Cognitive Training Based on EEG-Neurofeedback to Improve Working Memory: A Research Study on Healthy Volunteers with an Outlook on Preclinical Alzheimer's Disease

Thesis

for the degree of

doctor rerum naturalium (Dr. rer. nat.)

approved by the Faculty of Natural Sciences of Otto von Guericke University Magdeburg

by M.Sc. Beatrice Barbazzeni

born on August 03, 1992 in Verona (Italy)

Examiner: Prof. Dr. med. Emrah Düzel

Prof. Dr. med. Surjo R. Soekadar

submitted on: November 24, 2022

defended on: November 16, 2023

ABSTRACT

Working memory (WM) has been associated with alpha suppression which can be enhanced by reward expectation. The role of WM is relevant when dealing with neurodegenerative disorders, such as Alzheimer's disease (AD) causing progressive impairment of WM and underlying oscillations. Thus, understanding these processes would empower AD interventions. This thesis investigated whether providing individuals real-time neurofeedback (NF) about their ongoing oscillations can improve WM under high or low reward expectancies. In two double-blind experiments, sixty participants were trained over 5-days to suppress alpha power while receiving real-time or a control NF during a monetary rewarded delayed match-to-sample task (DMST), generating together 300 distinct EEG recording sessions. It was investigated whether NF training and monetary reward can enhance alpha suppression, consequently WM and whether any NF-training effect could be transferred to unrelated cognitive tasks. According to inter-individual variabilities in NF learning, it was also tested the effect of different mental strategies during maintenance. Hence, participants of *Experiment I* were instructed to perform a mental calculation task unrelated to the DMST, whereas participants of *Experiment II* to mentally rehearse the encoded visual object. Lastly, the effect of training was also explored on neighboring theta and beta frequency bands, related to memory processes. Results from *Experiment I* did show improved WM accuracy and reaction times (RTs) with a significant reward-anticipation effect. While no significant NF-training or reward-anticipation effects were found on enhancing alpha suppression, a reward-anticipation and NF effect was observed on theta suppression. Besides, a beta power decrease was unrelated to these factors. Results of *Experiment II* replicated improved WM performance with reward-anticipation effect, although neither NF-training nor reward-anticipation effects were found on oscillations and WM. Moreover, neither experiments demonstrated transfer effects of either WM or NF-training. Across both experiments, while during encoding enhanced WM accuracy over 5-days was found related to increased right parietal beta, faster RTs were found related to increased right parietal theta. During maintenance, increased right parietal beta was found to improve RTs, whereas increased left parietal beta was found to slow the performance. Despite a lack of NF-training benefits on WM, this exploratory analysis demonstrated how training-related improvements of WM are associated with oscillatory changes across training days. Based on these studies a proposal for an NF-training protocol was designed to explore declined cognitive-related oscillations in preclinical AD, providing the basis for a standard protocol to be further tested and developed.

TABLE OF CONTENTS

ABSTRACT i

CHAPTER 1: 1

INTRODUCTION ON COGNITIVE DECLINE IN AGING AND ALZHEIMER'S DISEASE 1

1.1 Chapter overview 1

1.2 Aging and Alzheimer's Disease (AD) 1

1.3 Cognitive decline in aging and AD 4

1.4 Overview on biomarkers in AD 9

1.5 Closing remarks 12

CHAPTER 2: 15

INTRODUCTION ON COGNITIVE TRAINING AND NEUROFEEDBACK BASED ON EEG 15

2.1 Chapter overview 15

2.2 Cognitive training to enhance cognitive performance 15

2.2.1 Cognitive training in healthy young adults 16

2.2.2 Cognitive training in healthy old and AD patients 19

2.3 Neurofeedback training based on electroencephalography (EEG) 21

2.3.1 An overview of electroencephalography (EEG) 21

2.3.2 An overview on EEG and neural oscillations 24

2.3.3 An overview on neurofeedback training based on EEG 32

2.3.4 NF training in healthy young adults 34

2.3.5 NF training in healthy old and AD 39

Healthy old individuals 39

Alzheimer's disease patients 43

2.4 The aim of my research work 49

2.5 The proposed research method based on neurofeedback 50

2.5.1 EEG recording and neurofeedback 50

2.5.2 EEG pre-processing and spectral analysis 53

2.6 Closing remarks 54

CHAPTER 3: 57

COGNITIVE TRAINING BASED ON EEG-NEUROFEEDBACK TO IMPROVE WORKING MEMORY IN HEALTHY VOLUNTEERS 57

3.1 Chapter overview 57

3.2 Introduction and scientific objective 57

3.3 Method 60

3.3.1 Participants 60

Experiment I 60

Experiment II 60

3.3.2. Experimental design 61

3.3.3 EEG recording and neurofeedback 62

3.3.4 EEG pre-processing and spectral analysis 62

3.3.5 Monetary rewarded Delayed Match-to-Sample task (DMST) 63

3.3.6 Transfer effect tasks 65

3.3.7 Questionnaire post-NF-training 66

3.3.8 Statistical analysis - separate for experiment I and experiment II 66
DMST 67
Transfer effect tasks 67
Questionnaire 67
Time-frequency analysis 67
3.3.9 Statistical analysis - Combined analysis across experiment I and II 68
3.4 Results: experiment I 71
3.4.1 DMST 71
3.4.2 Alpha power (7-13 Hz) 72
3.4.3 Theta power (4-7 Hz) 75
3.4.4 Low-beta power (13-20 Hz) 76
3.4.5 Transfer effect tasks 77
MST 77
Stroop tasks 77
3.4.6 Questionnaire 78
3.5 Results: experiment II 78
3.5.1 DMST 78
3.5.2 Alpha power (7-13 Hz) 80
3.5.3 Theta power (4-7 Hz) 81
3.5.4 Low-beta power (13-20 Hz) 82
3.5.5 Transfer effect tasks 85
MST 85
Stroop tasks 85
3.5.6 Questionnaire 86
3.6 Results: combined analysis across experiment I and II 86
3.6.1 Accuracy 86
3.6.2 RTs 92
3.7 Discussion 100
3.8 Conclusion 107
3.9 Closing remarks 109
CHAPTER 4: 113
NEUROFEEDBACK BASED ON EEG TO MODULATE ALPHA OSCILLATIONS IN PRECLINICAL ALZHEIMER'S DISEASE: A RESEARCH PROTOCOL 113
4.1 Chapter overview 113
4.2 Introduction and scientific objective 113
4.3 Method 114
4.3.1 Method validation: a comparison with previous studies 114
4.3.2. Participants 115
4.3.3 Experimental design 116
4.3.4 EEG recording and neurofeedback 116
4.3.5 EEG pre-processing and spectral analysis 117
4.3.6 Neurofeedback training task 118
4.3.7 Questionnaire post NF training 119
4.3.8 Statistical analysis 120

4.4 Closing remarks 120
CHAPTER 5: 123
GENERAL CONCLUSIONS 123
5.1 Summary 123
5.2 General discussion and future perspectives 125
5.2.1 The effect of neurofeedback training and working memory 125
5.2.2 Theta and beta oscillations underlying working memory processes and memory formation 128
5.2.3 The importance of standardized protocols to enhance the effectiveness of NF in the context of preclinical Alzheimer's Disease 131
5.3 Final remarks 134
REFERENCES 137
LIST OF FIGURES I
LIST OF TABLES II
LIST OF ABBREVIATIONS III
APPENDICES VI
WORDING OF THE DECLARATION OF HONOUR XIX

CHAPTER 1:

INTRODUCTION ON COGNITIVE DECLINE IN AGING AND ALZHEIMER'S DISEASE

1.1 CHAPTER OVERVIEW

In *Chapter 1* an overview of the aging process will be described in which a distinction from healthy aging to what characterized a pathologic process is briefly explored. Particularly, the interest of this chapter and more broadly of this doctoral thesis will be on focusing and describing the development of Alzheimer's disease (AD). Moreover, the understanding of the characteristics of cognitive decline characteristic of healthy aging will be compared with the progressive deterioration typically observed in AD across its clinical stages. To recognize any sign of early disease onset, the identification of specific biomarkers predicting AD development will also be shortly discussed. This chapter aims to provide a general understanding of the aging process and how this biological life event might dramatically deviate in the context of neurodegenerative diseases, such as AD. In particular, the focus would be on the investigation and the understanding of decreased cognitive functioning in healthy aging and how this episode clearly dissociates from the decline typically observed in AD. Finally, the detection of specific biomarkers, predicting early disease onset, is also of primary importance; beneficial for healthcare providers and caregivers giving the opportunity for potential interventions while improving patients' life.

1.2 AGING AND ALZHEIMER'S DISEASE (AD)

Aging is a process characterized by the progressive accumulation of molecular and cellular damage leading to structural and functional decline, in which the decrease of cognitive and physical capacity represents a relevant risk factor for disease development and lately death (WHO, 2018). Nevertheless, this process is neither linear nor consistent and broadly associated with an individual's age. In this frame, identifying healthy aging from pathological aging acquires significance in determining a person's life quality. Several factors have been identified influencing healthy aging throughout the entire life span such as physical and social environment (e.g., community, neighborhoods, home, and physical exercise), likewise genetic, personal, or social characteristics (e.g., sex, ethnicity, and socioeconomic status; WHO, 2018). Moreover, while considering the increased rate of the older population, aging represents one

of the highest risk factors for the development of several diseases, such as AD. AD is a debilitating neurodegenerative condition representing around 60-80% of dementia cases, and its rate is estimated to increase over the years (Alzheimer's Association, 2017). Particularly characterized by a progressive and deceptive memory decline, other cognitive functions are also impaired such as speech, visuoconstructional abilities, executive functions, and motor functions (Sacuiu, 2016); becoming a considerable issue for healthcare providers and caregivers. Cognitive and functional declines are projected to increase throughout the pathology (Logiudice and Watson, 2014) in which the progression of AD can be categorized into three main stages – mild, moderate, and severe – followed by death. Additionally, during the development of the disease, AD patients would manifest behavioral and psychological symptoms causing emotional suffering and discomfort. Although the specific pathological process and etiology (Piaceri et al., 2013), damaging the brain, is still hypothesized and not well defined (Sacuiu, 2016), several studies proposed that multiple subcortical nuclei would lead to the neurodegenerative process at the earliest stages of AD (Stratmann et al., 2016) and that genetic and environmental influences may also be recognized as the highest risk factors and determining causes (Grossberg & Desai, 2003; Livingston et al., 2017). To better define AD, Bateman et al. (2011) divided AD into two types: familial and sporadic. With the former, AD would develop based on a genetic characteristic and at an earlier onset, even though less than 1% of patients would be attributed to a familiar type. Differently, the latter would be characterized by "susceptibility genes" such as the APOE e4 (Corder et al., 1993) leading to disease development although not based on a recognizable genetic foundation (Piaceri et al., 2013).

A relevant topic under investigation is the possibility to detect early signs that can predict how the development of AD diverges from healthy aging (Ritchie et al., 2015; Mortamais et al., 2017), in which midlife represents a crucial point in this transformation (Ritchie et al., 2017); hence, the early detection would be beneficial while improving treatments and preventive measures. Moreover, several studies (Ewers et al., 2011; Serrano-Pozo et al., 2011) show that early signs of AD, such as progressive accumulation of amyloid-plaques, neurofibrillary tangles (NFT), and dysfunctional brain oscillations, can be detected several years or even decades before any noticeable cognitive decline; assuming a high correlation between the neurodegenerative process and cognitive dysfunctions. Indeed, before AD development, patients would show an intermediate stage called mild cognitive impairment (MCI), affecting different cognitive domains, particularly memory and attention. MCI, initially termed by the

DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 2013) as a minor neurocognitive disorder, would represent a transitional step in midlife, between healthy aging and the dementia onset although not all patients with MCI would progress into dementia; approximately 10-15% of patients with MCI would develop AD type of dementia (Roberts & Knopman, 2013). Memory and attentional complaints are characterized to be major signs both in early AD and in amnestic MCI (i.e., aMCI), in which cognitive decline would be observed as clinically relevant when compared to age-matched healthy individuals (Albert et al., 2011; Diagnostic and Statistical Manual of Mental Disorders, 2013). In this way, representing MCI as a probable stage leading to AD, the early detection of symptoms might mitigate and slow the worsening of conditions on daily living activities and cognitive functions while reducing its incidence rate (Petersen, 2009). However, the estimation of subjective cognitive decline might be unspecific throughout the performance of cognitive tests (e.g., Mini-mental State Examination test, MMSE or the Montreal Cognitive Assessment, MoCA), misleading the very mild AD detection in elderly and its early onset.

In addition, a target and specific treatment for AD and MCI has not been formalized yet and the majority of treatments are typically based on neuropharmacological approaches (e.g., donepezil, memantine, rivastigmine, and galantamine) finalized to delay the disease progression. Furthermore, due to the lack of effectiveness of these treatments in attenuating cognitive deficits (Casey et al., 2010; Čolović et al., 2013), several researchers (Knopman et al., 2012; Sperling et al., 2011) have tried to detect cognitive alterations and specific biomarkers in healthy aging that would appear ahead of MCI and predicting the progression toward AD. Although this topic will be further described in the following sub-chapter, and with a particular focus on neural oscillations, a short explanation will follow. Among these biomarkers, the evaluation of the electroencephalographic (EEG) recording combined with cognitive assessment could potentially detect early signs of a preclinical AD (pAD), allowing potential interventions. Based on EEG biomarkers, when compared to age-matched healthy aging controls, MCI and AD patients would show an increase in the relative power of slow oscillations such as delta and theta frequencies, associated with a decrease in the relative power of fast oscillations such as alpha, beta, and gamma frequencies. Hence, the relative amplitude of theta oscillations translated in an observable marker toward MCI and AD progression (Jelic et al., 2000); already detectable in elder individuals with evident complaints even 7 years before any diagnosed cognitive decline (Prichep et al., 2006). Moreover, structural neuroimaging has been implemented to identify any difference between typical age-related structural changes and

what is often observed in neurodegenerative disease. Several changes appear with a regional gray matter (Sowell et al., 2003) and white matter volume loss integrity (Leong et al., 2017), but also other studies found volume loss at those patterns characterizing neural networks (Leong et al., 2017; Jack et al., 2005; Enzinger et al., 2005).

When investigating cognitive functioning, the onset of symptoms might also depend on the global cognitive abilities reflected in the brain's architecture, due to the strength of neural connections (Stern, 2012). In this view, cognitive reserve, described as the ability to optimize and maximize cognitive functions, would represent the process that enables the efficient utilization of brain networks while coping against cognitive decline and brain pathology. In AD, reduced cognitive reserve might lead to working memory (WM) and attentional complaints with an overall brain structure and neural network deterioration (Stern, 2002). Consequently, having high cognitive reserve influenced by several factors such as high education, healthy lifestyle or occupational attainment would protect against progressive cognitive decline encountered in AD (Stern, 2012). This fact would advance the possibility of delaying AD progression through its stages.

In conclusion, depending on symptoms severity, on average, 20% of MCI patients can improve over time (Koepsell & Monsell, 2012). The pAD stage would increase the probability to recover cognitive functioning (Schultz et al., 2015). Thus, the absence of a specific intervention to restore cognitive functions leads to the development and experimentation of novel and unique methods to treat pAD and MCI, focusing on the neural substrate of cognitive reserve.

1.3 COGNITIVE DECLINE IN AGING AND AD

Representing aging as a relevant risk factor for dementia while considering the increased life expectancy of the older population, the importance of preventing the onset of neurodegenerative diseases, such as AD, assumes importance in promoting healthy aging. Based on a demographic statistic, in 2015, 8.5% of the global population was above the age of 65, and this rate is estimated to double by 2050, increasing to 16.7% (He et al., 2016). In this context, the World Alzheimer Report estimated that the number of elderlies affected by dementia might increase to more than one million by 2050 (Price et al., 2015). This fact would generate an impact on caregivers, healthcare providers, and the worldwide healthcare costs for each nation (Price et al., 2015). Being AD a considerable public health concern, it needs particular attention and investigation due to the progressive cognitive deterioration manifesting

at different rates and cognitive domains (Ballard et al., 2011; Schmidt et al., 2011). Indeed, progressive cognitive decline would be one of the most relevant characteristics of AD. The early identification of symptoms may help the improvement of patient care and planned treatment.

As described in the previous section, MCI represents a transitional stage between healthy aging and AD, although the pathological and physiological process might have already begun several years before any clinical diagnosis (Braak and Braak, 1997; Jack et al., 2009; Ritchie et al., 2015). The identification of this stage, defined as pAD, would be significant to delay the progression of dementia, although the discrepancy between normal and pathological aging is rather unclear. Thus, investigating relevant cognitive and neural changes during midlife indicating and separating health from pathological processes requires importance (Irwin et al., 2018). The assessment of cognitive functions would be useful in detecting any sign of impairment before any overt clinical signs and symptoms, even though the threshold between pAD and normal aging is still not well defined (Albert et al., 2011), and more findings are needed to better investigate this transitional stage. However, by collecting multiple studies Irwin et al., (2018) summarized evidence for the cognitive discrepancy between normal and pathological aging. Generally, cognitive abilities divided into different domains such as attention, memory, executive functions, language, and visuospatial abilities, tend to decline in aging (Lezak et al., 2012) but recognizing which type of change would be expected in the elderly or what would suggest the onset of a neurodegenerative disease is of primary importance. A clear understanding would decrease the risk of progressing into AD while improving life quality in patients and overall in the older population (Murman, 2015). According to a healthy aging process (Irwin et al., 2018), reduced performance on selected and divided attention is one of the most visible cognitive alterations, although lack of simple attention tasks should be mostly observed in advanced aging. Learning new abilities or retrieval of newly learned information would also decline dramatically when considering early dementia. In this regard, if the manipulation of newly learned materials is tested (working memory) or while performing multiple tasks (divided attention), performances decline with age. Furthermore, while retention of learned material is relatively maintained, retrieval would require cueing in aged individuals, as well as prospective memory (e.g., remembering to perform intended actions and tasks) would also be lately affected. When examining executive functions, performance on novel or complex tests declines, as well as on those tests that require inhibition of information. Also, abstraction, mental flexibility, or concept formation is likely

to decline while aging progressively. Differently, speech and language remain mostly intact even in advanced aging, although speech comprehension and ambiguous speech would show a progressive decline (Sommers, 1997) followed by decreased verbal fluency and verbal retrieval (Critchley, 1984). Lastly, also visuospatial processing and constructional praxis have been shown to deteriorate in healthy elders.

Considering now age-associated diseases (Irwin et al., 2018), cognitive dysfunctions can be caused by a broad range of risk factors damaging the brain (e.g., ischemia, head trauma, toxins, and neurodegenerative processes), albeit the fact that the separation between disease-related decline and normal aging is not simple and that cognitive decline in advance aging can be observed even without any form of dementia (Boyle et al., 2013a,b). As previously discussed, AD represents the most common cause of cognitive decline with increased age (Alzheimer's Association, 2014; Evans et al., 1989). Patients would mostly show clear memory and learning dysfunctions, followed by mild impairment in executive functions, language, and visuospatial processing in later stages. These cognitive changes would appear similar to normal aging but different by severity (Fjell et al., 2014; Morris and Price, 2001). In a study, Zhao et al. (2014) aimed to investigate the progression of cognitive dysfunction in AD patients, focusing on disease contributing factors. In the study, a total of 165 patients were analyzed in which their cognitive status was tested based on their MMSE scores. Results indicated that the scores declined over time although at different rates; particularly it was found that global cognition and executive functions were highly impaired rather than other domains (e.g., memory and language), and mostly in early-onset AD. With disease progression, toward moderate and more severe stages, then also other cognitive domains were also impaired. They found that memory appeared more affected in men whereas attention in women. Furthermore, high education was found to be associated with a rapid decline in visuospatial ability, while family history, hypertension, and cerebral vascular disease were contributing factors underlying disease progression. The authors concluded that understanding cognitive decline development in each domain would be of primary importance for clinicians and caregivers to provide better patient care and treatment. In this perspective, considering that the conversion rate from MCI to AD is almost 15% per year (Gauthier et al., 2006), this fact needs attention and investigation. Indeed, the cognitive decline observed at this stage can evolve into one or more cognitive domains. However, aMCI (in which only memory is affected) is mostly observed in the majority of patients before developing into AD.

The understanding of cognitive deficits in AD has been widely investigated, in which the majority of studies have mostly focused on memory complaints and their development during the progression of the disease. Among functions, episodic memory appears to be the most impaired, even in early AD. Studies suggested that this impairment would be the result of underlying dysfunctional processes such as the inability to learn new information (Storey et al., 2002; Hodges, 2000; Grober and Kawas, 1997); indeed, WM was found to be most impaired in AD (Collette et al., 1997). To better investigate how episodic memory would be affected concerning impaired learning, Germano and Kinsella (2005) proposed a theoretical framework of WM to speculate on those cognitive processes supporting the acquisition of new information and that would result in dysfunction in early AD. Based on extensive literature research, evidence supports the fact that learning deficits in early AD can be attributed to impaired encoding, even if retention or retrieval deficits were also considered (Hodges, 2000; Pasquier et al., 2001; Grober and Kawas, 1997; Albert et al., 2001). A possible way to investigate the mechanisms of impaired learning in early AD would be to consider the working memory model proposed by Baddeley (2000). Concerning the model, WM plays a role in learning while transferring information from a temporary to short-term storage, and successively to long-term storage representing episodic memory (Baddely, 2001; Bäckman and Small, 1998). Moreover, the understanding of learning deficits in early AD was also extended to the investigation of the WM storage capacity (Wilson et al., 1983), attentional processes (i.e., central executive) (Baddeley et al., 2001; Collette et al., 1999; Albert et al., 2001), and episodic buffer (Cannata et al., 2002; Carlesimo et al., 1998). In addition, all these WM processes have been investigated together, in which the isolation of specific component mechanisms under visible deficits would help the understanding of targeted memory complaints while improving interventions and life quality (Cherry et al., 1999).

