-hoc comparisons (Bonferroni corrected p -values) for the Go stimulus revealed significantly higher P3 amplitude in the parietal region ($M=3.94$, $SD=2.14$) relative to central ($M=2.70$, $SD=2.80$; $t(26)=4.61$, $p<0.01$) and frontal regions ($M=-0.50$, $SD=2.55$; $t(26)=10.18$, $p<0.001$) and in the central region relative to the frontal region ($t(26)=9.15$, $p<0.001$). However, for the Nogo-P3 amplitude was higher in the central region ($M=7.64$, $SD=3.80$) relative to parietal ($M=6.78$, $SD=3.17$; $t(26)= 3.37$, $p<0.01$) and frontal regions ($M=4.46$, $SD=3.51$; $t(26)= 8.35$, $p<0.001$) and in the parietal region relative to the frontal region ($t(26)= 4.50$, $p<0.001$). Moreover, the post-hoc comparisons revealed that the Nogo stimulus elicited a significantly higher P3 amplitude relative to the Go stimulus in the three regions (Frontal: $t(26)=8.41$, $p<0.001$; Central: $t(26)=8.72$, $p<0.001$; Parietal: $t(26)=6.40$, $p<0.001$).

These results replicated previous findings reporting the central topography of the Nogo-P3 component and the parietal topography of the Go-P3 component in the context of the cued Go/Nogo task (Eimer, 1993; Kopp, Mattler, Goertz, and Tist, 1996; Pfefferbaum et al., 1985; Simson, Vaughan, and Ratter, 1977).

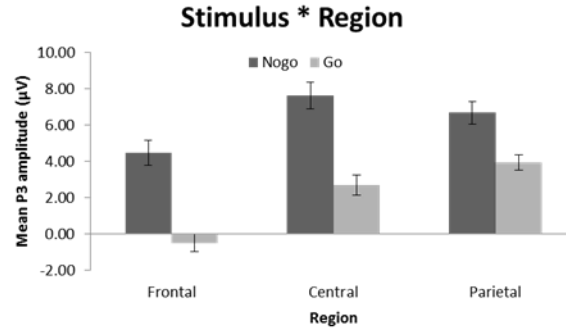


Figure 5.2. Two-way interaction of Stimulus and Region in mean P3 amplitude at pre-training. The graph shows that the mean P3 amplitude (μV) for Nogo stimulus was significantly higher in the Central when compared to Frontal and Parietal locations irrespective of NF protocol at pre-training. For the Go stimulus P3 amplitude was significantly lower in Frontal when compared to Central and Parietal Regions. Error bars depict standard error of the mean.

5.3.1.2. Pre- to post-training differences between NF protocols

Based on the previous analysis of the scalp distribution of the Nogo- and Go-P3 amplitude, the impact of the three NF protocols was analyzed in the regions where these ERP components were maximally observed. Figure 5.3. presents the original waveforms for Nogo stimulus in the central region and for Go stimulus in the parietal region before and after control, SMR and beta1 NF.

Differences in mean parietal Go and central Nogo-P3 amplitude were investigated in a two-way mixed-design ANOVA with the factors 2 TIME (Pre- vs. Post-training) x 3 PROTOCOL (control NF vs. SMR NF vs. beta1 NF). Figure 5.4. shows the mean P3 amplitude in the three NF protocols at pre- and post-training. Data and statistical values are presented in table 5.1. As shown in the table, for the mean Nogo-P3 the two-way ANOVA did not support the hypothesis of a differential impact of the NF (TIME x PROTOCOL: $F(2,24)=0.99$, $p=0.39$, $\eta_p^2= 0.08$). The main effects of TIME and PROTOCOL were also non-significant (TIME: $F(1,24)=1.88$, $p=0.18$, $\eta_p^2= 0.07$; PROTOCOL: $F(2,24)=0.11$, $p=0.90$, $\eta_p^2= 0.01$). The post-hoc comparisons failed to provide evidence of pre- to post-training Nogo-P3 amplitude changes in any of the three NF protocols (all $ps>0.10$).

A similar two-way ANOVA performed for the Go stimulus indicated a significant effect of the type of NF on the mean P3 amplitude in the parietal region (TIME x

PROTOCOL: $F(2,24)=4.27$, $p=0.03$, $\eta_p^2=0.26$). As shown in figure 5.3., the post-hoc comparisons revealed a significant increase in Go-P3 amplitude from pre- to post-training in SMR NF ($t(9)=2.31$, $p=0.03$) while the decrease observed in beta1 NF was not reliable ($t(8)=1.46$, $p=0.16$). Also, there was a marginal increase in Go-P3 amplitude in control NF ($t(7)=1.90$, $p=0.07$). For the Go-P3 amplitude the main effects of TIME and PROTOCOL were also non-significant ($ps>0.13$).

Table 5.1.

Means (standard deviations) and statistical results of the pre-training one-way ANOVAs and the pre- to post-training two-way ANOVAs on Mean Nogo- and Go-P3 amplitude, Hit Rate (H), False Alarm Rate (FA), d-prime (d'), Reaction Time (RT) Mean and Standard Deviation (RT-SD), percentage of Correct Trials (CT) to Go and Nogo stimuli included in ERP analyses after artifact rejection. Significant differences ($p < 0.05$) are highlighted in bold.

Source							One-way ANOVA			Two-way ANOVA								
	Pre-training			Post-training			Protocol			Time			Time x Protocol			Protocol		
	Control	SMR	Beta1	Control	SMR	Beta1	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2
<i>Mean P3</i>																		
Nogo	7.88 (1.89)	6.75 (4.05)	8.30 (4.63)	8.93 (1.87)	8.53 (3.96)	8.02 (5.55)	–	–	–	1.87	0.18	0.07	0.99	0.39	0.08	0.11	0.90	0.01
Go	3.94 (1.82)	3.26 (1.83)	4.63 (2.65)	4.92 (1.51)	4.33 (1.89)	3.92 (2.59)	–	–	–	2.51	0.13	0.09	4.26	0.03	0.26	0.26	0.77	0.02
H (%)	98.81 (1.56)	99.50 (0.85)	99.39 (0.74)	99.26 (1.08)	99.38 (0.52)	99.60 (0.94)	1.00	0.38	0.08	0.47	0.50	0.02	1.16	0.33	0.09	0.96	0.40	0.07
FA (%)	1.81 (2.05)	2.65 (1.78)	2.83 (3.77)	4.44 (3.23)	2.70 (1.97)	4.17 (3.77)	0.35	0.71	0.03	9.88	0.00	0.29	3.06	0.07	0.20	0.23	0.79	0.02
d'	4.82 (0.99)	4.80 (0.72)	4.90 (0.68)	4.42 (0.69)	4.95 (0.63)	4.46 (1.03)	0.04	0.96	0.00	1.49	0.23	0.06	1.12	0.34	0.09	0.41	0.67	0.03
<i>RT (ms)</i>																		
Mean	362.91 (58.90)	381.87 (91.45)	356.77 (67.80)	298.69 (40.33)	322.70 (64.91)	351.11 (87.06)	0.29	0.75	0.02	11.43	0.00	0.32	2.16	0.14	0.15	0.35	0.71	0.03
RT-SD	112.61 (16.81)	110.99 (28.68)	91.00 (28.52)	97.36 (30.81)	84.55 (21.33)	100.73 (46.00)	1.95	0.16	0.140	1.98	0.17	0.08	2.09	0.15	0.15	0.37	0.69	0.03
<i>CT (%)</i>																		
Go	94.61 (4.51)	91.69 (4.93)	92.50 (6.12)	85.94 (13.39)	96.44 (3.16)	90.21 (12.70)	0.71	0.50	0.06	1.14	0.30	0.05	4.00	0.03	0.25	0.81	0.46	0.06
Nogo	93.59 (4.65)	83.38 (13.27)	80.56 (21.24)	74.06 (18.48)	89.88 (5.42)	76.94 (24.22)	1.77	0.19	0.13	4.70	0.04	0.16	8.63	0.00	0.42	0.68	0.52	0.05

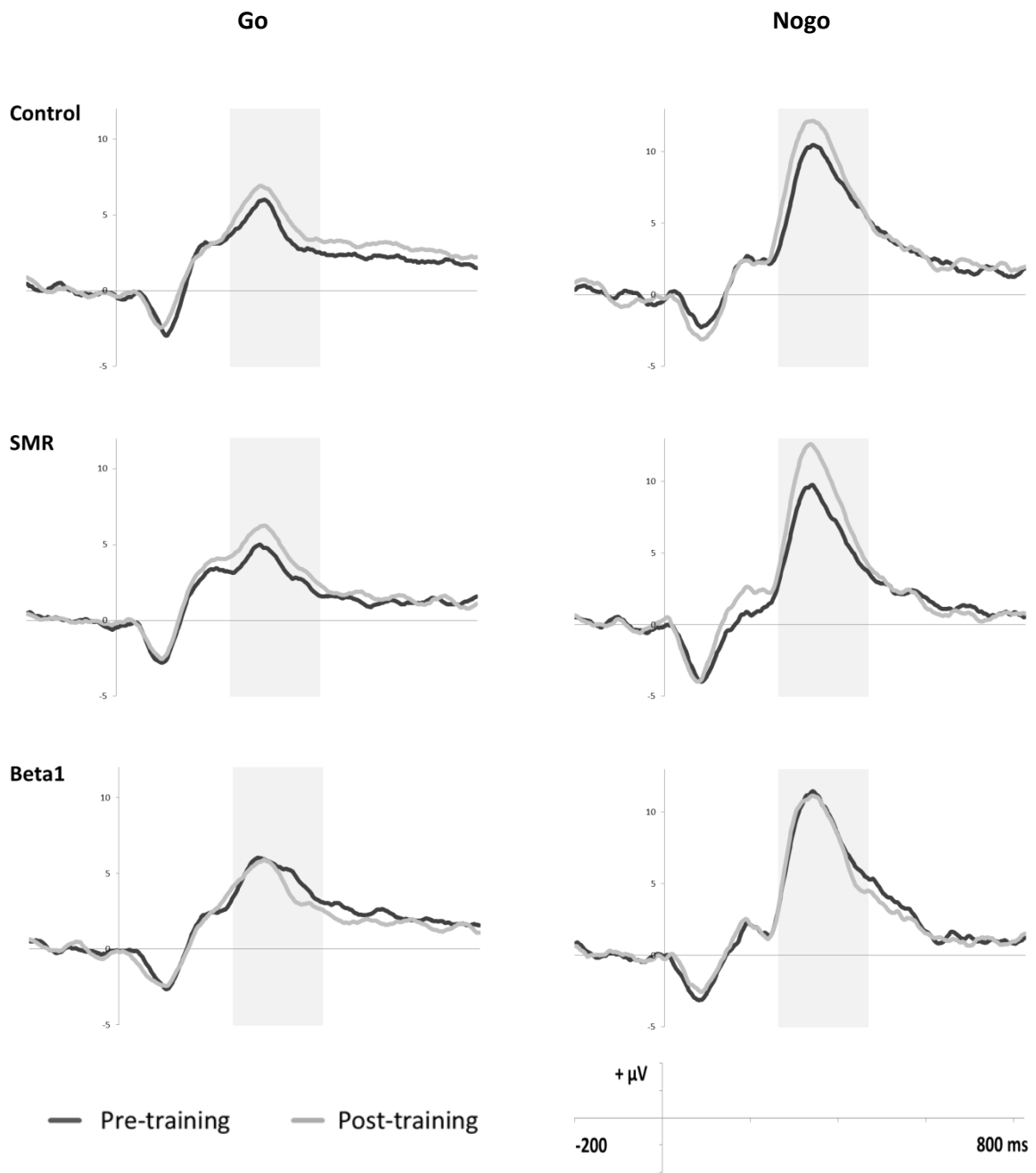


Figure 5.3. Grand-average of the parietal Go and central Nogo ERP waveforms for Control, SMR and beta1 NF at pre- and post-training. The shaded area represents the 250-450ms measurement window. Positive amplitude is displayed upwards.

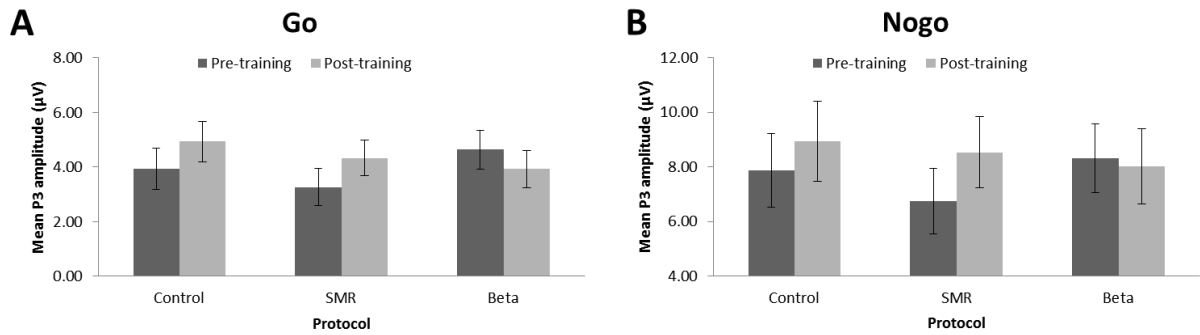


Figure 5.4. Mean parietal Go- and central Nogo-P3 amplitudes for control, SMR and beta1 NF at pre- and post-training. **(A)** Go-P3 amplitude was significantly increased in SMR NF, marginally increased in control NF and non-significantly decreased in beta1 NF. **(B)** Nogo-P3 amplitude was not significantly modulated by the NF protocol. Error bars depict standard error of the mean.

5.3.2. Hypothesis 2: Decreased RT and RT-SD as a function of SMR and beta1 NF

As can be observed in table 5.1., two one-way ANOVAs revealed that there were no initial differences between NF protocols in mean RT and RT-SD (all $p_s > 0.16$). The differential impact of the three NF protocols in mean RT and RT-SD were analyzed in two-way 2 TIME x 3 PROTOCOL mixed-ANOVAs.

5.3.2.1. Mean reaction time

As shown in fig. 5.5A, the mean RT decreased from pre-to post-training in the three NF protocols but predominantly in the control and SMR NF. As shown in table 5.1., the ANOVA revealed a significant main effect of TIME ($F(1,24)=11.43$, $p < 0.001$, $\eta_p^2 = 0.32$) indicating that the RT was significantly lower at post-training ($M=324.16$; $SD=64.10$) relative to pre-training ($M=367.18$; $SD=72.72$) irrespective of the NF protocol. This effect was driven by significant decreases in mean RT in control ($t(7)=2.79$, $p=0.01$) and SMR NF ($t(9)=2.84$, $p < 0.01$) but not in beta1 NF ($t(8)=0.26$, $p=0.80$). However, the TIME x PROTOCOL interaction was non-significant ($F(2,24)=2.16$, $p=0.14$, $\eta_p^2 = 0.15$), thus failing to provide evidence of a superior reduction of mean RT in the SMR and/or control NF

protocols relative to beta1 NF. Finally, the main effect of PROTOCOL ($F(2,24)=0.35$, $p=0.71$, $\eta_p^2=0.03$) was not significant.

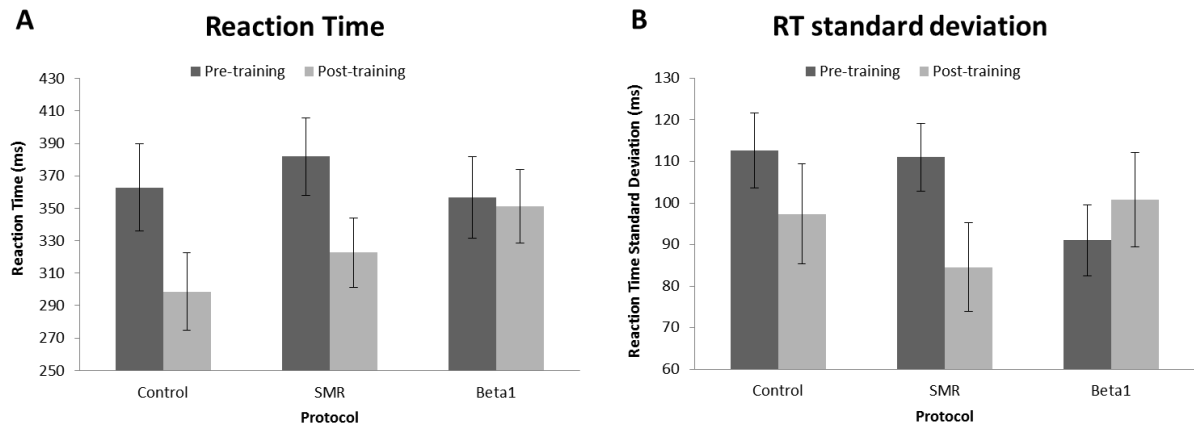


Figure 5.5. Two-way interaction of 2 Time x 3 Protocol for reaction time. The graphs show the effects at pre- and post-training of the three NF protocols on mean reaction time (RT) and reaction time standard deviation (RT-SD). **(A)** The mean RT was significantly decreased from pre- to post-training irrespective of the NF protocol. **(B)** There were no significant differences in RT-SD from pre- to post-training as a function of the NF. Error bars depict standard error of the mean.

5.3.2.2. Reaction time standard deviation

As shown in table 5.1. the two-way TIME x PROTOCOL mixed-ANOVA on RT-SD did not reveal significant main effects or interactions (all $ps>0.15$). However, as show in the figure 5.5B, post-hoc comparisons revealed a significantly decrease RT-SD in SMR NF ($t(9)=2.13$, $p=0.04$) but not in the other NF protocols (all $ps>0.28$).

5.3.3. Hypothesis 3: Increased performance rates and perceptual sensitivity as a function of SMR and beta1 NF

Table 5.1. summarizes the data and statistical results for mean d' , hit rate and false alarm rate at pre- and post-training for the three NF protocols. As can be observed in table, there were no differences between NF protocols at pre-training for any of the dependent variables (all $ps>0.38$). The differential impact of the three NF protocols in mean d' , hit rate and false alarm rate were analyzed in two-way 2 TIME x 3 PROTOCOL mixed-ANOVAs.

5.3.3.1. d'

Figure 5.6A, shows the pre-to post-training changes in d' for the three NF protocols. As shown in table 5.1, the two-way ANOVA on mean d' did not provide evidence of significant main effects or interactions (all p 's > 0.23). The post-hoc comparisons between pre- and post-training d' scores for each NF protocol were non-reliable (all p 's > 0.19).

5.3.3.2. Hit rate

The behavioral data for mean hit rate at pre- and post-training for each of the three NF protocols is presented in table 5.1. The mean percentage of hit rate showed a ceiling effect at pre- (M=99.23%; SD=1.05%) and post-training (M=99.41%; SD=0.84%). Figure 5.6B, shows the pre-to post-training changes in hit rate for the three NF protocols. Despite the apparent decreases in beta1 NF relative to the other two NF protocols, the TIME x PROTOCOL mixed-ANOVA on the mean hit rate revealed no reliable main effects or interactions (all p 's > 0.33), as shown in the table 5.1. The post-hoc comparisons between pre- and post-training hit rate scores for each NF protocol were non-reliable (all p 's > 0.11)

5.3.3.3. False alarm rate

The mean percentage of false alarms showed a floor effect at pre- (M=2.43%; SD=2.53%) and post-training (M=3.77%; SD=2.99%). As shown in figure 5.6C, the false alarm rate was increased after control NF and beta1 NF protocols and unchanged from pre-to post-training in SMR NF. As shown in table 5.1., the two-way TIME x PROTOCOL mixed ANOVA revealed a significant main effect of TIME ($F(1,24)=9.88$, $p<0.01$, $\eta_p^2=0.29$) indicating an increase in false alarm rate from pre- to post-training irrespective of the NF protocol. Additionally, the TIME x PROTOCOL interaction was marginally significant ($F(2,24)=3.06$, $p=0.07$, $\eta_p^2=0.20$). Post-hoc comparisons revealed that the percentage of false alarms increased significantly in control NF ($t(7)=3.34$, $p<0.01$) marginally in beta1 NF ($t(8)=1.82$, $p=0.08$) and non-significantly in SMR NF ($t(9)=0.07$, $p=0.94$). Finally, the main effect of PROTOCOL was not significant ($F(2,24)=0.23$, $p=0.79$, $\eta_p^2=0.02$).

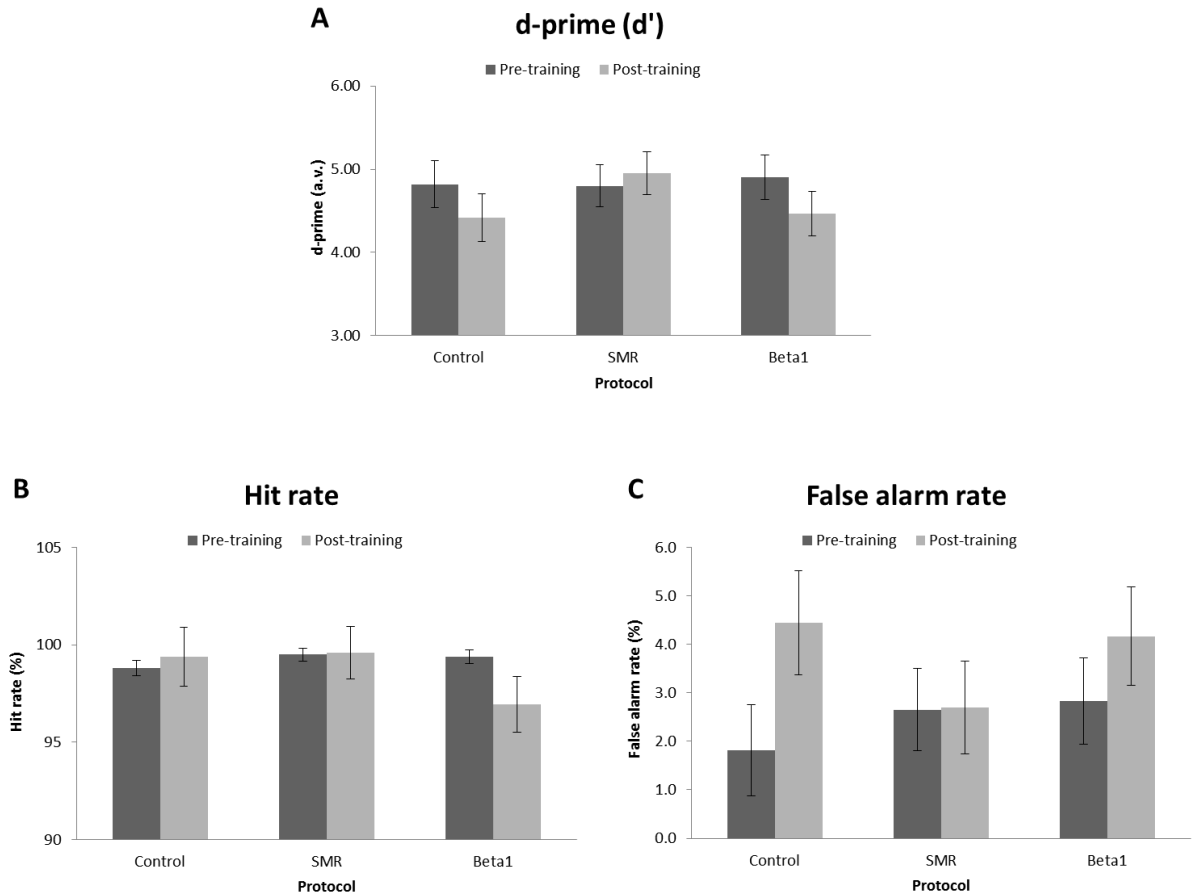


Figure 5.6. Two-way interaction of 2 Time x 3 Protocol for d' and performance rates. The graphs show the effects of the three NF protocols on d' (A), hit rate (B) and false alarm rate (C) at pre- and post-training. (A) d' was non-significantly changed from pre- to post-training as a function of the NF protocol. (B) The hit rate in beta1 NF was non-significantly decreased relative to the other NF protocols. (C) The false alarm rate was significantly increased in control NF, marginally increased in beta1 NF and non-significantly increased in SMR NF. Error bars depict standard error of the mean.

5.4. Discussion

The present experiment failed to provide supportive evidence of the contribution of SMR NF (or of the other NF protocols) to improve response inhibition. In fact, hypotheses that the SMR would be associated with increased Nogo-P3 amplitude (Hypothesis 1.1) and a decreased false alarm rate (Hypothesis 3.3) were not supported by the results. Furthermore, the false alarm rate was significantly increased in control NF and, according to hypothesis, marginally increased in beta1 NF (Hypothesis 3.3).

On the other hand, the results did not show the hypothesized involvement of beta1 NF with the facilitation of target detection and processing as would be evinced by increased in Go-P3 amplitude (Hypothesis 1.2), decreased mean RT (Hypothesis 2.1), increased d' (Hypothesis 3.1), increased hit rate (Hypothesis 3.2). However, the Go-P3 amplitude was significantly increased in SMR NF and marginally increased in control NF. The results were also suggestive of decreased mean RT and RT-SD in SMR NF, but not in the other NF protocols (Hypothesis 2.2).

5.4.1. Differential effects of low-beta NF on response inhibition

The present study was a first attempt to independently examine the specific contribution of SMR and beta1 NF protocols for improvements in response inhibition in a cued Go/Nogo paradigm. The present experiment failed to provide supportive evidence of the involvement of SMR NF in increasing the Nogo-P3 amplitude in a task that presented a high Go stimulus probability and required a previous response preparation. These results are in contradiction with previous research findings indicating an increased Nogo-P3 amplitude in ADHD children that were successful in regulating their brain activity in a mixed low-beta/theta NF protocol (Kropotov et al., 2005). Several methodological differences between the studies may account for the divergent conclusions. Firstly, there are obvious differences between the samples in terms of age and inhibitory deficits. While the deficits in inhibitory control were evident in Kropotov and collaborators' study (around 20% false alarm rate), in the present experiment the sample of high functioning adults produced only negligible false alarm rate at pre-training (<3% of the trials). Thus, the initial differences in efficiency of inhibitory control and the "floor effect" might explain the progress in ADHD children and the lack of it in high functioning adults. The higher Go stimulus probability relative to the

equiprobable cued-Go/Nogo task used by Kropotov and collaborators (2005), might have not been enough to impose the same level of inhibitory demands in high functioning adults as in ADHD children. An alternative explanation is that the differences in neuroplasticity between the two samples may have resulted in a functional reorganization that compensates initial deficits in response inhibition in children but not in young adults.

Another fundamental difference between the two studies relies on the NF protocols. While Kropotov and collaborators (2005) emphasized both SMR and beta1 amplitude enhancement relative to adjacent low and high frequencies in the EEG spectrum (1-30Hz), in the present study the effects of enhancing SMR and beta1 frequencies were independently trained without concomitant inhibition of other EEG frequencies. Finally, the higher number of NF session in that previous study (varying between 15 and 22) provided more training opportunities that might have been related to the higher cognitive improvements. The limitations regarding the differences between NF protocols and number of sessions and will be further discussed in section 12.3.1.

Despite the absence of response inhibition improvements, the examination of pre- to post-training changes in false alarm rates partially supported the claims of a differential impact of SMR NF and beta1 NF protocols in response inhibition. In line with previous studies (Egner & Gruzelier, 2004; Gruzelier, Foks, Steffert, Chen & Ros, 2014), the current one failed to provide supportive evidence of superior improvements in response inhibition following SMR NF but suggested a deterioration of inhibitory functions following beta1 and control NF. Importantly, while in previous studies it was unclear whether the failure to demonstrate improvements following the SMR/theta NF was related to the variable demands in response inhibition imposed by the TOVA task, in the present study the Go response probability of the Go/Nogo task was clarified. However, because the higher Go stimulus probability *per se* might have not been enough to impose a high demand on response inhibition in healthy adults, it remains unclear whether SMR NF may be involved with improved response inhibition in contexts of high response inhibition demands. These results are line with the proposal that the enhanced beta1 activity might be associated with an increase in the percentage of commission errors possibly because of an excessive arousal state (Egner & Gruzelier, 2001). The present study adds to these previous findings by demonstrating that the increase in false alarm rate were observed in conditions of high Go

stimulus probability. Possible reasons for the increased false alarm rate in control NF will be discussed in section 6.2.2.

Importantly, the global increase in the percentage of commission errors from pre- to post-training may be explained by an increase in difficulty of response inhibition determined by the decreased mean RT across the three NF protocols (see below). This explanation is in line with the observation that faster RTs increase the probability of unsuccessful behavioral inhibition (Lappin & Eriksen, 1966) and correlate with the increased amplitude of the Nogo-P3 component (Dimoska, Johnstone, & Barry, 2006; Smith, Johnstone, & Barry, 2006). However, this explanation is unlikely to account for the increased false alarm rate in beta1 NF because, contrary to observed in the control and SMR NF, no changes in response speed were evident in that group.

In sum, the results of the current experiment provided supportive evidence for a differential impact of the NF protocols in response inhibition. Although the results did not confirm the hypothesized improvements in response inhibition following SMR NF, there is evidence to believe that beta1 NF (but more clearly control NF) was associated with the hypothesized deterioration of response inhibition.