Another significant argument to be considered is the variability in the progression rate of symptoms in AD and comprehending symptoms severity of initial cognitive dysfunction would also acquire importance in predicting impairment severity of clinical progression in AD (Cummings, 2000). In this regard, Pillai et al. (2014) aimed to study whether specific cognitive deficits during the early disease stage would correlate to a specific disease progression; indeed, the possible prediction, based on recognized factors (Drachman et al., 1990), of a hypothetical clinical trajectory in MCI and early AD would be beneficial in healthcare management. Sixty-eight patients from the National Alzheimer's Coordinating Center (NACC) database with an autopsy-confirmed diagnosis of AD, an MMSE score of >15, and Clinical Dementia Rating

Scale-Global (CDR-SG) score ≤1 were included and examined in the study. An analysis was carried out to test any relation between neuropsychological performance at initial assessment and MMSE, CDR rate of change based on a mixed regression model. In the analysis, covariate factors such as age, sex, education, and APOE e4 were added to the model, and initial assessment performances were included as predictors. The evaluation of neuropsychological scores was extended to four cognitive domains including attention, executive functions, language, and memory, and for each domain-specific test, assessments were administered. Results showed that episodic memory performances were not predictors of either MMSE or Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) scores, whereas higher performances on digit span backward task were related to slower decline rate; a task assessing complex attention, executive functioning, information processing speed and generally related to WM. The initial WM and attention complaints indicator of early cognitive decline in AD (Summers and Saunders, 2012), would suggest that higher performances in these cognitive functions can be a marker of higher cognitive reserve (Stern, 2009). In general, the authors found that preserved functioning of WM and attentional processes were associated with slower decline in MMSE and CDR-SB scores whilst episodic memory deficits, mostly identified as relevant signs of initial AD pathology, were not an influential factor in determining the rate of decline on these scores. Furthermore, when investigating covariance factors, education has been recognized as a relevant variable in determining the rate of cognitive decline. According to Hall et al. (2007) and Pillai et al., (2011), higher education would generate a slower decline before dementia, but a faster decline after the onset of dementia and this process would be significantly related to cognitive reserve (Stern, 2009). Also, age resulted in a noticeable factor at diagnosis; higher age was associated with slower decline when assessing MMSE scores. With this study, Pillai et al. (2014) investigated and recognized valuable predictors of cognitive decline and related neuropsychological measures in MCI and early AD at initial assessment; essential for healthcare providers when establishing treatment plans. Hence, the understanding of specific cognitive markers at initial assessment would help identify proper care approaches and preventive measures of further clinical decline. The assessment of WM would require much more attention being a promising cognitive function able to delay the rate of impairment in AD.

1.4 OVERVIEW ON BIOMARKERS IN AD

The lack of specific and effective treatments in AD aimed the investigation of defined biomarkers, in which the early detection and recognition would increase the probability of differentiating and categorizing early stages of AD from other pathologies manifesting similar cognitive dysfunctions (Hamm et al., 2015). In support of the amyloid hypothesis framework (Hardy and Selkoe, 2002), several studies focused on identifying the progressive accumulation of amyloidogenic Aß peptides associated with familial AD mutations in which its early accumulation in specific brain regions would elicit dysfunctional neuronal activity patterns causing subsequent cognitive decline (Palop and Mucke, 2010). Based on this theory, developed treatments were aimed to decrease Aß accumulation, although these approaches resulted inefficiently and were accompanied by considerable side-effects, becoming unsuitable for AD interventions (Mikulca et al., 2014). In this regard, although several studies tried to investigate the reason for these ineffective results (Tamayev et al., 2012; Lauritzen et al., 2012; Goutagny et al., 2013; Willem et al., 2015), the need of discovering specific biomarkers at early disease onset and independently of the amyloid accumulation, remains an open debate.

The study of Hamm et al., (2015) suggested implementing EEG recording as an alternative and cost-efficient method to detect early AD, in which particular oscillatory activities would represent characteristic biomarkers of early disease onset. Indeed, cognitive processes would require the activation of different neuronal populations, in which the coordination of rhythmic activities of these groups generates neural oscillations (Womelsdorf et al., 2007). Among specific frequency bands (e.g., delta, theta, alpha, beta, and gamma), neural oscillations are associated with different brain activities that can be categorized as global states (e.g., delta waves during sleep) or specific behaviors (e.g., beta waves during motor activities; Pfurtscheller et al., 1998). Some others are instead related to specific cognitive processes; among these processes, WM has been associated with underlying theta oscillatory activities (Sauseng et al., 2010), representing the substrate of memory and learning. Differently, attentional processes have been linked to alpha oscillations represent inhibitory processes filtering out distracting information (Klimesch, 2012), whereas object recognition and other higher cognitive processes (including also WM) were associated with gamma activities (Debener et al., 2003; Herrmann et al., 2004a,b; Fries et al., 2001). In this perspective, the understanding of how neuronal oscillations are related to specific cognitive processes and behaviors acquired particular interest when investigating AD and the development of

neurodegenerative processes, in which the EEG signal would result promising in identifying pAD, consequently predictive of MCI and AD development (Hamm et al., 2015).

A review (Hamm et al., 2015), reported several studies in which the analyzed EEG signal was based on an eyes-closed resting-state paradigm, a high standardized and reproducible method to compare experimental results. It was found (Moretti et al., 2004; Osipova et al., 2005; Hsiao et al., 2013) that an increase in the relative power of slow oscillations (i.e., delta and theta) and a decrease in fast oscillations (i.e., alpha, beta, and gamma) was mostly observed in MCI and AD when compared to age-matched healthy individuals (Moretti et al., 2010; Czigler et al., 2008; van der Hiele et al., 2007). By comparing studies, the relative amplitude of theta oscillatory activities was identified as a potential biomarker for AD development and able to correctly detect (e.g., 85% classification rate) MCI (Jelic et al., 2000); indeed, Princhep et al., (2006) found increased theta power activity in aged individuals with cognitive complaints even 7 years before progressing to MCI. Nevertheless, further investigation is needed to confirm these results. Besides resting-state EEG analysis, the investigation of neural networks would result beneficial in understanding particular features characterizing AD; in fact, the increase of theta power was also found in other dementia types (e.g., Lewy bodies; Kai et al., 2005) as well as, increased relative gamma power might also be observed in healthy elderly after brain injuries (Hermann and Demiralp, 2005). To this, Hamm et al. (2015) suggested that combining behavioral tasks with EEG recording would overcome these misinterpretations while achieving more insights into AD pathology and its characterization. An example was offered by Garn et al. (2014), in which during the performance of a face-naming encoding mnemonic task, impaired EEG activities were correlated with MMSE scores; significant and sensitive indicators of disease severity.

Besides impaired theta activity, Mably and Colgin (2018) found that altered gamma oscillatory activity was observed while investigating cognitive impairments specific to particular diseases such as AD and Fragile X syndrome. Impaired spatial and episodic memory was related to degeneration in the entorhinal cortex and hippocampus (Hyman & Trojanowski, 1997), although how dysfunctional neural networks relate to impaired memory functions remains a topic under investigation. About the hypothesis that memory disturbances in AD are related to retrieval deficits from encoded information (Roy et al., 2016), rodents' models of AD would support this theory demonstrating that impaired slow gamma generated inefficient retrieval of stored spatial information during navigation (Mably et al., 2017). Moreover, several studies found decreased posterior alpha and beta powers in AD when compared to age-matched healthy

controls or MCI (Hsiano et al., 2013; Moretti et al., 2004; Osipova et al., 2005). These measures correlated with abnormal cerebral blood flow, MMSE scores (Babiloni et al., 2015; Lizio et al., 2011), and occipital and temporal grey matter density (Babiloni et al., 2015). Moreover, Babiloni et al. (2015) observed decreased alpha oscillations in occipital, parietal, and temporal brain regions in healthy aging individuals, although similar results in the alpha band were found in MCI (Koenig et al., 2005; Lizio et al., 2011); characterizing a bridge between healthy aging and AD. In other studies, individual alpha means peak frequency (IAF) was also found to decrease in AD (Garcés et al., 2014; Babiloni et al., 2015). However, further discussion should be considered due to the variability and complexity of different findings based on oscillatory activity measurements (e.g., in terms of amplitude and specific frequency bands). Thus, Stam (2014) suggested investigating AD based on neural network activities and neural connectivity, in which increased connectivity was mostly found in healthy old individuals (Buldú et al., 2011), whereas enhanced disconnection in AD (Lizio et al., 2011). Another study (Koelewijn et al., 2017) investigated and compared connectivity changes in AD and healthy old controls during a resting-state analysis by performing whole-brain, source-spaced magnetoencephalography (MEG) recording of neural oscillations at different frequencies. Analysis based on whole-brain neural oscillations and connectivity during resting state included sixteen AD patients, twenty-one healthy aging subjects, and also twenty-one young volunteers. Results demonstrated dysfunctional patterns in AD when compared to healthy old individuals. These dysfunctions were mostly localized to bilateral inferior parietal and superior temporal brain regions and associated with decreased alpha and beta activities in AD when compared to healthy old controls. Moreover, the default mode network (DMN) was further explored in which four functional networks were found in the beta band. Whilst network activities were mostly increased in healthy old and young volunteers, a decrease was observed in AD and mostly localized at the frontal areas. By Garcés et al. (2014), in which decreased functional and structural connectivity in the alpha band was observed in MCI at the inferior parietal regions, this evidence would confirm the result found by Koelewijn et al. (2017) of decreased activity at the alpha band, being AD the clinical progression from MCI. Thus, the results demonstrated in this study highlight the importance of clarifying how dysfunctional neural oscillations and connectivity at the alpha and beta band might be recognized as relevant AD markers, supporting the disconnection syndrome hypothesis in which AD would be characterized by specific characteristics impaired neural patterns instead of exacerbated aging.

In conclusion, understanding oscillatory activities across brain regions should be considered concerning cognitive, non-cognitive states, and quality of life, particularly when considering elders and AD patients. Thus, the study of Molin (2013), investigated any significant relation between oscillations (e.g., delta, alpha, theta, and beta) and brain regions based on a quantitative EEG (qEEG) analysis. The study aimed to examine any relationship between these oscillations and measures such as cognitive functioning, depression, and quality of life. Results showed a significant relation between older age and neural activity of theta and alpha localized posteriorly, and a significant correlation was also found when inspecting specific cognitive functions and scalp locations. Moreover, depression was found to be correlated with beta activity localized centrally, whereas the higher quality of life with increased frontal theta and posterior beta activity. Molin (2013) concluded that cognitive measures, depression, and quality of life can be related to the activity of specific neural oscillations localized at certain brain regions, indicating that these EEG markers could be considered when implementing novel interventions (e.g., neurofeedback). However, these were only preliminary results and several limitations were reported. Thus, further studies should be performed to reinforce the outcome of these findings.

1.5 *CLOSING REMARKS*

In *Chapter 1*, a description of the aging process and related cognitive decline was described. In particular, the focus was on differentiating healthy from pathological aging typically observed in neurodegenerative diseases such as AD. AD is a debilitant condition among the older population, representing 60-80% of dementia cases. Affecting several cognitive domains such as memory, executive functions, learning, speech, visuoconstructional abilities, and motor functions, AD is a considerable social concern. The immediate understanding of early disease onset is of primary importance when identifying proper understanding healthcare interventions. The high incidence rate, estimated to increase over the years, and the lack of a specific treatment to cure or delay the pathology, stimulate the research on investigating risks factors and possible causes and innovative methods and approaches to cope with the disease. Hence, being cognitive decline, a predicable event in aging, the early recognition of abnormal patterns would help the prediction of the clinical trajectory regarding cognitive and functional deterioration. Moreover, due to the importance of WM, preventing its functioning from declining would represent a valuable approach that needs to be further explored to delay the rate of cognitive impairment. In this perspective, pAD would also represent a relevant time

frame, in which the early detection of specific clinical biomarkers allows successful interventions before progressing into MCI and, successively, AD. Moreover, cognitive reserve is a valuable resource supporting the strength of neural networks to cope with cognitive decline. In addition to cognitive and behavioral assessments to evaluate pathological processes, the study of biomarkers is a promising approach that needs further investigation. Indeed, the early detection of specific marker characteristics of early disease onset might facilitate target interventions leading to better disease management. Besides brain volume loss or the accumulation of amyloid plaques and NFT, dysfunctional neural oscillations appeared as a central biomarker indicating early AD. Several studies found that impaired theta, alpha, and beta oscillations are implicated in the disease development and how these oscillations relate to the specific cognitive and non-cognitive states, localized at different brain regions. Thus, the possibility to early identify any form of AD, especially in the preclinical stages, would enhance the probability of delaying its progression and in rare cases also its recovery, supported by the development of innovative approaches to ensure feasible disease interventions.

CHAPTER 2:

INTRODUCTION ON COGNITIVE TRAINING AND NEUROFEEDBACK BASED ON EEG

2.1 CHAPTER OVERVIEW

In *Chapter 2*, innovative methods aimed to ameliorate and delay cognitive decline in aging will be described. Particularly cognitive training will play a central role in stimulating multiple cognitive functions while targeting the substrate of cognitive reserve. Several studies will support this evidence in healthy young and old volunteers and early-stage and more advanced AD patients. Moreover, after a short introduction to the electroencephalography (EEG) technique, the focus will describe neurofeedback training based on EEG, in which the modulation of specific neural oscillations underlying cognitive processes would represent a potential intervention in healthy aging and early AD. Studies will be reported highlighting the efficacy of implemented neurofeedback protocols in young, old, and AD patients. Limitations and further study considerations are also discussed when interpreting results and experimental procedures. Lastly, concerning the contents discussed in *Chapters 1* and *2*, an overview of the aim of this doctoral thesis will be presented and, in particular, the method implemented.

2.2 COGNITIVE TRAINING TO ENHANCE COGNITIVE PERFORMANCE

To date, there is no approach to directly target the neural substrate of cognitive reserve. Besides pharmacological interventions, cognitive training (CT) was proposed as an efficient method of ameliorating global cognition while training-specific tasks (Kallio et al., 2017, Gates, et al. 2020, Al-Thaqib et al. 2018) and is potentially effective in delaying cognitive decline (Herrera et al., 2012).

CT is a program aimed to practice on a set of standardized tasks. These tasks are created to reflect specific cognitive functions referring to components of fluid intelligence such as executive functions, attention, and working memory. Cognitive tasks can be presented in paper-and-pencil (Quayhangen et al., 1995; Quayhangen et al., 2000; Davis, Massman, & Doody, 2001; De Vreese et al., 1998; De Vreese & Neri, 1998; De Vreese et al., 2001) or computerized (Heiss, et al. 1993; Hofmann et al., 1996; Galante et al., 2007) form or may involve analogs of daily living activities (Neely, Vikstrom & Josephsson, 2009; Loewenstein et al., 2004; Farina et al., 2002). CT is also called *brain training* or *neurobics* because it recalls the hypothesis that

cognitive functions can be maintained or improved by exercising the brain; similar to how body fitness is improved by physical training (Simons et al., 2016). Indeed, CT includes interventions that aim to improve specific cognitive abilities such as problem-solving, reasoning, executive functions, and working memory; abilities that correlate with individual differences in academic achievements and the management and execution of daily life activities. Besides enhancing targeted training tasks, CT aims to transfer its effects while improving other cognitive functions (Katz, Shah & Meyer 2018), extending the efficacy and the applicability of this novel approach to several domains. For its purpose, CT is related to the concept of cognitive reserve, and it becomes particularly relevant when considering individual differences in susceptibility to age-related brain changes in healthy or in pathologic aging. Although little evidence supports the generalization of CT on functional outcomes and its long-term effects, the benefits on cognition are promising. Cognitive enhancement is possible in healthy aging, and in patients with cognitive deficits (van Heugten et al., 2016). Indeed, the enhancement with intensive training practice generates brain changes through the process of *neuroplasticity* (Park & Bischof, 2013): the neural functional and structural modification process in response to repeated experience and environmental stimulation (Shaw, Lanius & Vandendoel, 1994). Lastly, although newly developed training programs could be an interesting topic in the context of neurorehabilitation and clinical research, other aspects should be considered when investigating the outcome of studies on CT. These outcome measurements include daily functioning, self-efficacy, mood, life quality, and neuropsychological tests (van Heugten et al., 2016) that, taken together, would optimize the positive effects of CT on cognition.

2.2.1 COGNITIVE TRAINING IN HEALTHY YOUNG ADULTS

In the last decade, CT reached its popularity as an innovative method to improve cognitive abilities in the clinical population and in young adults. For this purpose, several approaches have been developed to sustain cognitive performance, psychological well-being, and academic achievements, such as computerized WM training (Jaeggi et al, 2008, 2010; Redick et al., 2013), commercial video games (Baniqued et al., 2014; Green and Bavelier, 2003), mindfulness (Mrazek et al., 2013) and physical exercise (Stroth et al., 2009; Erickson et al., 2011). In particular, WM received the highest attention from the scientific community, traditionally supported by computerized training methods (Au et al., 2015; Soveri et al., 2017a; Melby-Lervåg and Hulme 2013; Melby-Lervåg et al., 2016; Schwaighofer et al., 2015;

Karbach and Verhaeghen 2014). WM has been defined as the ability to hold a short amount of information in mind, easily accessible while executing a cognitive task. Since WM is mostly involved in planning, comprehension, reasoning, and problem-solving, it plays a significant role in information processing, executive functions, and learning (Cowan, 2014). Nowadays, work and learning are mostly based on digital technologies requiring constant switch of attention between tasks. Inevitably, this process would affect attention and concentration, slowing down the completion of the planned assignments. In this regard, based on neuropsychological and neuroimaging evidence, Savulich et al. (2019) created "Decoder": a newly developed game performed on an iPad to target CT of sustained visual attention. The study aimed to investigate the effects of CT in 75 healthy young adults randomly assigned to either a CT group (8 h of playing Decoder over four weeks) or an active control group (8 h of playing Bingo over four weeks) or a passive control group (performing general daily living activities). Results demonstrated the capability of Decoder as a CT method when compared with both control groups (active and passive). In particular, individuals trained with Decoder showed better performance on the Trail Making Test (TMT), increased target sensitivity (A') on the Cambridge Neuropsychological Test Automated Battery Rapid Visual Information processing (CANTAB RVP) test; both measures of improved sustained visual attention. Moreover, when compared to the passive control group, they reported significant differences in visual analog scales between the two gaming groups showing that Decoder generated higher enjoyment, task-related motivation, and alertness. The authors suggested that Decoder can be proposed as an innovative, drug-free method for enhancing sustained attention in healthy young individuals and the clinical population affected by attentional complaints. Furthermore, the possibility to enhance WM capacity through target-specific training has been demonstrated by several studies showing the effect of CT on a range of different cognitive skills (Chein & Morrison, 2010); thus, a variety of mental exercises and CT paradigms have been developed to improve cognitive performance. These approaches include attention (Tang & Posner, 2009), speed of processing (Dux et al., 2009), neurofeedback (Keizer, Verment & Hommel, 2010), dual-task (Bherer, Kramer & Petersen, 2008; Bherer et al., 2005), and perceptual (Mahncke et al., 2006) training. In an extensive review, Morrison & Chein (2011) investigated whether CT based on WM can be considered an efficient method to enhance WM capacity. In particular, they investigated the effect of WM training considering two methodological approaches: *strategy training* or *core training*. With the former, WM training is classified as domain-specific (McNamara & Scott, 2001) directed to assess encoding, maintenance, and retrieval. With the latter, WM is classified as domain-general (Klingberg, Forssberg & Westerberg,

2002), involving the repetition of demanding tasks, sequential processing, and frequent memory updating. Besides critical considerations of positive WM training success in the examined studies, the authors claimed its capability as an efficacious tool to enhance cognitive performance. Nevertheless, the authors considered some issues when interpreting the outcome of CT described in the literature. An alternative interpretation of positive training results relies on effort/expectancy effects (e.g., placebo effects, selection of the correct control group, selectivity or systematicity of transfer effects), type of training components and assessment tasks (i.e., generalization effects), lack of consistency between methodologies inducing conflicting findings (i.e., standardization of pre- post-assessment), and neural mechanisms activated by WM training. Recently, based on the Strategy Mediation Hypothesis (Laine et al., 2018) of WM training, Forsberg et al. (2020) investigated the effects of adopting external (given instruction) or internal (self-generated) training strategies in a single session of adaptive N-back task by comparing results between healthy young and old adults after a 30-min N-back training session. Half of the participants were instructed to use a visualization strategy, whereas, for the other half, no instructions were given. The pre-and post-test assessment included a criterion task (digit N-back), two untrained N-back tasks (letters and colors), and three other different WM tasks. The group who was instructed to adopt a visualization strategy increased some measures of the N-back tasks; although young participants did benefit more than older adults. However, this strategy did not enhance the performance of structurally different WM tasks. In addition, results demonstrated a significant association between N-back tasks performance and the type of self-generated strategies implemented by the uninstructed group and age group differences when adopting this strategy type. They suggested that Strategy Mediation may be considered when the mechanisms behind WM training are clearly understood and specifically when enhanced performance relates to the application of these strategies. Moreover, Zhao et al. (2019) investigated the effect of CT on prospective memory and related transfer-task effects. The study examined the outcome of an 8-days Virtual Week computer game in young volunteers compared with an active control group. Results showed significantly higher post-training performance in the trained than the control group. However, in a 3-month follow-up, these effects were no longer maintained indicating a short near-transfer effect. In addition, the game training did not prove to enhance performance on other near- and far-transfer tasks measuring general intelligence or various executive functions. Furthermore, the authors compared their results with previous findings (Zhao et al., 2018), revealing similarities of near- and far transfer effects suggesting the potential for prospective memory training in even younger participants.