5.4.2. Differential effects of low-beta NF on selective attention

The current experiment contributed to clarify the differential contribution of SMR and beta1 NF to the increased efficiency of task-relevant stimulus processing in the specific conditions of the cued Go/Nogo task. The results failed to support the hypothesis of a specific Go-P3 amplitude increment following beta1 NF. However, contrary to hypothesis, the Go-P3 amplitude was significantly increased in SMR NF and marginally increased in control NF (Hypothesis 1.2). These results are in line with previous evidence of increased Go-P3 amplitude in ADHD children under similar cued-Go/Nogo task conditions (Kropotov et al., 2005). However, that previous study was inconclusive regarding the differential contribution of SMR and beta1 NF to the effect because the NF protocol included both SMR and beta1 enhancement instructions. Furthermore, these results constitute a first evidence of specific increments in Go-P3 amplitude following SMR NF in healthy adults. A possible interpretation of this finding is that SMR NF may facilitate the top-down attentional control in situations of a previously prepared response to a frequent target stimulus, consistent with

the role of sensorimotor beta frequencies in response preparation (Zhang, Chen, Bressler, & Ding, 2008). Although the significant decreases in mean RT may be better explained by unspecific NF factors or practice effects, this effect was apparently driven by pre- to post-training decreases in control and SMR NF. Moreover, only SMR NF was associated with significant pre- to post-training decreases in RT-SD despite the absence of significant differences relative to other NF protocols. These results are in line with previous increments in response speed and moment-to moment consistency observed in variable contexts of Go stimulus probability (Egner & Gruzelier, 2004). Taken together these results are consistent with the interpretation that SMR may contribute to increased allocation of attentional resources (Go-P3 amplitude) and processing efficiency of task-relevant stimulus (decreased mean RT and RT-SD) in the context of previously prepared and highly probable responses.

However, the present results did not support the hypothesis of a superior performance accuracy following SMR NF in disagreement with previous observations of increased d' and increased hit rate in the TOVA and in a DAT following SMR/theta NF (Egner & Gruzelier, 2004). The failure to replicate these findings in a cued and prepotent Go response context suggests that the specific response priming and Go response probability context of the task may modulate the effects of SMR NF on performance accuracy.

Moreover, the present results did not support the hypothesis that beta1 NF would be associated with decreased RT in a frequent Go response context (Hypothesis 2.1). This finding is in disagreement with previous studies in which the beta1/theta NF was associated with decreased RT in variable conditions of Go response probability in the TOVA (Egner & Gruzelier, 2004) and in a cued-CPT task (Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011). The varying conditions response priming and Go stimulus probability of the tasks may explain this contradictory evidence. Speculatively, a decrease in mean RT to targets following the beta1 enhancement may only become evident in conditions of lower Go stimulus probability preceded or not by warning cues or in conditions of high Go stimulus probability without response priming.

5.4.3. Summary

In sum, the present findings were consistent with the contribution of SMR but not of beta1 NF to an increased allocation of attentional resources and processing efficiency of task-

relevant stimulus. Despite the involvement of the sensorimotor beta frequencies in motor and cognitive aspects of response inhibition, none of the NF protocols was associated with improvements in response inhibition in the context of a prepotent Go response. However, the current results are compatible with the interpretation that SMR NF may contribute to prevent an increase in commission errors despite increments in response speed and, therefore, of increasing inhibitory demands. In disagreement with previous proposals, there was no evidence that beta1 NF was associated with increased response speed leading to an increase in commission errors. Thus, the current experiment did not support the theoretical proposal that SMR NF in the right hemisphere would be associated with improved response inhibition to nontarget stimulus and that increased beta1 activity in the left hemisphere would be associated with increased efficiency of task-relevant stimulus processing (Othmer et al., 1999).

Chapter 6

General discussion and conclusions of study 1

6.1. Overview of the main findings

SMR NF was associated with increased attention to targets but not with inhibition

The results of the current study suggest that NF had different implications for the neural processing of target/Go stimulus in the two Go/Nogo tasks. Contrary to hypothesis, beta1 NF did not affect the Go-P3 amplitude in any of the tasks. However, SMR and, to some extent, control NF were associated with increased Go-P3 amplitude in the cued-Go/Nogo task but not in the three-stimuli oddball task. This difference in Go-P3 amplitude modulation in the two task was surprising given that this component indexes similar processes of allocation of attentional resources regardless of the Go stimulus probability (Pfefferbaum, Ford, Weller, & Kopell, 1985).

This difference may be explained by the higher response preparation imposed by the Go stimulus probability and the predictive warning cues (Bruin & Wijers, 2002; Thomas, Gonsalvez, & Johnstone, 2009) in the cued-Go/Nogo relative to the three-stimuli oddball task. Speculatively, the increased response preparation in the former task may have facilitated the process of allocation of attentional resources indexed by the Go-P3 amplitude increments associated with SMR and control NF. Unfortunately, the current study design does not allow for a direct test of whether a differential increase in response preparation in the foreperiod (i.e., between cue and stimulus presentation) might have contributed to differences in allocation of attentional resources in the two tasks. In fact, while in the cued-Go/Nogo task it would have been possible to extract measures of response preparation (such as the lateralized readiness potentials) in the three-stimuli oddball task the absence of warning cue conditions did not allow for an investigation of electrophysiological responses in the foreperiod. Along the same lines, the context of increased response preparation might have favored the increase response speed and consistency following SMR NF. In fact, despite

the non-significant differences relative to other NF protocols, the mean RT and RT-SD was decreased following SMR NF in the cued-Go/Nogo but not in the oddball task.

It could be argued that an increased response preparation state following control and SMR NF would have imposed higher demands on inhibition manifested by an increase in the Nogo-P3 amplitude (Groom & Cragg, 2015; Kok, Ramautar, De Rooter, Band, & Ridderinkhof, 2004; Randall & Smith, 2011; Smith, Jamadar, Provost, & Michie, 2013). Although this seems to have been the case (see fig. 5.4.), the Nogo-P3 amplitude increments were not significantly different from those in beta1 NF. However, it must be noticed that because response preparation and Nogo-P3 amplitude are only moderately correlated (Smith, Johnstone, & Barry, 2006), the absence of an increased Nogo-P3 amplitude does not invalidate the interpretation that the control and SMR NF might have contributed to an increase in response preparation.

The failure to observe improvements in unsuccessful inhibition (i.e., in false alarm rates) following SMR NF in both Experiment 2 and 3 was surprising in light of previous studies (Egner & Gruzelier, 2001; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Kropotov et al., 2005). Interestingly, the different response preparation and inhibitory demands imposed by the tasks was reflected by increased false alarm rates in the control and beta1 NF during the cued-Go/Nogo but not in the three-stimuli oddball task (see figures 4.6. and 5.6.). Taken together, these results suggest that in conditions of higher response preparation and/or inhibitory demands SMR NF might have had protective effect against the increases in false alarm rate. Thus, SMR might facilitate the allocation of attentional resources and processing efficiency of targets in situations of increased response preparation without compromising inhibitory control, while other NF protocols (notably the control condition, but also the beta1) might be associated with more error-prone behavior in contexts of the increased response preparation.

Speculatively, SMR NF may promote the regulation of the cortico-basal-ganglia-thalamic circuits involved in the integration of competing speed and accuracy demands (Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2010). This hypothesis is consistent with the proposed effects of SMR NF in regulating the excitability of thalamocortical circuits (Egner & Serman, 2006). However, the current experimental conditions do not allow for a clarification of whether SMR NF may promote a more efficient speed-accuracy trade-off.

Specific suggestions to investigate this question in future studies will be proposed in section 12.3.3.

Further, because control NF was also associated with a marginal increase in Go-P3 amplitude one cannot rule out the possibility that similar increments observed in SMR NF may reflect unspecific effects of NF. Thus, a replication of these findings in a larger sample size is needed to clarify the potential impact of SMR NF on the allocation of attentional resources to target stimulus and subsequent consequences for response execution and inhibition in different response preparation task contexts (see also section 12.3.3.).

The cognitive effects of SMR NF do not necessarily reflect increased SMR activity

Another surprising aspect of the present study was that SMR NF was associated with significant cognitive outcomes even in the absence of training- and frequency-specific SMR amplitude increments (Experiment 1). A possible explanation to these findings is that the learning measures might have failed to capture crucial changes in SMR oscillatory activity that may be linked to the enhanced modulation of the Go-P3 component. As previously discussed in section 1.1.2., several oscillatory mechanisms may be responsible for the increased amplitude of late ERP components. In fact, the effects of SMR NF on the Go-P3 amplitude may be explained by changes in evoked power, phase resetting and/or instantaneous phase alignment of task-relevant ongoing oscillations which are not necessarily captured by amplitude learning measures of Experiment 1. Although there is no current support to the contribution of SMR NF to changes in phase resetting during stimulus processing, this possibility gains particular strength in light of new evidence that it may influence SMR phase coherence between central and posterior electrodes in the resting state (Kober et al., 2015). Speculatively, it is possible that the attempt to influence the local SMR amplitude will bring about changes in interregional and local phase alignment in the same and different frequencies. Future studies may attempt to investigate whether the Go-P3 amplitude increments may have resulted from changes in evoked and/or phase oscillatory activity in one or more frequency bands.

Beta1 and RF NF were associated with increased inhibitory difficulties

The current study also provided support to the hypothesis that increments in beta1 activity (Experiment 1) might be associated with a (marginal) increase in false alarm rate in

the cued-Go/Nogo task (Experiment 3) but not in the three-stimuli oddball task (Experiment 2). The higher inhibitory demands of the cued-Go/Nogo highlighted the possible contribution of beta1 NF to increasing difficulties in withholding a prepotent response. Importantly, unlike control NF, there was no evidence that this increasing inhibitory difficulty might be explained by an increase in response speed.

The increased difficulty of inhibition is surprising in light of the evidence that beta activity promotes antikinetic behavior (Gilbertson et al., 2005; Joundi, Jenkinson, Brittain, Aziz, & Brown, 2012). On the other hand, these pattern of results appears to be in line with recent proposals linking beta activity with the facilitation of cue anticipation and processing (Kilavik, Zaepffel, Brovelli, MacKay, & Riehle, 2013). Speculatively, the increased commission errors in performance enhancement contexts may be explained by the an excessive facilitation of sensorimotor transmission following cue onset. Interestingly, the presence of a warning cue did not have a detrimental effect in false alarm rate in ADHD children (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Arns, Heinrich, & Strehl, 2014; Bakhshayesh et al., 2011). In that case in which the beta amplitude at pre-training might be relatively lower (Barry, Clarke, & Johnstone, 2003; Clarke, Barry, McCarthy, & Selikowitz, 1998), the increase in beta activity might have had a compensatory effect. Future work is needed to investigate whether beta1 NF might be related to detrimental performance effects in specific contexts of increased response preparation and inhibition demands. This could be achieved by orthogonally manipulating response priming (cue vs. no cue) and Go stimulus probability (high vs. low) as proposed in section 12.3.3.

6.2. Limitations and future directions

Several limitations of the current study warrant a caution interpretation of the findings and deserve further attention in future studies for their possible implications in learning and cognitive outcomes.

6.2.1. Failure to demonstrate independence of SMR and beta1 amplitude increments

The previously discussed patterns of cognitive change could not be related to frequency-specific increments in SMR and beta1 activity. Given that selective amplitude

increments between adjacent frequencies may only be obtained with the increasing number of sessions (Serman & Friar, 1972), a possible explanation for this failure may be the reduced number of sessions (for a further discussion see section 12.3.1.). The reduced number of sessions may have also limited the possibility of replicating previous across-session SMR amplitude increments (Doppelmayr & Weber, 2011; Hoedlmoser et al., 2008; Schabus et al., 2014).

Alternatively, the possibility of differentiating SMR and beta1 amplitude increments may be critically dependent on individual differences in the definition of the low-beta frequency bands. Given that the beta band frequency exhibits considerable inter-individual variability (Pfurtscheller, Stancák, & Edlinger, 1997) the SMR and beta1 frequencies may overlap in the traditionally defined frequency bands, such that increments in one sub-band may lead to increments in the other. In order to prevent this overlap and increase the trainability in a given frequency band some authors have recommended the individual adjustment of the frequency bands (Enriquez-Geppert et al., 2014a; Escolano, Aguilar, and Minguez, 2011; Hanslmayr et al., 2005; Zoefel, Huster, & Herrmann, 2011).

A further limitation of the present study concerns the different placement of the feedback electrodes in the three NF protocols. Although the different electrode placement follows the influential proposal that the regulation cortical activation and deactivation would be better achieved by increasing beta1 activity in the left hemisphere and SMR activity in right hemisphere respectively (Othmer, Othmer, & Kaiser, 1999), this might have resulted in confounding the effects of different types of NF training and hemispheric differences in sensorimotor beta reactivity. In order to address this limitation, future studies may consider monitoring SMR and beta1 amplitude changes from multiple scalp locations in both hemispheres or use a consistent electrode location.

6.2.2. Failure to replicate selective attention and response inhibition findings

Several methodological differences of the current study may explain that only partial support was provided to the differential effects of SMR and beta1 NF on selective attention and response inhibition. Firstly, the reduced number of sessions might have implicated fewer opportunities to develop and consolidate the kind of neural changes that correlate with improved modulation of those cognitive processes. However, the observation of significant

changes in performance suggests that factors other than insufficient training may have prevented the replication of some previous results.

Alternatively, the differences relative to previous studies may be related to the different sensitivity of the cognitive measures to the neurobehavioral changes induced by NF. For example, the increased P3b amplitude effect was observed by Egner & Gruzelier (2004) in an oddball task that imposed higher cognitive demands in terms of difficulty of target-standard discrimination and divided attention relative to those observed in Experiment 2. Moreover, the improvements in the false alarm rate associated with SMR learning (Egner & Gruzelier, 2001) were observed in a situation of variable Go stimulus probability and absence of warning cues that imposed lower response inhibition demands than Experiment 3. A related aspect is the presence of “ceiling and floor effects” in the behavioral measures – namely in hit and false alarm rates – which severely limited the possibility of determining whether the failure to observe the hypothesized cognitive effects was related to the NF manipulations or to the low sensitivity of the measures (for a further discussion see section 12.3.1.).

Another aspect that may explain the failure to replicate previous findings relates to the changes introduced in the NF protocols. Differently from most previous studies, the SMR and beta1 NF protocols did not emphasize theta and high-beta suppression. Since the suppression of these frequencies has been proposed to play a coadjuvant role in maintaining the attentional focus and postural composure during successful NF learning (Othmer et al., 1999), the failure to do so may have resulted in less than optimal SMR learning. However, because others have demonstrated the feasibility of enhancing SMR amplitude without concomitant theta and high beta suppression (e.g., Hoedlmoser et al., 2008; Kober, Witte, and Ninaus, 2013) this remains an open question. Regardless of its putative role in facilitating NF learning, theta suppression might have contributed to the changes in cognitive performance observed in previous studies. In fact, the involvement of theta oscillations in response inhibition (Harper, Malone, & Bernat, 2014) and deviance detection (Demiralp et al., 2001) suggests that the positive impact of the low-beta/theta NF protocols on cognitive performance may explained by enhancements in low-beta amplitude as much as by the suppression of theta amplitude. In agreement with this hypothesis, Study 2 examined the

effects of theta suppression NF on the same aspects of selective attention and response inhibition as the current study.

Finally, the absence of NF protocol specific cognitive improvements might be related to unanticipated cognitive effects in the control condition. In fact, RF NF was associated with unexpected increments in Go-P3 amplitude, response speed and false alarm rate. These cognitive changes might have been related to the higher cognitive and motivational demands of having to change the self-regulatory strategy from down- to up-regulation of random frequencies halfway through the training session. Although previous studies failed to report significant cognitive effects with similarly training strategies in RF NF (e.g., Doppelmayr & Weber, 2011), it is unclear whether these higher demands might have induced systematic changes in oscillatory activity with impact on cognitive performance rather than merely controlling for unspecific training effects (e.g., practice and placebo effects). Further studies are needed to ensure that experimental and control conditions are comparable in terms of motivational and/or cognitive aspects with possible implications for cognitive outcomes.

Chapter 7

Study 2: The effects of theta NF and beta1 NF on selective attention and response inhibition

7.1. Introduction

The two major goals of study 2 were to further clarify whether the theta and beta1 NF would be associated (1) with training-specific and frequency-specific theta amplitude decrement and beta1 amplitude increments and (2) with specific improvements in selective attention and response inhibition.

Moreover, Study 2 addressed several methodological limitations that might have been related to the failure to replicate previous cognitive improvements (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2001, 2004; Fuchs et al., 2003; Kropotov et al., 2005) following the independent manipulation of SMR and beta1 enhancement in Study 1.

7.1.1. Beta1 NF effects on selective attention and response inhibition

Beta 1 learning

Study 2 attempted to better clarify whether the beta1 amplitude could be selectively enhanced relative to other frequency-bands. In Study 1, despite the training-specific beta1 amplitude enhancement effect relative to controls, there was no evidence that the within-session amplitude changes in the beta1 frequency were larger than in other frequencies. Thus, the current experiment addressed several methodological limitations that could have prevented the observation of this frequency-specific effect.

Firstly, because the smaller number NF sessions relative to previous studies (see tables 1.1. and 1.2.) could have contributed to the absence of training-specific and cognitive enhancement effects, its number was increased (see section 8.2.3.) to provide comparable training opportunities relative to previous studies demonstrating successful modulation of theta (Vernon et al., 2003; Ros et al., 2009; Enriquez-Geppert et al., 2014) and beta

frequencies (Gruzelier et al., 2014a; Schabus et al., 2014; Kober et al., 2015). Moreover, it was assumed that the higher number of NF sessions would contribute to frequency-specific effects in the target frequencies (Lubar & Shouse, 1976; Serman & Friar, 1972).

Furthermore, in order to increase the responsiveness to NF interventions and reduce the probability of overlap with adjacent but functionally distinct frequencies (e.g., between SMR and beta1) the EEG frequencies were customized to the Individual Alpha Frequency (IAF) following previous recommendations (Escolano, Aguilar, & Minguez, 2011; Ghoshuni et al., 2012; Hanslmayr, Sauseng, Doppelmayr, Schabus, & Klimesch, 2005; Zoefel, Huster, & Herrmann, 2011). Admitting that the beta frequency can be decomposed into three low-beta (SMR, beta1, beta2) and three high beta (beta3, beta4, beta5) sub-bands, NF was focused on the middle range of the low-beta frequency in order to attempt to prevent an overlap with the adjacent high alpha and high beta bands. A complete description of the frequency bands will be provided in section 8.2.4. In order to keep with the nomenclature of the frequency bands used in the previous study, the SMR was considered to be the first frequency in the beta range, followed by beta1 and so on.

Moreover, it was not clear whether the training-specific effect in the beta1 frequency could be attributed to the within-session amplitude decrements in RF NF which were possibly related to the difficulty in maintaining a consistent self-regulatory strategy throughout the session. Thus, the current study introduced some modifications in RF NF condition. Similarly to the previous study, real-time visual NF was provided in selected frequencies of the spectrum other than the target frequencies. However, the participants were allowed to develop of a consistent self-regulatory strategy (i.e., either up- or down-regulation) throughout the session. Also differently from the previous study, the order of selected frequency bands and the up- and down-regulation instructions were randomized and counterbalanced between-subjects and between-sessions.

Cognitive effects of beta1 NF

Despite the involvement of beta activity in top-down control of attention and motor control and previous demonstrations of cognitive improvements following beta1/theta NF, Study 1 failed to provide evidence of the independent contribution of beta1 enhancement to those findings. However, in face of the available evidence and the methodological limitations

identified in the previous study (see section 6.2.) it would be premature to dismiss the possible contribution of beta1 enhancement NF to the improvements in selective attention and response inhibition.

Moreover, in Study 1 the false alarm rate was marginally increased in beta1 NF probably reflecting an increased difficulty in inhibiting a previously prepared and prepotent response. This warranted a reexamination of whether or not enhancements in the beta1 amplitude may have a detrimental impact on response inhibition (Egner & Gruzelier, 2001, 2004).

7.1.2. Theta NF effects on selective attention and response inhibition

The present study was a first attempt to independently investigate the implications of central midline theta suppression for selective attention and response inhibition improvements. In the previous study, the absence of concomitant suppression of theta amplitude in the SMR and beta1 NF protocols was advanced as a possible explanation for the failure to provide supportive evidence of these improvements. Although theta suppression has been assigned a coadjunctive role in maintaining the necessary attentional focus for successful self-regulation of sensorimotor beta activity (Serman and Shouse, 1980; Othmer et al., 1999), previous evidence of significant cognitive improvements associated with theta suppression (see section 1.2.4.3.) and the involvement of theta activity in cognitive control (see section 1.1.1.2. and 1.1.2.2.) suggest that it may play a more active role in the cognitive performance enhancement.

Theta learning

As noted above in section 1.2.3.1.3., previous studies low-beta/theta NF studies found supportive evidence of within-session theta amplitude decrements in both central (de Zambotti, Bianchin, Magazzini, Gnesato, & Angrilli, 2012; Gruzelier, Hirst, Holmes, & Leach, 2014; Ros et al., 2009; Vernon et al., 2003) and occipital regions (Beatty, Greenberg, Deibler, & O'Hanlon, 1974; Williams, Beatty, & O'Hanlon, 1975). However, other studies failed to corroborate these findings (Kober et al., 2015). Moreover, as discussed in section 1.2.3.2.3., there is no current evidence of across-session theta amplitude decrements in active (Doppelmayr & Weber, 2011; de Zambotti et al., 2012; Kober et al., 2015) or passive periods

(Becerra et al., 2012). As discussed in section 1.2.3.3.3., previous studies were also inconclusive regarding the frequency-specificity of the theta suppression effects (Becerra et al., 2012). Thus, the current study attempted to clarify whether within-session and/or across-session methods may capture the dynamic changes in theta amplitude induced by NF and whether those amplitude decrements were frequency-specific.

Cognitive effects of theta NF

The correlation of low tonic and high phasic theta amplitude with good cognitive performance (Klimesch, 1999) and the contribution of evoked theta power to the generation of the P3 component and automatic deviance detection (Demiralp et al., 2001; Yordanova et al., 2003) suggest that the suppression of ongoing oscillatory theta may be associated with increased P3 amplitude. Moreover, the association of theta activity with cognitive control suggests that the suppression of theta activity would be specifically novelty detection indexed by the P3a (Luu & Tucker, 2003; Cavanagh & Frank, 2014). Also based on previous evidence of that low pre-stimulus theta was associated with significant Nogo-P3 amplitude modulations in the Go/Nogo task (De Blasio & Barry, 2013; Harper, Malone, & Bernat, 2014; Kirmizi-Alsan et al., 2006) it was proposed that theta suppression NF would be associated with improvements in electrophysiological and behavioral indices of response inhibition. Additionally, there is currently evidence of the involvement of theta oscillations in performance consistency as measured by RT-SD in ADHD children and typically developing individuals across the life-span (McLoughlin, Palmer, Rijdsdijk, & Makeig, 2014; Papenberg, Hämmerer, Müller, Lindenberger, & Li, 2013) which may explain the decrease RT-SD following SMR/theta NF (Egner & Gruzelier, 2004),

7.2. Study 2 outline

Study 2 sought to investigate the differential electrophysiological and behavioural effects of theta and beta1 NF protocols on selective attention and response inhibition in three experiments. Despite acknowledging the limitations resulting from the failure to independently manipulate Go response probability and response priming effects in the two Go/Nogo tasks these were kept unchanged in Study 2. In fact, this would have implied

modifying the Go response probability in the two task (to keep a proportional ratio between Go and Nogo stimulus) and introducing two new tasks (i.e., an oddball task with response priming and a non-cued Go/Nogo task) with implications for task complexity and length. This would also have reduced the comparability with Study 1 and with the previous literature.

Experiment 4 investigated whether (1) the experimental manipulations of theta-suppression NF (theta NF) and beta1-enhancement NF (beta1 NF) were successful in inducing training- and frequency-specific amplitude changes in the frequencies of interest relative to a control condition (RF NF) and (2) to understand whether these effects would be differentially apprehended by within- and across-session methods in active and passive periods. Additionally, the present experiment addressed some methodological limitations of the previous study in control NF condition, in the number of NF sessions and in the definition of the target frequency bands.

Experiments 5 and 6 examined the electrophysiological and behavioural effects of theta and beta1 NF in the same two Go/Nogo tasks used in Study 1. Experiment 5 sought to examine the relative contribution of theta-inhibition and beta-enhancement to improvements in voluntary and involuntary selective attention in a three-stimuli oddball task (Hillyard, Squires, Bauer, & Lindsay, 1971; Hillyard & Kutas, 1983; Katayama, & Polich, 1996; Polich, 2007, 2012; Squires, Donchin, Herning, & McCarthy, 1977) as suggested by previous low-beta/theta NF (Arns et al., 2012; Bakhshayesh et al., 2011; Doppelmayr & Weber, 2011; Egner & Gruzelier, 2001, 2004; Kober et al., 2015).

Experiment 6 sought to examine the relative contribution of theta-inhibition and beta-enhancement to improvements in electrophysiological and behavioral indices of response inhibition in a cued Go/Nogo task as proposed by previous low-beta/theta NF studies (Bakhshayesh et al., 2011; Egner & Gruzelier, 2001, 2004). In this task, the lower probability of the Nogo stimulus relative to the Go target stimulus and the pre-stimulus preparation of a motor response imposed specific demands on response inhibition (Eimer, 1993; Kok, 1986; Pfefferbaum, Ford, Weller, & Kopell, 1985; Randall and Smith, 2011; Smith, Johnstone, & Barry, 2006, 2008).

Chapter 8

Experiment 4: Theta and beta1 learning

8.1. Hypotheses

Hypothesis 1: Training-specificity of within-session theta and beta1 amplitude changes in active periods.

It was hypothesized that:

- (1) Theta amplitude would be decreased within-sessions in active periods in theta NF relative to beta1 NF and control NF.
- (2) Beta1 amplitude would be increased within-sessions in active periods in beta1 NF relative to theta NF and control NF.

Hypothesis 2: Training-specificity of across-session theta and beta1 amplitude changes in active periods.

It was hypothesized that:

- (1) Theta amplitude would be decreased across-sessions in active periods in theta NF relative to beta1 NF and control NF.
- (2) Beta1 amplitude would be increased across-sessions in active periods in beta1 NF relative to theta NF and control NF.

Hypothesis 3: Training-specificity of within-session theta and beta1 amplitude changes in passive periods.

It was hypothesized that:

- (1) Theta amplitude would be decreased within-sessions in passive periods in theta NF relative to beta1 NF and control NF.
- (2) Beta1 amplitude would be increased within-sessions in passive periods in beta1 NF relative to theta NF and control NF.

Hypothesis 4: Training-specificity of across-session theta and beta1 amplitude changes in passive periods.

It was hypothesized that:

- (1) Theta amplitude would be decreased across-sessions in passive periods in theta NF relative to beta1 NF and control NF.
- (2) Beta1 amplitude would be increased across-sessions in passive periods in beta1 NF relative to theta NF and control NF.

Hypothesis 5: Frequency-specificity of theta and beta1 amplitude changes in active periods.

It was hypothesized that:

- (1) Theta NF would be associated with decreased mean theta amplitude but not with significant amplitude changes in other frequencies relative to beta1 NF and control NF on the average of active periods within-sessions.
- (2) Beta1 NF would be associated with increased mean beta1 amplitude but not with significant amplitude changes in other frequencies relative to theta NF and control NF on the average of active periods within-sessions.

Hypothesis 6: Frequency-specificity of theta and beta1 amplitude changes in passive periods.

It was hypothesized that:

- (1) Theta NF would be associated with decreased mean theta amplitude but not with significant amplitude changes in other frequencies relative to beta1 NF and control NF on the average of passive periods within-sessions.
- (2) Beta1 NF would be associated with increased mean beta1 amplitude but not with significant amplitude changes in other frequencies relative to theta NF and control NF on the average of passive periods within-sessions.

8.2. Methods and materials

8.2.1. Participants

Twenty-nine healthy adult students from Goldsmiths, University of London volunteered to take part in the experiment. Twenty-three participants were first-year psychology undergraduate students recruited through a Research Participation Scheme in return of course credit. Six participants were postgraduate students recruited through advertisement in the Campus and received monetary compensation of £50 at completion. All participants were right-handed and had normal or corrected-to-normal vision. None of the participants had previous experience with NF. Prior to the pre-assessment general information regarding the goals of the study and about EEG and NF procedures was given. Participants remained blind to the details of the experimental design and to the frequency-bands of interest. Participants gave written informed consent for participation in the study, which had previously been approved by the Department of Psychology Ethics Commission. Participants were screened for neuropsychiatric disorders and psychoactive substances use (see Appendix A). Participants were randomly allocated to one of three experimental conditions via rotation (starting with control NF condition) resulting in a control NF group consisting of 9 participants (5 females; mean age= 21.44 years; SD=4.03 years), a theta-inhibition NF group consisting of 10 participants (6 females; mean age= 22.60 years; SD=6.31 years) and beta1 NF group consisting of 10 participants (8 females; mean age= 21.7 years; SD=5.29 years). The mean age did not differ between groups as demonstrated by one-way ANOVA ($F(2,26)=0.13, p=0.88, \eta_p^2=0.01$).