2.2.2 COGNITIVE TRAINING IN HEALTHY OLD AND AD PATIENTS

With the increased life expectancy, cognitive decline due to aging represents a social concern (Baltes & Lindenberger, 1997). The increasing number of patients with AD or other dementia types (Prince et al., 2013) encourages the need to establish new effective and targeted treatments to postpone cognitive and functional decline. Although the focus of this doctoral thesis will be on documenting the efficacy of CT, other interventions include *cognitive stimulation* and *cognitive rehabilitation*. Cognitive stimulation (CS) is based on restorative strategies and mostly involves non-specific recreational and creative tasks. These activities involve recalling past memories, problem-solving, reading, and practicing conversational skills; tasks administered in a group setting modality (Aguirre et al., 2013; Clare et al., 2004; Sitzer et al., 2006). Cognitive rehabilitation (CR) is based on individualized approaches to develop compensatory strategies. These strategies focus on goals identification, visualization, training of procedural memory, and general approaches to improve daily living activities while coping with symptoms (Choi, et al., 2013; Clare et al., 2004; Sitzer et al., 2006). Unlike CS and CR, CT aims to stimulate cognitive reserves and neuroplasticity processes, in which high levels of brain activity are associated with less risk of developing age-related cognitive decline or dementia (Yong, 2016; Scarmeas et al., 2003). Thus, Herrera et al., (2012) investigated whether CT would have been efficient in reducing or delaying cognitive decline in individuals with aMCI considered at high risk to progress towards AD. They tested the efficacy of a 12-week computer-based memory and attention training program evaluating recognition for this scope. Individuals diagnosed with aMCI have been assigned to two groups; one group received the CT program, whereas a control group has been trained in cognitively stimulating activities. To assess the outcome of the computer-based training program, pre-and post-test measures (15 days before and after the training) have been compared, as well as a follow-up test was performed after six months to evaluate the duration of training benefits of the two training methods. Although only recognition was trained, they found improvement in both recognition and recall processes; memory components are usually impaired in individuals at risk of AD progression. This effect indicates a transfer of the training benefit between different cognitive mechanisms, supporting the idea that multi-domain computer-based CT can significantly improve cognitive functions. Additionally, they reported long-lasting beneficial effects after 6 months of the training sessions, indicating not only resistance to memory decline in MCI and demonstrating the efficacy of a computer-based memory and attention training program in patients with aMCI. Moreover, Hosseini et al., (2016), evaluated the effect of an 8-week

computer-based training program in older women with MCI. Twenty women have been assigned into two groups, where the group who received the training program has been compared to a control group. Before and at the end of the training program, reaction times (RTs), error number, and data processing speed have been measured using a Stroop task and a digit symbol coding test. When comparing pre-and post-test measures, results showed the training program's positive effect in reducing RTs, error number, and increasing data processing speed compared to the control group. These findings indicated the efficacy of computer-based training on different cognitive measures in older women with MCI, reflecting the possibility to stimulate brain plasticity processes by learning new tasks. This positive outcome would be relevant when considering the effect of cognitive decline on daily life activities. The optimization of age-related decline would have a considerable impact on life quality. Although the positive effect of CT on cognitive functions in healthy older adults, and patients with MCI has been reported, it remains unclear whether CT is effective in patients with dementia. In a meta-analysis, Sitzer, Twamley, and Jeste (2006) collected positive effects in implementing CT in AD, in which CT was able to support several cognitive and general functional abilities. It was found that the delay of cognitive decline was mostly associated with learning, solving cognitive problems, and the performance of instrumental activities of daily living (IADL) to increase independence. However, when interpreting the obtained results, several studies limitations were considered. These were the small number of investigated controlled studies, a small sample size of the reviewed studies, variability in results across studies generating difficult comparisons, few measures on functional abilities compared to cognitive tasks, and incomplete description of CT protocols leading to the lack of robust conclusion on the efficacy of CT in AD. Nevertheless, to better explore this topic, Kallio et al., (2017) investigated whether CT can improve or stabilize cognitive and other daily functions in patients with mild and moderate AD. Based on 31 randomized controlled trials (RCTs) a positive effect has been reported on 24 RCTs related to global cognition and training-specific tasks, particularly when intensive or specific CT programs were implemented. Less evidence has been reported of improved everyday functioning. The authors concluded that although positive results have been found in many trials, the study should have implemented an appropriate sample size, randomized methods, and complete datasets at follow-up sessions. Moreover, they suggested future high-quality RCTs with appropriate classification and specification of cognitive tasks in order to establish the effectiveness of CT in AD. Furthermore, Nousia et al. (2018) investigated the benefit of multidomain cognitive training (MCT) on the cognitive performance of patients with early-stage AD. In the study, 50 patients

have been randomly assigned to a 15-week training program group or a "waiting list" control group. The training program group received computer-based MCT and linguistic exercises. Episodic memory, delayed memory, word recognition, attention, executive function, processing speed, semantic fluency, and naming were assessed before and after the training in both groups. Results did show that in comparison to controls where the measured functions deteriorated over time, the training group improved the performance in word recognition, Boston Naming Test (BNT), semantic fluency (SF), clock-drawing test (CDT), digit span forward (DSF) and backward (DSB), trail-making test A (TMT A) and B (TMT B). They concluded that MCT has been efficient in enhancing delayed memory, naming, semantic fluency, visuospatial ability, executive functions, attention, and processing speed, emphasizing the cognitive-language performance of patients with early-stage AD. In conclusion to this subsection, although these studies were able to demonstrate the efficacy and the potential implementation of CT in improving cognitive functioning and functional abilities in healthy old and particularly in AD, robust evidence on CT remains limited and the quality of experimental designs should also be improved to increase reproducibility, standardization leading to more clear results (Bahar-Fuchs, Clare & Woods, 2013).

2.3 NEUROFEEDBACK TRAINING BASED ON ELECTROENCEPHALOGRAPHY (EEG)

Before moving to neurofeedback (NF), describing supporting evidence of its effectiveness in enhancing neural oscillations, and an overview of electroencephalography (EEG) will be given. In relation to this, the method described in this doctoral thesis was built on EEG-NF.

2.3.1 AN OVERVIEW OF ELECTROENCEPHALOGRAPHY (EEG)

EEG was born with Hans Berger, interested in investigating the activity of the human brain, and the first to relate this activity (e.g., alpha waves and cerebral metabolic activity) to specific cognitive processes (Berger, 1929). Thus, in electrophysiology, EEG is a method used to record the electrical activity by placing electrodes on the scalp that acquire the generated activity localized under the recorded surface. Often EEG is a non-invasive procedure when the electrodes are placed over the scalp, even though it becomes invasive when intracranial electrodes (i.e., iEEG) are involved and in which surgical intervention is needed (Wang et al., 2016). Essentially, EEG measures are voltage fluctuations generated by an ionic current within neurons (Niedermeyer & DaSilva, 2004; Rocha, 2020). The spontaneous electrical activity is

recorded by placing electrodes over different scalp locations, in which event-related potentials (ERPs; e.g., activity time-locked to a specific event of interest) or spectral content (e.g., neural oscillations at different frequencies bands) is investigated (Niedermeyer & DaSilva, 2004). Indeed, these two types of EEG activities represent the main application in cognitive science, cognitive psychology, psychophysiology, and neuroscience studies. Apart from scientific research, EEG has been widely implemented in the medical field, particularly as a diagnostic tool for epilepsy (Smith, 2005). However, other pathologies have been investigated while using EEG, such as brain tumors, brain injuries, inflammations, strokes, sleep disturbances, and neurodegenerative disorders (Mayo Clinic, 2020; Beres, 2017). When compared to other neuroimaging techniques (e.g., functional magnetic resonance imaging, positron emission tomography, magnetoencephalography, near-infrared spectroscopy, electrocorticography), EEG presents several advantages such as lower hardware costs, very high temporal resolution, tolerability to subject movements, silent, highly non-invasive, and possibly coupled with other techniques and paradigms (e.g., co-registration with functional magnetic resonance imaging). Nevertheless, a few disadvantages should be considered when implementing EEG. This includes a low spatial resolution because the recorded activity is only superficial (e.g., the inverse problem), long time in subject preparation to guarantee a proper recording, and relatively poor signal-to-noise ratio leading to the need for a relatively large sample size enabling the detection of valuable neural information (Hrishikesan, 2018; Alsharif et al., 2020). Moreover, EEG can be considered a powerful technique able to capture covert processes (e.g., when a response is not required; Mulholland, 2012), it can detect relevant neural activity even in the absence of any motor action (e.g., locked-in patients; Hinterberger et al., 2003). ERPs can be generated and identified even without attending to presented stimuli as well as, different stages of stimulus processing can be investigated (Sereno, Rayner & Posner, 1998), and lastly it can monitor variations in brain patterns occurring throughout the lifespan (Feinberg & Campbell, 2013).

Furthermore, to record the EEG activity, the method requires the placement of electrodes (wet or dry; Di Flumeri et al., 2019) on the scalp following the International 10-20 systems (Towle et al., 1993); a system to ensure a standard electrode location over the scalp properly named and numbered. To reduce impedance caused by dead skin cells and sweat, a conductive gel or paste is used to properly adhere to wet electrodes while guaranteeing artifacts reduction. The number of electrodes placed usually varies depending on the type of experiment, hardware, sample investigated (e.g., adults or neonates), and research hypothesis/goal. High-density

arrays (Stoyell et al., 2021; Toscano et al., 2020) can contain up to 256 electrodes, whereas low-density arrays (Soler et al., 2020; Kayser & Tenke, 2006) may contain way fewer electrodes, and different types of montage can be selected. During the recording, each electrode is linked to one input of a different amplifier (e.g., each pair of electrodes has one amplifier) and a common reference electrode. This is connected to the other input of each differential amplifier; in this way, the voltage between active electrodes and the reference electrode is amplified (Ebner et al., 1999; Ahmad, Ansari, & Dey, 2012). Moreover, EEG systems are digital nowadays, and an analog-to-digital converter is used for digitizing the amplified signal after being processed by an anti-aliasing filter (Burgess, 2014). Usually, sampling rates in the range of 256-512 Hz are used, although also other measures can be preferred. Once the acquired EEG signal is stored digitally, filters are applied to display the signal and to remove also artifacts caused by slow drift, line noise, environment, electrocardiogram activity, eye blinks, jaw, and other body movements, or increased impedance due to a disconnected electrode (Sazgar & Young, 2019). These filters can be categorized into low-pass, high-pass, band-pass, and notch filters (de Cheveigné & Nelken, 2019).

Furthermore, the EEG activity represents the summation of synchronous activity of neural populations with similar spatial orientation playing a relevant role in information processing (Engel et al., 2001; Aviyente et al., 2011). A typical adult human EEG signal is around 10-100 μV in amplitude measured from the scalp (Aurlien et al., 2004), and this activity can be rhythmic or transient. Based on the Fast Fourier Transform (FFT) analysis method, rhythmic activities are commonly decomposed into different frequency bands due to their special distributions and biological meaning (e.g., related to specific physiological and cognitive processes; Klimesch, 1999; Klimesch, 2012; Christof et al., 2016). Among these frequency bands, there is the delta (<4 Hz), theta (4-7 Hz), alpha (7-13 Hz), mu (8-13 Hz), beta (14-30 Hz), and gamma (> 30 Hz), although no agreement based on a standard system over these frequency ranges is yet confirmed and these ranges should only be taken as approximative measures, variable among studies (Newson, 2018).

Outlooking the main applications of EEG, neurofeedback represents one of the main methods initially proposed by Joe Kamiya in 1962 (Kamiya, 1962; Kamiya, 2011), and also represents one of the main fundamentals for brain-computer interfaces systems (BCI; Wan et al., 2016). In this perspective, recent research and industries focus on generating smaller, user-friendly, portable, and wireless EEG devices in which dry electrodes are preferable for their easy-to-use, and quicker setups (Casson et al., 2010), as well as in ear-EEG technologies. They are also

valuable solutions leading to longer and more tolerable EEG-recordings (Kappel, Mekeig & Kidmose, 2019; Kappel & Kidmose, 2018; Zhou et al., 2016) and preferable in real-life monitoring applications (Kappel, 2016; Bleichner et al., 2015; Fiedler et al., 2016; Nhat et al., 2020). Lastly, current EEG studies include machine learning applications (Lotte et al., 2018) in which algorithms are fed with acquired and pre-processed data, trained to detect different diseases, such as dementia (Ieracitano et al., 2020).

2.3.2 AN OVERVIEW ON EEG AND NEURAL OSCILLATIONS

In the previous *Subchapter 2.3.1,* an overview of EEG was given to explain the basic principles of this method. Moreover, a distinction was made between ERPs and oscillations, the spontaneous electrical activity that can be recorded by placing electrodes on the scalp. Due to the importance of detecting and investigating neural oscillations in NF training, this *Subchapter* will give an overview of what neural oscillations are.

In 1929 oscillations were initially observed in humans by Hans Berger, who identified the well-known alpha waves by measuring the electrical potential between two scalp electrodes with EEG (Berger, 1938). By observing a strong alpha rhythm during rest and cognitive activity, and even with the naked eye, it was concluded that this activity resulted from thousands of neurons oscillating in synchrony. Thus, while coordinating neuronal spiking, neural oscillations could represent the physiological substrate of cognitive functioning (Jensen, Spaak, & Zumer, 2019). However, despite the long history in the EEG investigation (Shaw, 2003), it is still debated which functional role neural oscillations have (Llinás, 2014). Nevertheless, the interest in studying neural oscillations and their functioning is gaining momentum in cognitive neuroscience. This fact is also supported by advances in neuroimaging techniques (e.g., MEG) which allow the identification of neural networks and source activities and a better investigation of neural mechanisms (Jensen, Spaak, & Zumer, 2019). It has been speculated that neural oscillations may play different roles such as feature binding, information processing (Senkowski et al., 2008), and transfer of this information (Brown, Kass, & Mitra, 2004; Johnson, 2000), but also the rhythmic production of motor outputs (Guertin, 2019). This fact is particularly relevant in the field of neuroscience in which the study of neural oscillations is aimed at investigating the functional role of these activities related to information processing and organization of this information (Solomon, Berg, & Martin 2002). In addition, the study of oscillations is particularly significant in the context of neurological disorders in which excessive synchronization causes the development of dysfunctional neural activity (e.g.,

seizures in epilepsy or tremor in Parkinson's disease) (Fisher et al., 2014; Ghosh et al., 2021; Sveinbjornsdottir, 2015).

Neural oscillations are the spontaneous electrical activity identified by rhythmic and repetitive patterns which originate in the neural tissue and are produced by a group of neurons whose electrophysiological activity is coordinated (Jensen, Spaak, & Zumer, 2019). These activities may consist of spike trains (Hodgkin & Huxley, 1952), local field potentials (Peyrache et al., 2012), or large-scale neural oscillations (Alavash, Tune, & Obleser, 2021). Neural oscillations, generated in the neural tissues, can be identified along with three different levels of organization such as the "micro-scale" (i.e., the activity generated by a single neuron), the "meso-scale" (i.e., the activity generated by a group of neurons), and the "macro-scale" (i.e., the activity generated by neurons located in different brain areas) (Haken, 1996), and where different mechanisms can be observed. For instance, when neural activity is generated within a single neuron (i.e., the "micro-scale"), oscillations may be observed in membrane potential or as action potentials that cause the activation of post-synaptic neurons. Therefore, (multiple) action potentials are generated due to changes in the electric membrane potential while giving rise to a sequence of spikes. Spikes are responsible for coding and transferring information throughout the brain, in which different patterns are detected in neural oscillations (Wang, 2010). However, when the membrane potential does not overcome the threshold to produce action potentials, neural oscillations can also be measured as a modulatory activity within the membrane potential. Differently, when the neural activity is generated by a group of neurons (i.e., the "meso-scale") through synaptic interactions and which produce synchronous activity patterns, this activity originates "macroscopic" oscillations measurable by the EEG, for example (Bruce, 2014; Abdul Kadir, Stacey, & Barrett-Jolley, 2018; Hodgkin & Huxley, 1952; Fingelkurts & Fingelkurts, 2004; Fingelkurts & Fingelkurts, 2005; Reif, 1965). The oscillatory activity produced by neural ensembles is often the result of feedback connections among neurons generating firing patterns that are actively synchronized. Therefore, when neurons interact with each other generate neural activities that oscillate at a different frequency than the (firing) frequency of every single neuron. Thus, when firing patterns of these neurons are synchronized, this synchronous pattern generates a synchronized input toward different cortical areas resulting in large-scale oscillatory activities (i.e., local field potentials), measurable with e.g., EEG or MEG. However, groups of neurons are not fully synchronized. Indeed, the frequency of large-scale neural oscillations is generated by a group of neurons whose firing pattern is rhythmically regulated so that it occurs simultaneously. For this reason, the frequency

of these oscillations does not necessarily match the firing pattern of every single neuron. Only when a common frequency regulates the activity of a large group of neurons, this would produce oscillations in the mean field (Wang, 2010). The endogenous activity produced by these groups of neurons results from local interactions between excitatory and inhibitory neurons (Cardin et al., 2009). Moreover, neurons that are paired in a neural network often generate spontaneous oscillations while communicating through synaptic interactions (Buzsáki, 2006; Traub et al., 1999; Wang, 2010). Thus, the phase and frequency are regulated by how the electrical membrane dynamics respond to the synaptic currents generating spontaneous oscillations in different frequency bands (Jensen, Spaak, & Zumer, 2019). Accordingly, this represents the "macro-scale", a level of organization in which the interaction of different brain regions can generate oscillations and in which time delays are extremely relevant. Indeed, different brain regions are coupled and the connections between these areas give rise to feedback loops. For instance, the connection between the thalamus and the cortex (i.e., the thalamocortical network) is well-known to produce oscillations in the alpha frequency range (Bollimunta et al., 2011; Suffczynski et al., 2001). Indeed, the alpha activity is one example of this "macroscopic" oscillation (Foster et al., 2017).

Independently of whether the oscillatory activity is recorded in terms of spike trains, local field potentials, or large-scale oscillations, the activity of time series data is characterized by specific parameters: frequency, amplitude, and phase. Thus, oscillations are described as a mix of sine waves and these waves have a frequency at a particular amplitude and phase varying over time (Jensen, Spaak, & Zumer, 2019). Usually, oscillations are recorded in the time domain, indicating the neural signal in this domain. However, oscillations are also defined in the frequency domain indicating how the signal's amplitude and phase vary over a frequency range. Therefore, several methods were proposed to investigate how neural oscillations vary in the time and frequency domains (Muthuswamy & Thakor, 1998; Mitra & Pesaran, 1999; Gross et al., 2013). Accordingly, these parameters can be extracted and analyzed by performing a time-frequency analysis (Cohen, 1995; Sejdić, Djurović, & Jiang, 2009). Indeed, throughout this analysis, it is possible to investigate the physiological properties of the neural signal and its correlation at the cognitive level. For instance, while considering the activity generated by large-scale neural oscillations, the synchronized activity of neural pattern (locally or between different areas), due to the modulation of amplitude, can be associated with cognitive functions (e.g., memory, perception, information processing, and motor activities) (Fries, 2005; Fell & Axmacher, 2011; Schnitzler & Gross, 2005; Baldauf & Desimone, 2014). Furthermore, these

activities can be measured e.g., with EEG which detects the spectral content of these recorded signals across different frequency bands (i.e., delta, theta, alpha, beta, gamma).

In several neuroscientific studies, a power spectral density (PSD) is computed across frequencies to investigate PSD changes over time and in response to task performances or events. The PSD of time series data denotes how the signal's power (i.e., amplitude square) is distributed with frequency (Jensen, Spaak, & Zumer, 2019). Moreover, the modulation in oscillatory power is indicated as the time-frequency representation (TFR) of power and computed by applying a sliding time window whose length can vary (Jensen, Spaak, & Zumer, 2019). For instance, the Morlet wavelets are a common method implemented to compute the power of oscillations. These wavelets are generated by a sinusoid tapered by windows with a Gaussian shape and centered at a specific point. Afterward, the wavelet transform applies the wavelet basis set to compute power and phase at each frequency level and across time (Jensen, Spaak, & Zumer, 2019). One advantage of the wavelets is that the product of the bandwidth and the length of the window stays constant, maintaining a constant time-frequency "area" over which the power is calculated and analyzed (Jensen, Spaak, & Zumer, 2019). Furthermore, being oscillatory activities the neural correlate of cognitive processes, several forms of neural synchrony across frequencies have been related to specific mechanisms such as neural binding and integration (Munia & Aviyente, 2019). In addition, due to the high temporal resolution of EEG allowing the detection of how oscillatory power and coupling vary over time, methods were proposed to describe the interplay across frequencies by computing within- and cross-frequency interactions (Jensen, Spaak, & Zumer, 2019). Cross-frequency coupling can be observed in different ways. It may involve the phase of amplitude (power) of a lower-frequency band and at the same time, the phase, amplitude, or frequency of a higher-frequency band (Colgin et al., 2009). For instance, a well-known type of this cross-frequency coupling is the phase-amplitude coupling (PAC), which is responsible for the integration across neural populations (Fries, 2005). PAC couples the phase of the lower frequency to the amplitude of the high frequency (Tort et al., 2010; Canolty & Knight, 2010; Jensen, Spaak, & Zumer, 2019), and thus, the amplitude of the high frequency is modulated by the phase of the low frequency (Munia & Aviyente, 2019). Other forms of cross-frequency coupling consist of phase/amplitude (Canolty & Knmighht, 2010; Cohen, 2009), phase/phase (Palva, Palva & Kaila, 2005), amplitude-to-amplitude (Voytek et al., 2010), and phase-frequency (Hyafil et al., 2015).