8.2.2. General procedure

The general procedure was identical to Experiment 1 (see section 3.2.2) except that sessions in the current experiment participants received eight (instead of six) NF sessions. Moreover, 3 minutes of eyes closed EEG was recorded in the pre-training and post-training assessment sessions for determination of the IAF. Thus, the participants attended a total of ten sessions in which the first and the last session were dedicated to EEG/ERP and behavioural outcome tasks (for details see sections 4.2.2. and 5.2.2.).

8.2.3. Neurofeedback Procedure

The NF procedure was identical to Experiment 1 (see section 3.2.3.) except that the participants received either theta-suppression, beta1-enhancement or control NF (see below). The NF sessions were distributed over three to four weeks according to the participants availability.

8.2.4. Neurofeedback training

EEG recording. EEG recording was identical to Experiment 1 (see section 3.2.4.) except that the peak-to-peak amplitudes were calculated to continuously extract EEG components customized to the IAF ranging from delta to gamma (see details of the frequency bands definition below). Furthermore, the scalp electrode was placed at Cz against a left earlobe reference electrode and ground electrode placed at the right earlobe according to the 10-20 electrode placement system irrespective of the NF protocol.

Frequency Bands. For purposes of feedback and statistical analyses, frequency band limits from delta to gamma bands were calculated individually for each participant according to the IAF. Frequency band limits determination followed the theoretical subdivision of three alpha bands outlined by Klimesch (1999). The subdivision of the low-beta band into SMR and beta1 frequency followed the 3 Hz bins bandwidth commonly encountered in the NF literature (e.g., Egner & Gruzelier, 2004). The resultant twelve frequency bands were defined as follows:

- delta (IAF – 8 Hz to IAF – 6 Hz);
- theta (IAF – 6 Hz to IAF – 4 Hz);
- alpha1 (IAF Hz – 4 Hz to IAF – 2 Hz);
- alpha2 (IAF Hz – 2Hz to IAF);
- alpha3 (IAF to IAF + 2 Hz);
- SMR (IAF + 2 Hz to IAF + 5 Hz);
- beta1 (IAF + 5 Hz to IAF + 8 Hz);
- beta2 (IAF + 8 Hz to IAF + 11 Hz);
- beta3 (IAF Hz + 11Hz to IAF + 14 Hz);
- beta4 (IAF Hz + 14Hz to IAF + 17 Hz);

- beta5 (IAF + 17 Hz to IAF + 20 Hz); and
- gamma (IAF + 20 Hz to IAF + 30 Hz).

Determination of the IAF. For the determination of IAF, the 3-minute long eyes closed EEG was resampled at 512 Hz and segmented in 2 second intervals (power resolution = 0.256 Hz). Fast Fourier Transform (FFT) was calculated on the full spectrum with a 10% Hanning window in BVA. The EEG signal was off-line band-pass filtered (0.1-100Hz) with a Butterworth Zero Phase 12 dB/oct filter. A notch filter (50Hz) was also applied. Ocular artefact correction was performed using Gratton and Coles method (Gratton, Coles, & Donchin, 1983). A sliding window of 500ms was applied and segments exceeding 100 μ V in any of the 64 scalp channels were rejected. IAF was determined by visually inspecting the pre-training EEG power spectrum for the peak of alpha power at Cz in order to maintain consistency with the NF training site. IAF ranged from 8 to 12 Hz (Mean=9.56, SD=0.95). A preliminary one-way ANOVA failed to reveal significant differences between the NF protocols in IAF ($F(2,26)=0.89$, $p=0.42$, $\eta_p^2=0.06$).

Neurofeedback task. The procedures of the neurofeedback task were identical to Experiment 1 (see section 3.2.4.) except that the video was shown prior to recording for one minute to reduce novelty effects of the feedback screens and allow for an adaption to the training settings. Also, to ensure the comparability of resting-state and training periods the same display was used in both conditions except that on the former the thresholds on the target-frequency band were disabled and the video kept on constant playback.

Feedback screens. In order to keep the participants motivated during the sessions the video displays were randomly selected from a set of eight. In this manner each participant was exposed to a different video every session. The feedback consisted of visual representations of peak-to-peak amplitude: two bar graphs, and a playing video. The bar graphs represented the frequency-band activity in the target-frequency band and the EMG band. The bars were green when the activity was on the correct side of a manually set threshold and turned red at overstepping it. A score point at the top-left of the screen was allotted for every two seconds of continuous above-threshold activity. The screens were randomly chosen from a set of eight so that participants were exposed to a different video every session. The videos

displayed animations that played in a continuous manner whenever the training requirements were met and stopped when they were not (see Reward contingencies section below). Appendix C shows an example of the feedback screens.

Feedback instructions and groups. The instructions for theta NF protocol emphasized keeping the bar graph representing the theta frequency's amplitude as low and for as long as possible, while the reverse was emphasized for the beta NF protocol. The participants in control NF protocol received suppression or enhancement instructions according to the pseudo-random counterbalanced order described above. In control NF group the participants received real-time feedback on the peak-to-peak amplitude of four different frequencies (alpha2, alpha3, beta3 and beta4). Note that to prevent possible leakage effects to the theta and beta1 frequencies the adjacent frequencies (e.g., delta and alpha1 and SMR and beta2) were purposively left out from the target frequencies used in control NF protocol.

Also, in order to cancel out possible effects of frequency order (e.g., alpha2 followed by alpha 3 and so on), of the type of frequency (low- vs. high-frequencies) and of training instruction (inhibition vs. enhancement) these factors were counterbalanced in a pseudo-random manner across sessions. Thus, from one session to the next the participants received real-time feedback in a different frequency, of a different type and with a different instruction. The participants in the control condition remained by blind regarding the changing training contingencies.

Reward contingencies. Reward contingencies were identical to the exposed in section 3.2.4.

8.2.5. EEG-Neurofeedback Data Processing

The processes of data preparation, artifact detection and peak-to-peak calculations were identical to those of Experiment 1 (see section 3.2.5.). The epoch-rejection rate per participant ranged from 3.81% to 7.10% (*Mean* = 5.51%, *standard deviation* = 0.77%). The percentage of rejected trials did not differ between groups as demonstrated by one-way ANOVA ($F(2,26)=0.33$, $p=0.54$, $\eta_p^2=0.04$).

8.2.6. Statistical Analyses

The statistical analysis procedures were identical to those of Experiment 1 (see section 3.2.6.).

8.3. Results

The within-session and across-session theta and beta1 amplitude changes in the three NF groups were separately analyzed for active and passive trials. The normalized within-session amplitude change in active periods was calculated for 8 periods. For passive periods there was only a single measure of normalized within-session change. Thus, four different analyses were performed (1) two-way 8 PERIOD x 3 PROTOCOL for within-session active periods, (2) one-way 3 PROTOCOL for within-session passive periods, (3) two-way 8 SESSION x 3 PROTOCOL for across-session active periods, and (4) two-way 8 SESSION x 3 PROTOCOL for across-session passive periods.

8.3.1. Training-specific learning

Hypothesis 1: Training-specificity of within-session theta and beta1 amplitude changes in active periods.

Within-session theta and beta1 amplitude changes in each of the NF protocols were investigated in separate two-way 8 PERIOD x 3 PROTOCOL ANOVAs with normalized amplitude change for each period relative to the first training period collapsed across sessions as the dependent measure.

Figures 8.1A and 8.1B show the within-session amplitude in the theta and beta1 frequencies for the three NF protocols. These were investigated in separate two-way 8 PERIOD x 3 PROTOCOL ANOVAs for theta and beta1 frequencies. The analyses indicated a marginally significant effect of PROTOCOL for theta ($F(2,26)=2.97, p=0.07, \eta_p^2=0.19$) but not for beta1 ($F(2,26)=0.73, p=0.49, \eta_p^2=0.05$). Contrary to hypothesis (Hypothesis 1), pairwise comparisons by independent t -tests failed to reveal training-specific decrements of mean theta amplitude in theta NF when compared to control NF ($t(17)=0.75, p=1.00$) and

beta1 NF ($t(18)=1.66, p=0.33$). However, the theta amplitude was marginally decreased in the control relative to beta1 NF ($t(17)=2.36, p=0.08$).

As shown in figures 8.1A and 8.1B, the analyses revealed significant PERIOD x PROTOCOL interaction effects in the theta ($F(8.18,106.28)=2.26, p=0.03, \eta_p^2=0.15$) but not in the beta1 frequency ($F(6.10,79.35)=0.50, p=0.81, \eta_p^2=0.04$). Descriptive statistics of theta and beta1 amplitude change and statistical results of between-subjects multiple comparisons for each period are presented in table 8.1. As shown in the table, theta amplitude change was marginally decreased in control relative to beta1 NF in periods 4, 6 and 7 (all other $ps>0.13$) and in theta relative to beta1 NF in period 7 (all other $ps>0.15$). None of the pairwise comparisons between control and theta NF were reliable (all $ps>0.26$).

Within-subject pairwise comparisons between periods relative to the first period performed for each NF protocol, revealed that in control NF the theta amplitude change was significantly decreased in all the periods (all $ps<0.05$). In theta NF, the theta amplitude was significantly decreased in periods 6 through 8 (all $ps<0.05$), marginally decreased in period 5 ($p<0.10$) and non-significantly decreased in periods 2 through 4 (all $ps>0.36$). Finally, in beta1 NF there was no evidence of theta amplitude decrements between the first and the remaining periods (all $ps>0.33$). The main effect of PERIOD was significant in the theta but non-significant in the beta1 frequency (theta: $F(4.09,106.28)=15.63, p<0.001, \eta_p^2=0.38$; beta1: $F(3.05,79.35)=0.67, p=0.58, \eta_p^2=0.03$).

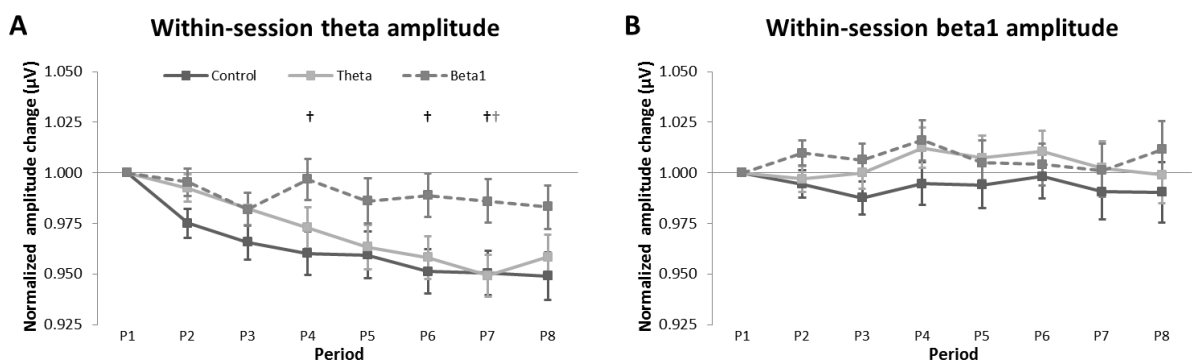


Figure 8.1. Within-session theta and beta1 amplitude change in active periods for control NF, theta NF and beta1 NF. The graphs represent the mean amplitude change in eight active periods (from P1 to P8) collapsed across eight training sessions relative to the first active period of each session for theta (A) and beta1 frequencies (B). Error bars depict standard error of the mean. Statistical significance level is represented by asterisks (†= $p<0.10$, *= $p<0.05$, **= $p<0.01$).

Table 8.1. Mean (and SD) of theta and beta1 amplitude change (μV) for each period (normalized to period 1 of each session) for control NF, theta NF and beta1 NF; independent t -tests (Bonferroni corrected p -values) between control NF, theta NF and beta1 NF.

Frequency	Period	Protocol						Independent t -test		
		Control		Theta		Beta1		Control vs. Theta	Control vs. Beta1	Theta vs. Beta1
		M	SD	M	SD	M	SD			
Theta	1	1.00	0.00	1.00	0.00	1.00	0.00	—	—	—
	2	0.98	0.03	0.99	0.01	1.00	0.02	1.78	2.07	0.30
	3	0.97	0.03	0.98	0.02	0.98	0.03	1.41	1.38	0.03
	4	0.96	0.04	0.97	0.02	1.00	0.04	0.86	2.48 †	1.67
	5	0.96	0.04	0.96	0.02	0.99	0.04	0.25	1.67	1.46
	6	0.95	0.03	0.96	0.02	0.99	0.05	0.45	2.45 †	2.06
	7	0.95	0.03	0.95	0.01	0.99	0.04	0.09	2.33 †	2.48 †
	8	0.95	0.04	0.96	0.02	0.98	0.04	0.59	2.14	1.60
Beta1	1	1.00	0.00	1.00	0.00	1.00	0.00	—	—	—
	2	0.99	0.02	1.00	0.02	1.01	0.02	0.28	1.68	1.44
	3	0.99	0.02	1.00	0.03	1.01	0.02	1.09	1.65	0.57
	4	0.99	0.03	1.01	0.03	1.02	0.03	1.21	1.47	0.26
	5	0.99	0.03	1.01	0.03	1.01	0.04	0.85	0.70	0.15
	6	1.00	0.03	1.01	0.03	1.00	0.03	0.82	0.40	0.43
	7	0.99	0.05	1.00	0.03	1.00	0.04	0.62	0.56	0.07
	8	0.99	0.05	1.00	0.03	1.01	0.05	0.42	1.04	0.64

†= $p < 0.10$, *= $p < 0.05$, **= $p < 0.01$

Hypothesis 2: Training-specificity of across-session theta and beta1 amplitude changes in active periods.

Figures 8.2A and 8.2B show the within-session theta and beta1 amplitude changes in active periods across-sessions in the three NF protocols. Across-session theta and beta1 amplitude changes as a function the type of NF protocol were investigated in separate 8 SESSION x 3 PROTOCOL mixed ANOVAs. Contrary to hypotheses, the SESSION x PROTOCOL interactions were non-significant for both frequencies (theta: $F(14,182)=0.86$, $p=0.60$, $\eta_p^2=0.06$; beta1: $F(14,182)=0.96$, $p=0.50$, $\eta_p^2=0.07$).

Means (and SD) of theta and beta1 amplitude change in active periods for each session are presented in table 8.2. As shown in the table, between-subject pairwise comparisons (Bonferroni corrected p -values) for each session did not provide evidence of significant within-session theta amplitude differences between control and theta NF (all $ps>0.44$), between control and beta1 NF (all $ps>0.15$), or between theta and beta1 NF (all $ps>0.20$). Similarly, for the beta1 frequency the post-hoc comparisons failed to show significant within-session beta1 amplitude differences between control and theta NF (all

$ps>0.43$), between control and beta1 NF (all $ps>0.14$), or between theta and beta1 NF (all $ps>0.51$).

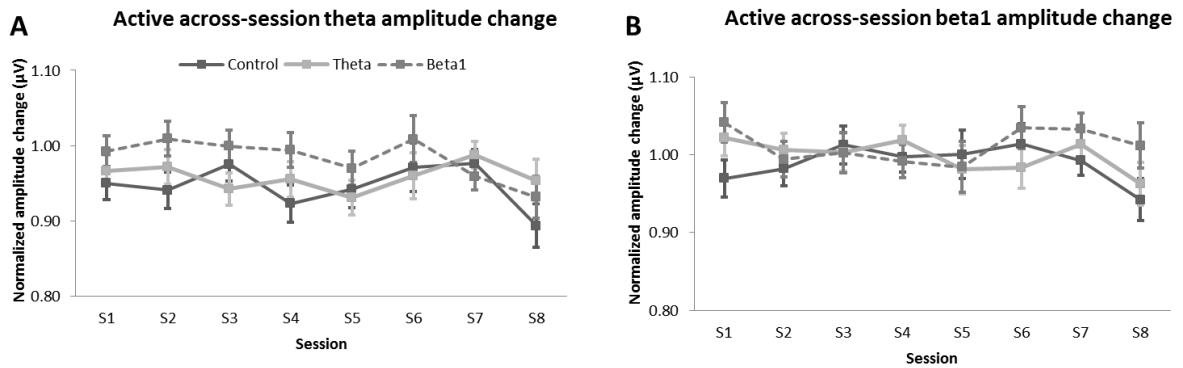


Figure 8.2. Across-session theta and beta1 amplitude change for control NF, theta NF and beta1 NF in active periods. The graphs represent the amplitude change in eight training sessions (from S1 to S8) for theta (A) and beta1 frequencies (B). Amplitude change was normalized relative to the first active period of the first session. Error bars depict standard error of the mean. Statistical significance level is represented by a cross and an asterisk (+= $p<0.10$; *= $p<0.05$, **= $p<0.01$).

The analyses also revealed a marginally significant effect of SESSION for the theta ($F(7,182)=1.86$, $p=0.08$, $\eta_p^2=0.07$) but not for the beta1 frequency ($F(7,182)=1.25$, $p=0.28$, $\eta_p^2=0.05$). However, the Bonferroni corrected post-hoc comparisons between sessions failed to provide evidence of significant changes in within-session theta amplitude (all $ps>0.20$). Post-hoc contrast within-subject contrasts also failed to provide evidence of linear effects of SESSION in both frequencies (theta: $F(1,26)=2.48$, $p=0.13$, $\eta_p^2=0.09$; beta1: $F(1,26)=1.40$, $p=0.25$, $\eta_p^2=0.05$). The main effect of PROTOCOL revealed marginally significant average within-session amplitude changes in the theta but not in the beta1 frequency (same as Hypothesis 1).

Table 8.2. Mean (and SD) of normalized theta and beta1 amplitude change (μV) in active and passive periods for each session and for control NF, theta NF and beta1 NF; independent *t*-tests (Bonferroni corrected *p*-values) between control NF, theta NF and beta1 NF.

Frequency	Session	Protocol						Independent <i>t</i> -test		
		Control		Theta		Beta1		Control vs. Theta	Control vs. Beta1	Theta vs. Beta1
		M	SD	M	SD	M	SD			
Theta (active)	1	0.95	0.06	0.97	0.05	0.99	0.08	0.57	1.45	0.90
	2	0.94	0.07	0.97	0.05	1.01	0.09	0.93	2.05	1.16
	3	0.98	0.07	0.94	0.04	1.00	0.09	1.08	0.78	1.91
	4	0.92	0.06	0.96	0.07	0.99	0.09	0.95	2.10	1.18
	5	0.94	0.05	0.93	0.08	0.97	0.08	0.33	0.85	1.22
	6	0.97	0.12	0.96	0.06	1.01	0.11	0.25	0.85	1.13
	7	0.98	0.07	0.99	0.05	0.96	0.04	0.45	0.67	1.15
	8	0.89	0.05	0.95	0.10	0.93	0.10	1.49	0.94	0.57
Beta1 (active)	1	0.97	0.08	1.02	0.05	1.04	0.09	1.51	2.08	0.58
	2	0.98	0.05	1.01	0.07	0.99	0.08	0.78	0.38	0.41
	3	1.01	0.07	1.00	0.07	1.00	0.09	0.26	0.30	0.03
	4	1.00	0.06	1.02	0.04	0.99	0.08	0.74	0.19	0.95
	5	1.00	0.08	0.98	0.11	0.98	0.10	0.43	0.35	0.08
	6	1.01	0.09	0.98	0.06	1.03	0.09	0.82	0.56	1.41
	7	0.99	0.07	1.01	0.03	1.03	0.07	0.77	1.48	0.73
	8	0.94	0.08	0.96	0.09	1.01	0.09	0.52	1.75	1.26
Theta (passive)	1	0.95	0.06	0.97	0.05	0.99	0.08	0.57	1.45	0.90
	2	0.94	0.07	0.97	0.05	1.01	0.09	0.93	2.05	1.16
	3	0.98	0.07	0.94	0.04	1.00	0.09	1.08	0.78	1.91
	4	0.92	0.06	0.96	0.07	0.99	0.09	0.95	2.10	1.18
	5	0.94	0.05	0.93	0.08	0.97	0.08	0.33	0.85	1.22
	6	0.97	0.12	0.96	0.06	1.01	0.11	0.25	0.85	1.13
	7	0.98	0.07	0.99	0.05	0.96	0.04	0.45	0.67	1.15
	8	0.89	0.05	0.95	0.10	0.93	0.10	1.49	0.94	0.57
Beta1 (passive)	1	0.97	0.08	1.02	0.05	1.04	0.09	1.51	2.08	0.58
	2	0.98	0.05	1.01	0.07	0.99	0.08	0.78	0.38	0.41
	3	1.01	0.07	1.00	0.07	1.00	0.09	0.26	0.30	0.03
	4	1.00	0.06	1.02	0.04	0.99	0.08	0.74	0.19	0.95
	5	1.00	0.08	0.98	0.11	0.98	0.10	0.43	0.35	0.08
	6	1.01	0.09	0.98	0.06	1.03	0.09	0.82	0.56	1.41
	7	0.99	0.07	1.01	0.03	1.03	0.07	0.77	1.48	0.73
	8	0.94	0.08	0.96	0.09	1.01	0.09	0.52	1.75	1.26

†= $p < 0.10$, *= $p < 0.05$, **= $p < 0.01$

Hypothesis 3: Training-specificity within-session theta and beta1 amplitude changes in passive periods.

Within-session theta and beta1 amplitude changes in passive periods were investigated in one-way between-subjects ANOVA. Data and statistical results are presented in table 8.3. For the theta frequency the analysis revealed a marginally significant effect of PROTOCOL ($F(2,26)=3.36$, $p=0.05$, $\eta_p^2<0.21$). As shown in figure 8.4B, post-hoc comparisons indicated that the within-session theta amplitude was significantly decreased in theta relative to beta1 NF ($t(18)=2.43$, $p=0.02$), marginally decreased in control relative to beta1 NF ($t(17)=2.01$, $p=0.06$) but not significantly different between control and theta NF ($t(18)=0.34$, $p=0.74$). Contrary to hypothesis, the main effect of PROTOCOL was not significant in the beta1 frequency ($F(2,26)=0.16$, $p=0.86$, $\eta_p^2=0.01$).

Hypothesis 4: Training-specificity of across-session theta and beta1 amplitude changes in passive periods.

Figures 8.3A and 8.3B show the theta and beta1 amplitude changes in passive periods across-sessions in the three protocols. Across-session theta and beta1 amplitude changes in passive periods was investigated in separate two-way 8 SESSION x 3 PROTOCOL mixed-ANOVAs. Table 8.2. presents means (and SDs) of average theta and beta1 amplitude change in passive periods relative to the first resting state period of each session.

In the theta frequency the analysis failed to reveal significant changes across sessions as a function of the type of NF (SESSION x PROTOCOL: $F(14,182)=0.86$, $p=0.60$, $\eta_p^2=0.06$). However, there was a marginal effect of SESSION ($F(7,182)=1.86$, $p=0.08$, $\eta_p^2=0.07$). Polynomial contrasts failed to provide evidence of a significant linear increment in theta amplitude change across sessions irrespective of the NF protocol ($F(1,26)=2.48$, $p=0.13$, $\eta_p^2=0.09$). Bonferroni corrected pairwise comparisons also failed to provide evidence of significant theta amplitude changes between sessions (all $p_s>0.20$).

In the beta1 frequency the main effect of SESSION ($F(7,182)=1.25$, $p=0.28$, $\eta_p^2=0.05$) and the interaction effect of SESSION x PROTOCOL ($F(14,182)=0.96$, $p=0.50$, $\eta_p^2=0.07$) were not reliable.

Table 8.3. Means (and SD) of the mean within-session amplitude change (μV) in active and passive periods for each frequency; statistical values of the between-subjects one-way ANOVAs and multiple comparisons by independent t -tests (Bonferroni corrected p -values) between control NF, theta NF and beta1 NF.

Source	Frequency	Protocol						ANOVA F	Independent t -test		
		Control		Theta		Beta1			Control vs. Theta	Control vs. Beta1	Theta vs. Beta1
		M	SD	M	SD	M	SD				
Active	Delta	0.957	0.03	0.968	0.03	0.997	0.02	5.38 *	0.87	3.17 *	2.34 †
	Theta	0.959	0.03	0.968	0.01	0.988	0.03	2.97 †	0.75	2.36 †	1.66
	Alpha1	0.973	0.02	0.989	0.02	0.992	0.02	2.25	1.67	1.99	0.33
	Alpha2	1.017	0.04	1.008	0.02	1.007	0.02	0.28	0.61	0.69	0.08
	Alpha3	1.032	0.05	1.014	0.02	1.016	0.04	0.55	0.97	0.85	0.12
	SMR	0.998	0.03	1.003	0.02	1.018	0.04	1.01	0.37	1.36	1.02
	Beta1	0.993	0.03	1.004	0.02	1.008	0.03	0.73	0.88	1.17	0.29
	Beta2	1.000	0.05	1.005	0.03	1.007	0.03	0.06	0.25	0.34	0.09
	Beta3	0.974	0.06	0.996	0.02	1.007	0.04	1.69	1.24	1.81	0.59
	Beta4	0.979	0.04	0.996	0.02	1.009	0.04	1.74	1.07	1.86	0.81
	Beta5	0.992	0.02	0.999	0.02	0.997	0.03	0.20	0.62	0.40	0.23
	Gamma	0.983	0.03	1.006	0.03	1.002	0.02	2.25	2.01	1.63	0.40
Passive	Delta	0.996	0.04	0.977	0.06	1.004	0.04	0.80	0.86	0.34	1.23
	Theta	0.967	0.05	0.960	0.04	1.011	0.05	3.36 †	0.34	2.01 †	2.43 *
	Alpha1	0.983	0.05	0.961	0.04	1.001	0.04	2.14	1.10	0.91	2.06 *
	Alpha2	1.036	0.09	0.988	0.04	1.009	0.08	1.00	1.42	0.80	0.63
	Alpha3	1.036	0.14	1.020	0.07	1.028	0.12	0.05	0.32	0.14	0.18
	SMR	0.997	0.07	0.995	0.04	1.041	0.09	1.33	0.06	1.35	1.45
	Beta1	1.001	0.05	1.001	0.04	1.011	0.06	0.16	0.03	0.49	0.48
	Beta2	0.993	0.08	0.998	0.06	1.013	0.06	0.24	0.17	0.66	0.50
	Beta3	0.960	0.10	0.975	0.06	1.019	0.06	1.62	0.41	1.71	1.33
	Beta4	0.961	0.08	0.976	0.04	1.012	0.08	1.32	0.46	1.57	1.14
	Beta5	0.989	0.03	0.980	0.04	0.992	0.06	0.20	0.47	0.11	0.60
	Gamma	0.996	0.04	0.977	0.06	1.004	0.04	0.80	0.86	0.34	1.23

† = $p < 0.10$; * = $p < 0.05$; ** = $p < 0.01$

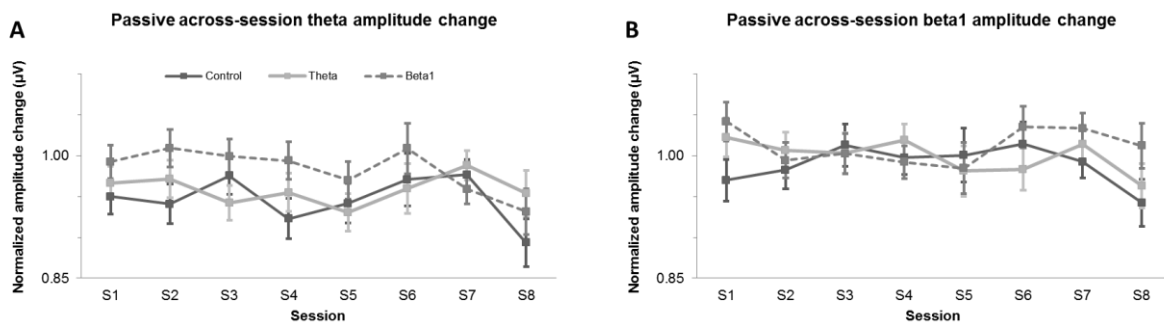


Figure 8.3. Across-session theta and beta1 amplitude change for control NF, theta NF and beta1 NF in passive periods. The graphs represent the amplitude change in eight training sessions (from S1 to S8) for theta (A) and beta1 frequencies (B). Amplitude change was normalized relative to the first passive period of the first session. Error bars depict standard error of the mean.

8.3.1. Frequency-specific learning

In order to investigate frequency-specific effects, the mean within-session amplitude change for eight frequencies ranging from delta to gamma was calculated for each NF protocol. Means (and SD) of within-session amplitude changes in the twelve frequencies in active feedback and passive resting state periods are presented in table 8.3. Frequency-specific effects were analyzed with two-way 12 FREQUENCY x 3 PROTOCOL mixed-ANOVAs for active and passive periods.

Hypothesis 5: Frequency-specificity of theta and beta1 amplitude changes in active periods.