As already described, in humans, neural oscillations can be measured by using non-invasive (e.g., MEG, EEG) but also by implementing invasive approaches such as single-unit recordings. Neural activity can be recorded either in terms of spikes (i.e., rhythm patterns of action potentials), in the absence of action potentials (Llinás & Yarom, 1986), or in terms of local field potentials (i.e., neurons that generate spikes with a synchronous rhythm). In general, the intensity of the recorded neural activities can be estimated by using quantitative models (Mureşan et al., 2008). Besides, in the cognitive sciences field, particularly in the context of "neurodynamics," neural oscillations can be investigated by implementing mathematical models. In fact, these models aim to relate neural activity patterns with brain functioning (Burrow, 1943) by using differential equations to explain the modulation of brain activities. In addition, from a physiological perspective, neural activity is also investigated with computational models and simulations (Trappenberg, 2010; Churchland, Koch, & Sejnowski, 1993; Dayan & Abbott, 2001; Gerstner et al., 2014).

Furthermore, neural oscillations can be evoked spontaneously or induced by an external event or stimulus (David, Kilner, & Friston, 2006). This activity can be generated either by the action of a single neuron or by a group of neurons. When an individual is not engaged in a task, spontaneous oscillations are the neural response to sensory inputs or motoric outputs. Thus, this type of neural activity is also called resting-state. However, the lack of stimulus processing should not be related to a noise process (Freyer et al., 2009). In addition, these spontaneous oscillations may also indicate the ongoing state of an individual such as whether the subject is awake, alert, or sleeping (e.g., the spontaneous fluctuation of alpha oscillations during wakefulness) (Laufs et al., 2003), but also this spontaneous activity is essential in perception (e.g., processing of incoming visual stimuli) (Mathewson et al., 2009; Busch, Dubois, & VanRullen, 2009; van Dijk et al., 2008). Differently, when an individual is engaged in an explicit task, the evoked neural activity is generated by sensory stimuli or motor responses (i.e., evoked potentials induced by a specific event that required the processing of received information). Activity patterns can be differentiated by changes in the frequency band, amplitude, or phase resetting. While frequency changes are observed also in terms of evoked and spontaneous oscillatory activities, oscillatory changes in amplitude are an example of induced activity. Indeed, amplitude changes reflect the induced neural activity underlying stimulus processing or motor preparation (e.g., the increase of gamma activity during cognitive effort) (Tallon-Baudry & Bertrand, 1999). In addition, the increase or the decrease in amplitude, associated with the activity observed in neural oscillations, is often indicated by a

process called event-related synchronization or desynchronization, respectively (Pfurtscheller & Lopes da Silva, 1999). Moreover, phase resetting can be observed when an input to a single neuron or a group of neurons resets the phase of the ongoing oscillatory activity (Tass, 2007). Therefore, spike timing within an individual neuron is related to periodic input, generating a process called phase locking (Izhikevich, 2007). However, phase resetting is also observed in a group of neurons where the phase of each of these neurons is regulated at the same time. Hence, phase resetting allows the synchronization of different neurons in several brain areas (e.g., spikes timing is phase-locked to the activity of the other neurons within the group) (Pikovsky, Rosenblum, & Kurths, 2001; Varela et al., 2001). In addition, through phase resetting, event-related potentials can be investigated (e.g., by EEG) reflecting the oscillatory activity that is phase locked to a stimulus or event repeatedly presented across trials (Makeig et al. 2002; Mäkinen, Tiitinen, & May, 2005).

From a functional perspective, neural oscillations observed in different frequency bands play a different role in cognitive processes. Gamma oscillations (i.e., frequency range of 30-100 Hz) are often related to higher-level processing of information. Thus, gamma activity would be responsible for processing and organizing neural information in time (Jensen, Spaak, & Zumer, 2019). Accordingly, gamma oscillations have been associated with synaptic integration. Furthermore, considering the importance of timing in neuronal firing, this process is highly coupled to the phase of gamma oscillations, where the level of gamma synchronization would work as a mechanism of control (Tiesinga et al., 2004). Hence, the stronger and tighter the synchronization in the sending areas, the stronger the feed-forward connection (Fries et al., 2001; Buffalo et al., 2011). For instance, this process of tight synchronization has been observed in MEG, and EEG human experiments in which increased gamma activity was related to increased attention (Gruber et al., 1999; Bauer et al., 2012; Siegel et al., 2008). Besides, gamma oscillations have also been considered responsible for communication between brain areas through coherence mechanisms (Bressler, 1996; Varela et al., 2001). Lastly, besides neural communication, synchronization in gamma activity has also been related to explaining the "binding problem" in object perception (Tallon-Baudry & Bertrand 1999; Gray et al., 1989; Engel & Singer 2001; Engel et al., 1999). Furthermore, the activity of alpha oscillations (i.e., frequency range of 7-13 Hz), originally investigated by Hans Berger in 1929 (Berger, 1938), has been observed during a state of relaxation and particularly increased with closed eyes. Similarly, the alpha activity was also defined as an "idling rhythm" because it represents an ideal state in which individuals are not involved in any specific task but awake (Jensen, Spaak,

& Zumer, 2019), although recent studies debate this fact supporting that alpha would serve as an inhibitory process during attention allocation (Foxe & Snyder, 2011; Klimesch, 2012; Jensen & Mazaheri, 2010). Indeed, several MEG and EEG studies investigated the functional role of alpha oscillations, demonstrating the role of alpha activity in memory processes (Klimesch et al., 1999; Jensen et al., 1999) and these results would contrast with the idea that alpha reflects an idling state or resting. Similarly, more recent research demonstrated increased alpha activity during a working memory task and associated this mechanism with active maintenance of memory representations (Palva & Palva, 2007) or with active inhibition of interfering information to enhance attention during maintenance (Klimesch et al., 2007; Foxe & Snyder, 2011; Bonnefond & Jensen, 2012). Having related alpha activity to inhibitory mechanism in the somatosensory system and where increased alpha activity was found related to the suppression of motor responses to distracting information (Haegens et al., 2012), these oscillations were also detected in the motor system (Sauseng et al., 2009). Besides, in human studies based on MEG and intracranial recordings, alpha band activity has also been observed in the auditory cortex (Gomez-Ramirez et al., 2011) which functional role was again associated with inhibitory processes in the auditory system (Weisz et al., 2011; Muller & Weisz, 2012). Moreover, the role of delta oscillations (i.e., frequency range of 1-4 Hz) has been associated with different tasks (Knyazev, 2012; Handel et al., 2007; Basar et al., 2001; Knyazev et al., 2009; Handel & Haarmeier, 2009) although there is support in favor of the idea that the phase of delta activity establishes the excitability of neural networks (Jensen, Spaak, & Zumer, 2019). Thus, it was found that the phase of delta oscillations can be modulated if the incoming input is anticipable. Hence, in these tasks, the delta activity can serve as a mechanism to block or facilitate an input that can be anticipated (Lakatos et al., 2008). In addition, in a MEG study, it was also found that the phase of the slower delta oscillations would control the activity of gamma oscillations. Thus, the gamma activity would show to be phase-locked to the delta phase (Handel & Haarmeier, 2009). Nevertheless, the mechanistic role of delta oscillations still requires a better investigation, particularly in tasks where the input can be predicted (Jensen, Spaak, & Zumer, 2019). Differently, the role of theta oscillations (i.e., frequency range of 4-7 Hz) has been associated with different functions and in particular responsible for the exchange of information between brain areas (Jensen, Spaak, & Zumer, 2019). Several animal studies reported phase synchronization between the hippocampal region and other areas. Hence, the hippocampal theta activity was found to be phase-locked to the theta oscillatory activity recorded in the prefrontal cortex (Siapas et al., 2005). Accordingly, this mechanism of phase synchronization observed in these two regions was also found to be related to memory

processes during a navigation task (Jones & Wilson, 2005; Colgin, 2011). Moreover, the involvement of theta phase synchronization was also reported in a working memory maintenance task. This synchronized oscillatory activity was identified in local field potentials and spike trains (Liebe et al., 2012). Similarly to delta oscillations, also theta oscillations were found to modulate higher-frequency bands. In particular, in animal studies investigating the rat hippocampus, gamma power activity was modulated by the phase of theta (Belluscio et al., 2012; Bragin et al., 1995). Indeed, the modulation in the gamma band and across frequencies due to theta was demonstrated to direct and route information in cortical and more subcortical regions related to memory (Colgin et al., 2009). However, the role of theta oscillations was also explored in human studies while investigating neocortical and hippocampal regions. Hence, it was found that intracranial theta activities were associated with working memory but also with long-term memory, and likewise, to animal studies, these oscillations were phase-locked to the activity in the gamma band (Canolty & Knight, 2010; Canolty et al., 2006). Lastly, in several studies based on EEG and MEG, strong theta activity was detected in frontal midline areas (Mitchell et al., 2008) and this activity was found to increase proportionally to increased cognitive effort in working memory tasks (Gevins & Smith, 2000; Scheeringa et al., 2009; Jensen & Tesche, 2002). Furthermore, beta oscillations (i.e., in the frequency range of 13-30 Hz) have been mostly related to the motor system (Baker, 2007) in both animal and human studies. Thus, it was observed that beta activity tends to decrease while anticipating sensorimotor processing (van Ede et al., 2011; Spaak et al., 2016), and similarly, beta oscillations were also related to information transfer between the motor cortex and the muscles (Kilner et al., 2000; van Elswijk et al., 2010). However, other studies observed beta oscillations in maintaining the status of large-scale networks (Engel & Fries, 2010). Indeed, a few MEG studies demonstrated that resting state networks were associated with functional connectivity in the band range of beta oscillations (Hipp et al., 2012; Brookes et al., 2011). And lastly, both human and animal studies attributed the beta band to a specific role in high-level cognitive processes such as decision-making (Haegens et al., 2011; Spitzer et al., 2010).

In conclusion, in this *Subchapter,* it was possible to describe the nature of neural oscillations while highlighting their role in the coordination of neural processing, measured both in animal and human studies. It was shown that this dynamic coordination was obtained by the phasic modulation of neural firing and related to the magnitude of neural oscillations. Thus, what can be observed at the cognitive level (e.g., task performance) is the outcome of these oscillations across different frequency ranges where the neural firing, coordinated and organized by these

oscillations, is associated with behavior (Jensen, Spaak, & Zumer, 2019). Having discussed what neutral oscillations are and their relation to cognitive functioning, in the next *Subchapter* an overview of NF training, a technique aimed at modulating neural oscillations, is presented.

2.3.3 AN OVERVIEW ON NEUROFEEDBACK TRAINING BASED ON EEG

Different from biofeedback, where individuals learn to attenuate, prevent and recognize body-physiological reactions related to specific pathological conditions (Frank et al., 2010), NF is applied to operate at the cognitive and neuronal levels. In NF, individuals are presented real-time feedback of their brain activities. These are generally based on EEG markers, aimed to self-regulate and enhance these signals without physical intervention; a similar practice to CT, although in CT, modifications in neural activities are secondary effects of enhanced cognitive performances. In NF, feedback signals represent learning goals, and individuals use this feedback to directly regulate and control their brain activation to consequently improve cognitive and behavioral functioning (Taya et al., 2015). In this regard, Hammond et al. (2010) named NF as *Neurotherapy*; an innovative and non-invasive method possibly implemented for treating several neurological and physiological dysfunctions. EEG-NF, particularly based on frequency/power parameters of the EEG signal, is one of the most common and efficient training methods; also, the applied method of this research thesis and further described in the following section. Other practices include slow cortical potential NF (SCP-NF) to improve slow cortical potentials (Christiansen et al., 2014), hemoencephalography (HEG) neurofeedback provides real-time feedback based on cerebral flow signals (Dias et al., 2012), functional Near-Infrared Spectroscopy (fNIRS) based neurofeedback (Lapborisuth at al., 2017) in which the neurofeedback signal is given in relation to the hemodynamic response, live Z-score neurofeedback (Collura et al., 2010), low-resolution electromagnetic tomography neurofeedback (LORETA) to identify phase, power and coherence parameters of the signal (Pascual-Marqui et al., 1994) and functional magnetic resonance imaging (fMRI) neurofeedback (Hurt, et al. 2014; Lévesque et al., 2006) to regulate brain activity from deeper areas under the cortex.

Several studies categorized NF as a kind of closed-loop BCI (Enriquez-Geppert, et al. 2017; Sitaram, et al. 2017, Jiang, et al. 2017); indeed, biomarkers derived from brain activities are feedback to the user supporting user's performances in modulating these patterns (Hartmann et al., 2011, Schestatsky et al., 2013; Zander & Kothe, 2011). In general, closed-loop NF application systems are implemented by software and a pre-processing pipeline that would

include data acquisition, online data pre-processing, feature extractions, generation of feedback signals, and the active involvement of the user through constant learning (Enriquez-Geppert, et al. 2017). The advantage of an NF based on EEG would be characterized by the high temporal resolution in acquiring the signal, suitable for generating real-time feedback of brain activities. At this stage, pre-processing procedures are applied to the acquired signal to remove or correct artifacts, representing the highest noise source. Afterward, specific features are selected and extracted. These features correspond to particular brain activities that the user aims to control and self-modulate. Based on these extracted features, a real-time feedback signal is generated and translated into a visual, auditory, tactile, or multi-modal stimulus presented and controlled by the active user. According to an established scale or threshold, the feedback signal represents the state of specific brain activities. Differently from other non-invasive neurostimulation techniques such as transcranial direct current (tDCS) or transcranial magnetic (TMS) stimulation (Hameed et al., 2017), during NF the user is positively engaged in a continuous learning process to modulate and self-control the targeted brain pattern while optimizing neural signals to meet the intended direction.

By exploring the importance of neural oscillations in terms of amplitude/power or phase/coherence, NF was mostly implemented to investigate those mechanisms underlying cognitive and behavioral processes. Different NF protocols were proposed to explore the various events observed in the EEG spectral activity (Marzbani et al., 2016). These NF protocols may differ in the chosen frequency band, scalp electrode displacements, the EEG recording at different activity states during eyes-open or eyes-closed, and the cognitive process under investigation. Although the scope of NF is to observe and stimulate changes at the cognitive and behavioral level, the intervention on specific neural networks and processes may not always guarantee the expected and desired results.

Furthermore, based on different training protocols, NF was also implemented for treating epileptic (Strerman, & Egner, 2006), ADHD (Butnik, 2005) patients, in addictions (Scott, Kaiser, Othmer & Sideroff, 2005), depression and anxiety (Hammond, 2005) but also in monitoring specific neurological lesions (Bearden, Cassisi, & Pineda, 2003), and treating chronic pain (Middaugh & Pawlick, 2002). Moreover, besides clinical applications, other research studies did focus on healthy young volunteers investigating the effects of NF in improving cognitive, athletic, and artistic performances (Budzynski, 1996; Egner & Gruzelier, 2004; Gruzelier, Egner & Vernon, 2006; Hanslmayer, Sauseng, Doppelmayr, Schabus &

Klimesch, 2005; Vernon, 2005; Vernon, Egner, Cooper, Comton, Neilands, Sheri & Gruzelier, 2003).

In general, the application of NF embraces the idea that the modulation of the neural signals would consequently generate changes at the cognitive states (Klimesch, 1999; Klimesch, Vogt & Doppelmayer, 2000; Klimesch, Schack & Sauseng, 2005; Sauseng & Klimesch, 2008). The possibility to monitor in real-time cognitive processes might support related learnings (Baldwin & Penaranda, 2012), and also the identification of individual markers (e.g., EEG) underlying these processes would optimize the training of performances (Mathewson et al., 2012). Nevertheless, either the modulation aims to regulate dysfunctional activities (e.g., in the clinical population), or intended to enhance these patterns in healthy individuals, the relation between cognitive performances and underlying neural signals has to be taken correlational or even casual (Sauseng & Klimesch, 2008).

2.3.4 NF TRAINING IN HEALTHY YOUNG ADULTS

Considering the healthy population, EEG-NF is primarily directed to modulate and enhance specific neural oscillations (related to specific frequency ranges) to promote positive cognitive and motor functioning changes. Based on this framework in which the modulation of specific EEG activities can reorganize neural networks under cognitive tasks (Anguerra et al., 2013), the outcome of NF training should be addressed by investigating its effect at the neural and behavioral levels measuring the EEG activity and related behavioral performances. To enhance learning processes while considering individual differences, a functional connectome approach was also proposed to explore the functionality of neural networks and how distributed brain regions interact to support cognitive functioning. Through this approach, the real-time monitoring of cognitive states related to individual identified neural markers (EEG activities) would facilitate learning and, consequently performances (Taya et al., 2015). Anyway, to enhance the reliability of these neural and behavioral changes the inclusion of a control condition in the experimental design is appropriate and necessary when evaluating NF training outcomes.

In a review, Rogala et al. (2016) explored the effects of several EEG-NF protocols by inspecting the scientific literature. Considering that several EEG-NF approaches performed on healthy individuals lack scientific rigor, uncontrolled and nonspecific factors, mostly ignored when designing valid experimental methods, these studies have been investigated to guarantee

reliable conclusions. From a list of 86 relevant reports, 43 experiments including a control group were considered. From this list, only 28 well-controlled studies were selected, where the success ratio (SR) for EEG and behavioral effects were calculated demonstrating that in these selected studies the EEG-NF training could influence the amplitude of the specific EEG activity and behavior, particularly when alpha or theta were considered as targeted frequency bands. In the study, two features resulted positively correlated with power changes of selected EEG frequency bands: the use of protocols that focus on a reduced number of selected frequencies and the multiple numbers of electrodes implemented during the NF training. However, no evidence has been found supporting the relationship between EEG power changes and targeted behavioral outcomes. Moreover, the authors highlighted the "do's" and "don'ts" list, which should be considered when developing future EEG-NF protocols. Within the don'ts, one major finding was the negative impact when implementing several frequency bands between the generated NF-signal and the rate of training success. Ros et al., (2013) reported the negative effect on behavior when involving different frequency bands. Indeed, the interdependence of EEG frequencies may affect behavioral changes in modulating neighboring frequencies trained in the opposite direction by canceling out the effect of up-regulating the target band. Similarly, behavioral changes may be due to the up-regulation of neighboring frequencies instead of the trained frequencies of interest. On the other hand, within the do's the position of electrodes based on well-identified sources of targeted EEG frequencies would bring the expected spectral changes. Indeed, positioning multiple electrodes on a specific region increases the possibility of generating feedback signals specific to the targeted activity. In this regard, optimal studies should identify the right electrode locations based on previous studies of anatomical and functional regions associated with different behavioral tasks (i.e., the frontoparietal network involved in attentional processes).

Cognitive abilities are essential for educational achievements, social and vocational skill training. In particular, memory represents a relevant key feature for executing different cognitive tasks, and its performance contributes to overall cognitive functioning. In this context, it is relevant to pay attention to those strategies used to enhance memory performance. In recent years, neurofeedback training has become a promising method to enhance memory capabilities. However, the lack of consistency in the scientific literature would lead to further exploration of its potential. In particular, several factors have been considered when evaluating the effectiveness and methodological similarity between studies, such as the selected frequency band and related spectral power changes (Klimesch, 1999; Zoefel, et al. 2011; Hanslmayr, et

al., 2005; Escolano et al., 2014; Bauer, 1976; Lecomte & Juhel, 2011; Rasey et al., 1995; Reiner et al., 2014; Enriquez-Geppert et al., 2014; Burgess & Gruzelier, 1997), the presence or not of control group conditions (Zoefel et al., 2011; Lecomte & Juhel, 2011), and the choice of open or blind experiments. In this regard, Farnia et al. (2017), investigated the effect of two different NF training protocols: beta up-training and low alpha/high alpha ratio suppression on memory performance. In a double-blind experiment, thirty healthy volunteers performed ten 30-minutes NF training sessions. Participants were randomly assigned into three groups: beta up-training and theta down-training, low alpha/high alpha ratio suppression, and sham training. To evaluate the effect of each NF training protocol on memory, the Wechsler memory scale (WMS-R) was performed before and after the training method. Results showed that no significant differences were observed between participants in age, gender, marital status, and psychological condition. However, both NF training protocols demonstrated their validity in enhancing memory performance when compared to the sham control group. Farnia et al. concluded that NF training has the potential to improve memory. Still, future studies are needed to address the effects of training in healthy individuals or patients with cognitive impairments. Furthermore, the effectiveness of NF training has been demonstrated by Engelbregt et al., (2016) who evaluated the long-term effects of frontal beta EEG-NF training on healthy subjects and how changes in EEG activity were combined with altered cognitive performance. In the study, twenty-five subjects were randomly assigned to either an active or sham NF (control group) training performing fifteen 45-minutes training sessions. Resting-state EEG was recorded before the NF training, within one week after the training, and in a 3-years follow-up session. Moreover, cognitive performance was measured using an abbreviated version of the Groninger Intelligentie Test (GIT; Luteijn et al., 2004). Results did show that when compared to the sham NF, the active NF training group did increase beta activity, and this increase was maintained over three years, although the NF training did not prove to be more efficient than the control in enhancing cognitive performance.

Neurofeedback training aims to support individuals in completing specific functions or tasks with greater efficiency and less error rate. Based on an extended literature examination, Vernon (2005) reported that NF training has been mainly implemented to enhance sport, cognitive and artistic performance. By reviewing these studies, the author concluded that the use of NF seems plausible to train individuals to re-organize patterns of cortical activity attempting to improve performance, although the variable outcomes between studies made their results and conclusions equivocal. To increase scientific validity and reliability of outcome measures, a

few recommendations were pointed out such as, measuring pre-and-post EEG baselines to monitor activity changes due to the training, utilizing a moving EEG baseline measurement to check for possible changes in arousal, and including an active control group that receives the same experimental procedure as the NF group. In addition, by obtaining pre-and-post training behavioral measurements, it would be possible to correlate EEG changes with behavioral performance.

Moreover, based on the growing interest in NF training as a potential method in enhancing cognitive and behavioral performance, Vernon et al. (2009), investigated those methodological factors, mostly unexplored, that can influence training outcomes. By inspecting these factors, the article aimed to highlight unanswered questions stimulating future research in developing more effective NF training protocols. Based on previous works, the review (Vernon et al., 2009) focused on those studies investigating alpha NF training for performance enhancements. Several methodological factors were considered; such as NF training schedule, reward threshold, feedback type, unidirectional vs. bidirectional training, target frequency range, eyes open vs. eyes closed NF training, and index of learning. The review concluded that a possible association could be established between alpha activity modulations and mood/cognition changes. NF training represents a valid method to enhance behavior, although not enough agreement exists on those factors leading to the published results. In an attempt to identify the most effective NF training paradigms, specific factors were observed. Indeed, practicing a short session of 20-30 minutes would already elicit EEG and behavioral changes without inducing fatigue or boredom, although these EEG changes might be short-lasting, and several sessions would be required to achieve the desired goals. In this regard, whether several sessions grouped within a short period or diluted across days/weeks would generate better results remains an unsolved topic. Another relevant factor is the reward threshold (fixed or variable), where a threshold based on resting-state EEG measures would be more reliable than choosing a fixed amplitude level or time. Feedback modalities demonstrated their effect, as well, in influencing the training outcomes; pleasant sounds were able to elicit more positive results than unpleasant ones, particularly when matched with visual feedback. Furthermore, bidirectional NF training paradigms were shown to be more effective than unidirectional training, highlighting that NF training based on identifying the IAF ranges would be preferable to training based on fixed frequency ranges. Eyes closed training was able to determine different and distinct behavioral and cognitive changes when compared to eyes open NF training. Lastly, the authors suggested that the observed learning processes are confirmed when individuals would be able to control

the EEG signal, in terms of inhibition or enhancement, relative to a measured baseline and in the absence of constant feedback information. Moreover, learning to control the feedback signal raised ambiguous results; the physiological and attentional state of the participant could vary during the training leading to different oscillatory power changes (Lynch & Paskewitz, 1971; Plotkin & Rice, 1981; Rice & Blanchard, 1982). Participants may be more attentive at the beginning of the training because of the unfamiliar setting but get more relaxed during the training, influencing over time their power activities. Therefore, having a control group to which an invalid or no feedback is given would address this concern, although several studies demonstrated that even when providing invalid feedbacks participants were able to control their oscillatory activity (Strayer et al., 1973; Lynch et al., 1974; Lindholm & Lowry, 1978), while others showed no effects when valid feedback was given (Beatty, 1971; Beatty, 1972). Due to methodological discrepancy and different behavioral states between control and contingent groups, the ability to control feedback signals due to NF training is ambiguous. Biswas and Ray (2019) implemented an experimental paradigm to investigate whether the same participant's valid, invalid, and neutral feedback conditions would have generated different effects on enhancing alpha power. In particular, they investigated if valid feedback had a stronger effect on alpha power than invalid or neutral/constant feedback. In addition, participants were free to either use or ignore the provided feedback, investigating a possible correlation between alpha power enhancement and subjective level of attention or relaxation. Twenty-four participants executed five training sessions receiving valid, invalid, or constant auditory feedback during the eyes-closed state. Results showed that in those participants who could not sustain their alpha power, giving valid feedback helped them in sustaining alpha power during trials more than giving invalid or neutral feedback. Moreover, participants who showed greater enhancement of alpha power were those who did not pay greater attention to the neurofeedback tone. Although the results showed short-term effects of valid feedback on alpha power maintenance, the authors concluded that alpha NF training when compared to a control condition can help maintenance and enhancement of power activity, particularly in those subjects who are not able to sustain for longer periods their alpha power and or they attend to feedback passively.

2.3.5 NF TRAINING IN HEALTHY OLD AND AD

HEALTHY OLD INDIVIDUALS

As mentioned in the previous section, cognitive decline in elders represents an unavoidable progressive process (Baltes & Lindenberger, 1997) becoming a relevant healthcare topic to be further discussed. This fact stimulated several researchers to develop innovative tools exploiting cognitive reserves while maintaining cognitive functions, such as CT (Baltes et al., 1989). WM and executive functions are mostly affected due to cognitive deterioration – higher-level functioning that is essential for an individual's well-being while carrying out daily living activities. Besides CT, to ameliorate physiological and functional mechanisms against progressive deterioration in aging, advanced approaches were suggested. In this regard, NF has proposed that subjects learn to self-modulate and control real-time brain signals through feedback, a method to maintain and preserve cognitive reserve from declining (da Paz & Tomaz, 2020). In most studies, due to the easier application and probability of obtaining positive results, NF training protocols were designed and applied on healthy young individuals, although some other studies investigated its application in the aging population proving successful results in preserving multiple cognitive functions.

Fernandez et al. (2008) investigated in a group of over 60 years old healthy participants the effect of NF training in which participants were assigned to either an experimental or control group. Before the beginning of the experiment, several parameters such as baseline intelligence quotient (IQ), blood pressure, cholesterol, and hearing were tested. IQ measures were also tested again after the training in all participants. Successively, the experimental group underwent 30 EEG-NF training sessions lasting 30 minutes each tuned to theta oscillations, whereas the control group underwent the same number and duration of training sessions but received a sham/placebo NF. Results did show that the control group, who received a sham NF, demonstrated no changes in the EEG spectrum, whereas the experimental group who received the real NF training protocol improved verbal comprehension and correspondent changes at the alpha and beta oscillations. Fernandez et al. concluded that NF training could be potentially applied to aid older individuals, in whom EEG spectrum abnormal neuronal patterns would manifest the possible development toward cognitive deterioration. In a similar study (Becerra et al., 2012) investigating theta suppression, fourteen healthy old individuals tested on several cognitive tasks before and after the training, were pseudo-randomly assigned to either an experimental group who received the NF or a control group who received a sham NF

over 30 training sessions each lasting 30 minutes. Results demonstrated that the group who underwent the NF training treatment showed enhanced theta suppression differently from the control group. These oscillatory enhancements promoted changes at the absolute power of alpha and improvements associated with WM functioning and verbal comprehension. Furthermore, Angelakis et al. (2007) examined the effect of the NF method aimed to increase peak alpha frequency (PAF) over 30 training sessions. In the study, six healthy old volunteers were randomly assigned to either an experimental or a control group while receiving distinct NF protocols. The experimental group was trained on enhancing PAF, while the control group was instructed to enhance alpha amplitude localized at the POz site. To test the effect of the different implemented NF protocols, before and after the training alpha oscillations recorded at the occipital regions and corresponding cognitive abilities were inspected. From the results, the experimental group was able to enhance PAF, as well as, the control group to enhance alpha amplitude at POz. In addition, they found the effect of NF on alpha oscillations in the experimental groups was localized at the frontal regions with improved processing speed and executive functions, whereas improved verbal, visual, and WM functions were particularly found in the control group. Albeit with a few limitations such as small sample size and different training protocols, the study demonstrated the effect of NF training in improving cognitive functioning in healthy old individuals while enhancing oscillatory activities.

CT and NF training is frequently implemented separately; hence, a combined approach would be suggested to explore their potential effect on neurorehabilitation. In this regard, Portugal et al. (Portugal, 2013a; Portugal et al., 2013b) proposed a combined approach by examining the effect of NF training when combined with cognitive tasks. They hypothesized that the combined training protocol would have generated greater performances over the NF training alone. Thus, a combined neurorehabilitation protocol based on NF was designed targeting alpha and theta power up-training localized at the Fz site. Following the newly suggested protocol, several cognitive tasks such as the N-Back Task and the Corsi Block-Tapping Task were combined with the NF. Ten healthy old individuals performed eight-day training sessions during the study and were assigned with either the NF-combined approach or the NF-single protocol. Results showed that those participants assigned to the NF-single protocol improved performances on WM tasks such as the Digit Span and Matrix Rotation, suggesting positive effects in this specific cognitive domain, although no parallel improvements were observed in other tasks such as the Stroop task or in the TMT indicating that no transfer effect of WM training was extended to other domains. Moreover, the experimental group, undergoing the

combined NF protocol demonstrated higher results in performing both the Digit Span and Matrix Rotation tasks but again with no transfer effects over the TMT and Stroop task. The authors advanced the hypothesis that a combined approach coupling CT with NF may have a greater effect in enhancing cognitive performances. Meanwhile, increased alpha and theta regulatory activities were observed independently of the NF training protocol implemented when investigating the EEG spectrum. Despite positive findings, these results can only be considered preliminary, and no clear conclusions should be claimed regarding effective NF interventions. Indeed, a few study limitations such as the small sample size, the absence of a control group, and inter-individual differences were considered.

Being WM, executive functions, and attentional processes primarily affects aging, Wang and Hsieh (2013) investigated the effect of NF training on improving attention and WM processes by comparing its effects in the older and young subjects. The absence of detailed guidelines and procedures aimed to guarantee which NF protocol would be more effective in slowing an individual's cognitive decline. The study proposed a training protocol to achieve two purposes. First, a comparison between EEG patterns in old and healthy young participants was carried out based on EEG recording. Second, those dysfunctional EEG patterns associated with altered cognitive functions were observed and identified. Based on these two purposes, the study involved the participation of thirty-two volunteers trained to increase theta oscillatory activity at the frontal vertex (Fz). From the obtained results, WM and attention process improved significantly, motivating the possibility that NF protocols successfully applied to younger individuals might also be applied to the elders while guaranteeing positive outcomes. Furthermore, considering attentional complaints, one possible consequence of the executive functioning deterioration during aging, Bielas, and Michalczyk (2021), investigated whether the implementation of NF targeting executive functions in elders would have enhanced the overall executive functioning. The experimental design consisted of twenty NF training sessions (30 minutes each) targeting the up-regulation of beta (12-22 Hz) localized at the Cz. Besides, Stroop and Simon’s tasks were administered to investigate whether NF training would have also ameliorated attentional control. Thus, RTs were measured during the task execution at the end of the NF training protocol. When comparing a control group, who was not exposed to the NF protocol, to the group who received the NF beta up-training, the latter reported improved RTs, concluding that cognitive functioning, particularly targeting executive functions, can be enhanced by implementing an NF training method.

Moreover, through the scientific literature, different training protocols were suggested but it is still debatable whether longer or shorter training protocols would be equally effective in ameliorating dysfunctional oscillations and cognitive decline in aging. In this regard, Reis et al. (2016) tested whether even a short but intensive NF training would have been equally effective in enhancing WM performance in the elderly. In the study, four experimental groups were designed in which the NF training protocol was aimed to target alpha and theta oscillations in healthy aging volunteers. These groups, differently assigned to participants, were: NF alone, NF + CT, CT alone, and sham NF, each consisting of one daily 30-minutes training session distributed over eight days. Results demonstrated that the group who received the NF training alone showed increased alpha and theta power, as well as, improved cognitive performance in a Matrix Rotation task. Differently, moderate performance improvement on the same cognitive task but without any neurophysiological improvements was observed in those groups who received the combined NF with CT or the CT approach alone. In the context of NF based BCI research (Enriquez-Geppert, et al. 2017; Sitaram, et al. 2017, Jiang, et al. 2017), Gomez-Pilar (2016) proposed a combined NF training with a motor imagery-based BCI (MI-BCI) to investigate whether this application would have improved cognitive functions by stimulating neuroplasticity processes. In the study, sixty-three old participants were enrolled, in which 31 were assessed to test this MI-BCI application while the others were assigned to a control group. Successively, the Luria neuropsychological test was performed among participants and their scores were compared between the two groups. Based on those frequencies selected to evaluate cognitive changes, increased relative power in 12, 18, and 21 Hz were observed in the NF group. When investigating cognitive functioning after the training, visuospatial, oral language, memory, and intellectual functions improved significantly. In conclusion, it was possible to confirm the validity of the study and novel application, in which NF was combined with MI-BCI, in enhancing cognitive performances in the elderly. Memory and attention represent central functions in elders, in which innovative training protocols were suggested to stimulate cognitive reserves in this domain. Particularly, the sensorimotor rhythm (SMR) training protocol was proposed (da Paz et al., 2018). In this study, da Paz et al. (2018) proposed an SMR protocol aimed to improve WM performances in older adults. Hence, participants were assigned to either an NF training, a sham NF, or a control condition. Results demonstrated enhanced visual WM performances, as well as, increased theta and beta power at the frontal whereas alpha at the temporal regions for those who underwent the NF training protocol. On the other hand, improved WM task performances were observed in those who

received the sham NF but without any significant EEG power spectrum changes. Lastly, the control group demonstrated neither improvement in WM nor enhanced EEG power spectrum.

The availability of several NF training protocols lacks a defined common criterion when defining rigorous procedures. This regards the choice of selected frequencies, the number of experimental sessions, sample size, the coupling with cognitive tasks, channel locations, the definition of a control/placebo group, and the type of protocol in terms of up or down-regulation of selected frequencies. To conclude this section, it was possible to see that the described studies would suggest and demonstrate that NF training is capable of exploiting brain reserves in the elderly while supporting brain and cognitive activities. Thus, NF training can be used to modulate the EEG activities underlying cognitive and behavioral processes in which particular focus should be given on assessing WM and attention functions; having demonstrated to gain promising results from the intervention of NF.

ALZHEIMER'S DISEASE PATIENTS

As previously discussed, AD represents one of the most relevant neurodegenerative conditions in the aging population, in which the progressive loss of memory coupled with other impairments is a remarkable sign of the disease. Particularly, relevant symptoms are progressive cognitive, affective and behavioral functioning decline, leading to decreased autonomy while performing even simple daily tasks (Livingston et al., 2017). Source of considerable healthcare concern due to the increasing rate of dementia among the aging population (Corrada et al., 2008, 2010), the lack of established treatments leads to the experimentation of innovative methods aimed at valuing cognitive reserve and brain plasticity processes. Among novel methods, previous studies involving healthy volunteers and several clinical populations demonstrated the efficacy of NF training on improving neural activities, cognitive and affective functioning while stimulating brain plasticity (Arns et al., 2017; Sitaram et al., 2017; Thibault et al., 2018). Thus, considering cognitive decline a prominent characteristic of dementia, the combination of CT and NF with operant conditioning was proposed as a potential complementary treatment toward the modulation of the underlying neural activities.

In respect to the possibility of detecting EEG markers predictive of early disease onset, Luijmes et al. (2016) aimed to implement NF training to enhance cognitive performances in pharmacologically treated patients whose quantitative EEG (qEEG; Kanda et al., 2009)

activities were typical of AD pathology and following the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) guidelines (McKhann et al., 1984). In the study, ten patients, who received the NF training program, were compared with 123 AD patients who received the typical intervention recommended for this clinical population. The NF training consisted of 30 sessions, in which individual-specific protocols were designed to self-regulate the EEG activities recorded over the midline electrodes. Before and after the treatment, each experimental group underwent the Cambridge Cognitive Examination (CAMCOG) test to assess the functionality of multiple cognitive domains. Regarding EEG-based reliable change index (RCI), it was found that, unlike those patients who received the usual typical treatment, those who underwent the NF training manifested a higher stabilization of cognitive functions in which learning memory resulted in the most improvement. Moreover, recall memory and recognition were improved after undergoing the NF training and concluding that the NF training generated positive benefits on cognitive functions compared to the treatment typically administered in AD. In a further RTC study, Jirayucharoensak et al. (2019), examined the effect of a newly developed game-based NF training aimed to improve cognitive performances in sixty-five aMCI patients compared to fifty-four healthy elders. Three different experimental groups were designed, and in which participants were assigned: the game-based NF training, the exergame-based cognitive training, and the "care as usual" (CAU) group. Representing the CAU group as the common approach to possibly improve cognitive performances in MCI, the control condition was assigned to the exergame group. To improve attention span and overall cognitive performance, the gamified NF training consisted of five games. Successively, the investigation of NF training effects on neural oscillations was based on measuring the relative power of beta (12-32 Hz) and alpha (8-12 Hz) frequencies recorded at the AF3 and AF4 scalp locations in which the up-regulation of beta/alpha power ratio was measured as an index of attentional level changes. In addition, in a test and retest phase, participants' scores on the Cambridge Neuropsychological Test Automated Battery (CANTAB) were compared between experimental groups to investigate the reliability of the newly gamified NF training method over the other two groups. It was found that rapid visual processing, attention, and spatial working memory (SWM) functions were mostly enhanced in healthy old and aMCI participants, who underwent the NF training, although other functions such as pattern recognition and short-term visual memory, remarkable in aMCI, were not found to be improved. Moreover, no effects of NF were observed on the spatial span (SSP) CANTAB test; a test evaluating attention span and some aspects of WM abilities. However, the exergame

intervention, but not CAU, demonstrated its capability in improving the SSP test. In this case, among healthy old and aMCI, the exergame was considered a better intervention in targeting attention span and assessing WM compared to the NF. In a non-controlled pilot study, Jang et al. (2019) investigated the application of EEG-based and vascular NF in five MCI patients trained over 16 sessions to up-regulate beta (12-15 Hz) oscillations on F6 scalp location based on an individual strategy. Results showed that patients improved their performance after the training in the Korean version of the MoCA scale and in certain domains of the Central Nervous System Vital Signs (CNSVS) neurocognitive test battery, in which memory and cognitive fitness, attention, RTs, and executive functions were evaluated. In particular, higher performance on the N-back task and a higher correlation between the power of beta and the number of sessions was found, albeit few study limitations to be considered before interpreting the results. In a similar study design (Lavy et al. 2019), 11 MCI patients were trained to increase alpha power (8-10 Hz) over Pz among ten experimental sessions. Results demonstrated a positive correlation between peak alpha frequency and the number of training sessions. Moreover, patients improved their composite memory verbal and non-verbal memory recall, in which memory performance was maintained at the four weeks follow-up. However, a robust conclusion cannot be drawn due to the lack of a control group. Recently, in the non-controlled study of Li et al. (2020), 40 MCI patients were trained to self-regulate alpha power and beta (13-30 HZ)/alpha (8-13 Hz) power ratio in 10 NF sessions. A significant increase of delta, theta, alpha, and beta band connectivity was observed, although no behavioral outcomes were measured.

When investigating relevant hallmarks in dementia, particularly in AD, the most frequent divergences in qEEG, cerebral perfusion, increased slow oscillatory activities, or dominant alpha frequency reduction were identified. The possibility to identify early disease onset based on the detection of these markers, and in this context dysfunctional EEG patterns, stimulated several types of research in NF aimed to target and ameliorate those patterns. The study of Berman and Frederick (2009) investigated the capability of NF training on ameliorating dysfunctional oscillations in patients diagnosed with dementia and whether this intervention would have been efficient in restoring cognitive processes such as memory and executive functions. Two groups were designed in which patients were randomly assigned to either an NF training representing the experimental condition or a “waiting list” representing a control condition. Successively, before and after the experiment, qEEG analysis (to identify and localize dysfunctional oscillations needed to be normalized) and neuropsychological tests were

assessed in both group conditions. According to the procedure, for the group who underwent the NF protocol, the training consisted of 30-40 (30 minutes each) sessions in which the feedback signal was based on visual, auditory, or tactile modalities. From the obtained results the authors were able to observe improved cognitive functioning in different domains. Particularly verbal and visual memory were influenced the most, discussing the possibility to implement NF training in early dementia to improve memory and learning.

Although AD is the most common type of dementia cases, other types should also be considered and investigated. Dementia is a neurodegenerative disorder in which the progression of cognitive dysfunction relates to the particular dementia type (e.g., AD, vascular or multi-infarct dementia, frontotemporal, Lewy Body) and its understanding would influence target interventions. In this regard, Surmeli et al. (2016), aimed to explore the effect of NF training in AD and vascular dementia (VD). Twenty participants took part in the study in which nine were diagnosed with AD whereas eleven were diagnosed with VD, and all patients were treated with cholinesterase inhibitors and antidepressant medications. To assess and identify dysfunctional oscillations, based on an individual-specific EEG training protocol, participants of each group underwent a qEEG analysis. The NF training was comprehensive of 10-96 training sessions (60 minutes each) and cognitive functions were also assessed with MMSE test. In general, the results were positive. Indeed, MMSE scores improved significantly, particularly regarding the orientation and recall sub-scales, independently of the dementia type, indicating the optimal NF training outcome on cognition. Furthermore, a reduction in the Clinical Global Impression (CGI) scale was also found when comparing before and after the intervention. When analyzing the qEEG patterns, five patients were not categorized as belonging to the dementia cohort anymore, and the other five were able to decrease their probability of being classified in the dementia database. Overall, the effect of NF was to reduce aberrant theta activity while enhancing alpha and beta power, and a significant decrease in interhemispheric coherence was also observed. However, study limitations should also be considered. Indeed, Surmeli et al. sustained the feasibility of NF potentially effective in treating dementia. These findings are only preliminary. The lack of a control group and experimental blindness represents a significant limitation, accompanied by the fact of having a small sample size generating doubtful conclusions.