Figure 8.4A presents the within-session amplitude changes in the twelve frequencies in active periods for each of the three NF protocols. The two-way mixed ANOVA revealed a significant main effect of FREQUENCY ($F(11,286)=10.87, p<0.001, \eta_p^2=0.30$) and a nearly significant interaction effect of FREQUENCY x PROTOCOL ($F(22,286)=1.57, p=0.05, \eta_p^2=0.11$). The effects of the three protocols on each of the twelve frequencies were explored by one-way ANOVAs and *t*-tests. As can be seen in table 8.3., apart from the previously described effects in the theta frequency (section 8.3.1.), also significant differences in within-session amplitude were found between the NF protocols in the delta frequency ($F(2,26)=5.38, p=0.01, \eta_p^2=0.29$) but not in other frequencies (all $p_s>0.13$). Post-hoc comparisons revealed that the within-session delta amplitude was significantly decreased in the control relative to beta1 NF ($t(17)=3.17, p=0.01$) and marginally decreased in the theta relative to beta1 NF ($t(18)=2.34, p=0.08$) but was not significantly different in the control relative to theta NF ($t(17)=0.87, p=1.00$). The analysis also indicated that the main effect of PROTOCOL was not reliable ($F(2,26)=1.17, p=0.33, \eta_p^2=0.08$).

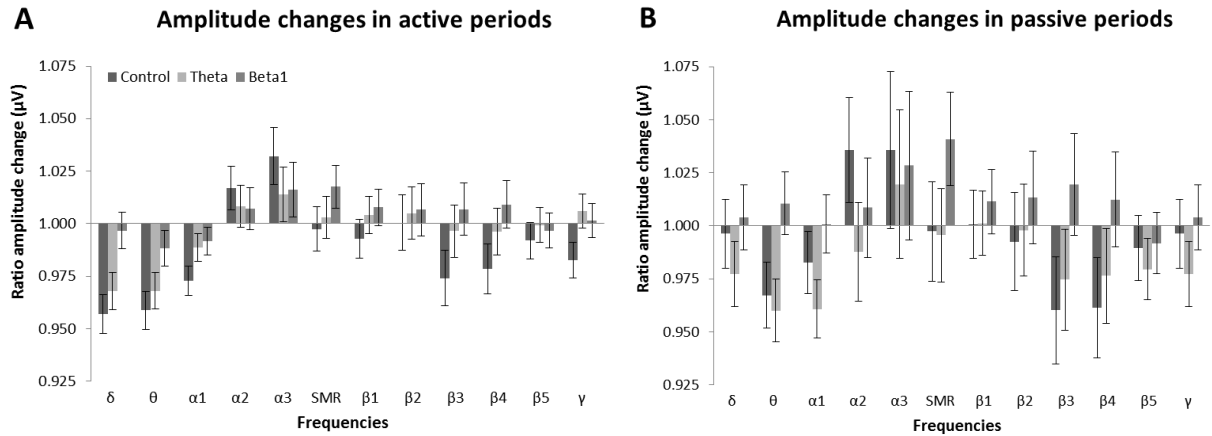


Figure 8.4. Within-session amplitude change in different frequency bands for control NF, theta NF and beta1 NF protocols. The graphs indicate the mean within-session amplitude change from delta to gamma frequencies for active periods (normalized to the first active period of each sessions) (A) and passive periods (normalized to the first passive period of each session) (B). Error bars depict standard error of the mean. Statistical significance level is represented by asterisks (* $p < 0.05$ and ** $p < 0.01$).

Hypothesis 6: Frequency-specificity of theta and beta1 amplitude changes in passive periods.

The mean amplitude changes in passive periods for the frequencies ranging from delta to gamma for each of NF protocols are shown in figure 8.4B. The two-way mixed ANOVA indicated significant main effect of FREQUENCY ($F(11,286)=2.82$, $p < 0.01$, $\eta_p^2=0.10$). However, the post-hoc comparisons failed to provide evidence of reliable differences between the twelve frequencies (all $p_s > 0.32$). The analysis also revealed a non-reliable interaction effect of FREQUENCY x PROTOCOL ($F(22,286)=0.83$, $p=0.69$, $\eta_p^2=0.06$). As shown in table 8.3., despite this non-significant interaction, the post-hoc comparisons additionally revealed a within-session alpha1 amplitude decrement in the theta relative to beta1 NF ($t(18)=2.06$, $p < 0.05$) while other pairwise comparisons were not reliable (all $p_s > 0.28$). The analysis further indicated a non-significant main effect of PROTOCOL ($F(2,26)=0.95$, $p=0.40$, $\eta_p^2=0.07$).

8.4. Discussion

A major goal of the current study was to investigate the training- and frequency-specificity of theta suppression and beta1 enhancement using within- and across-session methods. The results partially supported the hypothesis that the three NF protocol would have a differential impact on within-session amplitude changes in both active and passive periods, but only in the theta frequency (Hypothesis 1 and 3). However, they failed to provide supportive evidence of across-session amplitude changes in theta and beta1 frequencies irrespective of whether active or passive periods were considered (Hypothesis 2 and 4). Moreover, the type of NF also modulated the within-session delta amplitude in active periods (Hypothesis 5) but no significant within-session amplitude changes in other frequencies were observed in the passive periods (Hypothesis 6).

8.4.1. Within-session training- and frequency-specificity

8.4.1.1. Training-specific within-session amplitude changes

The three NF protocols had a differential impact on within-session amplitude changes in theta but not in beta1 frequency. Additionally, in the theta frequency the results evinced a distinct pattern of within-session amplitude changes in active and passive periods.

Theta

Contrary to hypothesis, the analysis indicated of a trend towards within-session theta amplitude decrements in RF NF control condition, but not in theta NF, when compared to beta1 NF (Hypothesis 1). Firstly, it should be noticed that this difference did not reach statistical significance and, therefore, warrants replication in a larger sample before further conclusions can be drawn. Nevertheless, this result is surprising in light of the particular training regime and of the previous literature using similar RF NF as a control condition. In fact, because RF NF training did not emphasize the suppression of theta activity (or any of the adjacent delta and alpha1 frequencies) this result cannot be explained by the direct effect of the NF intervention. Moreover, this theta suppression effect following RF NF is in disagreement with one previous study (Doppelmayr & Weber, 2011). However, the two studies are difficult to compare because of differences in the learning measures (within vs.

across-session) and in the training instructions of the RF condition (counterbalanced up- and down-regulation vs. up-regulation).

Alternatively, theta suppression following RF NF may be considered epiphenomenal to unspecific brain processes involved in NF such as time on task and cognitive effort. However, time on task is unlikely to explain this effect because theta amplitude tends to increase rather than decrease over time in both resting and vigilance task conditions (Brismar, 2007; Paus et al., 1997; Wascher et al., 2013). Assuming the involvement of more active processes, theta suppression might be explained by a decrement in cognitive effort relative to the first active period of each session (i.e., the normalization period) possibly related to the difficulty in maintaining a consistent self-regulatory strategy throughout the session. This explanation would be consistent with the modulation of theta amplitude by cognitive effort (Gevins, Smith, McEvoy, & Yu, 1997; Klimesch et al., 2001; Wascher et al., 2013) and with previous evidence of fm-theta amplitude increments when NF training promoted the active use of specific self-regulatory strategies and required higher cognitive effort relative to Sham NF (Enriquez-Geppert et al., 2014a, 2014b). In turn, the absence of variations in within-session theta amplitude in Sham NF (Enriquez-Geppert et al., 2014a, 2014b; Kober et al., 2015) might be explained by the lower cognitive effort involved in these conditions. Given the speculative nature of this explanation, more studies are needed to investigate whether the variations in within-session theta amplitude might reflect changes in cognitive effort. Future studies should consider ensuring the comparability of control (e.g., sham or RF) and other experimental NF conditions in terms of cognitive effort by monitoring subjective measures of effort and self-regulatory strategies.

The failure to provide evidence of training-specific within-session theta amplitude decreases in active periods (Hypothesis 1) in theta NF is in disagreement with previous results obtained during SMR/theta (de Zambotti et al., 2012; Gruzelier et al., 2014a; Ros et al., 2009; Vernon et al., 2003) and theta suppression NF (Beatty, Greenberg, Deibler, and O'Hanlon, 1974; O'Halon, Royal, & Beatty, 1977; Williams, Beatty, & O'Hanlon, 1975). Several aspects may have contributed to these different outcomes. Firstly, the control for training-specificity was different between studies. Contrary to previous studies (de Zambotti et al., 2012; Gruzelier et al., 2014a; Ros et al., 2009; Vernon et al., 2003), the current one also monitored within-session theta amplitude changes in other NF protocols. Thus,

differently from the current study, training-specificity could not be inferred from those previous ones. Moreover, in those studies it was unclear whether the within-session theta amplitude decrements were an epiphenomenon of increasing the synchronization in the higher frequencies (i.e., SMR and other beta frequencies) or a direct manifestation of an attempt to desynchronize the lower ones.

Also differently from the present study, in Beatty and colleagues investigations the evidence of training-specific theta suppression was obtained relative to a theta enhancement NF condition. In the latter, the theta amplitude was enhanced relative to the baseline and therefore this condition could not provide an unbiased measure of within-session theta amplitude changes (O'Halon, Royal, & Beatty, 1977; Williams, Beatty, & O'Hanlon, 1975). Moreover, the training-specific theta suppression effect was obtained during a single-session in which the prolonged time on task may have provided more opportunities to counteract the increasing theta activity over time. In the current experiment, it may have been more difficult to further decrease theta amplitudes because the NF sessions had a shorter duration. Moreover, the theta amplitude might have been already low because of its scarcity in healthy adults that have not been sleep deprived or subject to tiring and monotonous tasks.

According to hypothesis, in passive periods the theta amplitude was significantly decreased within sessions in theta NF relative to beta1 (Hypothesis 3). However, the absence of such decrements in active periods questions whether this result can be interpreted as the culmination of training. Moreover, the nearly significant decreases in passive periods in RF relative to beta1 NF and the absence of differences between theta and RF NF suggest that unspecific effects of NF may equally explain these effects. These results could be interpreted as an increment in theta amplitude, possibly reflecting increased mental effort in beta1 NF.

Beta1

In the beta1 frequency there was no evidence of training-specific effects in active periods. These results are in disagreement with previous observations of within-session beta1 amplitude increments following beta1 NF relative to control NF condition (Experiment 1, Hypothesis 1). Three methodological differences relative to that previous study might explain this disagreement. Firstly, in the current experiment the beta1 frequency was defined relative to IAF (IAF + 5 Hz to IAF + 8 Hz), while in the previous one it was defined

according to an arbitrary sub-band categorization (15-18 Hz). However, because the mean IAF was 9.5 Hz (see section 8.2.4) this is unlikely to have resulted in actual differences in beta1 frequency band definition between studies. Another methodological difference concerns the training regime in the control condition. In the previous study, RF NF showed a more pronounced within-session beta1 amplitude decrement than that observed in the current experiment. This might have contributed to the significant differences between RF and beta1 NF protocols in the former but not in the latter study. Finally, the different position of the active electrode (Cz) relative to the previous study (C3) might equally explain the difficulties in enhancing the beta1 amplitude in the present experiment. Further work is needed to investigate whether the success of the beta1 amplitude enhancement depends on such factors as the electrode location and the type of control condition.

There was also no evidence supporting the hypothesis of training-specific beta1 amplitude increments in passive periods (Hypothesis 3). These results are in line with those of Study 1 (Experiment 1, Hypothesis 3) and similarly suggest that the resting state beta activity rapidly returns to baseline levels after beta1 NF.

In sum, the absence of training-specific theta amplitude decrements and beta1 amplitude increments relative to control NF suggests that these changes were undistinguishable from unspecific NF effects such as time on task and cognitive effort. The lack of further within-session amplitude changes may be related to “floor and ceiling effects” in theta and beta frequencies respectively justified by the relative scarcity of theta and abundance of beta in healthy adult subjects during vigilance states (Amzica & Lopes da Silva, 2011). Future studies are needed to investigate whether the pre-training absolute and/or relative theta and beta1 amplitude may play a critical role in NF learning as suggested for the SMR frequency (Rutterford & Pacheco, 2011).

8.4.1.2. Frequency-specific within-session amplitude changes

In the present experiment the frequency-specificity of theta and beta1 NF was examined in the spectrum of EEG frequencies ranging from delta to gamma. In active periods, there was evidence of specific within-session delta amplitude decrements in the RF and theta NF relative to beta1 NF. This result is in disagreement with the hypothesis that the theta and beta1 NF protocols would be associated with frequency-specific effects in the theta

and beta1 frequencies respectively (Hypothesis 5). Again, this is a surprising outcome given that none of these NF protocols attempted to manipulate delta amplitude. Although this might reflect a partial overlap between delta and theta frequencies, unspecific effects of NF may also contribute to delta amplitude changes. In this regard, delta oscillations have been related to motivational processes involved in the detection of salient internal and external signals (Lakatos et al., 2008; Knyazev, 2012) that might be crucially important to feedback learning. Interestingly, the modulation of delta amplitude as a function of the type of NF was only observed in active periods suggesting that it might reflect the involvement of an active learning process. Future studies are needed to replicate these results and investigate whether the within-session modulation of delta amplitude might reflect distinct motivation processes between NF protocols.

Contrary to observed in the active periods, a non-significant FREQUENCY x PROTOCOL interaction suggested that the within-session amplitude change from pre- to post-training in the different frequencies was not significantly modulated by the type of NF protocol. Nevertheless, the pairwise comparisons revealed within-session theta and alpha 1 amplitude decrements in the theta relative to beta1 NF. These effects are unlikely to represent the culmination of the training process because no such effects were observed in active periods. Alternatively, this result suggests a differential effect of the two NF protocols in counteracting the increased amplitude of slow frequencies usually associated with increased mental fatigue and lower arousal (Wascher et al., 2013).

8.4.1.3. Across-session training-specific effects

Another major goal of the present experiment was to investigate across-session theta and beta amplitude changes in both active and passive periods. Contrary to hypothesis (Hypothesis 2), there was no evidence of across-session beta1 amplitude increments despite the higher number of NF sessions and the individualization of the beta1 frequency relative to Study 1 (Experiment 1, Hypothesis 2). These results are in line with a previous failure to increase beta1 amplitude across sessions (Doppelmayr & Weber, 2011). Also contrary to hypothesis (Hypothesis 2), in the theta frequency the within-session amplitude was not significantly decreased across-sessions irrespective of the NF protocol. These results are in agreement with previous studies that failed to observe across-session theta amplitude

decrements after SMR/theta NF and beta1/theta NF (de Zambotti et al., 2012; Doppelmayr & Weber, 2011; Kober et al., 2015). In passive periods, there was no evidence of training-specific across-sessions amplitude changes in theta and beta1 frequencies (Hypothesis 4).

Taken together, the current evidence suggests that amplitude changes in the theta and beta1 frequencies are perhaps better captured by within-session than by across-session learning indices. Speculatively, the modulation of these frequencies may critically depend on the purposeful engagement of particular self-regulatory strategies which, once developed, are unlikely to have a facilitative effect from one session to next. Another aspect that may have contributed to the failure to observe linear amplitude changes across-session in both frequencies was the inconsistency of the learning strategies over time. Thus, future studies would do well in monitoring the consistency of these strategies across training sessions.

8.4.4. Summary

In sum, the present study confirmed that within-session amplitude changes in active and passive periods provide potentially complementary information regarding the NF learning process. In fact, theta NF was associated with significant within-session theta amplitude decrements in the passive but not in the active periods. However, these decrements are difficult to attribute to the effects of feedback (which was only provided in active periods) and to time on task (which has been associated with increments in theta amplitude). Moreover, the observation of theta amplitude decrements in active and passive periods associated with RF NF suggests that these may reflect unspecific effects of NF. Interestingly, both RF and theta NF were associated with within-session delta amplitude decrements in active but not in passive periods suggesting that delta frequency may play a role during active feedback learning. In the beta frequency, there was no evidence of training-specific within-session learning in active and passive periods. The present study also failed to evince across-session changes in both theta and beta1 frequencies, suggesting that within- and across-session measures may provide non-overlapping information regarding the learning process.

Chapter 9

Experiment 5: The effects of theta and beta1 on selective attention

9.1. Hypotheses

Hypothesis 1: Increased P3a and P3b amplitude as a function of theta and beta1 NF

It was hypothesized that:

- (3) P3b amplitude would be increased in beta1 NF relative to theta and control NF conditions and in theta NF relative to control NF ($\text{beta1} > \text{theta} > \text{control}$).
- (4) P3a amplitude would be increased in theta NF relative to beta1 NF and control NF conditions and in beta1 NF relative to control NF ($\text{theta} > \text{beta1} > \text{control}$).

Hypothesis 2: Decreased RT and RT-SD as a function of theta and beta1 NF

It was hypothesized that:

- (3) RT would be decreased in beta1 NF relative to the theta and control NF and in theta NF relative to control NF ($\text{beta1} < \text{theta} < \text{control}$).
- (4) RT-SD would be decreased in theta NF relative to control and beta1 NF and in beta1 NF relative to control NF ($\text{theta} < \text{beta1} < \text{control}$).

Hypothesis 3: Increased performance rates and perceptual sensitivity as a function of theta and beta1 NF

It was hypothesized that:

- (4) d' would be increased in beta1NF relative to the theta and control NF and in theta NF relative to control NF ($\text{beta1} > \text{theta} > \text{control}$).
- (5) Hit rate would be increased in beta1 NF relative to theta and control NF and in theta NF relative to control NF ($\text{beta1} > \text{theta} > \text{control}$).
- (6) False alarm rate would be decreased in theta NF relative to control and beta1 NF and in control NF relative to beta1 NF ($\text{theta} < \text{control} < \text{beta1}$).

9.2. Methods

9.2.1. Participants

The same twenty-nine participants of Experiment 4 took part in the present study (see section 8.2.1. for details). After excluding trials with artifacts and averaging the ERP waveforms one participant from beta1 NF was excluded from the analysis for having less than thirty correct trials in at least one of the stimulus conditions at either pre- or post-training. Table 9.1. presents demographic data for the remaining twenty-eight participants. The mean age and the mean IAF did not differ between NF protocols as confirmed by one-way ANOVAs (Age: $F(2,25)=0.11, p=0.89, \eta_p^2<0.01$; IAF: $F(2,25)=0.95, p=0.40, \eta_p^2= 0.07$).

Table 9.1. Descriptive statistics of age (mean and SD), gender (frequency) and IAF (mean, SD and range) by NF protocol after excluding one participant with insufficient number of correct trials per stimulus condition.

NF	Age		Gender			IAF		
	M	SD	Male	Female	Total	M	SD	Range
Control	21.44	4.03	4	5	9	9.22	0.67	8 -10
Theta	22.60	6.31	4	6	10	9.80	0.92	9 -12
Beta1	22.00	5.52	2	7	9	9.44	1.13	9 - 11
Total	22.04	5.23	10	18	28	9.50	0.92	8 - 12

9.2.2. Stimulus and procedure

The three-stimuli oddball task was presented to the subjects before and after the NF sessions in counterbalanced order with the cued Go/Nogo task (Experiment 6). The order of presentation had no effect in either the P3 amplitude for target, nontarget and standard stimuli or the behavioral measures of RT and accuracy.

Stimuli and procedures were identical to those of Experiment 2 of Study 1 (see section 4.2.2.).

9.2.3. EEG recording and analysis

EEG recording.

EEG recording was identical to Experiment 2 (see section 4.2.3.).

EEG data analysis.

EEG pre-processing was performed in EEGLAB (Delorme and Makeig, 2004). EEG data was re-referenced to the average of the Left and Right earlobes and high-pass filtered (0.05 Hz). EEG continuous recordings were visually inspected to remove extreme EEG artifacts prior to an infomax Independent Component Analysis was performed for correction of ocular artifacts. EEG data was then segmented relative to stimulus onset (1000ms pre-stimulus to 1000 ms post-stimulus) and trials exceeding 100 μ V were automatically identified and rejected on visual inspection.

EEG analysis was performed in Fieldtrip (Oostenveld, Fries, Maris, and Schoffelen, 2011). Only correct trials (correct response to target and correct non-response to standard and nontarget on the 0 to 1000ms interval post-stimulus onset) were analyzed and submitted to baseline correction (-200 to 0ms relative to stimulus onset). A minimum of 30 trials per condition were used to calculate individual ERP components. One-hundred random permutations were performed on thirty correct trials of each condition in order to ensure that the same number of trials per condition were used and that the individual waveforms resulted from a random selection of the number of available trials per condition. Hence, the individual mean P3 amplitudes represent the average amplitude of a hundred randomly generated waveforms each of which was based on an average of 30 artifact-free segments.

The target-standard and nontarget-standard difference waves and respective mean P3 amplitude were calculated for frontal, central and parietal regions according to the procedures described in section 4.2.3.

Percent of correct ERP trials.

After excluding segments with artifacts, the percentage of correct trials for each type of stimulus was calculated for each participant and averaged across groups. Descriptive statistics of the mean percentage of correct responses to target, nontarget and standard stimuli are presented in table 9.2. Pre-training differences between the three NF protocols were

investigated with separate one-way ANOVA for each type of stimulus. As shown in the table, the NF protocols differed significantly in the percentage of correct standard and nontarget stimuli ($p < 0.05$), but not in the percentage of correct target stimulus ($p > 0.24$). Post-hoc comparisons revealed a marginal lower percentage of correct non-responses to standard stimuli in the beta1 relative to RF NF ($t(27) = 2.46$; $p = 0.06$) but not between beta1 and theta NF or between theta and RF NF (all $p > 0.16$). The percentage of correct non-responses to nontargets was significantly lower in the beta1 relative to RF NF ($t(27) = 2.64$; $p = 0.04$) while other pairwise comparisons were non-significant (all $p > 0.16$).

Additionally, the differences in the percentage of correct trials from pre- to post-training as a function of the NF were analyzed in separate two-way 2 TIME x 3 PROTOCOL mixed-ANOVAs for each type of stimulus. As can be seen in table, the non-significant TIME x PROTOCOL interactions showed that the NF protocols did not differ significantly in the percentage of correct responses from pre- to post-training (all $p > 0.28$). However, the significant main effects of TIME indicate that the percentage of correct standard and nontarget stimuli increased from pre- (Standards: $M = 84.67\%$, $SD = 11.36\%$; Nontargets: $M = 89.50\%$, $SD = 8.46\%$) to post-training (Standards: $M = 90.18\%$, $SD = 8.70\%$; Nontargets: $M = 94.79\%$, $SD = 7.59\%$). On the other hand, the percentage of correct target stimulus was not significantly changed as a function of the moment of assessment. Moreover, a significant main effect of PROTOCOL indicated that in beta1 NF the overall percentage of correct standard stimulus was lower relative to control NF ($t(16) = 2.71$; $p = 0.04$) and marginally lower relative to theta NF ($t(17) = 2.53$; $p = 0.06$). Despite these pre- to post-training and NF protocol differences in the percentage of correct trials, the method of calculating the individual ERP waveforms ensured that the same number of correct trials was used at pre- and post-training in the three NF protocols (see previous section).

9.2.4. Behavioral data analysis

Reaction time data preparation

RT and RT-SD analysis were performed on the same correct target trials used for ERP analysis after the exclusion of artifacts.

Performance rates and d-prime data preparation

Performance rates (hit rate to targets, false alarm to standards and false alarm to nontargets) were calculated for all the available trials before artifact rejection. The procedure for the calculation of d-prime scores was as described in section 4.2.4.

9.2.5. Statistical analysis

Specifications of statistical packages and criteria were provided in section 3.2.6.

9.3. Results

9.3.1. Hypothesis 1: Increased P3a and P3b amplitude as a function of theta and beta1 NF

9.3.1.1. Pre-training differences between NF protocols

Figure 9.1. shows the grand average of the stimulus-locked ERP elicited by the target-standard and nontarget-standard difference waves in frontal, central and parietal regions at pre-training irrespective of NF protocol. The figure shows a large positive deflection with maximal peak amplitude around 300ms in parietal electrodes for target-standard (P3b) and a smaller positive deflection around 300ms with maximal peak in central electrodes after nontarget-standard (P3a).

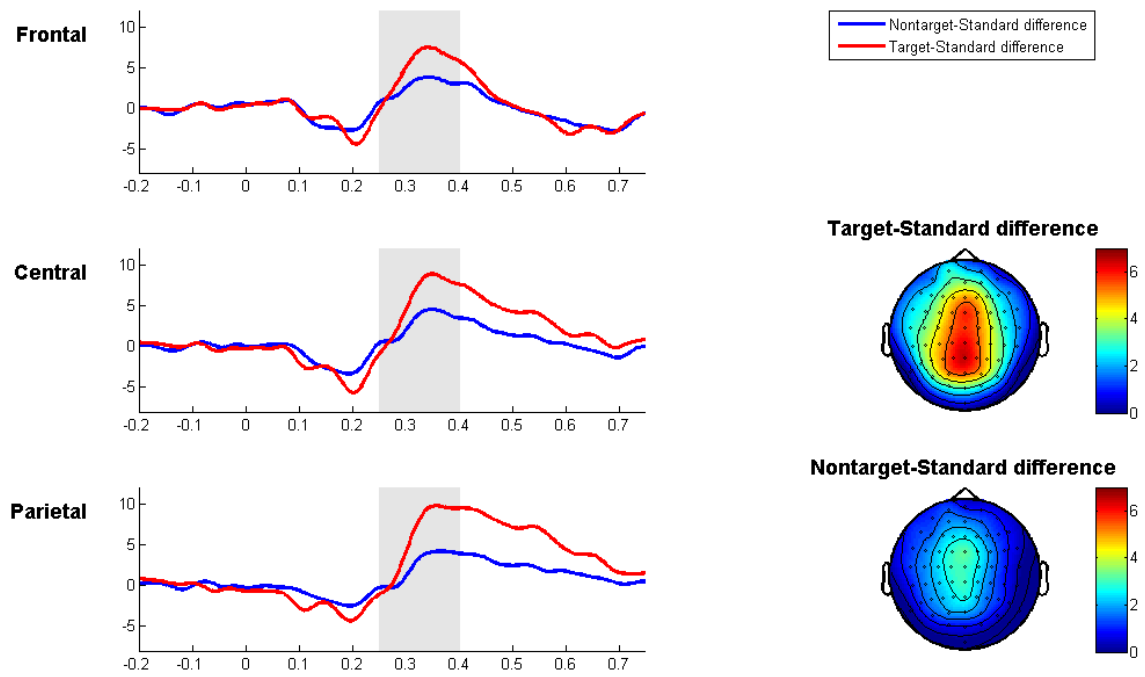


Figure 9.1. *Left.* Grand average of the stimulus-locked ERP of target-standard and nontarget-standard difference waves in midline frontal, central and parietal regions at pre-training irrespective of the NF protocol. The shaded area represents the 250-400ms measurement window. Positive amplitude is displayed upwards. *Right.* Distribution of the target-standard and nontarget-standard difference waves.

A three-way 2 STIMULUS (target-standard vs. nontarget-standard) x 3 REGION (frontal vs. central vs. parietal) x 3 PROTOCOL (Control vs. Theta vs. Beta1) mixed-design ANOVA for the mean P3 amplitude at pre-training yielded significant main effects of STIMULUS ($F(1,25)=36.56, p<0.01, \eta_p^2=0.59$) and REGION ($F(1.39,34.89)=3.99, p=0.04, \eta_p^2=0.14$) as well as a significant interaction of STIMULUS x REGION ($F(1.29,32.11)=10.61, p<0.01, \eta_p^2=0.29$). The main effect of PROTOCOL ($F(2,25)=0.63, p=0.54, \eta_p^2=0.05$) and the interactions involving the between-subject variable were non-significant (STIMULUS x PROTOCOL: $F(2,25)=0.05, p=0.95, \eta_p^2<0.01$; REGION x PROTOCOL: $F(2.79,34.89)=0.59, p=0.61, \eta_p^2=0.05$; STIMULUS x REGION x PROTOCOL: $F(2.57,32.11)=1.73, p=0.18, \eta_p^2=0.12$).

As shown in fig. 9.2., the post-hoc comparisons (Bonferroni corrected p -values) for the target-standard revealed that the P3 amplitude was significantly higher in the parietal ($M=12.38$, $SD=4.42$) relative to the frontal region ($M=10.05$, $SD=4.97$; $t(27)=3.22$, $p=0.01$) and marginally higher in the parietal relative to central region ($M=11.26$, $SD=5.09$; $t(27)=2.54$, $p=0.05$). The target-standard P3 amplitude was marginally higher in the central region relative to the frontal region ($t(27)=2.52$, $p=0.06$). However, for the nontarget-standard the P3 amplitude was not significantly different between parietal ($M=6.42$, $SD=3.27$) and central regions ($M=6.66$, $SD=3.77$; $t(27)=0.35$, $p=1.00$), between parietal and frontal regions ($M=6.22$, $SD=3.56$; $t(27)=0.32$, $p=1.00$) and between central and frontal regions ($t(27)=1.27$, $p=0.64$). Finally, the post-hoc comparisons revealed that the P3 amplitude was significantly higher for the target-standard difference waves relative to the nontarget-standard difference waves in the three regions (Frontal: $t(27)=4.75$, $p<0.001$; Central: $t(27)=5.43$, $p<0.001$; Parietal: $t(27)=6.85$, $p<0.001$).

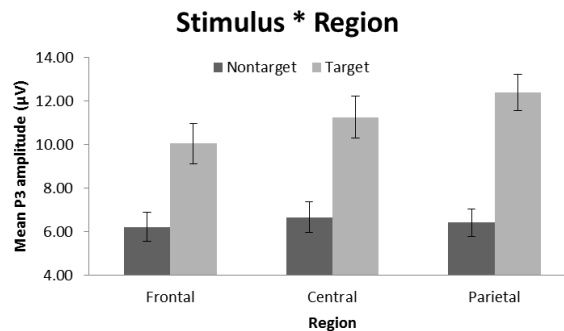


Figure 9.2. Two-way interaction of Stimulus and Region in mean P3 amplitude at pre-training. The graph shows the mean P3 amplitude (μV) for Target-Standard and Nontarget-Standard stimulus in three Regions (Frontal, Central and Parietal) irrespective of NF protocol. For Target-Standard the P3 amplitude was larger at Parietal electrodes, while for Nontarget-Standard the P3 amplitude did not differ significantly between regions. Error bars depict standard error of the mean.

Table 9.2.

Means (standard deviations) and statistical results of the pre-training one-way ANOVAs and the pre- to post-training two-way ANOVAs on Target-Standard (T-S) and Nontarget-Standard (N-S) P3 amplitude, Hit Rate (H), False Alarm Rate (FA) to Standards (S) and Nontargets (N), d-prime (d') to Target-Standard (T-S) and Target-Nontarget (T-N), Reaction Time (RT) Mean and Reaction Time Standard Deviation (RT SD), percentage of Correct Trials (CT) to Targets (T), Standards (S) and Nontargets (N) included in ERP analyses after artifact rejection for each of the three NF protocols. Significant differences (p<0.05) are highlighted in bold.

Source	Pre-training						One-way ANOVA			Two-way ANOVA								
	Pre-training			Post-training			Protocol			Time			Time x Protocol			Protocol		
	Control	Theta	Beta1	Control	Theta	Beta1	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2
<i>Mean P3</i>																		
T-S	13.92 (4.65)	11.32 (5.43)	11.91 (2.48)	12.74 (3.42)	12.25 (9.06)	12.50 (6.09)	-	-	-	0.02	0.89	0.00	0.59	0.56	0.04	0.22	0.81	0.02
N-S	7.45 (3.89)	5.42 (4.11)	7.12 (3.19)	6.32 (2.14)	6.04 (4.16)	7.56 (4.45)	-	-	-	0.00	0.98	0.00	0.62	0.54	0.05	0.62	0.55	0.05
H (%)	97.09 (3.54)	100.00 (0.00)	99.09 (1.50)	98.61 (1.57)	99.06 (2.03)	98.75 (2.06)	4.40	0.02	0.26	0.04	0.85	0.00	2.87	0.08	0.19	2.39	0.11	0.16
FA (%)																		
S	0.14 (0.18)	0.11 (0.17)	0.18 (0.21)	0.14 (0.13)	0.80 (0.16)	0.07 (0.11)	0.32	0.73	0.02	2.24	0.15	0.08	0.94	0.40	0.07	0.27	0.77	0.02
N	1.78 (2.11)	0.90 (0.99)	1.44 (1.33)	0.67 (0.16)	0.80 (1.03)	0.89 (1.45)	0.80	0.46	0.06	2.88	0.10	0.10	0.72	0.50	0.05	0.38	0.69	0.03
d'																		
T-S	4.87 (0.49)	5.26 (0.16)	4.96 (0.40)	5.05 (0.27)	5.20 (0.28)	5.15 (0.33)	2.92	0.07	0.19	1.94	0.18	0.07	1.35	0.28	0.10	2.39	0.11	0.16
T-N	4.04 (0.48)	4.54 (0.14)	4.22 (0.33)	4.38 (0.32)	4.44 (0.25)	4.38 (0.36)	5.33	0.01	0.30	3.11	0.09	0.11	3.22	0.06	0.20	2.85	0.08	0.19
RT (ms)																		
Mean	566.30 (166.28)	514.22 (99.57)	545.11 (133.54)	591.92 (158.24)	491.65 (114.26)	606.28 (124.15)	0.36	0.70	0.03	2.20	0.15	0.08	2.90	0.07	0.19	1.09	0.35	0.08
RT SD	105.86 (26.78)	105.76 (20.78)	101.71 (13.54)	105.30 (27.62)	91.27 (29.23)	102.85 (30.95)	0.12	0.89	0.01	1.03	0.32	0.04	1.22	0.31	0.09	0.24	0.79	0.02
CT (%)																		
T	88.00 (8.94)	91.60 (4.20)	84.00 (13.64)	88.00 (9.74)	88.44 (8.99)	94.00 (9.71)	1.50	0.24	0.11	0.43	0.52	0.02	0.08	0.92	0.01	2.37	0.11	0.16
S	89.42 (5.76)	87.05 (9.64)	77.31 (14.29)	92.58 (5.46)	93.08 (8.11)	84.56 (9.96)	3.42	0.05	0.21	8.30	0.01	0.25	0.39	0.68	0.03	4.56	0.02	0.27
N	93.33 (3.00)	91.20 (6.27)	83.78 (11.46)	96.22 (2.73)	95.60 (8.32)	92.44 (9.99)	3.86	0.03	0.24	12.87	0.00	0.34	1.32	0.28	0.10	2.56	0.10	0.17

9.3.1.2. Pre- to post-training differences between NF protocols

The pre- to post-training effects of the three NF protocols were analyzed in the region where the P3a and P3b components reached the maximal amplitude. This corresponded to the average of frontal, central and parietal regions for nontarget-standard (P3a) and to the parietal region for target-standard (P3b). The means (and standard deviations) of the P3 amplitude of target-standard and nontarget-standard difference waves in the three NF protocols at pre- and post-training are shown in table 9.2. These effects were investigated in separate two-way mixed-ANOVA with 2 TIME (pre- vs. post-training) x 3 PROTOCOL (Control vs. Theta vs. Beta1) for target-standard and nontarget-standard.

Figures 9.3. and 9.4. present the target-standard and nontarget-standard difference waveforms and the mean P3 amplitude for each of the three NF protocols at pre- and post-training respectively. As suggested by the figures, the statistical analysis did not support the hypothesis of a differential impact of the three NF protocols on the neural processing of targets (TIME x PROTOCOL: $F(2,25)=0.59$, $p=0.56$, $\eta_p^2=0.04$). As shown in the table 9.2., the main effects of TIME and PROTOCOL for target-standard difference waves were also not reliable ($ps>0.81$). Moreover, the post-hoc comparisons failed to provide evidence of pre- to post-training target-standard amplitude changes in any of the three NF protocols (all $ps>0.44$).

Similarly, the type of NF did not significantly modulate the nontarget-standard P3 amplitude from pre- to post-training (TIME x PROTOCOL: $F(2,25)=0.62$, $p=0.54$, $\eta_p^2=0.05$). Again the main effects of TIME and PROTOCOL were not reliable for the nontarget-standard difference waves ($ps>0.55$). The post-hoc comparisons failed to provide evidence of pre- to post-training nontarget-standard amplitude changes in any of the three NF protocols (all $ps>0.37$).

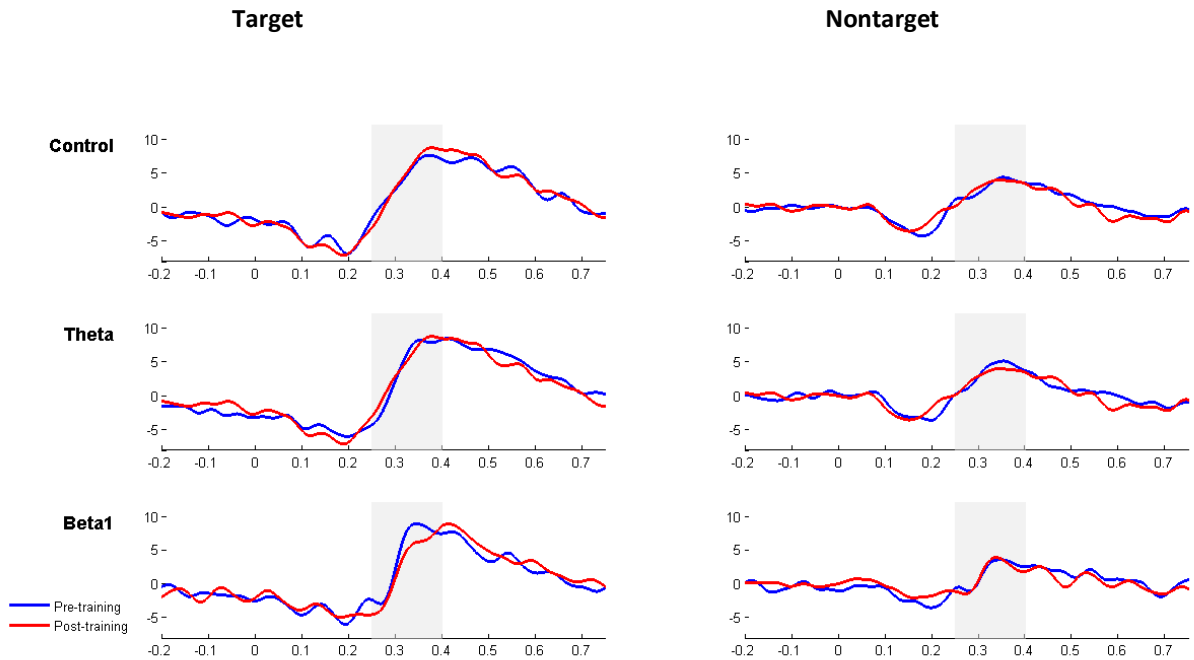


Fig. 9.3. Grand-average of the parietal target-standard difference and average nontarget-standard difference ERP waveforms for control, theta and beta1 NF at pre- and post-training. The shaded area represents the 250-400ms measurement window. Positive amplitude is displayed upwards.

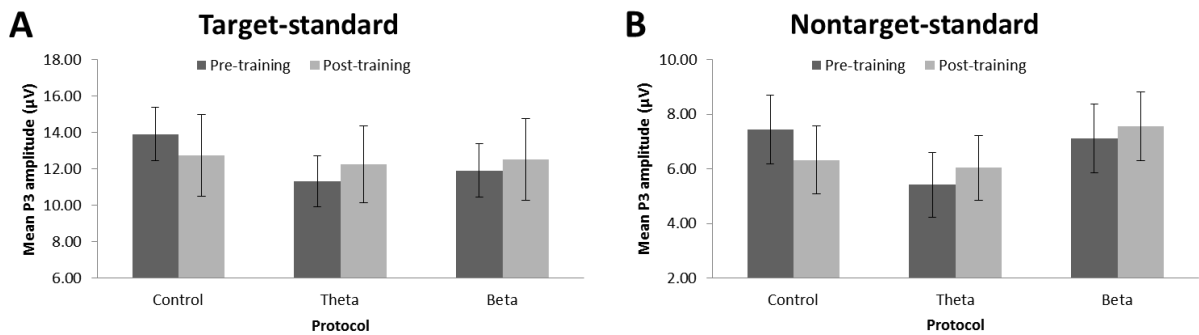


Figure 9.4. Mean P3 amplitude of the target-standard and nontarget-standard difference waveforms for control, theta and beta1 NF at pre- and post-training. Both target-standard **(A)** and nontarget-standard P3 amplitudes **(B)** were not significantly modulated by the type NF protocol. Error bars depict standard error of the mean.

9.3.2. Hypothesis 2: Decreased RT and RT-SD as a function of theta and beta1 NF

Table 9.2. summarizes the data and statistical results of RT and RT-SD at pre- and post-training for the three NF protocols. As can be observed in table, two one-way ANOVAs revealed that there were no initial differences between NF protocols in mean RT and RT-SD (all $p_s > 0.70$). The differential impact of the three NF protocols in mean RT and RT-SD were analyzed in separate two-way 2 TIME (Pre-training vs. Post-training) x 3 PROTOCOL (Control vs. Theta vs. Beta1) mixed-ANOVAs.

9.3.2.1. Mean reaction time

As shown in fig. 9.5A, the mean RT was decreased in theta NF and increased in control and beta1 NF from pre- to post-training. As shown in table 9.2., there was a marginally significant TIME x PROTOCOL interaction ($F(2,25)=2.90, p=0.07, \eta_p^2=0.19$). Bonferroni corrected post-hoc comparisons indicated that the mean RT was significantly increased in beta1 NF ($t(8)=2.41, p=0.02$), while the mean RT changes in control and theta NF were not reliable ($p_s > 0.32$). As also shown in the table, the main effects of TIME and PROTOCOL were not reliable ($p_s > 0.15$).

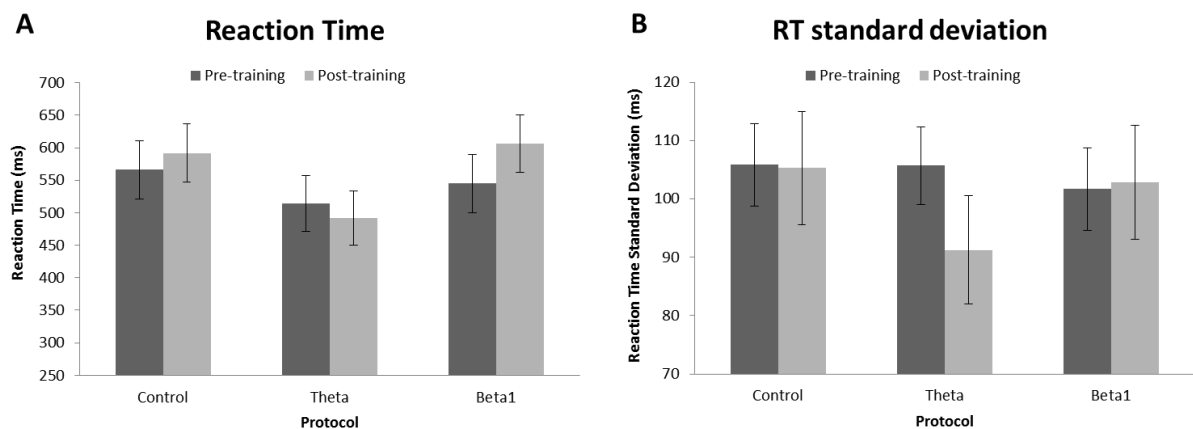


Figure 9.5. Two-way interaction of 2 Time x 3 Protocol for reaction time. The graphs show the effects at pre- and post-training of the three NF protocols on mean reaction time (RT) and reaction time standard deviation (RT-SD). **(A)** The significant Time x Protocol interaction revealed an increase in mean RT in beta1 NF. **(B)** RT-SD was significantly decreased in theta NF. However, the Time x Protocol interaction was non-significant. Error bars depict standard error of the mean

9.3.2.2. Reaction time standard deviation

Figure 9.5.B shows that the RT-SD was decreased from pre- to post-training in theta NF but not in the other NF protocols. However, as shown in table 9.2., the two-way mixed-ANOVA did not reveal significant main effects or interactions ($ps>0.31$). Despite the absence of a significant TIME x PROTOCOL interaction, the post-hoc comparisons revealed a marginally decreased RT-SD in theta NF ($t(9)=1.89, p=0.07$) but no significant changes in the other NF protocols ($ps>0.89$).

9.3.3. Hypothesis 3: Increased performance rates and perceptual sensitivity as a function of theta and beta1 NF

Table 9.2. summarizes the data and statistical results for target-standard d' , target-nontarget d' , target hit rate, standard false alarm and nontarget false alarm at pre- and post-training for the three NF protocols. As can be observed in the table, at pre-training separate one-way ANOVAs for each variable revealed significant differences between NF protocols in hit rate and d' between nontargets and standards and a marginal significant difference in d' between targets and standards. As shown in figures 9.6A, 9.6B and 9.7A, the d' between targets and standards (T-S), the d' between targets and nontargets (T-N) and the hit rate (H) were marginally or significantly lower in the control relative to theta NF (d' T-S: $t(17)=2.28, p=0.09$; d' T-N: $t(17)=3.21, p=0.01$; H: $t(17)=2.90, p=0.02$) but not significantly different between control and beta1 NF or between theta and beta1 NF (d' T-S: $ps>0.26$; d' T-N: $ps>0.15$; H: $ps>0.18$). No initial differences in standard and nontarget false alarm rates were observed between NF protocols ($ps>0.46$). The differential impact of the three NF protocols in these variables were analyzed in separate two-way 2 TIME x 3 PROTOCOL mixed-ANOVAs.

9.3.3.1. Target-standard d'

Figure 9.6A shows the effects of the three NF protocols on target-standard d' from pre-to post-training. As shown in table 9.2., the two-way TIME x PROTOCOL mixed-ANOVA did not yield any significant main effects or interactions (all $ps>0.11$). Post-hoc comparisons only indicated non-significant pre- to post-training target-standard d' differences in the three NF protocols (all $ps>0.14$).

9.3.3.2. Target-nontarget d'

As shown in figure 9.6B, from pre- to post-training the target-nontarget d' increased in control and beta1 NF and was slightly decreased in theta NF. The two-way ANOVA confirmed a marginal significant TIME x PROTOCOL interaction ($F(2,25)=3.22$, $p=0.06$, $\eta_p^2=0.20$). Post-hoc comparisons confirmed a significantly increased target-nontarget d' in control NF protocol ($t(8)=2.63$, $p=0.01$) and non-significant pre- to post-training differences in the other two NF protocols ($ps>0.24$). As shown in table 9.2., the main effects of TIME and PROTOCOL were also marginally significant.

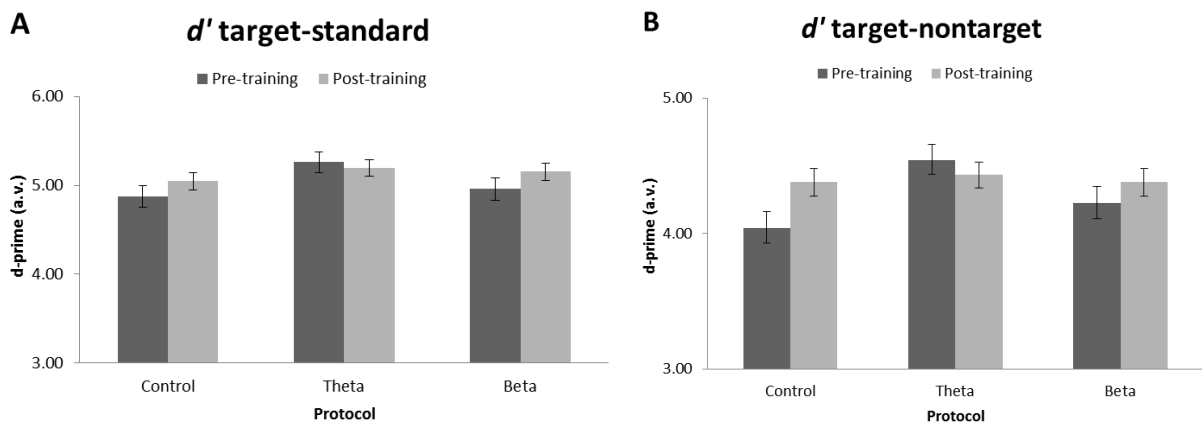


Figure 9.6. Two-way interactions of 2 Time x 3 Protocol for d' -prime (d'). The graphs show the d' target-standard (A) and d' target-nontarget (B) at pre- and post-training for the three NF protocols. At pre-training, in control NF the d' target-standard was marginally lower and the d' target-nontarget was significantly lower relative to theta NF. The d' target-nontarget was significantly increased from pre- to post-training in control NF, but was not significantly changed in the other NF protocols. Error bars depict standard error of the mean.

9.3.3.3. Target hit rate

As shown in figure 9.7A, the mean hit rate increased in control NF and decreased in theta and beta1 NF from pre- to post-training. As shown in table 9.2., the statistical analysis revealed a marginal significant TIME x PROTOCOL interaction ($F(2,25)=2.87$, $p=0.08$, $\eta_p^2=0.19$). Post-hoc comparisons confirmed a marginally increased hit rate in control NF protocol ($t(8)=1.88$, $p=0.06$) and non-significant pre- to post-training differences in the other

two NF protocols ($p_s > 0.21$). As shown in table 9.2., the main effects of TIME and PROTOCOL were not reliable ($p_s > 0.11$).

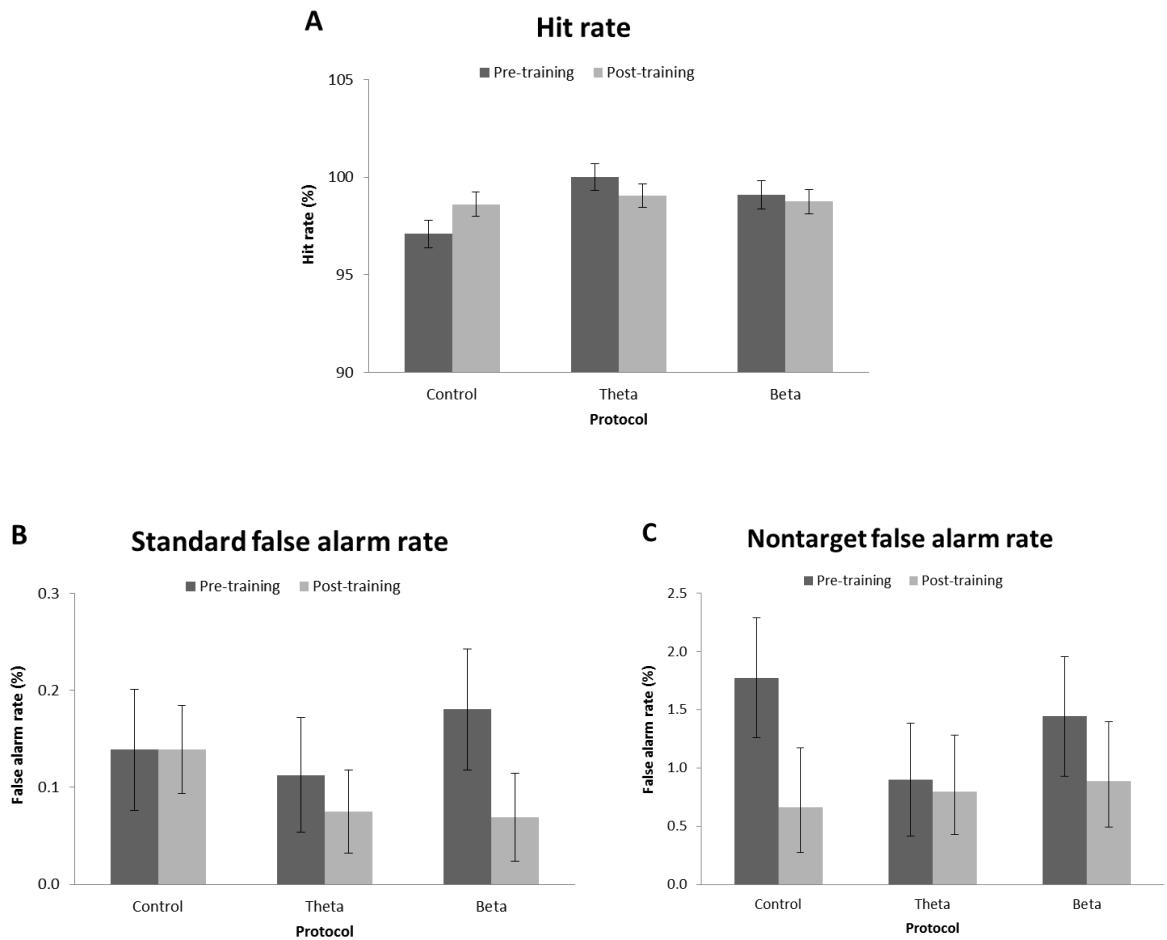


Figure 9.7. Two-way interaction of 2 Time x 3 Protocol for performance rates. The graphs show the percentage of hit rate for targets **(A)**, the percentage of false alarm rate for standards **(B)** and the percentage of false alarm rate for nontargets **(C)** at pre- and post-training for the three NF protocols. In control NF the hit rate was significantly decreased at pre-training and marginally increased from pre- to post-training **(A)**. The false alarm to standards decreased from pre- to post-training in beta1 NF **(B)** and the false alarm to nontargets decreased from pre- to post-training in control NF **(C)**. Error bars depict standard error of the mean.

9.3.3.4. False alarm rate for standards

As shown in figure 9.7B, the false alarm rate for standards was decreased from pre-to post-training in theta and beta1 NF. As shown in table 9.2., the two-way TIME x

PROTOCOL mixed-ANOVA revealed no reliable main effects or interactions (all $p_s > 0.10$). Despite the absence of a significant TIME x PROTOCOL interaction, post-hoc comparisons revealed a marginally decreased false alarm rate in beta1 NF ($t(8)=1.91, p=0.07$) and non-significant changes from pre- to post-training in the control and theta NF ($p_s > 0.50$).

9.3.3.5. False alarm rate for nontargets

As shown in figure 9.7C, the false alarm rate for nontargets was decreased from pre- to post-training in theta and beta1 NF. As shown in table 9.2., the two-way TIME x PROTOCOL mixed-ANOVA revealed no reliable main effects or interactions (all $p_s > 0.15$). Despite the absence of a significant TIME x PROTOCOL interaction, post-hoc comparisons revealed a marginally decreased false alarm rate in control NF ($t(8)=1.83, p=0.08$) and non-significant changes from pre- to post-training in the theta and beta1 NF ($p_s > 0.37$).

9.4. Discussion

The ERP analysis did not support the hypotheses that the three NF protocols would be associated with differential neural response to infrequent nontarget (P3a) and target (P3b) stimuli (Hypothesis 1.1 and 1.2). However, the behavioral analyses suggested that the type of NF had differential impact on measures of selective attention and response inhibition. Contrary to hypothesis, the mean RT was increased in beta1 NF rather than decreased (Hypothesis 2.1). Moreover, the increments in target-nontarget d' and hit rate were observed in control NF condition which are likely to represent a rectification of lower performance at pre-training rather than a real performance advantage of RF NF (Hypothesis 3.1 and 3.2). Moreover, the current experiment indicated a differential impact of the type of NF protocol on false alarm rate. Also contrary to hypothesis (Hypothesis 3.3), beta1 and control NF but not theta NF were associated with marginal decreases in false alarm rate for standards and nontargets respectively.

The next sections will examine several methodological differences relative to previous studies that might have been related to the failure to replicate differential electrophysiological and behavioral effects of theta and beta1 NF on selective attention and response inhibition in the context of a three-stimuli auditory oddball.

9.4.1. Electrophysiological and behavioral effects of beta1 NF

ERP components

The present experiment investigated the hypothesis that beta1 NF would be associated with a superior increment in the P3 amplitude to infrequent target (P3b) stimuli relative to the other NF protocols (Hypothesis 1.1). In agreement with the results of Experiment 2, the current ones failed to replicate previous findings that suggested an advantage of beta1 NF in the modulation of the P3b amplitude (Egner & Gruzelier, 2004). In Experiment 2, it was proposed that the failure to replicate this effect could have been related to the lower number of NF sessions relative to that previous study (six vs. ten). However, the increment in the number of NF sessions, numbering eight in the present experiment, might have not been enough to significantly impact the neural generators of the P3b. Alternatively, the failure to observe specific NF effects in the P3b amplitude might be related to the absence of significant increments in beta1 activity in the present study (for a further discussion see section 11.2.1.). Additionally, the present experiment failed to support the hypothesis that the P3b amplitude increment effect would be better explained by theta suppression rather than by the enhancement of beta1 activity.

Behavioral responses

Furthermore, it was hypothesized that the higher efficiency of task-relevant stimulus processing following beta1 NF would be reflected by increments in response speed (Hypothesis 2.1), d' (Hypothesis 3.1) and hit rate (Hypothesis 3.2) from pre- to post-training. Contrary to prediction, beta1 NF was associated with increased mean RT (Hypothesis 2.1) relative to the control and theta NF protocols. This deterioration of processing efficiency in beta1 NF is in disagreement with previous studies indicating a decrease in mean RT after beta1/theta NF (Bakhshayesh et al., 2011; Egner & Gruzelier, 2004) and with the absence of significant changes in RT following both SMR and beta1 NF in Experiment 2. However, a nearly significant interaction effect warrants caution in the interpretation of these findings and replication in a large sample. Future studies may attempt to clarify whether the increased RT may be explained by increased motor inhibition in agreement with the proposed role of

the beta oscillation in maintaining the current motor/cognitive set in a low Go response probability context (Engel & Fries, 2010) and in promoting the inhibition of the motor system (Ritter, Moosmann, & Villringer, 2009; Picazio et al., 2014). Also it would be interesting to investigate whether this increased RT effect would be specific to infrequent responding contexts, characterized by prolonged inactivity which may contribute to decrease the motor cortex excitability.