As previously discussed, the possible regulation of abnormal neural oscillations would stimulate neuroplasticity and cognitive reserves. This fact is particularly promising when investigating alternative methods to treat AD and its early stages. Recently, the pilot study of

Marlats et al. (2020) investigated the effect of a different NF protocol on cognitive performances in twenty-two MCI patients, although only twenty were able to complete the experiment. The protocol consisted of 20 training sessions targeting (SMR)/theta, distributed over ten weeks. In particular, the aim was to entrain SMR (12-15 Hz) rhythms, while up-regulating SMR frequencies and down-regulating theta (4-8 Hz) and beta (21-30 Hz) frequencies localized at the Cz site. Moreover, patients were tested on their EEG patterns and neuropsychological scores (dependent variables) in a test, re-test, and follow-up assessment. From the MoCA, Goldberg Anxiety Scale (GAS), and the Wechsler Adult Intelligence Scale-IV (WAIS-IV), it was found that WM, episodic memory, and few psycho-affective dimensions (e.g., lower anxiety, fewer cognitive complaints, and better wellness) improved after completion of the NF training program. These results potentially supported the implementation of NF in cognitive rehabilitation while slowing the clinical progression of MCI, and also, at the four weeks follow-up, cognitive and EEG improvements were maintained although the MoCA score returned to their baseline levels. Furthermore, based on the fact that slow oscillations tend to increase whilst fast oscillations tend to decrease in dementia, Marlats et al. aimed to test whether the NF training would have reinforced alpha and beta oscillations while decreasing delta and theta oscillations and whether by ameliorating these oscillations it would have benefited related impaired cognitive processes. They found significant differences in the EEG spectrum between baseline and after NF training; consequently, alpha and theta were enhanced significantly at rest. Nevertheless, to support robust conclusions in which the NF intervention would enhance brain activities, although still debatable is the outcome of increased theta activity, a few study limitations must be considered such as the lack of a control group and small sample size.

To briefly summarize what has been discussed so far, the application of NF in dementia targeting specific neural oscillations underlying related cognitive processes, resulted in a valuable alternative to usual medical approaches, particularly higher beneficial effects were found when applied at the early stages of the disease. By stimulating neuroplasticity and exploiting cognitive reserve, NF would positively influence the disease by delaying its progression and the overall cognitive decline. Nevertheless, despite most studies that have mostly investigated the effect of NF on cognitive processes, non-cognitive states have been less explored. Thus, the study of Kaufmann et al. (2019) aimed to examine the effect of NF training on non-cognitive processes involving a patient diagnosed with minor neurocognitive disorders (MND). The study investigated whether the effect of NF, besides improving

cognitive functions, would have been transferred to non-cognitive symptoms manifested by the disease such as altered sleeping and depression. The experiment, consisting of six training blocks over twelve sessions, aimed to apply and compare two different NF protocols targeting SMR and alpha asymmetry (AA), in which a neuropsychological assessment was conducted before and after the NF. Based on the research hypothesis, depressive symptoms would have been regulated by the AA-NF application, whereas sleeping, memory, and attention by applying SMR-NF. Results proved that AA-NF but not SMR-NF was found to generate higher NF training results on neural oscillations, cognitive and non-cognitive functioning, in which memory and sleep but not attention or depression benefitted from this type of intervention. Hence, NF training confirmed its effectiveness in regulating cognitive and non-cognitive states even in MND; a valuable method to be considered an alternative to typical pharmacological interventions.

In conclusion to this section, it was possible to demonstrate that NF resulted in a valuable alternative and solution to regulate and enhance neural oscillations and cognitive processes, especially when these results are dysfunctional due to progressive neurodegenerative processes. NF, suggested as a feasible complementary treatment in dementia, besides improving cognitive functions it has been also proposed to target brain regions and neural networks related to the processing of emotions; in fact, more than 70% of dementia patients would be affected by a variety of psychological symptoms (e.g., anxiety, depression, apathy) (Lyketsos and Lee, 2004; Craig et al., 2005; Steffens et al., 2005) and NF would result in a beneficial method to induce symptoms improvements (Johnston et al., 2010; Linhartovà et al., 2019).

However, considering the variability among research studies when establishing NF protocols, a few limitations should be considered. A large sample size, blind experiments, the inclusion of a control group, selected frequencies, and channel locations, duration and amount of training sessions, and the choice of cognitive tasks targeting specific cognitive mechanisms are a few examples when designing accurate experiments. In addition, level of education, social engagement, active lifestyle, and other psychological, motivational or social determinants would require attention having a great impact on stimulating cognitive reserve and neuroplasticity; necessary to maximize NF training outcomes in dementia. So far, NF has been described in scientific research, however, several for-profit clinics mostly spread in Europe and North America aimed to treat several pathological conditions. Indeed, these clinics are aimed to advertise and encourage the application of NF training as an authentic and original method

enhancing and regulating several cognitive processes and underlying neural activities; a drug-free intervention, non-invasive and harmless. By offering the medical support of professionals, for-profit clinics rely on the investment of high technology EEG systems to guarantee optimal results within just a few training sessions, although the biggest downside of these services is characterized by very high costs and mostly unaffordable due to longer treatment periods.

Even so, NF and its operating mechanisms need further investigation to better understand cognitive and behavioral mechanisms corresponding to different brain activity patterns. And lastly, considering distinct neural patterns that characterize dementia patients, such as particular EEG frequency alterations in AD and MCI (Cassani et al., 2018), these features represent useful biomarkers with predictive power (Mehler & Kording, 2018; Micoulaud-Franchi et al., 2019); hence; NF while generating an "endogenous" stimulation would be implemented to regulate biomarkers improving cognitive functions targeting residual neural plasticity (Mirmiran et al., 1996; Prichep, 2007).

2.4 THE AIM OF MY RESEARCH WORK

Based on the scientific background described so far and the need to stimulate further investigations toward innovative methods, the current research project, reported by Barbazzeni, Speck and Düzel (2023), was aimed to improve WM in healthy volunteers by combining CT with EEG-NF. In two experiments, a novel NF method coupled with a memory task was proposed to explore the effect of NF training on alpha oscillations, particularly on enhancing alpha power suppression, and consequently its effect on improving cognitive performances. In addition, WM training effects were also investigated concerning the modulation of neighboring frequency bands such as theta and beta oscillations, typically involved in memory processes.

Moreover, following the results and the experience gained by implementing the developed NF method in a research study involving healthy volunteers, an alternative EEG-NF training protocol was proposed to potentially regulate dysfunctional oscillations in a group of pAD when compared to age-matched healthy controls. This research protocol based on NF was suggested as an additional approach to CT and current treatments in pAD. Besides, it aims to be tested and improved by further research in the field of dementia, particularly targeting early disease onset.

Hence, in *Chapter 3*, the scientific objective, method, and results from the first investigation involving healthy volunteers will be reported and discussed. Whereas, in *Chapter 4*, an overview of the suggested research protocol designed for pAD will be described.

2.5 THE PROPOSED RESEARCH METHOD BASED ON NEUROFEEDBACK

2.5.1 EEG RECORDING AND NEUROFEEDBACK

In this Subchapter, a general description of the developed NF method is presented and as reported by Barbazzeni, Speck and Düzel, (2023). The description regards the recording setup, data acquisition, signal pre-processing and spectral analysis, generation, and visualization of the NF signal. Moreover, in *Chapter 3* the specific experimental design and signal analysis procedures concerning the study with healthy volunteers are explained. In *Chapter 4*, adaptations of the experimental design and signal analysis procedures to meet the requirements of the proposed research protocol for pAD are reported.

As described by Barbazzeni, Speck and Düzel, (2023), to record the EEG signal tuned to the alpha frequency band, one set of OpenBCI (http://www.openbci.com/) Gold Cup Electrodes (see Fig. 1) were used. The OpenBCI Gold Cup Electrodes are made of a 1-meter color-coded ribbon cable with 10 passive gold electrodes that were paired with an OpenBCI board to sample EEG activity. The OpenBCI Gold Cup Electrodes include 26 gauge traded wire, single female header termination per cable, Insulation: PVC rated to 80*C and Overall OD: 1.45mm/0.057". A Multi-Cap Cup (https://www.gvb-gelimed.de), OneStep Cleargel (https://eeg-gel.de/en/produkte.php) EEG conductive gel, and Ten20 Conductive paste (http://www.openbci.com/) were used to adhere the electrodes to the scalp. To potentially avoid eye movement and blink artifacts generated from frontal areas, ten gold scalp electrodes were placed over posterior sites. Hence, the electrodes were placed over the central, parietal, and temporal areas according to the 10-20 International System for electrodes placement, except for one electrode placed right at the beginning of the ear canal. The selected channel locations were TP8, C4, in ear-EEG, C3, P4, Pz, P3, TP7, TP9, and TP10. "The right mastoid (TP10) was used as a reference for all electrodes, the left mastoid (TP9) as a noise-canceling, ground electrode." For a better signal quality, impedance was kept below 5kΩ for scalp and in the ear electrodes, respectively. Furthermore, eight channels were used for the NF-training. These channels were TP8, C4, ear-EEG, C3, P4, Pz, P3, and TP7.

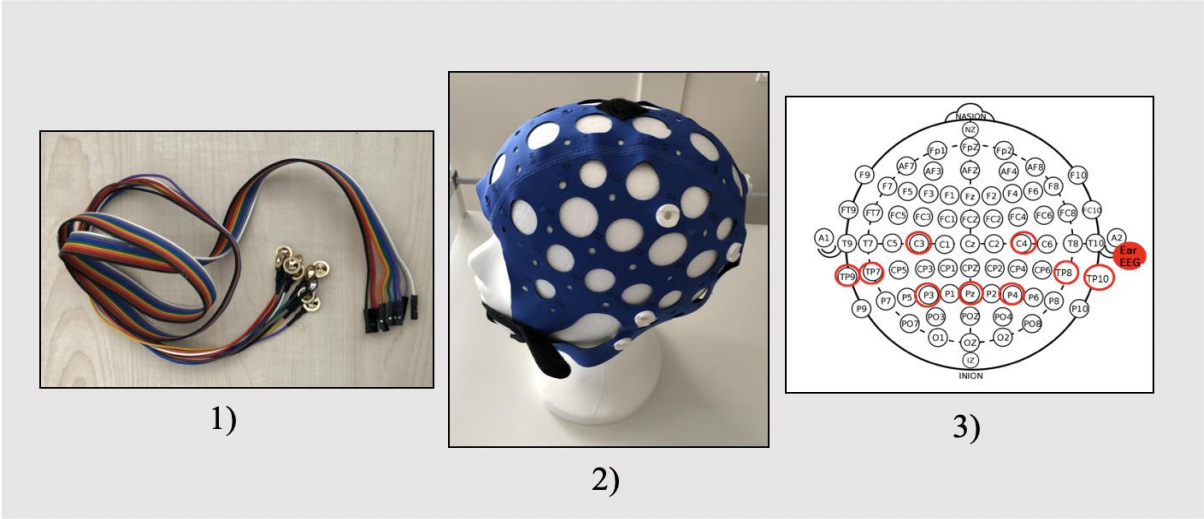

Fig. 1 EEG recording setup 1) *Representation of the OpenBCI Gold Cup Electrodes used to record the EEG signal from the selected locations.* ***2)*** *Representation of the Multi-Cap Cup used to locate the gold cup electrodes on the scalp.* ***3)*** *Simple representation of the electrode locations according to the 10-20 International System.*

The acquired EEG signal was sampled by using OpenBCI Cyton Biosensing Board (http://www.openbci.com/): an Arduino-compatible 8-channels neural interface with a 32-bit processor (see Fig. 2). The Cyton Board system communicated wirelessly to a Macbook Pro (13-inch, 2018), processor 2.3 GHz Intel Core i5, 8 GB memory, via the OpenBCI USB Dongle using RFDuino radio modules. The Cyton Board could also communicate wirelessly to any mobile device or tablet compatible with Bluetooth Low Energy (BLE). To generate the NF signal based on alpha power, a band-pass FIR (finite impulse response) filter was applied based on the individual's alpha range. The individual's alpha range was always estimated in a separate baseline, preceding each training session. The individual's alpha range was computed during an eyes-open EEG recording while participants were instructed to observe for 2 min a fixation cross displayed on a computer screen (see Fig. 3). To construct a time-frequency representation of the signal with a good time and frequency localization, an FFT was applied to the band-pass filtered signal to transform the continuous-time signal into its frequency domain. Moreover, to generate the NF signal the continuous signal was segmented into sliding windows of 0.25 s in which the FFT was applied on each sliding window. Besides, an additional delay of 0.24 s was added to consider for the signal acquisition, preprocessing time, and NF generation. Therefore, 0.49 s was the time period indicating the delay between the recorded EEG signal and the NF. Successively, during task performance, for each experimental trial, the NF signal based on the absolute alpha power was normalized with its respective baseline (6 s), recorded at the beginning of each trial. Hence, the signal was streamed back to the participant in the form of a visual NF on a computer screen. Lab streaming layer (LSL,

https://github.com/sccn/labstreaminglayer) in Python was implemented to provide the online processing and the real-time NF required by the training method.

Furthermore, to test the efficacy of the NF method, a feedback-control condition was also proposed. As will be described in *Chapter 3*, the experimental procedure included an NF-training group (NF) and a control group (CO). Being alpha power suppression the oscillation of interest, the NF-group was trained to increase alpha suppression by receiving a real-time NF signal that was related to the ongoing relative power of an individual's alpha activities. Differently, the CO-group was treated as an active control condition, and even though they received the same experimental instructions to increase alpha suppression, they were trained based on a feedback signal generated by random numbers. In both conditions, groups visualized the feedback signal being displayed as a white ball moving in real-time and displayed on the computer screen (see Fig. 3). A move of the white ball closer to the top of the screen indicated successful alpha power suppression. A move closer to the baseline line indicated lower alpha suppression, thus an increase in alpha power. Both groups were encouraged to control the movement of the white ball closer to the top of the screen. The Macbook Pro was used to execute the entire experiment.

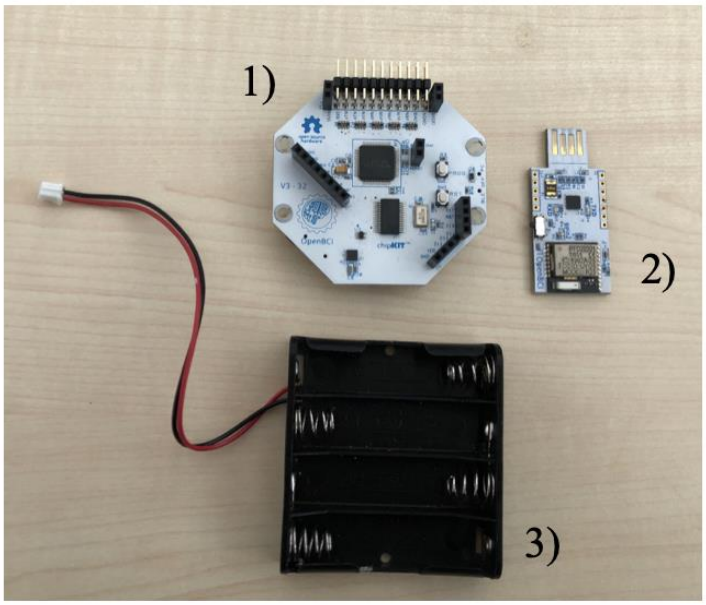

Fig. 2 OpenBCI Cyton Board (8-channels) and USB Dongle. 1) *Representation of OpenBCI Cyton Biosensing Board.* ***2)*** *Representation of the USB Dongle.* ***3)*** *Battery case connected to the Cyton Biosensing Board.*

Fig. 3 Detection of the individual's alpha range. *As part of the NF-training protocol, before the start of each training session, an individual's alpha range was identified during an eyes-open baseline block of 2 minutes, in which participants were asked to observe a fixation cross displayed on a computer screen. By applying a Fast-Fourier Transform, an individual's alpha range was estimated for each participant and successively applied as the individual's alpha range during each NF-training session (2 times for each training day).*

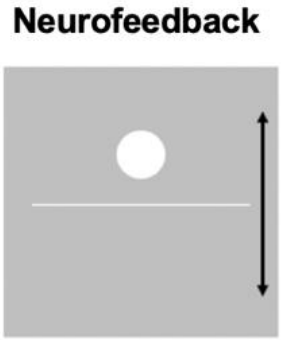

Fig. 4 Schematic representation of the real-time neurofeedback. *The neurofeedback signal was baseline normalized for each trial. While performing the task, during the maintenance period, a white line was set in the middle of the screen, indicating the participant's alpha power at baseline (trial-by-trial). A white ball was moving toward the middle-upper side of the screen when the participant was increasing alpha suppression. In contrast, it was moving closer to the baseline line when the participant was decreasing alpha suppression.*

2.5.2 EEG PRE-PROCESSING AND SPECTRAL ANALYSIS

In this Subchapter, general EEG-preprocessing and signal analysis methods are reported. The description is presented by Barbazzeni, Speck and Düzel, (2023). Moreover, in *Chapter 3* the specific procedures used to analyze the research study involving healthy volunteers are described. In *Chapter 4* the suggested analyses designed for the research protocol involving pAD patients are presented.

"The EEG activity from the OpenBCI system was recorded in volts (V)." Once the data were acquired, the signal was pre-processed and analyzed. In the first pre-processing phase, EEGLAB version eeglab_15x (Delorme & Makeig, 2004) toolbox in MATLAB 2018b (MATLAB and Statistics Toolbox Release 2018b, The MathWorks, Inc., Natick, Massachusetts, United States) was used to import raw EEG data, events of interest, channel locations and to interpolate (possible) bad channels. After this phase, MNE software version

0.18 (Gramfort et al., 2014) in Python (Gramfort et al., 2013) was used to proceed with further analysis. Once the pre-processed data were loaded, the raw EEG signal was epoched for each experimental condition of interest and each training block (i.e., a block is considered as a set of trials). To remove artifacts and to reject bad trials, the "Autoreject" API library in Python (Jas et al., 2016; Jas et al., 2017) was applied. Autoreject API is an algorithm that automatically rejects and repairs bad trials based on their peak-to-peak amplitude; indeed, an individual threshold can be set to reject pre-processed trials presenting artifacts. Furthermore, the signal was further analyzed in MATLAB 2018b by performing a time-frequency analysis with the Morlet Wavelets method in which the signal was filtered in a frequency range of 2-20 Hz with 0.5 Hz resolution (Barbazzeni, Speck & Düzel, 2023).

For averaged epochs and selected alpha frequency range, the analyzed EEG signal indicating the NF event (20 s) was normalized relative to the baseline event (6 s) and according to the decibel log-ratio formula (10*log10(Activity\Baseline)) (Cohen, 2014). However, only 5 s (from 1 to 6 s) of the baseline period were considered for this analysis to avoid possible edge effects. The time-frequency analysis was performed for each participant, channel, experimental condition, and training session across days. Moreover, a grand average between subjects was conducted to analyze the power of alpha for each training session, experimental condition, channel, and group across days (Barbazzeni, Speck & Düzel, 2023).

2.6 CLOSING REMARKS

In *Chapter 2* innovative methods to enhance cognitive functions by targeting the substrate of the cognitive reserve were described. Among these approaches, CT was proposed to ameliorate global cognition while training-specific tasks; potentially effectively delaying cognitive decline. Related to the concept of cognitive reserve influencing age-related brain changes, stimulating neuroplasticity CT demonstrated its efficacy in generating long-term effects while enhancing cognitive functioning not only in healthy young and old volunteers and patients with mild and more advanced AD. WM received the highest attention among different cognitive domains due to its involvement in planning, comprehension, reasoning, problem-solving, information processing, and learning. Indeed, several studies demonstrated the capability of CT in improving performances compared to control groups. Thus, CT was a promising approach, especially when considering the impact that cognitive decline has on daily life activities and the possibility of recovery would ameliorate the quality of patients' life. Moreover, NF was proposed as an alternative approach to current interventions, a method

aimed to self-regulate and enhance brain activation through real-time feedback of brain signals. Mostly based on EEG, NF focuses on optimizing neural oscillations to investigate neurocognitive functions and mechanisms underlying cognitive and behavioral processes. Successfully applied in healthy young volunteers to enhance cognitive and motor performances, the implementation in healthy old individuals, found particular interest while maintaining and preserving cognitive reserve from declining. Commonly demonstrated across studies, the improvement of theta oscillations has transferred beneficial effects on ameliorating alpha and beta oscillations. Besides, also PAF was found to be improved by applying NF training. Furthermore, oscillatory activities were demonstrated to benefit from implementing this novel approach and related cognitive functions. In this regard, combined approaches were suggested in which NF was coupled with CT to enhance its effects. WM, attention, and executive functions, usually affected by cognitive decline, were found to benefit the most from applying these methods. Indeed, the greatest challenge in medical research is aimed at delaying the progression of dementia rate, and NF was found to be effective in stimulating neural plasticity while preventing functions to decline in mild and moderate AD. However, due to the proposal of different NF training protocols and the variability of results among studies, several factors should be considered to establish more standardized, reproducible, and effective protocols underlying the experimental procedures. Finally, based on past research, the aim of this thesis was briefly outlined, as well as, the proposed NF method and analysis procedures were described. Hence, an EEG-NF training method combined with CT and targeting alpha oscillations was proposed to improve WM in healthy volunteers. Besides, the method has been further extended by designing an NF protocol proposal to potentially regulate dysfunctional alpha and theta oscillations in pAD. The applied NF method is discussed in *Chapters 3* and *4*, respectively.