Although the specific mechanisms by which beta1 NF may impact response speed are still unclear it is worth noting that a delay in the P3b peak latency could be detected at post-training in the beta NF (see fig. 9.3.). The P3 latency has been taken a measure of stimulus evaluation and/or response selection time with some studies suggesting that it constitutes an independent processes (e.g., Kutas, McCarthy, & Donchin, 1977; Magliero, Bashore, Coles, & Donchin, 1984) and other showing a positive correlation with RT (e.g., Makeig et al., 2004). In order to clarify whether the increased mean RT may be explained by a delay in stimulus evaluation time or in response selection further post-hoc analyses are needed to investigate the effects of the three NF on P3b latency. An increase in the P3b latency would suggest that the participants in beta1 NF group required additional stimulus evaluation and/or response selection time. Alternatively, if beta1 NF affects mainly the post-decisional processes an increase in mean RT without changing the P3 latency would be expected. Future studies should also take into consideration that the P3b latency may be described in terms of one or more underlying components: a first component may reflect stimulus evaluation, while a second one may be related to response selection time (Verleger, 1997; Dien et al., 2004; Verleger et al., 2005, 2015).

Further, the hypothesis that theta suppression would explain the decreased mean RT in low-beta/theta NF was also not confirmed by the results. Thus, the NF conditions that may have been related to the decreases in mean RT in previous beta1/theta NF studies remain unclear. A possible explanation is that the decreased mean RT observed in previous studies may have resulted from the concertation of theta and high beta inhibition with beta1 enhancement emphasized in those NF protocols (e.g., Egner & Gruzelier, 2004). While the specific involvement of high beta inhibition in the cognitive enhancement effects remains unexplored, the present study suggests that, contrary to theta suppression, beta1 NF might be counterproductive in terms of increasing the processing speed of task-relevant information.

Also contrary to hypothesis, the present experiment failed to provide supportive evidence of increased target-standard d' and target-nontarget d' (Hypothesis 3.1) and hit rate (Hypothesis 3.2) in the beta1 relative to the other NF protocols. This is in agreement with previous studies that showed that beta1/theta NF was not associated with higher performance accuracy (Bakhshayesh et al., 2011; Egner & Gruzelier, 2004). The “ceiling effects” in performance accuracy observed in theta and beta1 NF may have prevented further increases in target detection and perceptual sensitivity.

Interestingly, the target-nontarget d' was significantly increased from pre- to post-training in control NF relative to other NF protocols and nearly significant increases in hit rate and decreases in false alarm for nontargets. These differences may also be explained by an initial lack of compliance with the instructions which might have determined the significantly lower pre-training scores in these measures observed in control NF. Alternatively, these improvements may be related to the more efficient detection of task-relevant stimulus and inhibition of distractors in control NF. Taking into consideration that RF NF was focused on the regulation of alpha and high beta, the increased performance accuracy in that condition would be consistent with the role of alpha (Dockree et al., 2007; Klimesch, 2012; Gruber et al., 2014) and beta (Wróbel, 2000; Bekisz and Wróbel, 2003; Lee et al., 2013; Sacchet et al., 2015) frequencies on attention processes. However, as shown in Experiment 4, there was no evidence of an advantage of control NF in the modulation of alpha and beta frequencies. Instead, the within-session delta and theta amplitude decrements may explain the general improvements in cognitive performance (Klimesch, 1999; Lakatos et al., 2008; De Blasio & Barry, 2013) observed in control NF condition.

Finally, in disagreement with a previous proposal that the beta1/theta NF would be associated with excessive arousal state determining a faster yet error prone behavior (Egner & Gruzelier, 2004), beta1 NF was not associated with an increase in the false alarm rate. On the contrary, despite the absence of a significant TIME x PROTOCOL interaction there was evidence that beta1 NF was associated with a decrease in false alarm rate from pre- to post-training (Hypothesis 3.3.). Future studies are needed to clarify the specific NF conditions that might have been related to improvements in response inhibition in the three-stimuli oddball task.

9.4.2. Electrophysiological and behavioral effects of theta NF

ERP components

The present experiment investigated the possibility that theta NF would be associated with a superior P3 amplitude increment to infrequent nontarget (P3a) stimuli relative to the other two NF protocols (Hypothesis 1.2). The failure to observe this effect was surprising in light of previous demonstrations of the involvement of evoked theta oscillatory activity in the generation of the P3 component (Demiralp, Ademoglu, Comerchero, & Polich, 2001; Yordanova et al., 2002, 2003). Thus, whether the suppression of theta activity may have been related to previous improvements in P3 amplitude (Egner & Gruzelier, 2004) remains unclear.

Behavioral responses

In agreement with the proposed association of low tonic theta amplitude with improved cognitive control, the present experiment suggested a decreased RT-SD after theta NF (Hypothesis 2.2). The present results suggest that theta NF may have promoted a reduction in the moment-to-moment fluctuations in behavioral performance. However, the absence of a significant TIME x PROTOCOL interaction warrants a cautious interpretation and replication of these findings.

In disagreement with the proposed relation between theta suppression and increased performance monitoring, there was no evidence of decreased false alarm rate in theta NF (Hypothesis 3.3.). The analyses revealed that neither the false alarm for standards nor the false alarm for nontargets were significantly decreased from pre- to post-training as a function of the type of NF. Again, the nearly flawless performance in theta NF at pre-training may have determined a “floor effect” that prevented further decrements in false alarm rates at post-training.

In sum, despite the involvement of theta and beta oscillations in goal-directed selective attention (Voytek et al., 2015; Womelsdorf & Everling, 2015) there is currently no evidence that the modulation of their amplitude by NF may impact fundamental neural processes associated with selective processing of task-relevant information. Future studies are needed to explore the hypothesis that an increment of the top-down control of stimulus selection may be related to the facilitation of the long-range coherent activity of theta and

beta frequencies (Womelsdorf & Everling, 2015) rather than with power modulations of these frequencies in local neural populations.

9.4.3. Summary

The current experiment provided inconclusive results regarding the differential impact of theta and beta1 NF on selective attention and response inhibition. The increased RT and decreased false alarm rate suggest that beta1 NF might be related to improvements in response inhibition. Additionally, the decreased RT-SD in theta NF suggests a diminished performance variability which may be explained by an increase in cognitive control. However, the absence of statistically significant TIME x PROTOCOL interactions recommends the replication of these results in a larger sample before any conclusions can be reached regarding the advantage of a specific NF for performance improvements.

Chapter 10

Experiment 6: The effects of theta and beta1 on response inhibition

10.1. Hypotheses

Hypothesis 1: Increased Go and Nogo-P3 amplitude as a function of theta and beta1 NF

It was hypothesized that:

- (3) Nogo-P3 amplitude would be increased in theta NF relative to beta1 and control NF and in beta1 NF relative to control NF ($\text{theta} > \text{beta1} > \text{control}$).
- (4) Go-P3 amplitude would be increased in beta1 NF relative to theta and control NF conditions and in theta NF relative to control NF condition ($\text{beta1} > \text{theta} > \text{control}$).

Hypothesis 2: Decreased RT and RT-SD as a function of theta and beta1 NF

It was hypothesized that:

- (5) RT would be decreased in beta1 NF relative to the theta and control NF and in theta NF relative to control NF ($\text{beta1} < \text{theta} < \text{control}$).
- (6) RT-SD would be decreased in theta NF relative to control and beta1 NF and in beta1 NF relative to control NF ($\text{theta} < \text{beta1} < \text{control}$).

Hypothesis 3: Increased performance rates and perceptual sensitivity as a function of theta and beta1 NF

It was hypothesized that:

- (7) d' would be increased in beta1NF relative to the theta and control NF and in theta NF relative to control NF ($\text{beta1} > \text{theta} > \text{control}$).
- (8) Hit rate would be increased in beta1 NF relative to theta and control NF and in theta NF relative to control NF ($\text{beta1} > \text{theta} > \text{control}$).

- (9) False alarm rate would be decreased in theta NF relative to control and beta1 NF and in control NF relative to beta1 NF (theta < control < beta1).

10.2. Methods

10.2.1. Participants

The same twenty-nine participants of Experiment 4 took part in the present study (see Methods Experiment 4 for details). One participant was excluded from the analysis for having less than twenty correct trials in at least one of the four stimulus conditions (Left-cue Go, Left-cue Nogo, Right-cue Go, Right-cue Nogo) at either pre- or post-training. The same participants were included in experiments 5 and 6 (demographic data is presented in Table 9.1).

10.2.2. Stimulus and procedure

The stimuli and procedure were identical to those of Experiment 3 (see section 5.2.2.).

10.2.3. EEG recording and analysis

EEG recording.

EEG recording specifications were identical to Experiment 2 (see section 4.2.3).

EEG data analysis.

EEG data analysis and pre-processing were identical to Experiment 3 (see section 5.2.3.).

Percent of correct ERP trials.

Preliminary analyses with one-way ANOVA at pre-training failed to reveal any significant influence of the type of cue (right vs. left) in the percent of correct trials for both Go and Nogo stimuli (Go: $F(1,27)=0.63$, $p=0.43$, $\eta_p^2=0.02$; Nogo: $F(1,27)=0.15$, $p=0.70$, $\eta_p^2<0.01$). Subsequent analysis were performed on collapsed left- and right-hand primed Go and Nogo trials. Descriptive statistics of percent of rejected trials in the Go/Nogo task are

presented in table 10.1. As shown in the table, separate one-way ANOVA at pre-training failed to reveal any significant differences between NF protocols for the percent of correct Go and Nogo trials ($ps > 0.96$). However, there was a significant increase in the percentage of correct Go trials from pre- (M=80.69%, SD=14.26%) to post-training (M=88.25%, SD=12.53%; $F(1,25)=7.94$, $p < 0.01$, $\eta_p^2 = 0.24$) and a marginal increase in the percentage of correct Nogo trials from pre- (M=81.38%, SD=13.06%) to post-training (M=86.43%, SD=12.53%; $F(1,25)=3.05$, $p = 0.09$, $\eta_p^2 = 0.11$). All other main and interaction effects were non-reliable (all $ps > 0.27$).

10.2.4. Behavioral data recording and analysis

Reaction time data preparation

Reaction time data preparation was identical to Experiment 3 (see section 5.2.4). The rejection rate of Go trials with response latencies below 100 ms or above 1200ms was 0.05%.

d-prime data preparation

d-prime data preparation was identical to Experiment 3 (see section 5.2.4).

10.2.5. Statistical analysis

Statistical analyses was identical to Experiment 3 (see section 5.2.5).

10.3. Results

10.3.1. Hypothesis 1: Increased Go and Nogo-P3 amplitude as a function of theta and beta1 NF

In the present experiment the hypotheses relative to the differential impact of the three NF protocols in the Nogo-P3 and Go-P3 amplitude (Hypotheses 1.1 and 1.2) were investigated for original waveforms at pre-training (section 10.3.1.1) and from pre- to post-training (section 10.3.1.2).

10.3.1.1. Pre-training differences between NF protocols

Figure 10.1 shows the grand average of the stimulus-locked ERP elicited by the frequent Go and infrequent Nogo stimuli in frontal, central and parietal regions at pre-training irrespective of NF protocol.

The pre-training differences between the NF protocols in the mean P3 amplitude of three scalp regions were investigated in a three-way 2 STIMULUS (Go vs. Nogo) x 3 REGION (Frontal vs. Central vs. Parietal) x 3 PROTOCOL (Control vs. Theta vs. Beta1) mixed-design ANOVA. This analysis yielded significant main effects of STIMULUS ($F(1,25)=47.76, p<0.01, \eta_p^2=0.65$) and REGION ($F(2,50)=36.73, p<0.01, \eta_p^2=0.59$) as well as a significant interaction of STIMULUS x REGION ($F(1.45,35.37)=38.29, p<0.01, \eta_p^2=0.61$). The main effect of PROTOCOL ($F(2,25)=0.66, p=0.53, \eta_p^2=0.05$) and the interactions involving the between-subject variable were non-significant (STIMULUS x PROTOCOL: $F(2,25)=1.38, p=0.27, \eta_p^2=0.10$; REGION x PROTOCOL: $F(4,50)=1.10, p=0.37, \eta_p^2=0.08$; STIMULUS x REGION x PROTOCOL: $F(2.83,35.37)=1.60, p=0.21, \eta_p^2=0.11$).

As shown in figure 10.2, for the Go stimulus the post-hoc comparisons (Bonferroni corrected p -values) revealed significantly higher P3 amplitude in the parietal region ($M=4.58, SD=2.76$) relative to central ($M=3.63, SD=3.52; t(27)=3.00, p=0.02$) and frontal regions ($M=1.06, SD=2.24; t(27)=8.31, p<0.001$) and in the central region relative to the frontal region ($t(27)=6.88, p<0.001$). However, the Nogo-P3 amplitude was higher in the central region ($M=7.09, SD=4.06$) relative to parietal ($M=5.77, SD=3.75; t(27)=5.22, p<0.001$) and frontal regions ($M=5.10, SD=3.01; t(27)=6.93, p<0.001$) but not in the parietal region relative to the frontal region ($t(27)=1.81, p=0.25$). Moreover, the post-hoc comparisons revealed that the P3 amplitude was significantly higher for Nogo stimulus relative to Go stimulus in the three regions (Frontal: $t(27)=9.25, p<0.001$; Central: $t(27)=7.46, p<0.001$; Parietal: $t(27)=2.43, p=0.02$).

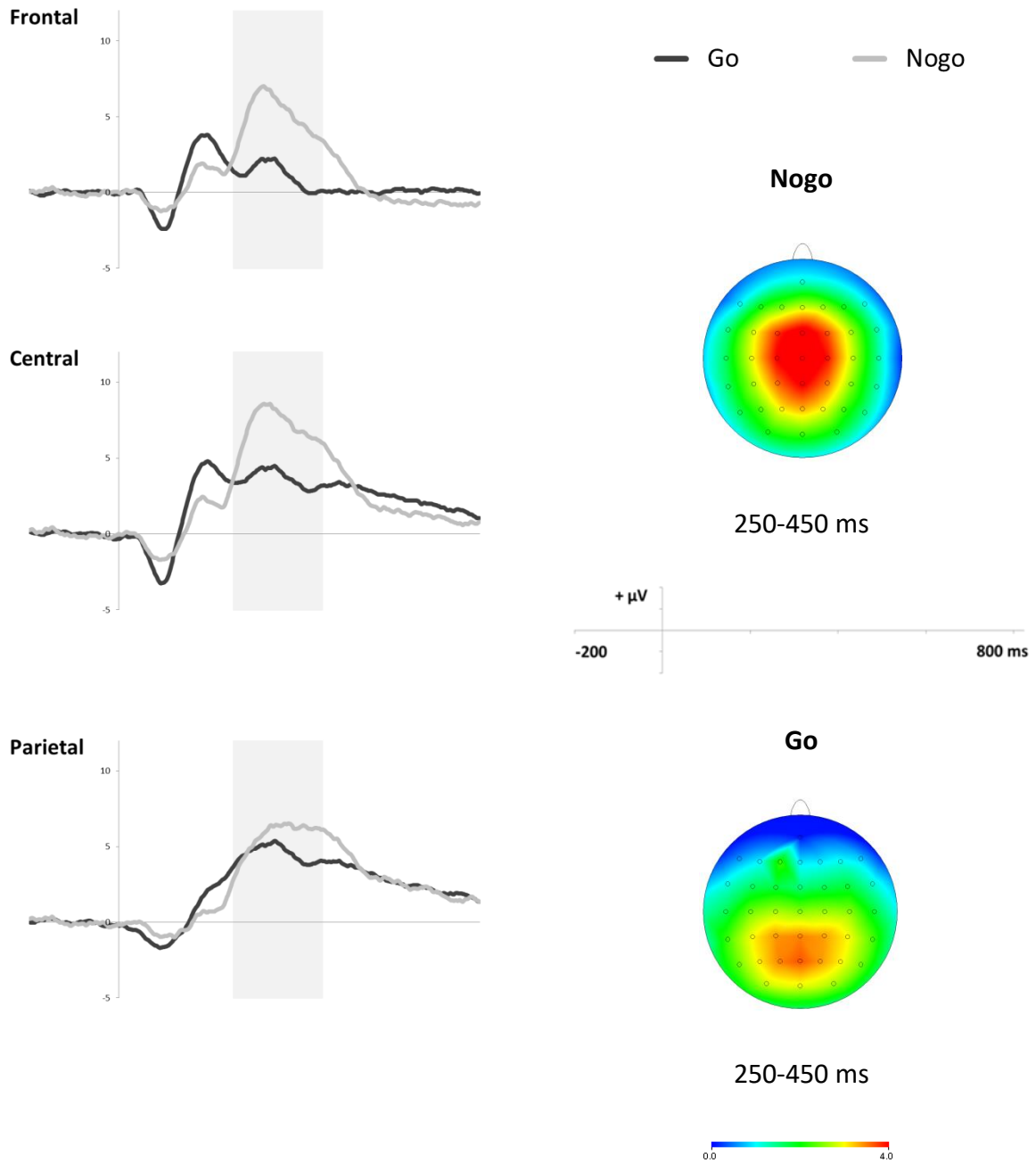


Figure 10.1. *Left.* Grand average of the stimulus-locked ERP original waveforms elicited by the Go and Nogo stimuli in midline frontal, central and parietal regions at pre-training irrespective of the NF protocol. *Right.* Distribution of the P3 amplitude for the Go and Nogo stimuli. Positive amplitude is displayed upwards.

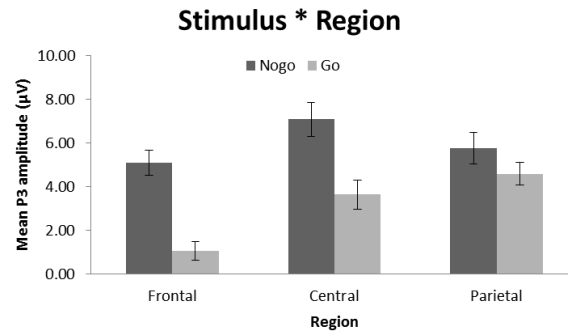


Figure 10.2. Two-way interactions of Stimulus and Region in mean P3 amplitude at pre-training. The graph shows that the mean P3 amplitude (μV) for Nogo stimulus was significantly higher in the Central when compared to Frontal and Parietal locations irrespective of NF protocol at pre-training. For the Go stimulus P3 amplitude was significantly higher in Parietal when compared to Frontal and Central Regions. Error bars depict standard error of the mean.

10.3.1.2. Pre- to post-training differences between NF protocols

Based on the previous analysis of the scalp distribution of the Nogo- and Go-P3 amplitude, the impact of the three NF protocols was analyzed in the regions where these ERP components were maximally observed. Figure 10.3. presents the original waveforms for Nogo stimulus in the central region and for Go stimulus in the parietal region before and after control, theta and beta1 NF.

The differences in mean parietal Go and central Nogo-P3 amplitude were investigated in separate two-way mixed-design ANOVAs with the factors 2 TIME (Pre- vs. Post-training) x 3 PROTOCOL (control vs. theta vs. beta1). Figure 10.4. shows the mean P3 amplitude in the three NF protocols at pre- and post-training.

As shown in table 10.1, the two-way ANOVA did not support the hypothesis of a differential impact of the NF on the mean Nogo-P3 amplitude (TIME x PROTOCOL: $F(2,25)=0.81$, $p=0.46$, $\eta_p^2=0.06$). The main effects of TIME and PROTOCOL were also non-

significant ($p_s > 0.44$). The post-hoc comparisons failed to provide evidence of pre- to post-training Nogo-P3 amplitude changes in any of the three NF protocols (all $p_s > 0.12$).

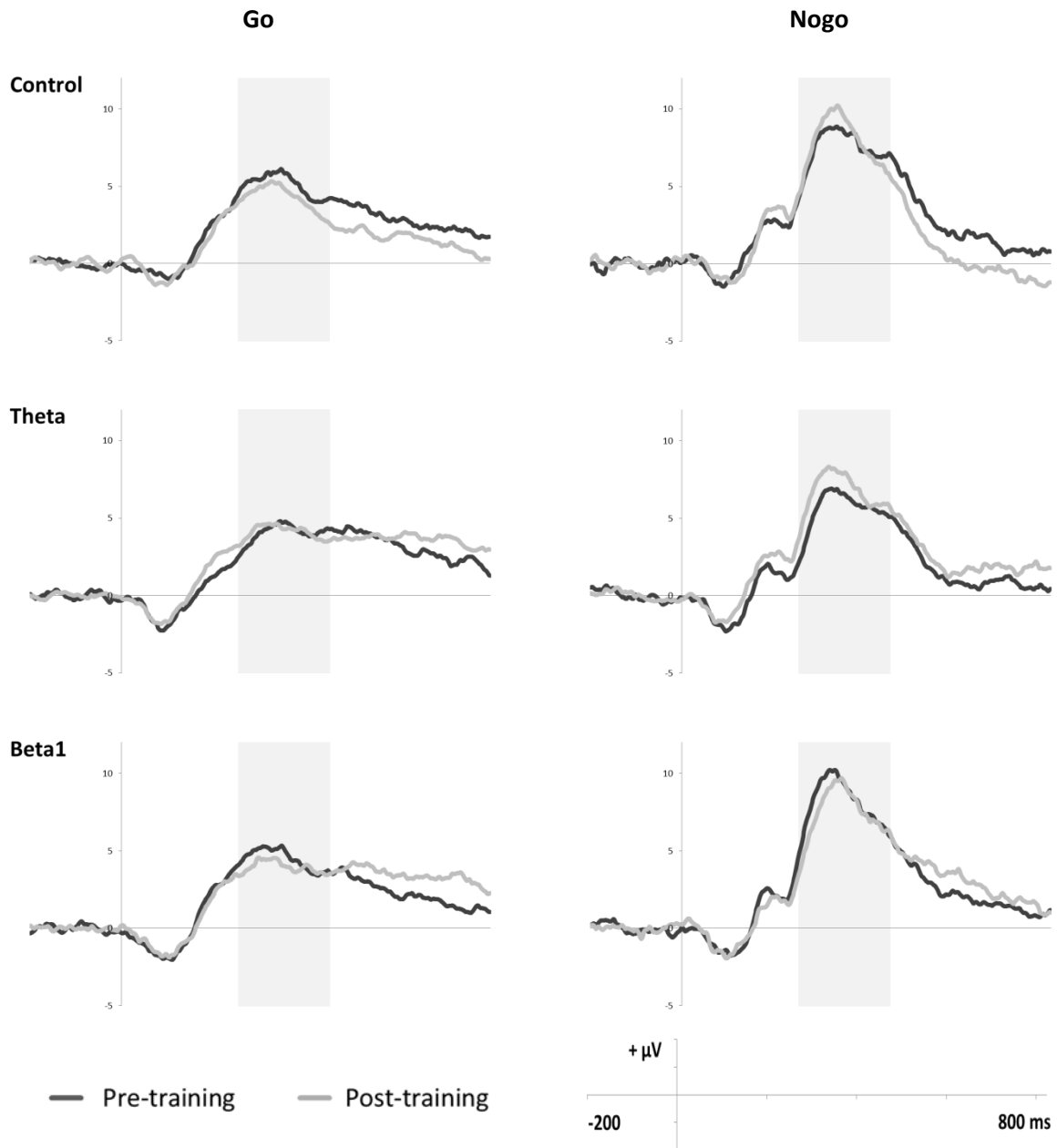


Figure 10.3. Grand-average of the parietal Go and central Nogo ERP waveforms for control, theta and beta1 NF at pre- and post-training. The shaded area represents the 250-450ms measurement window. Positive amplitude is displayed upwards.

Similarly, the two-way ANOVA performed for the Go stimulus indicated a non-significant effect of the type of NF on the mean P3 amplitude (TIME x PROTOCOL: $F(2,25)=0.43$, $p=0.66$, $\eta_p^2=0.03$). For the Go-P3 amplitude the main effects of TIME and PROTOCOL were also non-significant ($ps>0.66$). The post-hoc comparisons failed to provide evidence of pre- to post-training Go-P3 amplitude changes in any of the three NF protocols (all $ps>0.23$).

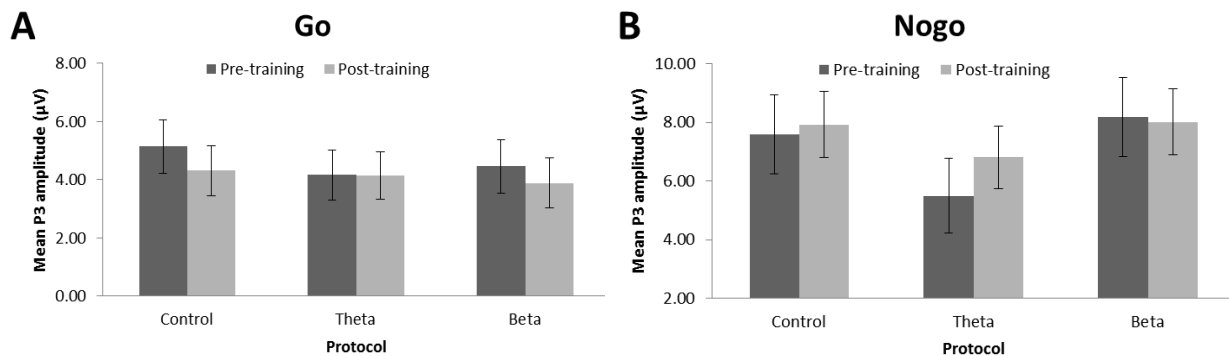


Figure 10.4. Mean parietal Go- and central Nogo-P3 amplitudes for control, theta and beta1 NF at pre- and post-training. **(A)** The parietal Go-P3 and the central Nogo-P3 amplitude **(B)** were not significantly different at pre- and post-training in any of the NF protocols. Error bars depict standard error of the mean.

10.3.2. Hypothesis 2: Decreased RT and RT-SD as a function of theta and beta1 NF

As can be observed in table 10.1., two one-way ANOVAs revealed that there were no initial differences between NF protocols in mean RT and RT-SD (all $ps>0.32$). The differential impact of the three NF protocols in mean RT and RT-SD were analyzed in two-way 2 TIME x 3 PROTOCOL mixed-ANOVAs.

Table 10.1.

Means (standard deviations) and statistical results of the pre-training one-way ANOVAs and the pre- to post-training two-way ANOVAs on Mean Nogo- and Go-P3 amplitude, Hit Rate (H), False Alarm Rate (FA), d-prime (d'), Reaction Time (RT) Mean and Reaction Time Standard Deviation (RT SD), percentage of Correct Trials (CT) to Go and Nogo stimuli included in ERP analyses after artifact rejection for each of the three NF protocols. Significant differences ($p < 0.05$) are highlighted in bold.

Source							One-way ANOVA			Two-way ANOVA								
	Pre-training			Post-training			Protocol			Time			Time x Protocol			Protocol		
	Control	Theta	Beta1	Control	Theta	Beta1	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2
<i>Mean P3</i>																		
Nogo	7.59 (2.84)	5.50 (4.50)	8.17 (4.52)	7.93 (1.95)	6.81 (3.98)	8.01 (3.77)	–	–	–	1.04	0.32	0.04	0.81	0.45	0.06	0.84	0.44	0.06
Go	5.14 (2.38)	4.15 (2.28)	4.46 (3.50)	4.31 (2.25)	4.15 (2.52)	3.88 (2.93)	–	–	–	1.51	0.23	0.06	0.43	0.66	0.03	0.16	0.85	0.01
H (%)	96.22 (3.42)	95.96 (6.19)	98.53 (1.39)	97.27 (3.41)	94.27 (15.46)	98.66 (1.49)	1.02	0.38	0.08	0.01	0.92	0.00	0.25	0.78	0.02	0.80	0.46	0.06
FA (%)	3.60 (3.60)	2.91 (2.53)	2.43 (2.62)	3.37 (2.75)	1.84 (2.14)	1.56 (1.78)	0.36	0.70	0.03	2.33	0.14	0.09	0.28	0.76	0.02	1.02	0.38	0.08
d'	3.99 (0.84)	4.09 (0.79)	4.42 (0.64)	4.10 (0.87)	4.45 (0.75)	4.69 (0.63)	0.80	0.46	0.06	4.30	0.05	0.15	0.36	0.70	0.03	1.24	0.31	0.09
<i>RT (ms)</i>																		
Mean	395.86 (64.32)	402.66 (108.30)	410.17 (132.26)	386.04 (104.41)	348.13 (91.70)	389.70 (100.80)	0.04	0.96	0.00	5.52	0.03	0.18	1.30	0.29	0.09	0.16	0.86	0.01
RT SD	140.83 (35.73)	126.66 (29.34)	116.97 (34.59)	127.76 (44.16)	113.09 (40.27)	121.29 (36.24)	1.18	0.32	0.09	2.19	0.15	0.08	1.35	0.28	0.10	0.56	0.58	0.04
<i>CT (%)</i>																		
Go	81.67 (11.25)	79.69 (17.98)	80.83 (13.92)	86.60 (14.12)	93.00 (6.63)	84.65 (13.22)	0.04	0.96	0.00	7.94	0.01	0.24	1.36	0.27	0.10	0.24	0.79	0.02
Nogo	82.22 (10.47)	80.63 (15.65)	81.39 (13.76)	85.00 (13.30)	90.88 (6.80)	82.92 (16.12)	0.03	0.97	0.00	3.05	0.09	0.11	0.99	0.38	0.07	0.27	0.77	0.02

10.3.2.1. Mean reaction time

As shown in fig. 10.5A, the mean RT decreased from pre- to post-training in the three NF protocols. As shown in table 10.1., the ANOVA revealed a significant main effect of TIME ($F(1,25)=5.52$, $p=0.03$, $\eta_p^2=0.18$) indicating that the RT was significantly lower at post-training ($M=373.68$; $SD=97.06$) relative to pre-training ($M=402.89$; $SD=101.75$) irrespective of the NF protocol. Furthermore, the TIME x PROTOCOL interaction was non-significant ($F(2,25)=1.30$, $p=0.29$, $\eta_p^2=0.09$) thus failing to provide evidence of a superior reduction of mean RT in the theta relative to control and beta1 NF. However, the post-hoc comparisons indicated a pre- to post-training decrease in mean RT in theta NF ($t(9)=2.71$, $p=0.01$) but not in other NF protocols (all $ps>0.34$). Finally, the main effect of PROTOCOL ($F(2,25)=0.16$, $p=0.86$, $\eta_p^2=0.01$) was not significant.

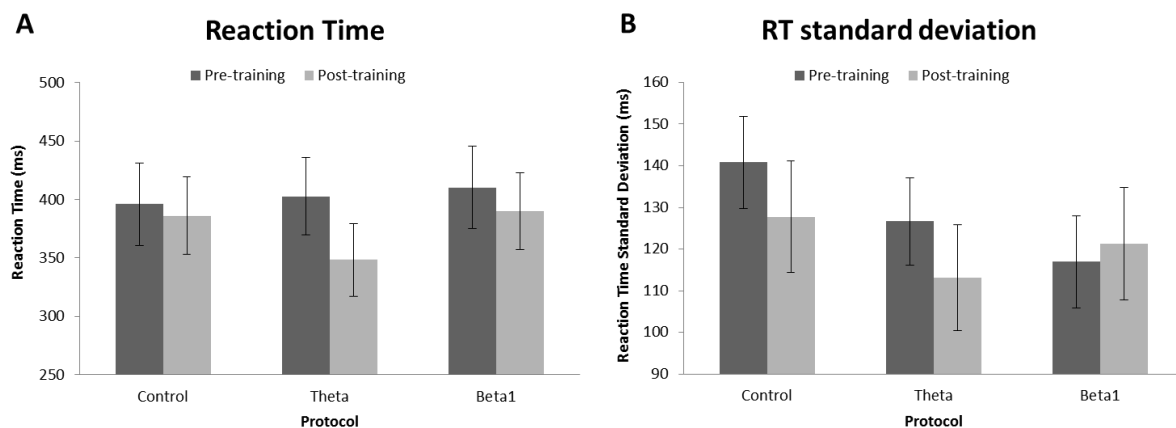


Figure 10.5. Two-way interaction of 2 Time x 3 Protocol for reaction time. The graphs show the variation in mean reaction time (RT) and reaction time standard deviation (RT-SD) from pre- to post-training in the three NF protocols. **(A)** The mean RT was significantly decreased from pre- to post-training irrespective of the NF. **(B)** The RT-SD decrease in the theta and control NF were non-significant. Error bars depict standard error of the mean.

Reaction time standard deviation

Figure 10.5B shows the differential impact of the three NF protocols on RT-SD. As shown in table 10.1., the two-way TIME x PROTOCOL mixed-ANOVA did not reveal significant main effects or interactions (all $ps>0.15$) suggesting that the RT-SD was not significantly different at pre- and post-training and was not influenced by the type of NF.

The post-hoc comparisons failed to provide evidence of pre- to post-training RT-SD changes in any of the three NF protocols (all $ps>0.12$).

10.3.3. Hypothesis 3: Increased performance rates and perceptual sensitivity as a function of theta and beta1 NF

Table 10.1. summarizes the data and statistical results for mean d' , hit rate and false alarm rate at pre- and post-training for the three NF protocols. As can be observed in table, there were no differences between NF protocols at pre-training for any of the dependent variables (all $ps>0.38$). The differential impact of the three NF protocols in mean d' , hit rate and false alarm rate were analyzed in two-way 2 TIME x 3 PROTOCOL mixed-ANOVAs.

10.3.3.1. d'

As can be observed in figure 10.6A, d' was increased from pre-to post-training in in the three NF protocol. As shown in table 10.1, the two-way ANOVA revealed a nearly significant effect of TIME ($F(1,25)=4.30$, $p=0.05$, $\eta_p^2=0.15$) indicating a higher d' at post-training ($M=4.41$, $SD=0.77$) relative to pre-training ($M=4.16$, $SD=0.76$). The same analysis did not reveal other significant main effects or interactions (all $ps>0.31$). The post-hoc comparisons failed to provide evidence of pre- to post-training d' changes in any of the three NF protocols (all $ps>0.10$).

10.3.3.2. Hit rate

The mean percentage of hit rate alarms showed a ceiling effect at pre- ($M=96.87\%$; $SD=4.27\%$) and post-training ($M=96.65\%$; $SD=9.34\%$). Figure 10.6B shows the percent hit rate changes from pre- to post-training in the three NF protocols. As shown in table 10.1, the TIME x PROTOCOL mixed ANOVA failed to reveal significant main effects or interactions (all $ps>0.46$). The post-hoc comparisons failed to provide evidence of pre- to post-training hit rate changes in any of the three NF protocols (all $ps>0.54$).

10.3.3.3. False alarm rate

The mean percentage of false alarms showed a floor effect at pre- ($M=2.43\%$; $SD=2.53\%$) and post-training ($M=3.77\%$; $SD=2.99\%$). As shown in figure 10.6C, the false

alarm rate was decreased in the three NF protocols. However, as shown in table 10.1, the statistical analysis with a two-way TIME x PROTOCOL mixed ANOVA did not reveal significant main or interaction effects (all $ps>0.14$). The post-hoc comparisons failed to provide evidence of pre- to post-training false alarm rate changes in any of the three NF protocols (all $ps>0.19$).

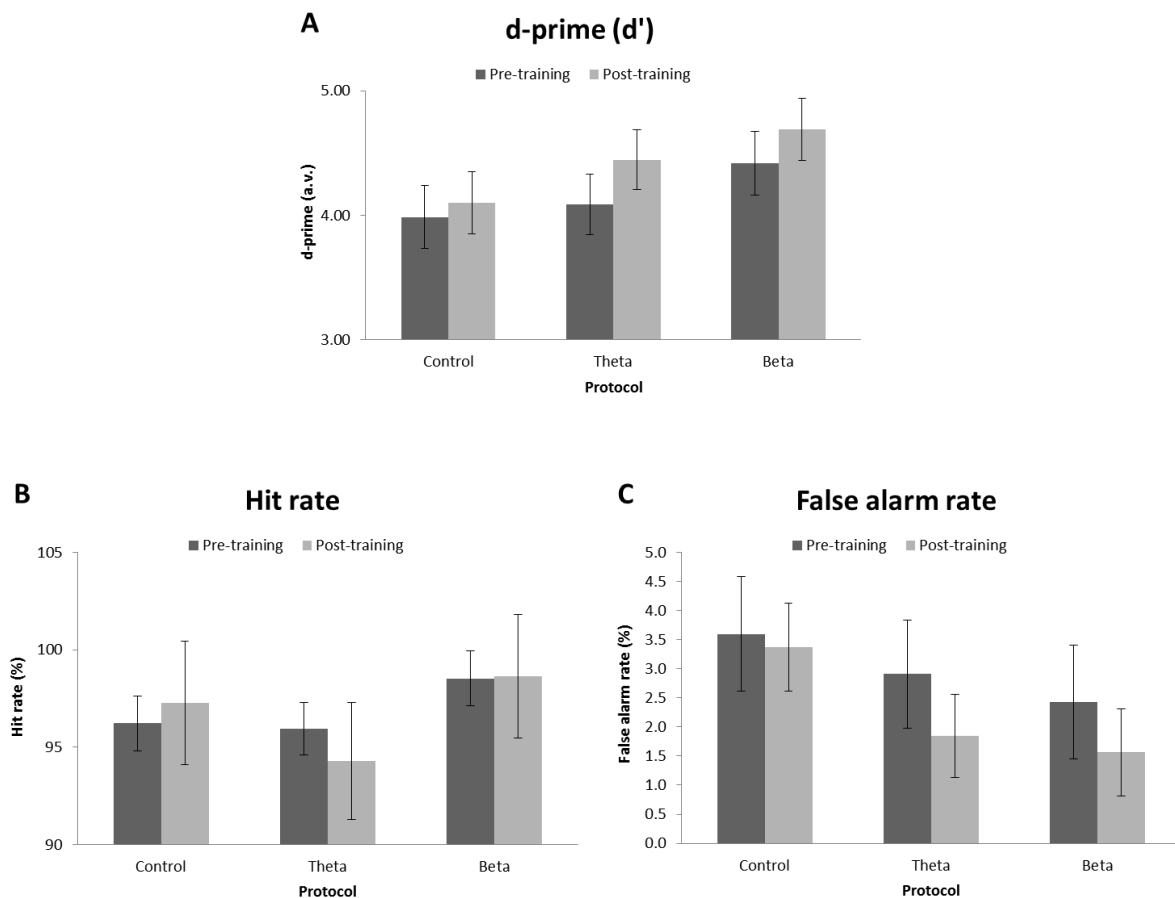


Figure 10.6. Two-way interaction of 2 Time x 3 Protocol for d' and performance rates. The graphs show the effects of the three NF protocols on d' (**A**), hit rate (**B**) and false alarm rate (**C**) at pre- and post-training. (**A**) d' was significantly increased from pre- to post-training irrespective of the type of NF. There were no significant changes in hit rate (**B**) or in false alarm rate (**C**) from pre- to post-training in the three NF protocols. Error bars depict standard error of the mean.

10.4. Discussion

The results of the current experiment failed to provide evidence of the hypothesized differential impact of theta NF and beta1 NF protocols in response inhibition and target stimulus processing in the cued Go/Nogo task.

10.4.1. Differential effects of theta and beta1 NF on response inhibition

The efficiency of response inhibition was measured by the Nogo-P3 amplitude and by the false alarm rate. The present experiment failed to provide supportive evidence that theta NF (or other NF protocols) would be associated with improved successful response inhibition as indexed by an increase in the Nogo-P3 amplitude (Hypothesis 1.1) and unsuccessful response inhibition as manifested by a decreased false alarm rate (Hypothesis 3.3).

In Study 1 (see section 6.2.2.) it was hypothesized that the failure of to replicate Nogo-P3 amplitude increases (Kropotov et al., 2005) and false alarm rate decreases (Egner & Gruzelier, 2001; Gruzelier, Foks, Steffert, Chen, & Ros, 2014) following SMR and beta1 NF could have been related to the absence of theta suppression instructions. Moreover, the involvement of the theta frequency in response inhibition (Barry, De Blasio, De Pascalis, & Karamacoska, 2014; De Blasio & Barry, 2013; Kirmizi-Alsan et al., 2006) would suggest that theta suppression rather than the enhancement of low-beta frequencies might have been implicated in those improvements. However, despite noticeable increments in Nogo-P3 amplitude and decrements in false alarm rate in theta NF, these were not statistically significant relative to the other NF conditions. Thus, the results of the present experiment suggest that theta suppression alone was not a sufficient condition to observe significant improvements in response inhibition.

Several aspects may have contributed to these results. Firstly, the previous evidence of increments in the Nogo-P3 amplitude following low-beta/theta NF (Kropotov et al., 2005) was obtained in ADHD children and not in healthy adults. Contrary to ADHD children that typically present lower Nogo-P3 amplitude (Liotti, Pliszka, Higgins, Perez, & Semrud-Clikeman, 2010), the absence of such initial deficits among high functioning subjects may have contributed to the failure to observe further cognitive improvements.

Another explanation for the failure to replicate previous reductions in commission errors in healthy adults might be related to differences in the type of NF protocol and in the task conditions. In previous studies, SMR enhancement with concomitant theta and high-beta suppression was associated with reductions in commission errors in the TOVA (Egner & Gruzelier, 2001; Gruzelier et al., 2014b). In Study 1 (see Experiment 3), differently from other NF protocols, SMR NF was not associated with increased false alarm rate despite increased response speed. Thus, it is possible that the SMR/theta NF protocol might be associated with superior response inhibition improvements relative to theta suppression and SMR enhancement NF in isolation. For instance, theta suppression might have a facilitative role in SMR learning that was found to correlate with improvements in response inhibition (Egner & Gruzelier, 2001).

Moreover, the lack of response inhibition improvements in the current experiment can be explained by a floor effect in the false alarm rate which is a likely consequence of low response inhibition demands of the task to high functioning adults. However, previous studies have found response inhibition improvements with even less demanding Go/Nogo tasks and equally few commission errors (Egner & Gruzelier, 2001) suggesting that the task conditions may not be a significant impediment to observe progress in situations of optimal performance context. Further, it is worth noting that the correlative nature of those findings and the lack of control for unspecific NF effects (see section 1.2.5.) warrants a cautious interpretation of those previous findings. Thus, future research is needed to investigate whether theta and beta1 NF may have a significant impact on response inhibition in optimal performance contexts by using more sensitivity measures.

Additionally, the results failed to show a contribution of theta NF to improve other behavioral indices of inhibition such as RT-SD (Hypothesis 2.2). Given that Experiment 3 failed to provide evidence of a specific effect of SMR NF RT-SD, it was reasoned that theta suppression may have been, at least in part, associated with RT-SD decrements in SMR/theta NF (Egner & Gruzelier, 2004). However, in the present experiment conditions there was no evidence that theta NF was associated with such effect. Chapter 11 will further discuss the implications of theta NF for RT-SD as a function of the task context.

Finally, the present experiment contributed to clarify the role of beta1 NF on response inhibition. Following Experiment 3, the current experiment confirms that beta1

NF was not associated with significant changes in Nogo-P3 amplitude. Importantly, contrary to hypothesis (Hypothesis 3.3) the current experiment did not replicate the trend towards increased false alarm rate observed in previous ones (Egner & Gruzelier, 2001; Experiment 3). Further work is necessary to clarify whether these differences might be related to active electrode location effects. Interestingly, , unlike present and past studies that used Cz- left earlobe, CPz-FCz or C3-C4 montages (Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Doppelmayr & Weber, 2011; Egner & Gruzelier, 2004) those previous increments were associated with left-hemispheric beta1 amplitude increments (C3-contralateral earlobe).

In sum, the current experiment did not allow for a full clarification of the specific effects of beta1 enhancement and theta suppression on response inhibition. Despite addressing potential methodological limitations of the previous study (by increasing the number of NF sessions and individualizing the frequency bands), the present experiment still failed to replicate those effects. The small sample size of the current experiment might have also limited the statistical power to detect differences between the NF protocols. Thus, more studies are needed to attempt to replicate these findings with a larger sample size.

10.4.2. Differential effects of theta and beta1 NF on Go stimulus processing

The results did not show the hypothesized involvement of beta1 NF with the facilitation of target detection and processing efficiency in the cued Go/Nogo task. In line with the previous study (Experiment 3), the analysis failed to provide supportive evidence that beta1 NF was associated with increased Go-P3 amplitude (Hypothesis 1.2.). These results are in disagreement with previous increments in Go-P3 amplitude effect on an equiprobable Go/Nogo task observed in ADHD (Kropotov et al., 2005). However, as noticed for the Nogo-P3 amplitude, the absence of initial neural and behavioral deficits in the present sample may explain the failure to observe further increments in Go-P3 amplitude.

Contrary to hypothesis beta1 NF was not associated with decreased mean RT (Hypothesis 2.1) relative to the other NF conditions. Thus, the present results failed to corroborate previous findings implicating the beta1/theta NF with decreased RT in ADHD children but also in healthy adults (Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser,

2011; Egner & Gruzelier, 2004). Importantly, the results suggest theta suppression NF rather than beta1 NF might be associated with a pre- to post-training decrease in mean RT. However, in the absence of a significant TIME x PROTOCOL interaction it cannot be claimed that theta NF had a superior effect to other NF protocols in improving the efficiency of Go stimulus processing.

The inconsistent findings relative to previous studies may be related to some important differences in the task conditions. While in the present experiment the Go stimulus probability was higher than that of the Nogo stimulus, in previous studies the Go stimuli had a low probability (Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011) or high and low Go stimulus probability conditions were analyzed together (Egner & Gruzelier, 2004). Chapter 11 will further discuss the differential impact of theta NF and beta1 NF on Go stimulus processing efficiency as a function of Go stimulus probability (see section 11.1.2.). Additionally, the difference relative to previous studies may be explained by the absence of concomitant theta and high-beta inhibition which might have affected beta1 learning and the coupling of lower and higher frequencies as will be discussed in section 11.1.1.

Finally, following Experiment 3 and other previous studies (Bakhshayesh et al., 2011; Egner & Gruzelier, 2001, 2004), the results failed to demonstrate an association of beta1 NF with increases in correct target detection or hit rate (Hypothesis 3.2). Taken together the present experiment confirmed that beta1 NF is unlikely to contribute to a more efficient processing of target detection and processing in the particular conditions of the cued-Go/Nogo task. As a corollary of the absence of significant changes in performance rates (hit and false alarm), the present experiment failed to provide evidence of increased perceptual sensitivity as a function of the type of NF protocol (Hypothesis 3.1).

10.4.3. Summary

The current experiment suggests that the theta suppression and beta1 enhancement alone were not associated with improvements in response inhibition and Go stimulus processing in healthy adults. Despite evidence of improvements in ADHD children (Bakhshayesh et al., 2011; Kropotov et al., 2005) and in non-controlled studies with healthy adults (Egner & Gruzelier, 2001) the NF conditions that might have been associated with

these effects remain unclear. The low response inhibition demands of the task and reduced number of sessions and statistical power might have prevented the observation of significant effects NF. Further work is needed to replicate these results with a larger sample and to take into consideration the response inhibition demands of the task for healthy adults.

Chapter 11

General discussion and conclusions of study 2

11.1. Overview of the main findings

Study 2 aimed at investigating the role of theta-inhibition NF and beta1 NF in selective attention and response inhibition improvements in three experiments. Contrary to hypothesis, Experiment 4 showed that during NF (i.e., in active periods) delta and theta activity were increased in beta1 NF relative to RF NF and delta activity was marginally increased in beta1 NF relative to theta NF. The results of Experiments 5 and 6 confirmed that the three types of NF had a differential effect on performance as a function of the different Go/target probability and response priming conditions of the tasks.

Beta1 NF was associated with task specific increased RT

The type of NF had a significant impact on mean RT in the three-stimuli oddball but not in the cued-Go/Nogo task. In the latter task, despite pre-to post-training decreases in mean RT it could not be claimed that theta NF had a superior improvement effect relative to other NF protocols. On the other hand, in the oddball task beta1 NF was associated with a significant increase in mean RT to an unpredictable target, but such effect was not observed when the target had a higher probability and was preceded by a warning cue. This differential increase in mean RT suggests that beta1 NF might have interfered with the processes of stimulus evaluation, response selection and/or movement execution upon detection of a deviant stimulus but not when the target stimulus was frequent.

In the oddball task, beta1 NF was also associated with an apparent delay of the P3b latency which possibly reflects increased stimulus evaluation time (Kutas et al., 1977) that might, in turn, explain the increased mean RT. Following the proposal that the latency of late ERP components may be explained by changes in phase and evoked oscillatory activity, a possible line of enquiry for future work would be to investigate whether this delayed P3 latency may be related to changes in phase resetting and enhanced post-stimulus

evoked delta and theta activity. This explanation would be consistent with the increased delta and theta amplitude in beta1 NF observed in Experiment 4. Interestingly, the visual inspection of the waveforms does not suggest a delay in the P3b latency in cued-Go/Nogo task (Experiment 6) in which the target stimulus was frequent. This difference may be explained by the role of theta dynamics in situations that imply a need for control such as the detection of a deviant task-relevant stimulus in the oddball task but not in the detection of a frequent target (Cavanagh & Frank, 2014). Moreover, in face of the previous literature it seems legitimate to conclude that the within-session increment in slow wave activity may reflect a decrease in the arousal state (Arns, Conners, & Kraemer, 2012; Barry, 2004; Howells, Stein, & Russell, 2010; Monastra et al., 2005), that might have contributed to the increased latency of the P3b and mean RT.

Control NF was associated with task specific increased hit rate and d'

Control NF condition was associated with increased hit rate and d' in the three-stimuli oddball (Experiment 5) but not in the cued-Go/Nogo task (Experiment 6). Moreover, control NF was associated with decreased within-session delta and theta (Experiment 4). Taken together these findings suggest that the decreased pre-stimulus theta activity might be associated with a reduction of performance fluctuations and increased vigilance to infrequent targets (Makeig and Jung, 1996). Contrary to the oddball task, the higher Go stimulus probability and the presence of warning cues in the cued-Go/Nogo task might have prevented initial performance declines. However, as noted in section 9.4., it is possible that these performance increments in the oddball task reflect only the correction of an initial failure to comply with the instructions rather than a real performance advantage.

Nevertheless, the hypothesis that these performance enhancements may be causally related to the decreased pre-stimulus theta activity merits further investigation. Future studies are needed to clarify whether differences in pre-stimulus theta power induced by NF may predict changes in hit and error rates in averaged trials time-frequency analysis (Makeig & Jung, 1996). Unfortunately, in the current experiment the low number of missed targets at pre- and post-training does not allow for a meaningful statistical comparison between different conditions.

Delta and theta up- and down-regulation may be associated with distinct effects on selective attention and response inhibition

In contrast with previous studies (Vernon et al., 2003; Ros et al., 2009; de Zambotti et al., 2012; Gruzelier et al., 2014a), it was demonstrated that the theta amplitude was significantly decreased (in control and theta NF) relative to other NF comparison conditions (beta1 NF). Moreover, the current study suggests that the up- and down-regulation of slow frequencies (delta and theta) might have distinct cognitive effects on selective attention and response inhibition. In the selective attention domain, the down-regulation of theta amplitude might have been related to improved performance accuracy in control NF, while the up-regulation of theta amplitude in beta1 NF might have been related to increased stimulus evaluation and/or response selection time.

However, the modulation of delta and theta activity did not influence the response inhibition processes in both Experiment 5 and 6. Interestingly, these results are in line with previous demonstrations that fm-theta up-regulation had a significant impact on executive functions that implicated proactive (e.g., memory updating) but not reactive cognitive control (e.g., response inhibition) (Wang & Hsieh, 2013; Enriquez-Geppert et al., 2014a). Further work is needed to determine whether the down- and up-regulation of delta and theta amplitudes might have distinct cognitive effects and whether they reflect specific or unspecific effects of NF. As discussed in section 8.4.1.1., theta modulation might reflect distinct cognitive effort requirements of the NF (Enriquez-Geppert et al., 2014b).

Alternatively, previous improvements in response inhibition might have been related to changes in EEG parameters other than decreased theta power. In fact, although theta power was often decreased following SMR/theta NF (Gruzelier, Hirst, Holmes, & Leach, 2014a; Ros et al., 2009; Vernon et al., 2003), no previous study demonstrated a causal relationship between those decrements and improved response inhibition. In fact, increased post-stimulus power and phase coherence in the theta (Cavanagh & Frank, 2014) and beta frequencies (Alegre et al., 2004; Picazio et al., 2014; Swann et al., 2009) could have contributed to the cognitive control and response inhibition improvements observed in previous studies.

Finally, the current experiment failed to provide supportive evidence of the involvement of theta suppression in promoting a decrease in RT-SD (Egner & Gruzelier,

2001, 2004; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Monastra, Monastra, & George, 2002). However, it is worth noting that RT-SD was marginally decreased in theta NF in the three-stimuli oddball but not in the cued-Go/Nogo task. Importantly, this improvement was obtained in a low target probability context that imposes a higher demand to performance monitoring abilities. However, the absence of a significant decrease in RT-SD relative to other NF conditions advises a cautious interpretation of these findings.

11.2. Limitations and future directions

The absence of training- and frequency-specific amplitude changes clearly limits the interpretation of the differential cognitive effects of the three NF protocols. The within-session delta and theta amplitude changes suggest that beta1 NF might differ from the control and theta NF in terms of motivation and cognitive effort. However, further work would be needed to investigate whether this interpretation is supported by differences in subjective ratings of effort and motivation. Moreover, it is unclear whether differences in motivation and cognitive effort might have interfered with the main task in the theta and beta1 NF (i.e., to enhance beta1 activity and decrease theta activity relative to controls).

On the other hand, the within-session amplitude increments in slow frequencies may reflect increased mental fatigue and lower arousal (Wascher et al., 2013) in beta1 NF. However, it is unclear whether these amplitude increments underpinned the failure to replicate previous improvements in selective attention following beta1/theta NF (Bakhshayesh et al., 2011; Egnér & Gruzelier, 2004). A task for future studies will be to clarify whether the beta1/theta NF might better control for within-session amplitude increments in the slow frequencies relative to beta1 NF and whether the two protocols may have distinct effects on cognitive performance.

Thus, the present findings were inconclusive regarding the independent role of theta suppression and beta enhancement on selective attention and response inhibition improvements in healthy adults. This might have been related to previously discussed “ceiling and floor effects” in theta and beta1 amplitude as well as in the cognitive performance measures. This limitation and possible ways to tackle it in future studies will be further discussed in section 12.3.1.

Chapter 12

Conclusions

12.1. General discussion of studies 1 and 2

The experimental work constituting this thesis can now be evaluated in relation to the two main purposes of the thesis: (1) to investigate the feasibility of successfully modulating the EEG amplitude of the theta and low-beta frequencies (section 12.1.1.) and (2) to clarify whether theta suppression and/or low-beta enhancement would be associated with improvements in selective attention and response inhibition (section 12.1.2.). After summarizing the main findings, several methodological limitations of the present experimental work will be discussed and directions for future studies will be proposed (section 12.1.3.).

12.1.1. Learned modulation of theta and beta frequencies

The feasibility of inducing training- and frequency-specific modulations of theta and low-beta activity was investigated with within- and across-session methods during active feedback and passive resting state periods. Two major conclusions could be derived from the current experimental work. Firstly, there was limited evidence of training-specificity. In fact, even when there was evidence of superior amplitude changes in one NF condition relative to another this was not true relative to a third one. As an example, training-specific beta1 amplitude increments were observed between beta1 and control NF but not between beta1 and SMR NF. Moreover, it was not possible to demonstrate that the amplitude changes were frequency-specific. This probably reflects the fact that (1) the amplitude changes in one oscillatory frequency may induced changes in other parameters of brain oscillatory activity in the same or in different frequencies and that (2) common or unspecific aspects to every type of NF may constrain the oscillatory activity in certain frequencies. Besides searching for comparable control conditions in terms of motivational and cognitive implications, it would be important to redefine the criteria for determination of NF learning based on newer assumptions of brain oscillatory activity. This would

include (1) the investigation of cross-frequency amplitude-amplitude and phase-amplitude coupling phenomena and (2) disentangling the effects of neurostimulation on the physiological parameters of interest (i.e., power or coherence) from those of self-regulatory processes by comparing NF with other forms of neurostimulation that do not require an active engagement of the participants (e.g., TACS).

A second aspect that emerges from the present research is that active feedback and passive resting state describe different phenomena involved in NF. Even in the same frequency, the amplitude changes across active feedback do not necessarily match those in the passive resting state periods. For instance, in Study 1 there was evidence of training-specific beta1 amplitude increments relative to controls in active feedback periods but not in passive resting state. Conversely, Study 2 revealed that between theta and beta1 NF there was only evidence of training-specific theta amplitude decrements in passive periods but not in active ones. Since previous studies also noticed conflicting evidence between feedback and resting state learning indices (Hoedlmoser et al., 2008; de Zambotti et al., 2012; Witte et al., 2013), a task for future research may be to systematically investigate for each frequency which learning index may be causally linked to the desired cognitive changes. For example, theta amplitude increments in active but not in passive periods may be causally related to increased post-stimulus theta power.

12.1.2 Central midline theta and sensorimotor beta effects on selective attention and response inhibition

A major goal of the thesis was to investigate the differential effects of NF on selective attention and response inhibition in two Go/Nogo tasks that imposed specific demands on these processes. In this respect, the two experimental studies made important advancements to our current understanding of the independent contribution of theta suppression and sensorimotor beta enhancement for cognitive enhancement.

Selective attention

SMR NF was associated with increased target stimulus processing efficiency evinced by increased Go-P3 amplitude, decreased mean RT and decreased RT-SD. However, except for the increased Go-P3 amplitude there was no evidence that SMR NF was associated with improved cognitive performance relative to other NF protocols, namely

RF NF. These results corroborate previous findings that SMR but not beta1 NF may be related to improved target stimulus processing efficiency (Doppelmayr & Weber, 2011) and provide first evidence of the proposed functional differentiation between left-hemispheric beta1 NF and right-hemispheric SMR NF (Othmer et al., 1999). However, the cognitive implications of SMR NF could not be attributed to SMR amplitude enhancement. As discussed in section 6.1., SMR NF might have contributed to influence oscillatory mechanisms other than SMR amplitude. The increased amplitude of the Go-P3 component suggests that SMR NF might have influenced the evoked activity in low frequencies that contribute to the P3 component and/or the mechanism of phase resetting and phase alignment of task-relevant oscillations. Moreover, the fact that control NF was also associated with nearly significant and significant changes in Go-P3 amplitude and RT suggests that the cognitive improvements in SMR NF were not different from a placebo intervention.