CHAPTER 3:

COGNITIVE TRAINING BASED ON EEG-NEUROFEEDBACK TO IMPROVE WORKING MEMORY IN HEALTHY VOLUNTEERS

3.1 CHAPTER OVERVIEW

Chapter 3 describes the main research study of this thesis and as reported by Barbazzeni, Speck and Düzel, (2023). In the introduction, the research aim will be discussed, focusing on the scientific objective and research hypotheses. Moreover, the method will cover the experimental design, in which the developed NF method, described in *Chapter 2*, has been adapted for this study design, as well as, the analysis. Afterward, the results, their interpretation, and discussion will follow. Lastly, the conclusion will summarize, discuss, and compare the main findings with previous studies reported in the literature. In addition, an overview of *Chapter 4* will be given.

3.2 INTRODUCTION AND SCIENTIFIC OBJECTIVE

Previously discussed in *Chapters 1* and *2*, WM supports the execution of cognitive tasks by temporarily maintaining a short amount of information in mind. Thus, the involvement of WM in planning, comprehension, reasoning, and problem-solving makes its functioning relevant during information processing, executive functions, and learning (Cowan, 2014). Therefore, how can WM be explained concerning neural oscillations? Is there a way to improve WM by training and modulating underlying neural oscillations?

After presenting a stimulus-generating sensory experience, the maintenance of that information encoded in WM is believed to be associated with the sustained activity of neural oscillations. Indeed, this neural activity is needed to retain the previously encoded item toward generating a behavior directed to a goal (Malecki, et al., 2009). Moreover, the momentary maintenance of encoded information through WM is likely related to alpha-band oscillations in which two relevant attentional mechanisms have been proposed: suppression of irrelevant items and selection of those items that should be maintained (Klimesch, 2012). The selection of these items is necessary because these can control the access to our knowledge by semantically orienting attention in time, space, and context (Klimesch, 2012). Thus, while considering alpha oscillations, the response to a stimulus or task performance generates either a decrease or an

increase in its power activity. Hence, this process is called alpha desynchronization or synchronization, respectively (Klimesch et al., 1994; Klimesch, 1997). Particularly, the presentation of a stimulus was found to elicit alpha desynchronization as a mechanism of anticipatory attention. A greater desynchronization has been related to higher performance in a discrimination test (Ergenoglu, et al., 2004; Hanslmayr, et al., 2005) and cognitive load while executing a WM task (Kardan et al., 2020). Moreover, while investigating the effect of motivation expectancies on cognitive performance and neural oscillations, Malecki, et al., (2009) were able to demonstrate that the implementation of monetary reward during the performance of a delayed match-to-sample task (DMST) was capable of boosting cognitive performances by modulating the amplitude and topography of sustained neural activity, as well as, by inhibiting distracting information occurring during the retention period. Similarly, the study of Pornpattananangkul and Nusslock (2016) found that while performing a learning task, the expectation of a monetary reward was related to increased alpha suppression, highlighting the effect of anticipatory reward on neural activities and cognitive performances. Consequently, given alpha suppression and its relation to cognitive functioning, different studies explored the capability of NF training on alpha power to enhance the performance on cognitive tasks by improving the underlying neural activities (Biswas et al., 2019; Hanslmayr et al., 2005; Zoefel et al., 2011). Although it is still debated whether enhanced cognitive performance correlates with an increase (Escolano et al., 2011; Hsueh et al., 2016; Wei et al., 2017) or a decrease (Hanslmayr et al., 2012; Klimesch et al., 1996; Klimesch et al., 1997; Klimesch, 1999) in alpha power, this research thesis was aimed to investigate which role NF training of alpha power suppression plays when associated to reward expectancies and consequently, which effect these modulated oscillations have on WM performances. Moreover, the overall effect of training across days and participants was also observed while investigating neighboring frequencies bands such as theta and beta oscillations, typically involved in memory processes.

In a double-blind study design, sixty participants were randomly assigned to two groups and trained over 5-days to increase alpha suppression receiving either a real-time NF or a control NF (CO, control condition) of their ongoing alpha oscillations during the performance of a monetary-rewarded DMST. To assess the interaction between the effect of NF-training and reward-anticipation on WM, in half of the trials, participants could have expected monetary reward for correct task performance, whereas in the other half and independently of task performance, no reward could have been expected. Furthermore, it was investigated whether

NF training of alpha suppression would have facilitated the performance of untrained and unrelated cognitive tasks by generating transfer effects. Lastly, two studies, namely *Experiment I* and *Experiment II*, were conducted following the same experimental design but different concerning the instructions given during maintenance. In particular, according to inter-individual differences in NF learning, the aim was to compare the effect of implementing different mental strategies during maintenance to strengthen alpha power suppression and, consequently WM performances. In *Experiment I,* research participants were engaged in a mental calculation (MC) task that was unrelated ("far" effects) to the DMST. In *Experiment II,* research participants were required to visually rehearse the sample image through mental imagery (MI) task that was related ("near effects) to the DMST. In both studies, these mental strategies were applied during maintenance and executed in parallel to the control of the alpha-level by receiving the real-time or control NF.

In *Experiment I* and *Experiment II* the following hypotheses were tested:

I. NF training is capable of increasing alpha power suppression while performing the DMST. Throughout the training, the increase of alpha power suppression would be significant in the NF-group compared to the CO-group;

II. The anticipation of a monetary reward for those trials in which a reward is expected (reward trials) would generate a greater increase of alpha power suppression when compared to those trials in which no reward is expected (non-reward trials). This effect would be particularly remarked in the NF-group compared to the CO-group;

III. Improved WM performances during the DMST would be related to enhanced alpha suppression and reward expectancies. Hence, this effect would be mostly observed in reward compared to non-reward trials and in the NF-group compared to the CO-group;

IV. Transfer effects facilitating the performance of unrelated and untrained cognitive tasks would be observed in the NF-group compared to the CO-group due to the effect of enhanced alpha power suppression;

V. The increase of alpha suppression would be higher when implementing MI during *Experiment II* compared to a MC during *Experiment I.* Indeed, MI, closely related to DMST, would generate "near" effects, whereas MC "far" effects on alpha power and WM performances;

VI. By combining *Experiment I* and *Experiment II,* it would be possible to measure participants' memory performance across training days and how WM performances relate to the change of particular oscillatory activities measured during the encoding and maintenance periods.

3.3 METHOD

3.3.1 PARTICIPANTS

"The study was approved by the Ethics Committee of the University Hospital Magdeburg (approval number 205/19). The study protocol was explained in detail to all participants prior to signing the consent form, and withdrawal from the study was possible at any time. Participant confidentiality was maintained, and anonymous codes were assigned to participants. The exclusion criteria were neuropsychiatric disorders, history of epilepsy, chronic abuse (e.g., alcohol, drugs, analgesics, or other substances), participation in other clinical trials, and claustrophobia." (Barbazzeni, Speck & Düzel, 2023).

EXPERIMENT I

"Thirty healthy young volunteers (13 males, 17 females; mean age = 25.04; SD = 2.428) took part in the experiment and were randomly assigned to two groups (NF vs. CO). Participants were trained over five consecutive days in a double-blinded experiment. Fifteen participants (mean age = 24.74, SD = 2.743) received real-time NF of alpha power (NF group). Fifteen participants (mean age = 25.33, SD = 2.024) received control NF (CO-group)." (Barbazzeni, Speck & Düzel, 2023).

EXPERIMENT II

"Thirty healthy young volunteers (18 males, 12 females; mean age = 24.826; SD = 2.313) took part in the experiment and were randomly assigned to two groups (NF vs. CO). Participants were trained over five consecutive days in a double-blinded experiment. Fifteen participants (mean age = 24.600, SD = 2.847) received a real-time NF of alpha power (NF group). Fifteen participants (mean age = 25.053, SD = 1.578) received a control NF (CO-group)." (Barbazzeni, Speck & Düzel, 2023).

3.3.2. EXPERIMENTAL DESIGN

The same study design was executed in *Experiment I* and *Experiment II*, although it differed only by the instructions given during maintenance.

In a double-blind study design, thirty healthy volunteers were randomly allocated to two experimental groups (NF vs. CO) according to the "sealed envelope system" (Torgerson & Roberts, 1999; Kim & Shin, 2014). With eyes closed, the experimenter chose one of two matching envelopes, that were previously shuffled, and indicating the type of training treatment (i.e., NF or CO) . "The experimenter assistant was in charge of reading the content and assigning participants to the corresponding group." For the entire duration of the training, the experimenter and participants were blind about the type of assigned training.

All visual stimuli were displayed on a computer screen of size = 1680x1050 pixels, width = 47.5 cm, luminosity = 80, contrast = 80, and visual angle = 10° 25' 0.36".

Before the training, a familiarization session preceded five consecutive training days. During the familiarization session, participants were explained the experimental procedure, the NF method, and how to execute the training task through a short practice. Afterward, the experiment started. An individual's alpha range was computed during a different baseline session and preceding each DMST performance for each daily session. Each training day consisted of two DMST runs (i.e., a run is considered as a set of trials) of 15 min each. A rest between these runs was given to avoid any effect of fatigue.

Participants were instructed to apply a mental strategy while monitoring their alpha level to enhance alpha suppression during maintenance. Thus, in *Experiment I*, participants were required to execute a MC task (Kawabata, 1974; Lin et al., 2012; Magosso et al., 2019). This task consisted of performing a mental subtraction aimed at sustaining attention. Differently in *Experiment II*, participants were required to implement a MI task. This second strategy consisted of visually rehearsing the *sample image* previously encoded. Moreover, research participants were also trained to suppress their alpha power while receiving real-time NF or CO feedback displayed on the screen in this period. Hence, participants assigned to the NF-group were trained to increase their alpha suppression, receiving real-time feedback of their ongoing individual alpha power. Differently, participants assigned to the CO-group, although also instructed to increase their alpha suppression, received a feedback signal created by a series of random numbers. In both experimental groups, the feedback signal was visualized on

the screen in the form of a white ball moving in real-time. In the NF-group the movement of the ball was proportional to the relative power of alpha. Particularly, a movement toward the top of the computer screen denoted successful alpha suppression, while a movement closer to the baseline line denoted an increase in alpha power. In the CO-group, the movement of the white ball followed the same logic although generated by random numbers, and thus unrelated to the relative power of alpha. The description is reported by Barbazzeni, Speck and Düzel, (2023).

Furthermore, to test transfer effects, before starting the training and at training completion, both groups performed two additional cognitive tasks (i.e., transfer effect tasks). Lastly, at the end of the experiment, a questionnaire was given to investigate participants' opinions of the entire experiment and training outcome.

3.3.3 EEG RECORDING AND NEUROFEEDBACK

The method implemented to record the EEG activity and to generate the NF signal was described in *Chapter 2 Subchapter 2.5.1*. However, the method has been adapted and further described in this study (Barbazzeni, Speck & Düzel, 2023).

As relevant component of the NF training method before the performance of each daily DMST session, an individual's alpha range was measured during a 2 min eyes-open baseline session. During this separate session, research participants were required to relax and observe a fixation cross displayed on the screen. By applying the FFT, the individual's alpha range was computed based on three different frequency ranges and while considering the lower and upper alpha limits: 6-10 Hz, 7-11 Hz, and 8-12 Hz. Thus, the frequency range that would have shown the highest frequency power was selected as the individual's alpha range. Successively, based on the estimated individual's alpha range, an individual NF training was performed for each DMST session.

3.3.4 EEG PRE-PROCESSING AND SPECTRAL ANALYSIS

The general EEG pre-processing and analysis procedure described *Chapter 2 Subchapter 2.5.2*. However, adapted analyses for the current study are reported below.

As described in Barbazzeni, Speck and Düzel, (2023), for each DMST session, pre-processed EEG data were epoched for reward and non-reward trials. Each epoch consisted of five events,

including a time period (i.e., epoch length) of 31s. Epochs included the time period from *baseline* (1st event) to the end of the *probe image* (5th event) appearance. Moreover, after artifact rejection and the Morlet Wavelets analysis, the signal corresponding to theta (4-7 Hz), alpha (7-13 Hz), and low-beta (13-20) frequency bands were extracted. The analyzed signal, computed during the maintenance period (i.e., *NF event*), has been normalized (i.e., *baseline event*) for averaged epoch and selected frequency band. The time-frequency analysis was computed for each subject, channel location, reward condition, and training day followed by the grand average among participants. In the entire research study (*Experiment I* and *Experiment II*) 300 distinct EEG recording sessions were analyzed.

3.3.5 MONETARY REWARDED DELAYED MATCH-TO-SAMPLE TASK (DMST)

The DMST has been widely implemented to investigate WM processes for learned associations (Chusadama, 2010). The task implemented in this research study was a modified version of the common DMST and developed to evaluate WM performance for encoded stimuli (see Fig. 5). According to the request of participants, the task was displayed in two possible languages (English or German).

Each trial started with a baseline (6 s) in which participants were instructed to relax and observe a fixation cross. This period was followed by the presentation of a visual cue (1 s) to test reward-based motivation effects. The cue indicated whether correct performance in the current trial would have been rewarded or not. Hence, a blue square indicated a reward trial, whereas a red square indicated a non-reward trial. Afterward, a trial-unique visual object (i.e., the *sample image*) was presented to participants for 2 s. This event was followed by a delay (maintenance period) in which the NF training was executed for a period of 20 s, while applying the corresponding mental strategy according to *Experiment I* or *II*. This maintenance period was also necessary to investigate whether participants could maintain the encoded information in their WM. Then, the trial terminated with the presentation of a *probe image* displayed for 2 s. At this stage, participants were asked to choose whether the probe image was a matching (“old”\”alt”), or a similar but new (“new”\”neu”), non-matching version of the sample previously presented by pressing a button on a keyboard. The button presses were counterbalanced for each DMST run within participants. Moreover, in reward trials, correct performances were followed by a reward that was displayed as a “50-cent” image (1 s), while incorrect performances were followed by a grey screen (1 s). Differently, in non-reward trials,

correct and incorrect performances were followed by a grey screen (1 s). To assess WM performance, accuracy and RTs were measured during the recall process.

A list containing 878 computer-generated stimuli was randomized and these randomized stimuli were subdivided into 10 DMST sessions, displayed over 5-days of training. Each training day consisted of 2 DMST sessions. Each DMST session included 24 trials: 12 reward trials and 12 non-reward trials. Moreover, each reward condition consisted of 6 matching and 6 non-matching probes that were presented in random order. Hence, 48 trials (subdivided for each condition) were presented daily across the training.

In accordance with the signal detection theory (Verde et al., 2006), the accuracy score in the DMST was computed based on the difference between Hit Rates (HR) and False Alarm Rates (FARs). More precisely, when the *sample image* was "old" and the *probe image* classified as "old", a Hit denoted a correct performance. Differently, when the *sample image* was "new" but the *probe image* was classified as "old", a False Alarm denoted an incorrect performance.

Psychopy (Peirce et al. 2019) in Python was used for the presentation and timing of all stimuli implemented in the DMST. The description of the task is reported by Barbazzeni, Speck and Düzel, (2023).

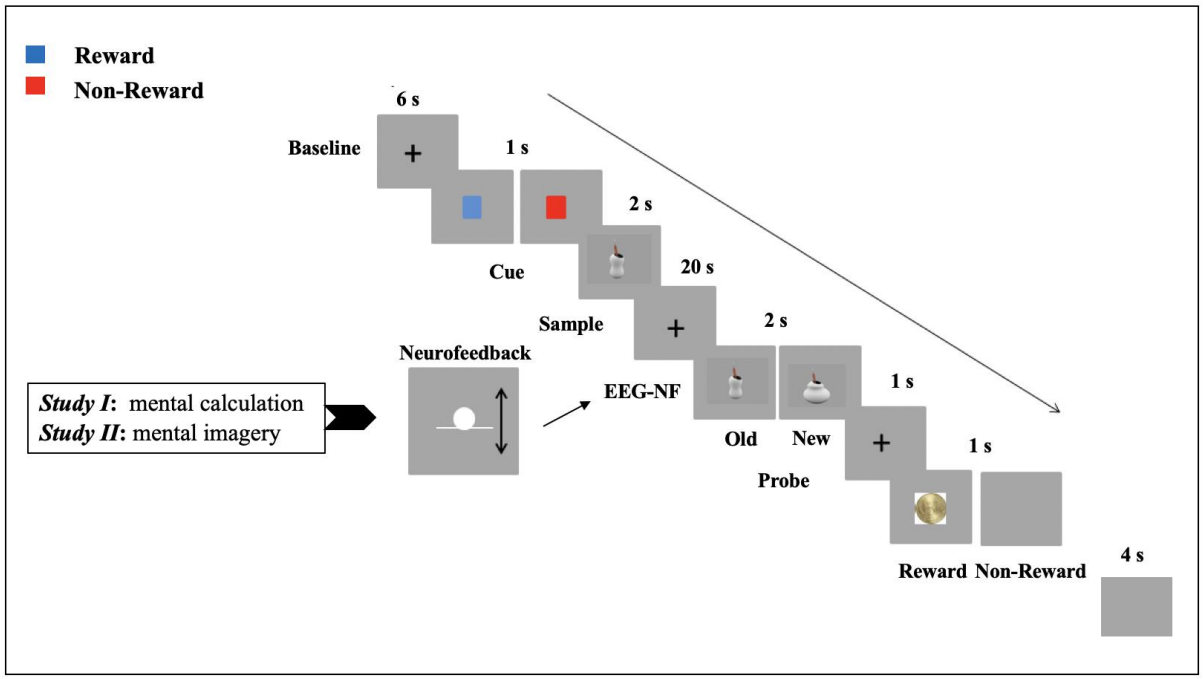

Fig. 5 Single-trial representation of the monetary-rewarded DMST. *Each trial started with a baseline of 6 s, recording alpha oscillations at rest while participants were observing a fixation cross. Successively, a colored cue was presented for 1 s. The cue was red or blue. A red square would have anticipated a non-monetary reward condition in which no reward was given. Thus, this condition was independent of task performance. A blue square*

would have anticipated monetary reward, and this condition was dependent on WM task performance. Afterward, a sample image, represented by a visual object, was displayed for 2 s. This event was followed by neurofeedback. During this event, called maintenance, the feedback signal was displayed for the 20 s as a white ball moving in real-time. During this period, research participants were instructed to control and regulate the ball's movement by applying a mental strategy. In Experiment I, participants were engaged in a mental calculation task, whereas in Experiment II, participants were engaged in a mental imagery task by mentally rehearsing the sample image. In both cases, the goal was to control the movement of the ball toward the top of the screen, away from the baseline line. While the ball's movement toward the top was inversely proportional to the relative power of the alpha power in the NF-group, in the CO-group the movement of the ball was generated by random numbers. Then, the probe image was presented for 2 s, and participants were required to choose either "old" or "new". In this period, RTs were estimated. Based on the cue condition (i.e., a predictor of reward or non-reward) and subjects' performance, a monetary reward was displayed or not for 1 s and presented as a 50-cent image or grey screen in case of no reward or incorrect performance. A short pause of 4 s between trials was given, displayed as a grey screen to switch from one trial to the other (Barbazzeni, Speck & Düzel, 2023).

3.3.6 TRANSFER EFFECT TASKS

To test whether NF-training would have generated transfer effects on unrelated and untrained cognitive tasks, the Mnemonic Similarity Test (MST) and the Stroop task were used. Transfer effect tasks were performed pre (before day-1) and post (after day-5) the NF-training and presented in two possible languages (English or German) depending on the choice of participants.

An adapted version of the MST (Stark et al., 2013) was used. In a first phase (i.e., incidental study phase) research participants were displayed 128 images of visual objects on the screen for 2 s. Participants were required to judge each visual stimulus as "indoor" \ "innen" or "outdoor" \ "aussen" by pressing different buttons on a keyboard. In a second phase (i.e., test phase), participants were required to discriminate objects, displayed for 2 s, as "old" \ "alt" (repetitions), "similar" \ "änlich" (lures) and "new" \ "neu" (foils) by pressing different buttons on a computer keyboard. In relation to the previous study phase, ''old'' visual objects were already presented, ''similar'' visual objects were similar but different, and ''new'' were never presented before. "The test phase included 192 trials: 64 repetitions, 64 lures, and 64 foils."

Furthermore, in the Stroop task (Simons, 1935), several words were presented for 2 s with various colors and meanings. "Word colors and word meanings were congruent or not." Participants were required to read the word colors (phase 1) or the word meaning (phase 2) of the presented words. "The task consisted of 280 trials, equally divided for each phase." The choice of colors was: "green" \ "grün", "blue" \ "blau", "yellow" \ "gelb", and "red" \ "rot".