Taking together the results of both studies, there was no evidence that beta1 NF was associated in improvements in electrophysiological or behavioral indices of selective attention. Unlike other NF protocols, beta1 NF was not associated with significant increases in Go-P3 amplitude or decreases in mean RT and RT-SD in Study 1. These results suggest that beta1 NF had poorer selective attention outcome compared to placebo RF and ineffective SMR NF interventions. Moreover, in Study 2 beta1 NF was associated with increase mean RT and with an apparent increase in the P3b latency in the oddball task, suggesting that the increased response latency to infrequent targets might be related to increased stimulus evaluation time as well as with a slower movement execution. Further work is needed to investigate whether the increased P3b latency effect holds true and to determine whether it might explain the increased mean RT. However, the absence of frequency-specific beta1 amplitude increments in Study 1 and increased delta and theta activity relative to the other two NF protocols in Study 2 warrants caution in attributing these outcomes to increased beta1 activity. Although these results are in disagreement with the previous suggestion that beta1 NF might contribute to increased cortical arousal responsible as indicated by increases P3b amplitude and decreased mean RT (Egner & Gruzelier, 2004), it must be noticed that this previous study also failed to provide

supportive evidence of frequency-specific beta1 amplitude increments (Egner et al., 2004). Thus, the potential cognitive effects of increased beta activity remain unclear.

The results of Study 2 were inconclusive regarding the cognitive effects of central midline theta suppression. Firstly, the presence of significant delta amplitude decrements in control and theta NF relative to beta1 NF did not allow a full clarification of the specific effects of theta suppression. Then, it is unclear whether the theta amplitude decrements in passive periods obtained in theta NF can be explained by the NF intervention because no significant theta decrements were observed in active periods. Moreover, the increased perceptual sensitivity (in control NF) and decreased RT mean and SD (in theta NF) suggest that reductions in amplitude of low frequencies was associated with selective attention improvements. Conversely, when pre-stimulus theta amplitude increases as a function of NF training (e.g., as in beta1 NF) the detection of infrequent target stimulus may become slower.

Response inhibition

In line with previous studies (Gruzelier et al., 2014b; Egner & Gruzelier, 2004; Bakhshayesh et al., 2011), the results of the two present ones were inconclusive regarding the independent effects of theta suppression and SMR and beta1 enhancement on response inhibition. Study 1 investigated the proposed functional role of right-hemispheric SMR NF in improving response inhibition (Othmer et al., 1999; Egner & Gruzelier, 2004). In contrast with the other NF protocols, the false alarm rate did not increase after SMR NF suggesting that it might contribute to increased response preparation without affecting response inhibition. However, Study 2 did not replicate the increases in false alarm rate in other NF protocols and even provided evidence of marginal decreases in false alarm rates in the oddball task for both control and beta1 NF. Thus, the previous interpretation that SMR NF may prevent increments in false alarm rate may not hold true when compared to other NF protocols.

Study 2 investigated whether theta suppression may account for previous effects of SMR/theta and beta1/theta NF on response inhibition (e.g., Kropotov et al., 2005). As previously noted, both control and theta NF were associated with decreased delta and theta activity relative to beta1 NF. However, contrary to theta NF, control NF was related to

decreased false alarm rate to nontargets. Moreover, beta1 NF was also associated with decreased false alarm rate but to standard stimulus. Thus, the differential effects of NF modulation of theta amplitude on false alarm rate remain elusive. Study 2 also failed to replicate previous Nogo-P3 amplitude enhancement effects (Kropotov et al., 2005) in high functioning adults.

Following the proposal that enhanced beta1 activity could be associated with faster-yet-more-error-prone behavioral performance (Egner & Gruzelier, 2001, 2004), the two experiments also attempted to investigate the effects of beta1 NF on response inhibition. However, Study 1 and 2 provided conflicting evidence of the impact of beta1 NF on false alarm rate. Study 1 indicated that beta1 NF was associated with a marginal increase in false alarm rate in the cued-Go/Nogo task which was not replicated in Study 2. In the latter beta1 NF was even associated with decrease false alarm rate to standards. Several differences between studies might explain these different outcomes. Besides negligible differences resulting from the individualization of the frequency bands, in Study 1 the beta1 activity was enhanced in the left hemisphere as opposed to the central midline location in Study 2. Moreover, while the results of Study 1 could be related to training-specific beta1 amplitude increments, those of Study 2 could be better explained by increased delta and theta activity than by increased beta1 activity relative to other NF protocols. As previously noted, because beta1 amplitude was not selectively increased relative to other frequencies, it remains unclear whether the marginal increase in false alarm rate can be attributed to the beta1 activity. Finally, the difference in the number of beta1 NF sessions between studies might explain the different response inhibition effects. In the future, differences in performance related to the hemispheric specificity and with the number of sessions should also be object of systematic study.

In sum, the two studies were inconclusive regarding the specific effects of NF that might contribute to increased processing efficiency of target stimulus as evinced by increased Go-P3 amplitude, decreased mean RT and RT-SD, increased d' and increased hit rate. Although both SMR (in Study 1) and RF NF (in both Study 1 and 2) were associated with specific cognitive improvements these NF protocols could not be related to a specific pattern of EEG amplitude changes. The results were also inconclusive regarding the specific conditions associated with improved response inhibition. Increased error rates were

evinced following both beta1 and RF NF which had distinct effects on beta1 activity. This suggests that factors other than enhanced beta activity might have accounted for the increased false alarm rate proposed in previous studies (Egner & Gruzelier, 2001, 2004).

Importantly, the analysis here reported did not allow for the establishment of a causal relationship between the increased behavioral and electrophysiological responses and NF-induced changes in the oscillatory activity at pre- and/or post-stimulus. Further work is needed to investigate this temporal and causal relationship in interactive ERP paradigms in which the self-induced modulations of theta and beta amplitude may be used as an independent variable as suggested in section 1.1.1.

12.2. Theoretical and practical implications

The experimental work of this thesis attempted to contribute to the ongoing debate concerning the differential impact of SMR and beta1 NF frequencies enhancement (Doppelmayr & Weber, 2011; Egner & Gruzelier, 2001, 2004; Othmer et al., 1999) and theta suppression (Becerra et al., 2012; Gruzelier et al., 2014; Gruzelier, 2014c; Ros et al., 2009) on cognitive performance. However, the failure to provide evidence of frequency-specific SMR and beta1 enhancements and of theta suppression hindered the possibility of establishing a relationship between the different types of NF modulation and the specific cognitive effects.

Is there a causal relationship between NF and cognitive outcomes?

So far, the relationship between NF modulation and cognitive outcomes, when demonstrated, has been correlational in nature (e.g., Kober et al., 2015). This correlational evidence is insufficient to establish a cause-and-effect relationship between NF modulation and cognitive effects. For example, training-specific amplitude changes may be observed in frequencies other than those targeted by the NF interventions. In the experimental work presented here (Study 2), beta1 NF was associated with increased delta and theta amplitude relative to controls. Thus, a positive correlation between increased beta activity and improvements in cognitive performance would be spurious. A more direct way to establish a causal link would be to compare the effects of NF designed to modulate power and/or connectivity in certain frequency bands with those of other forms of neurostimulation (e.g.,

TACS). If TACS reverses or has similar effects to those of NF a causal link between a specific frequency modulation and behavior can start to be established. Moreover, in order for a cause-and-effect relationship to be established a temporal link between NF modulation and the resultant cognitive effect must be demonstrated. This would imply not only training participants to acquire voluntary control over certain parameters of brain activity (e.g., local power and coherence) but also to make stimulus presentation contingent on voluntarily controlled signals. Finally, for a causal link to be established the cognitive effects cannot be better explained by the stimulation in other candidate task-relevant frequencies.

Another important theoretical question concerns the mechanisms by which NF-induced changes in oscillatory activity, namely amplitude, might be causally linked to changes in the amplitude and latency of ERP components. It was proposed that the increased Go-P3 amplitude following SMR NF may reflect increased evoked power or phase-locking of task-relevant low frequency oscillations (Başar-Eroglu, Başar, Demiralp, & Schürmann, 1992; Demiralp et al., 2001; Doppelmayr, Klimesch, Pachinger, & Ripper, 1998; Polich, 1997; Yordanova, Kolev, & Başar, 1998; Yordanova et al., 2002; Yordanova, Rosso, & Kolev, 2003). A recent study suggests that local increases in central SMR amplitude may be related to decreased phase coherence of SMR activity between central and posterior sites (Kober et al., 2015). Thus, the possible influence of SMR NF on mechanisms of stimulus evoked amplitude and instantaneous phase alignment might explain its implications for ERP amplitude. Further analyses are needed to investigate whether changes in post-stimulus evoked power or in phase locking may have been related to increased Go-P3 amplitude in SMR NF.

It was also proposed that the increased RT latency following beta1 NF could be explained by an increase in stimulus evaluation as evinced by an increased latency of the P3b. Although NF-induced changes in ERP latency were not object of study in the current experimental work, an increased ERP latency may be explained by a decreased in oscillatory frequency of task relevant oscillations and/or by an increase in phase concentration around a later time point. Further work is needed to investigate whether the increased oscillatory activity in lower frequencies associated with beta1 NF might explain the increased P3b latency.

In sum, there is still limited evidence of how NF-induced amplitude changes may be causally related to functional changes in ERP amplitude and latency. In order to explore whether such relationship exists future research would do well to (1) explore changes in parameters of oscillatory activity other than pre-stimulus power such as inter-trial phase coherence and post-stimulus evoked power, (2) compare the frequency-specific NF effects with those of TACS and (3) to investigate the temporal relationship between NF-induced amplitude changes and stimulus evoked activity in trial-by-trial analysis.

Can the concertation of multiple frequencies explain the cognitive effects of NF?

Another theoretical challenge for future research is to explain the how NF may promote changes at the level of functional networks and influence higher order cognitive activity. Although NF protocols that combine the enhancement (e.g., low-beta) and suppression (e.g., theta and high-beta) of different frequencies may present increasing interpretational difficulties relative to simpler ones, they may better reflect the complexity of brain operations requiring the coordination of multiple networks. It is possible that a significant impact on cognitive activity may only be achieved by coordinating distributed neuronal processes involving the oscillatory activity in multiple frequency bands (Canolty & Knight, 2010; Varela, Lachaux, Rodriguez, & Martinerie, 2001). For instance, the cross-frequency phase-amplitude coupling of theta and beta frequencies was found to provide a mechanism for sequential encoding of items in working memory (Engel & Fries, 2010), behavioral inhibition (Knyazev, 2012) and cortico-subcortical communication (Schutter, Leitner, Kenemans, & van Honk, 2006). Thus, it is possible that in order to influence complex cognitive functions, such as response inhibition, NF protocols may need to promote the concertation of different brain oscillations. Future research should compare the learning and cognitive outcomes of simpler (e.g., SMR NF) and more complex (e.g., SMR/theta) NF protocols and investigate their impact at the level of local and distributed networks.

What are the potential practical applications of theta and low-beta NF?

Since the ultimate goal of NF research is to validate protocols for enhancing cognitive functions in clinical and typically developing populations, we now turn to the

potential practical applications of the experimental work of this thesis. A first potential application of SMR NF (and to some extent theta-suppression NF) is in clinical disorders that have been characterized by reduced P3 amplitude, increased RT and/or RT-SD such as cognitive decline associated with initial phases of dementia and normal aging (Phillips et al., 2013; Smart et al., 2014), development disorders such as ADHD (Barry et al., 2003b; Liotti et al., 2010; Senderecka et al., 2012) and traumatic brain injury (Stuss et al., 2003). However, the brain mechanisms behind these cognitive improvements must be clarified before clinical protocols can be developed and tested in clinical trials. Moreover, the potential benefits to clinical improvements must be rigorously assessed.

Another area of potential interest is in optimal performance and cognitive enhancement contexts, such as in sports, in which the evidence of efficacy of NF in response preparation and selection has remained limited to date (Park, Fairweather, and Donaldson, 2015; Ring, Cooke, Kavussanu, McIntyre, & Masters, 2015; Thompson, Steffert, Ros, Leach, & Gruzelier, 2008). In this area the P3b amplitude and latency as well as in RT and RT-SD have been proposed to differentiate the performance of experts from that of novices (Nakamoto & Mori, 2008, 2012). Thus, theta suppression and SMR NF interventions may offer the promise of being translated into significant cognitive performance improvements.

12.3. Methodological limitations and future directions

12.3.1. Factors affecting learning-specificity and cognitive performance effects

Although methodological limitations have already been separately discussed for each study in chapters 6 and 11, they will be reconsidered here focusing on the commonalities between the studies. These can be classified as limitations regarding (1) the method of individualizing the frequency bands, (2) the modifications introduced in the NF protocols, (3) the number of sessions, (4) the presence of ceiling and floor effects (5), and the reduced statistical power.

Method of frequency band individualization

It could be argued that the failure to show the expected training-specific theta amplitude decrements and beta1 amplitude increments in Study 2 may be related to the particular method of individualizing the frequency bands. Although it has been suggested that the alpha frequency may be adopted as a common reference for individually adjusting the frequency bands (Klimesch, 1999), especially for the determination of the transition frequency between theta and alpha (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998), other methods could have been used. In particular, when frequencies other than alpha are considered, the maximal synchronization peak during activation tasks may be an alternative feasible method to determine the individual frequency peak. This method has been successfully adopted in previous fm-theta enhancement NF studies which used a range of executive functions tasks to determine the individual fm-theta (Enriquez-Geppert et al., 2014a). Post-movement event-related synchronization following activation tasks (e.g., motor preparation or imagery) has also been adopted to determine the dominant sensorimotor beta frequency (Pfurtscheller et al., 1997; Pfurtscheller & Lopes da Silva, 1999; Neuper & Pfurtscheller, 2001). Thus, future studies would do well in following previous suggestions of functionally differentiating beta frequencies based on individually defined oscillatory patterns of beta reactivity (e.g., to motor inhibition) rather than using the classically defined frequency bands or beta band adjustments according to the IAF (Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes da Silva, 1999).

Modifications of the low-beta NF protocol

The attempt to clarify the independent contribution of theta suppression and of SMR and beta1 enhancement for the cognitive improvements determined the exclusion of theta suppression from the SMR and beta1 NF protocols. This modification might have been related to the failure in replicating previous electrophysiological and behavioral effects and to provide evidence of SMR (Study 1) and beta1 learning (Study 2). For instance, the increased slow wave activity might have been related to the decreased behavioral performance in beta1 NF in Study 2.

As previously mentioned, complex cognitive operations typically rely on the concertation between low and higher frequencies rather than on a single frequency.

Moreover, theta suppression might be of importance in maintaining the attentional focus and in signaling early drowsiness stages (Makeig & Jung, 1996) necessary for successful low-beta conditioning (Sterman & Shouse, 1980; Othmer et al., 1999). Thus, it is an empirical question for future studies to investigate whether SMR/theta and beta1/theta NF may be related to different cognitive outcomes and involve different changes in oscillatory activity when compared to SMR and beta1 NF.

Reduced number of NF sessions

The reduced number of NF sessions might explain the failure to provide supportive evidence of training- and frequency-specific effects as well as evidence of specific cognitive outcomes. Based on clinical non-randomized studies, it has been assumed that the magnitude of the amplitude change in the target frequencies and the differentiation between amplitude changes in the target and nontarget adjacent frequencies increases with the increasing number of sessions (Lubar & Shouse, 1976; Sterman & Friar, 1972).

However, it remains unclear whether a linear relationship between the number of NF sessions and an higher learning specificity and cognitive performance can be claimed. As an example, significant Go-P3 and training-specific beta1 amplitude increments were observed in Study 1 where the number of NF sessions was lower, but not in Study 2 where it was higher. These results suggest that the number of NF sessions required to yield significant learning and cognitive outcomes may vary from one EEG frequency to the other and probably depend on the complexity and amenability of the cognitive functions for plastic change. Future research would do well in designing controlled studies attempting to clarify the relation between training- and outcome-specificity and the number of NF sessions.

Ceiling and floor effects

Another important methodological limitation was the possible presence of ceiling and floor effects in the learning and cognitive outcome measures. Although in principle the electrophysiological measures (peak-to-peak amplitude and mean amplitude of the ERP components) may not be constrained by the same inherent measurement and physiological limits as the behavioral measures, in practice these measures may also be subject to ceiling effects (Picton et al., 2000). For instance, a ceiling effect was observed in the oddball task

with the progressive increment of the target-to-target interval, a known determinant of the P3 amplitude (Gonsalvez & Polich, 2002). In the current experimental work, the pre-training high levels of beta activity and low levels of theta activity in healthy young adults could have determined “ceiling and floor effects” that can explain the failure to demonstrate significant training-specific amplitude changes (e.g., in SMR NF or in theta NF) relative to controls.

The presence of “ceiling and floor effects” was most evident in the behavioral measures of the oddball and cued Go/Nogo tasks. For instance, the hit rate scores concentrated around maximal values (ceiling effect), while the false alarm rates concentrated around minimal values (floor effect). This has probably inflated the probability of Type II errors, that is, the possibility that differences between the NF protocols at post-training might have gone undetected because of the reduced variance in the independent variables. These effects might have resulted from the combination of a high functioning sample with the relatively low cognitive demands of the tasks.

In order to avoid these effects, future studies may consider increasing the task difficulty by manipulating the inter-stimulus interval, the difficulty of stimulus discrimination (in the three-stimuli oddball task) and the Go/Nogo stimulus probability (in the Go/Nogo task) in order to prevent these effects. Alternatively, other paradigms (SST and Go/Nogo task with RT deadline) may be more adequate to investigate response inhibition improvements in healthy adults. Future studies may also consider testing the differential effects of theta and beta1 NF in conditions of pre-training increases in theta power or decreases in beta power. Such conditions of increased theta/beta ratio are frequently encountered in ADHD (Arns et al., 2012; Barry, Clarke, & Johnstone, 2003; Clarke, Barry, McCarthy, & Selikowitz, 1998) and in drowsiness (Makeig & Jung, 1996; Takahashi, Shinomiya, Mori, & Tachibana, 1997).

Statistical significance and power

An important limitation in interpreting some of the present findings was that the post-hoc comparisons had an exploratory nature when not protected by significant TIME x PROTOCOL interactions (e.g., reduced RT-SD in theta NF). This represents an increased risk of incurring in type I error (rejecting the null hypothesis of no statistical differences

between NF protocols, when the null hypothesis is true). The failure to observe significant interaction effects might have been related to the reduced statistical power, which represents an increased risk of incurring in type II errors (accepting the null hypothesis, when there is in fact a true statistical difference).

The reduced power is a severe limitation shared by most NF and cognitive neuroscience studies (Button et al., 2013). Based on the reported effect size, the statistical power for each of the statistical tests could be calculated². In face of the small observed power, one cannot be certain that the rejection of the alternative hypotheses corresponds to the absence of real differences in performance after NF. Relying on the statistical conventions, in order to observe a desired power of 0.80 in the three-stimulus oddball task (minimizing the risk of accepting the false null-hypothesis to 20%), the calculations recommended sample sizes as high as 120 subjects. Thus, future studies investigating the effects of NF may consider significantly increasing the samples sizes.

12.3.2. Difficulty in determining the effects of NF on voluntary and involuntary aspects of selective attention

A major methodological limitation of the present study was the impossibility of determining whether the NF protocols would differentially affect the voluntary and involuntary mechanism of selective attention. The posterior distribution of the P3 amplitude to nontargets (P3a) was in agreement with the proposal that in an easy target-standard discrimination context this component may reflect the updating of the memory representation rather than the involuntary capture of attention (Hagen et al., 2006).

In a previous study, the P3 amplitude enhancement effect was observed in anterior and posterior sites in conditions of high target-standard discrimination difficulty (Egner & Gruzelier, 2004) suggesting that both P3a and P3b components might have been enhanced. Future studies would do well to replicate these findings in a difficult target-standard discrimination three-stimuli oddball paradigm in which the distinct topography of the frontal-P3a and parietal-P3b components may provide more specific indications of the nature of the selective attention mechanisms involved (e.g., Sawaki & Katayama, 2009).

² The calculation of the statistical power using G*Power software (Faul, Erdfelder, Lang, and Buchner, 2007) was based on η_p^2 for F-tests. The software also provides an estimation of the required sample size for the desired level of power (effect sizes were calculated as in SPSS).

Alternatively, future studies could introduce a novel stimulus which is recognized to elicit the same fronto-central effect.

12.3.3. Failure to independently manipulate Go response probability and response priming

The P3 amplitude has a similar functional significance in the context of the oddball and in that of the cued-Go/Nogo task (Pfefferbaum et al., 1985). Therefore, it is surprising that SMR NF was associated with P3 amplitude increments to a frequent Go target but not to an infrequent one.

The three stimuli oddball and the cued Go/Nogo were designed to maximize the possibility of detecting selective attention and response inhibition effects in accordance with the main goals of the thesis. However, the Go stimulus probability and the precedence by a warning cue were not orthogonally manipulated in the two tasks. While in the three-stimuli oddball task the low probability Go response was never preceded by a warning cue, in the cued Go/Nogo task the high probability Go response as always preceded by a facilitating response priming. This resulted in different levels of response preparation and top down control in the pre-stimulus period (Boulinguez, Ballanger, Granjon, & Benraiss, 2009) in the two tasks (lower in the three-stimuli oddball and higher in the cued Go/Nogo). that are difficult to attribute to the independent effects of stimulus probability or to response priming. In order to tackle this limitation future studies should consider orthogonally manipulate the Go response probability and the degree of previous response preparation as within-subject factors in the context of the same task.

Moreover, the cued-Go/Nogo task to be used in future studies should allow for the testing of specific predictions regarding improvements in speed-accuracy trade-off as suggested by increased response speed without affecting the false alarm rate following SMR (Experiment 3) and theta NF (Experiment 6). This could be achieved by comparing conditions in which the cue prompts response speed or accuracy in a counterbalanced design. A manipulation of response speed would also have the advantage of better elucidating the possible effects of NF on successful and unsuccessful response inhibition. In fact, despite increases in response speed in both tasks (see figures 4.4., 5.5. and 10.5.) this might have not been enough to substantially increase the difficulty of response

inhibition (Dimoska, Johnstone, & Barry, 2006). Future studies should also consider manipulating the difficulty of inhibition by imposing restrictions on RT deadline (Benikos, Johnstone, & Roodenrys, 2013). Finally, the comparison of cue and no cue conditions allows for the testing of specific hypothesis regarding differential effects of beta activity in cue processing (Kilavik, Zaepffel, Brovelli, MacKay, & Riehle, 2013) which might explain the increased false alarm rate in beta1 NF (Experiment 3).

12.3.4. Statistical comparison of different ERP components

Another factor that may present difficulties in the interpretation of the current findings results from the impossibility of comparing effects from different brain regions within the same experiment. For instance, while in the three-stimuli oddball task both P3a and P3b presented a maximal parietal amplitude allowing for the statistical analysis of effects associated with the stimulus condition (i.e., targets vs. nontargets) in the cued-Go/Nogo task this was not possible given the regional differences of the effects (central for the Nogo stimulus and parietal for the Go stimulus). It could be argued that the option to run different analysis for each type of stimulus could risk increasing the type II error. However, because parietal and central effects could not be included in the same analysis, this allowed the possibility of running the analysis in the two tasks with the same level of type II error protection, therefore increasing their comparability. An alternative procedure would have been to follow-up an omnibus analysis including the factors region and stimulus with planned comparisons in the regions and stimulus of interest.

12.4. Final conclusions

The experimental data constituting this thesis has provided supportive evidence of the differential effects of different types of NF on psychophysiological indices of target information processing efficiency such as the Go-P3 amplitude, the mean RT and the RT-SD. Although these findings replicate previous indications of differential effects of SMR and beta1 NF (Egner & Gruzelier, 2004; Doppelmayr & Weber, 2011), there was no evidence of superior cognitive performance following SMR NF when compared to a

control NF condition or of training-specific SMR amplitude increments. Moreover, these effects were only observed in the cued-Go/Nogo task.

Despite inconclusive evidence regarding training-specific theta amplitude decrements, the results were also suggestive of the contribution of theta suppression NF to increased processing efficiency of target stimulus information. However, the RT-SD in the oddball task and mean RT in the cued-Go/Nogo task were not significantly decreased relative to other NF conditions. Importantly, the failure to provide evidence of training-specific beta1 amplitude increments in one of the studies limited the possibility of drawing more definite conclusion regarding the role of beta1 NF in selective attention and response inhibition.

In sum, the current experimental work was not conclusive regarding the conditions that might have contributed to the improvements in target processing efficiency. Despite the fundamental importance of demonstrating the training- and frequency-specificity of the NF interventions, this may not be enough to establish a causality link between NF and changes in cognitive performance. In fact, the present research showed that changes in cognitive performance may occur independently from NF-induced amplitude modulations and that training-specific effects are not necessarily predictive of cognitive improvements. In this respect, it would be important to investigate which parameters of brain oscillatory activity elicited by NF may be causally related to the modulation of ERP amplitude and latency and with the changes in behavioral performance.

13. References

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Appendices

14.1. Appendix A: Screening questionnaire

Neurofeedback Frequency-Specific Effects on Late Event-Related Potentials

Screening Questionnaire

ID number: _____ Age: _____ Gender: _____ CODE: _____

Before taking part in this experiment it is important that we know some things about your medical history as this might influence EEG recording and make you ineligible to take part.

Please answer the questions below by ticking the boxes. After you've done it, please verify that you're eligible for the experiment.

Have any of the following ever happened to you?	Yes	No
Traumatic brain injury (with loss of consciousness)		
Acute intoxication (leading to coma or severe loss of consciousness)		
Drug or alcohol addiction		
Neurological disorder (brain tumor, epilepsy, stroke, multiple sclerosis, other)		
Psychiatric disorder (major depression, anxiety disorder, bipolar disorder, psychosis, other)		

Are you currently taking any medication with a psychoactive effect?	Yes	No
Antidepressants		
Stimulants		
Antipsychotics		
Mood stabilizers (including antiepileptics or anticonvulsants)		
Anxiolytics (benzodiazepines, other)		
Depressants (sedatives, hypnotics, other)		

Hand preference	Left	Right
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Thank you for having completed the questionnaire. If you ticked NO in every box you may participate in the experiment. Please, bring the filled questionnaire with you for the initial session or send it to m.pimenta@gold.ac.uk (Miguel Pimenta).

14.2. Appendix B: Neurofeedback instructions

Instructions

In the coming weeks you will take part in a neurofeedback training study. As you now know from the EEG session, your brain works partly on electrical activity which we can measure using these electrodes. The electrical activity in your brain happens in certain frequency ranges, for example, there is slower activity when you're asleep, and faster activity when you are trying to solve a math problem.

This image shows you the electrical activity that's going on in your brain right now. The higher the peaks the more activity you are creating at certain frequencies. As you can see there is continuous movement, there is natural variation over time of the EEG (and in brain waves). So, it is believed that we can gain some degree of control over this activity. In this study we are trying to find out if that is indeed the case and to what extent people can influence their brain activity. In a moment you will be shown a screen which responds to a specific frequency range. Over the weeks you will be training to influence your brain's activity within this frequency range by means of the feedback the screen provides to you. Try to keep the EEG activity within the range for as long as possible as well as to be aware of what makes it work.

We can only have a certain degree of control over our brain activity. The way you can gain control over your brain activity is by learning from the feedback you're being given. So you have to pay attention to what happens in the screen, but you shouldn't try too hard. There will not always be a correspondence between what you are intending to do and what your brain does. Also, you shouldn't play tricks, just pay passive attention to what happens and see if you can keep the game from stopping. We cannot tell you exactly how to do this because it is different for everybody, and do not be disappointed if you don't get it or if you can't stay above this threshold the whole time. There will always be some variation.

Try as much as possible to relax your jaw, neck and shoulder muscles as it might create electromuscular activity that will interfere with the EEG reading. Information on electromuscular activity will also be displayed.

Each training session will have 10 trials. Each trial is 2.50 in duration. During the first and last trials try to keep the EMG within range and don't bother with the EEG activity. Each time we will compare whatever you do during your training to the previous period.

14.3. Appendix C: Examples of feedback displays

Figures A, B and C are examples of visual representations used for NF. In the first study, the participants received NF in the target frequency through two types of visual displays (A and B). In the first half of the session, the moving video in right side of display A represented successful SMR or beta1 enhancement or the successful suppression of the target frequency in the control NF. The bar graph in the left side of the screen represented the EMG activity. In the second half of the session, the enlarged blue circle represented the enhancement of the target frequency, while the green square represented EMG. In the second study, the visual representation of successful enhancement or inhibition was provided both by the video and the leftmost bar graph as shown in display C. The rightmost bar graph represented EMG activity. As shown in the figure, the bar graph turned green when the the peak-to-peak amplitude was enhanced above the threshold (invisible) or suppressed below the threshold (horizontal line crossing the vertical axis) according to instructions. In both studies, the participants obtained points for fulfilling both target and EMG conditions.

A

B



c