"The presentation and timing of all stimuli in the MST and Stroop task were controlled using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com) and Psychopy in Python (Pierce et al. 2019), respectively." Based on the

signal detection theory, the performance of the MST and the Stroop task were computed on the accuracy rates. The description of the task is reported by Barbazzeni, Speck and Düzel, (2023).

3.3.7 QUESTIONNAIRE POST-NF-TRAINING

A questionnaire was given to participants at experiment completion (day-5), following the MST and Stroop task performance. The questionnaire was given in two possible languages (English or German) depending on the choice of participants. Twelve questions were asked in a customized 6-points Likert scale, where:

- 1 = “absolutely not good” \ “überhaupt nicht gut”
- 2 = “not good” \ “nicht gut”
- 3 = “slightly not good” \ “ein bisschen nicht gut”
- 4 = slightly good” \ “ein bisschen gut”
- 5 = “good” \ “gut”
- 6 = “very good” \ “sehr gut”

or from:

- 1 = “absolutely not difficult” \ “überhaupt nicht anstrengend”
- 2 = “not difficult” \ “nicht anstrengend”
- 3 = slightly not difficult” \ “ein bisschen nicht anstrengend”
- 4 = “slightly difficult” \ “ein bisschen anstrengend”
- 5 = “difficult” \ “anstrengend”,
- 6 = “very difficult” \ “sehr anstrengend”

and in a “yes" \ “ja” and “no” \ “nein” scale. The twelve questions are reported in *Appendix A* and presented by Barbazzeni, Speck and Düzel, (2023).

3.3.8 STATISTICAL ANALYSIS - SEPARATE FOR EXPERIMENT I AND EXPERIMENT II

The statistical analyses were performed using SPSS software version 26.0 as reported by Barbazzeni, Speck and Düzel, (2023).

DMST

Behavioral performances were measured in terms of accuracy and RTs, and analyzed with two-way mixed repeated-measures ANOVAs. The within-subjects factors included the independent variables training "day" (including 5 levels: day-1, day-2, day-3, day-4, day-5) and "reward condition" (including 2 levels: reward, non-reward). The between-subjects factor included the variable experimental "group" (NF-group versus CO-group), whereas the variable "gender" was used as the covariate on the mean distribution. The covariate "gender" was discarded only when analyzing the accuracy results because found to significantly impact the results. However, this choice did not affect the analysis because the factor "gender" was unrelated to the hypothesis under investigation. In case the Mauchly's Sphericity Test assumption was violated, any corrected ANOVAs results were made with Greenhouse-Geisser correction.

TRANSFER EFFECT TASKS

A between- and within-subject analysis based on a non-parametric statistic was used to analyze the performance of the MST and Stroop task. The Mann-Withney U (two-independent samples) Test was used to analyze the performance between-subjects, whereas the Wilcoxon Signed Ranks (two-related samples) Test was used to analyze the within-subject performance. In the Mann-Withney U Test, the parameter "U" denotes the test statistic. The parameter "N" denotes the mean rank. In the Wilcoxon Signed Ranks Test, the parameter "T" denotes the sum of ranks. The parameter "z" denotes the Z statistic.

QUESTIONNAIRE

The answers from the questionnaire were analyzed in relation to the frequencies and computed according to the median distribution. In particular, the percentage value corresponding to the most frequent answer was considered as the result.

TIME-FREQUENCY ANALYSIS

The power of theta, alpha, and low-beta was statistically analyzed with a three-way mixed repeated-measures ANOVAs. The within-subjects factors included the independent variables training "day," "reward condition", and "channel" location (including 3 levels: P4, Pz, P3). The between-subjects factor included the variable experimental "group", whereas the variable "gender" was used as the covariate on the mean distribution. Due to problems occurring during

signal recording, one participant (from the CO-group, in *Experiment II*) was removed only from this analysis because considered an outlier (i.e., generating EEG data which deviated from the normal distribution). In case the Mauchly's Sphericity Test assumption was violated, any corrected ANOVAs results were made with Greenhouse-Geisser correction. In some exceptions ($\varepsilon > .75$), the Huynh-Feldt correction was used.

3.3.9 STATISTICAL ANALYSIS - COMBINED ANALYSIS ACROSS EXPERIMENT I AND II

A combined analysis across experiments was performed to investigate how WM improvements observed across the 5-days of training were related to the modulation of specific neural oscillations measured at (*sample image*) encoding and maintenance periods. Thus, participants of *Experiment I* and *II* were combined to create an entire sample (n = 60; female = 29, male = 31, mean age = 24.95, SD = 2.389). One research participant (from the CO-group, in *Experiment II*) was excluded from the analysis because considered an outlier (as previously explained), and thus the analyzed sample included 59 subjects.

For this analysis, the relative power for theta, alpha, and low-beta bands measured during encoding and maintenance was investigated only for channels P4 and P3 located at the parietal regions. Oscillatory activities occurring during encoding (*sample image* presentation) were investigated only considering the first 1000 ms of the encoding period. The reason is related to previous findings. Indeed, several electrophysiological studies have already demonstrated that the encoding process occurs rapidly (Ranganath & Paller, 1999). It was suggested memory encoding can be influenced by the early activity of beta (Deiber et al., 2007) and alpha (Nenert et al., 2012; Kleberg et al., 2014) oscillations already occurring within 500 ms after the onset of a stimulus. Differently, the effect of theta oscillations (Osipova et al., 2006; Kleberg et al., 2014; Guderian et al., 2009) tend to be observed over longer intervals which usually includes a time period not less than 1000 ms after the onset of a stimulus. Therefore, the encoding period was divided into two-time windows of 500 ms each (S1 and S2, respectively). The time window S1 included the encoding period from 0 to 500 ms. The time window S2 included the encoding period from 500 to 1000 ms. Moreover, the extracted and the analyzed signal associated with each time window was normalized to the baseline. To perform the normalization, only the last 500 ms of the baseline period before stimulus (i.e., *sample image*) onset were considered.

To perform this exploratory analysis, a Linear Mixed-Effect Model (LMM) (Pinherio & Bates, 2004) analysis was conducted to investigate any relationship between WM performances and

oscillatory changes observed across the 5-days training. Indeed, the LMMs are good alternatives to the commonly used repeated-measures ANOVAs. Two main advantages are usually considered when implementing an LMM. Firstly, instead of limiting the variance factor into an error term, the LMM allows the specification of random effects (e.g., subjects). Thus, the variance associated with the defined term can be better distributed. Secondly, compared to the ANOVAs, the LMM can better deal with possible missing data. Therefore, a few studies have preferred to apply LMM in their analysis (Walker, Redfern, & Oleson, 2019; Rund et al., 2016; Yuki et al., 2019; Magezi, 2015).

To predict accuracy and RTs performances (dependent variables), alternative hypothesis models were designed and compared to a null hypothesis model. The models were built under the assumption that:

- **H_1**(alternative hypothesis models): the observed WM performance across the training days was explained by the intervention of specific experimental factors occurring during the encoding and the maintenance periods, even when controlling the variability in performance across days and participants;

- **H_0**(null hypothesis model): the observed WM performances across training days were explained by the random variability in performance, and thus unrelated to any experimental factor.

All models were designed by using the restricted maximum likelihood (REML). H_1 models consisted of different fixed effect coefficients considered as continuous or categorical variables. Examples of continuous variables were "frequency bands" (i.e., the relative power of alpha, theta, and low-beta oscillations) estimated for each "channel" (i.e., P4 and P3 location), during "encoding" (i.e., S1 and S2 time windows), or "maintenance" (20 s time period), and training "day" (i.e., day-1 = 1, day-2 = 2, day-3 = 3, day-4 = 4, day-5 = 5). Examples of categorical variables were the "reward condition" (i.e., A: "non-reward"; B: "reward", where condition B was compared to the reference level A), and "group" (i.e., A: "CO"; B: "NF", where condition B was compared to the reference level A). Furthermore, a random effect was also defined to investigate the variability in WM performance across the 5 training days and participants. The random effect included a slope (fixed effect: "day") and the intercept varied by subjects.

In a first exploratory analysis phase, 3 models were built and only main effects were considered. When investigating the encoding period, the (full) alternative hypothesis H_1 model consisted of 16 predictors: " *'Accuracy (or RTs) ~ 1 + Group + Day + Reward + P4_S1_Alpha + P3_S1_Alpha + P4_S2_Aalpha + P3_S2_Alpha + P4_S1_Theta + P3_S1_Theta + P4_S2_Theta + P3_S2_Theta + P4_S1_Beta + P3_S1_Beta + P4_S2_Beta + P3_S2_Beta + (1 + Day|Subject)'*. " During the maintenance period, the full H_1 model consisted of 10 predictors: " *'Accuracy (or RTs) ~ 1 + Group + Day + Reward + P4_Alpha + P3_Alpha + P4_Theta + P3_Theta + P4_Beta + P3_Beta + (1 + Day|Subject)'*. " Moreover, the statistical significance of alternative hypothesis H_1 models were analyzed in comparison to the null hypothesis H_0 model. Hence, H_0 was a nested model of H_1 which was built including the intercept, one predictor, and the same H_1 random effect: " *'Accuracy (or RTs) ~ intercept + Day + (1 + Day|Subject)'*. " Thus, the model adequacy of H_1 over H_0 was analyzed with the maximum likelihood (ML) ratio test.

In a second phase, *post-hoc* analyses were performed to investigate, eventually, interaction effects between those factors that were found significant from the previous analysis. Hence, 3 models were built to predict WM performances. Only prediction on accuracy during the maintenance period was no longer explored because no particular neural oscillations were found significantly related to accuracy improvements (in the first analysis phase). When investigating mean accuracy during the encoding period, the interaction model H_1 model consisted of 8 predictors: " *'Accuracy ~ 1 + Group + Day + Reward + P4_S2_Beta + Group*P4_S2_Beta + Reward*P4_S2_Beta + Day*P4_S2_Beta + (1 + Day|Subject)'. "* Differently, mean RTs during encoding were investigated with an interaction model H_1 model consisting of 7 predictors: " *'RTs ~ 1 + Group + Day + Reward + P4_S1_Theta + Group*P4_S1_Theta + Day*P4_S1_Theta + (1 + Day|Subject)'. "* During the maintenance period, mean RTs was assessed with an interaction model H_1 model consisting of 11 predictors: " *'RTs ~ 1 + Group + Day + Reward + P4_Beta + P3_Beta + Group*P4_Beta + Group*P3_Beta + Day*P4_Beta * Day*P3_Beta + P4_Beta*P3_Beta + (1 + Day|Subject)'. "* Also, in this phase, the model adequacy of interaction models H_1 over H_0 was analyzed with the maximum likelihood (ML) ratio test.

The LMM investigation was conducted in MATLAB 2018b. The graphs were generated using R software version 1.4.1106 (R Core Team, 2017; Ripley, 2001; Aiken and West, 1991). Furthermore, mean differences between experimental conditions and groups were compared by applying a paired sample t-test and independent t-test analyses. These analyses were

conducted in SPSS software version 26.0. A description of the combined analysis across *Experiment I* and *II* is reported by Barbazzeni, Speck and Düzel, (2023).

3.4 RESULTS: EXPERIMENT I

All the results and related statistics from *Experiment I* and described in this section are reported by Barbazzeni, Speck and Düzel, (2023).

3.4.1 DMST

Accuracy was investigated across 5-days (see Fig. 6.1). A significant main effect of "day" ($F_{(4,112)} = 8.302$, $p = .000$, $\eta_p^2 = .229$) indicated improved performances through the training. However, the improvement in accuracy was not influenced by reward-anticipation. Indeed, a significant main effect of "reward" ($F_{(1,28)} = 2.557$, $p = .121$, $\eta_p^2 = .084$) was not found. Moreover, no differences in accuracy performances were observed between groups. Thus, a non-significant main effect of "group" ($F_{(1,28)} = 1.101$, $p = .303$, $\eta_p^2 = .038$) was found across 5-days and as indicated by the interaction "day*group" ($F_{(4,112)} = 1.374$, $p = .247$, $\eta_p^2 = .047$). Furthermore, improved accuracy was unrelated to either the NF-training or reward-anticipation effects. Between groups, the interaction between NF-training and reward-anticipation was not significant ("day*reward*group": $F_{(4,112)} = .606$, $p = .659$, $\eta_p^2 = .021$).

Moreover, RTs were investigated across 5-days (see Fig. 6.2). A significant main effect of "day" ($F_{(2.800,75.601)} = 3.318$, $p = .027$, $\eta_p^2 = .109$) indicated improved performances through the training. In addition, a significant reward-anticipation effect was found on enhanced RTs performances as indicated by a significant main effect of "reward" ($F_{(1,27)} = 8.344$, $p = .008$, $\eta_p^2 = .236$). However, RTs performances did not differ between groups. Thus, a non-significant main effect of "group" ($F_{(1,27)} = .034$, $p = .856$, $\eta_p^2 = .001$) was found across 5-days and as indicated by the interaction "day*group" ($F_{(2.800,75.601)} = .232$, $p = .861$, $\eta_p^2 = .009$). Furthermore, faster RTs were unrelated to either the NF-training or reward-anticipation effects. Between groups, the interactions between NF-training and reward-anticipation was not significant ("day*reward*group": $F_{(4,108)} = 1.486$, $p = .212$, $\eta_p^2 = .052$).

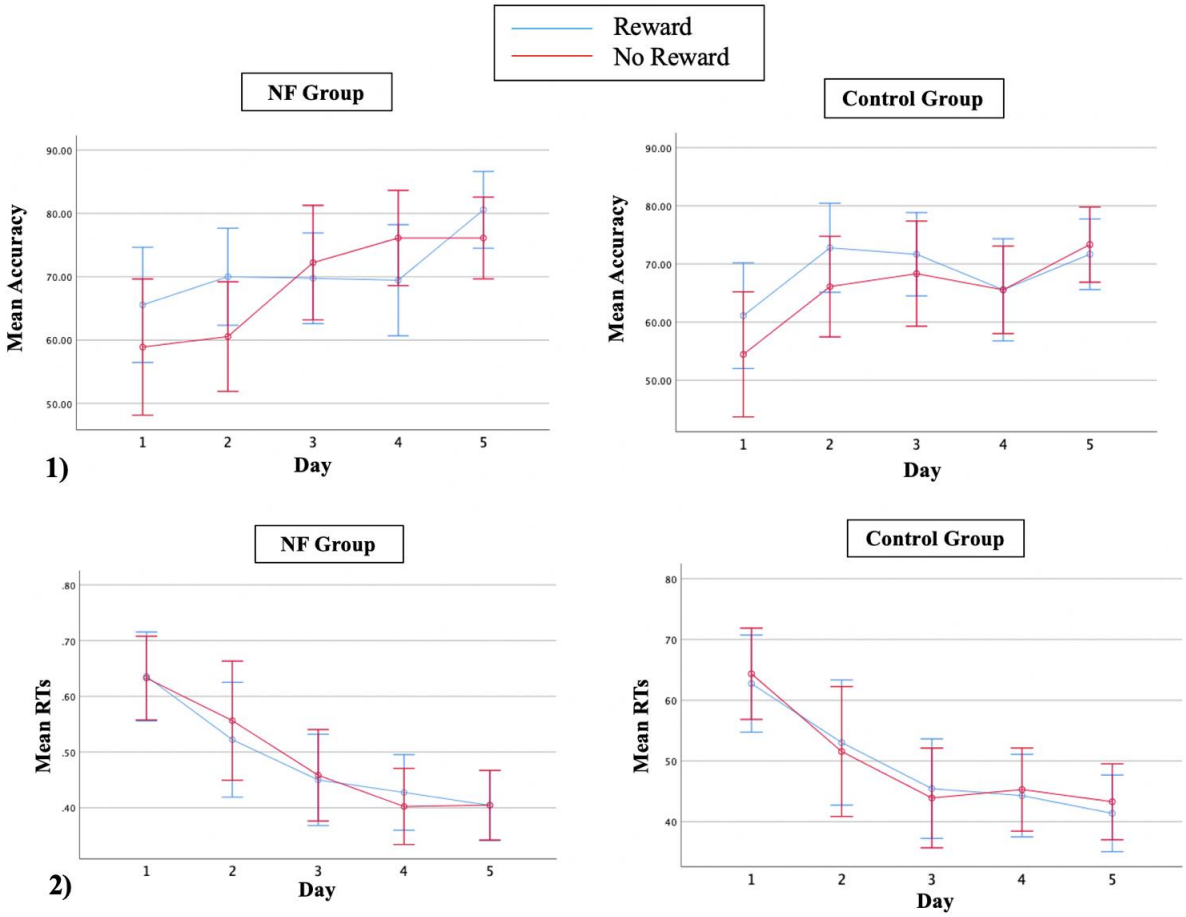

Fig. 6 Results of mean accuracy and reaction times in Experiment I. 1) *Mean accuracy is presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean accuracy.* ***2)*** *Mean RTs are presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean RTs. In all figures, blue lines indicate behavioral performance in response to the reward condition. Red lines indicate behavioral performance in response to the non-reward condition. Error bars indicate 95% confidence intervals (CI) with covariate gender in all figures. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

3.4.2 ALPHA POWER (7-13 HZ)

The relative power of alpha was investigated across 5-days (see Fig. 7). Although alpha power tended to decrease, power changes across training days were not significant. Thus, a non-significant main effect of "day" ($F_{(2.543,68.672)}$ = 1.480, p = .232, η_p^2 = .052) was found. In addition, a similar trend was observed in both groups, and no significant differences in alpha power were found. Indeed, the main effect of the "group" ($F_{(1,27)}$ = .467, p = .500, η_p^2 = .017) was not significant. In addition, no significant differences in alpha power were found in response to the reward conditions. Hence, a reward-anticipation effect on alpha power suppression was not found and the main effect of "reward" ($F_{(1,27)}$ = 1.031, p = .319, η_p^2 = .037) was not significant. Moreover, no differences in alpha power were found across training days regarding the interaction between the NF-training and reward-anticipation effects. Indeed, the

interaction "day*reward*group" ($F_{(2.617,70.668)}$ = .390, p = .734, η_p^2 = .014) was found not significant. The relative power of alpha was also investigated by comparing only day-1 and day-5. Hence, the interaction "day*reward*channel" ($F_{(2,54)}$ = 4.743, p = .013, η_p^2 = .149) was found significant. The effect of this interaction indicated that a decrease in alpha power was observed on day-5 compared to day-1 and across all the analyzed parietal channel locations. This decrease in alpha power was observed in reward compared to non-reward trials from day-1 (MD = .009, SEM = .046) to day-5 (MD = -.117, SEM = .084). Nevertheless, this interaction effect was not further investigated.

From the observation of the time-frequency analysis (see Fig. 8.1), it was noticed that on day-1 in reward-trials and after the encoding period, a consistent alpha suppression was found in the NF-group although only during the initial 7 s of the maintenance period. Differently, this pattern was not observed in the CO-group. Thus, a paired t-test *post-hoc* analysis was performed to investigate whether the level of alpha-suppression (in channel P4, on day-1, for reward-trials) during this period was different between the two groups. It was found that on average alpha power was higher in CO than NF (M = .24049, SD = .63725, SEM = .16454, 95% CI[-.11241, .59339]) but the difference was not significant (t_{14} = 1.462, p = .166). Hence, no NF-training effect on alpha suppression was observed.

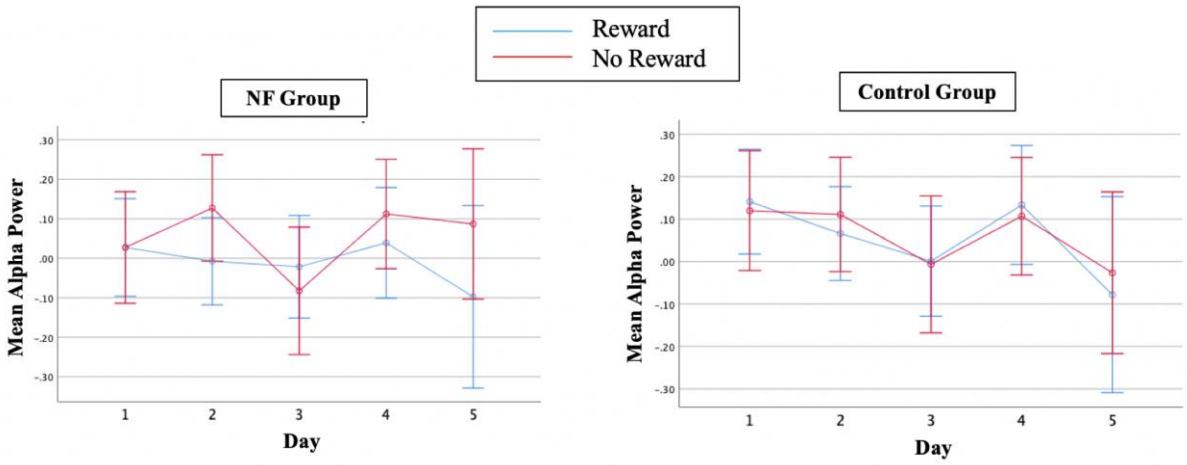

Fig. 7 Results of mean alpha power in Experiment I. *The analysis was performed on parietal channel locations P3, Pz, and P4 and the presented signal indicates the grand average across these channel locations. Mean alpha power is presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean alpha power. In both figures, blue lines indicate data from the time-frequency analysis and in response to the reward condition. Red lines indicate data from the time-frequency analysis and in response to the non-reward condition. In both figures, error bars indicate 95% confidence intervals (CI) with covariate gender. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

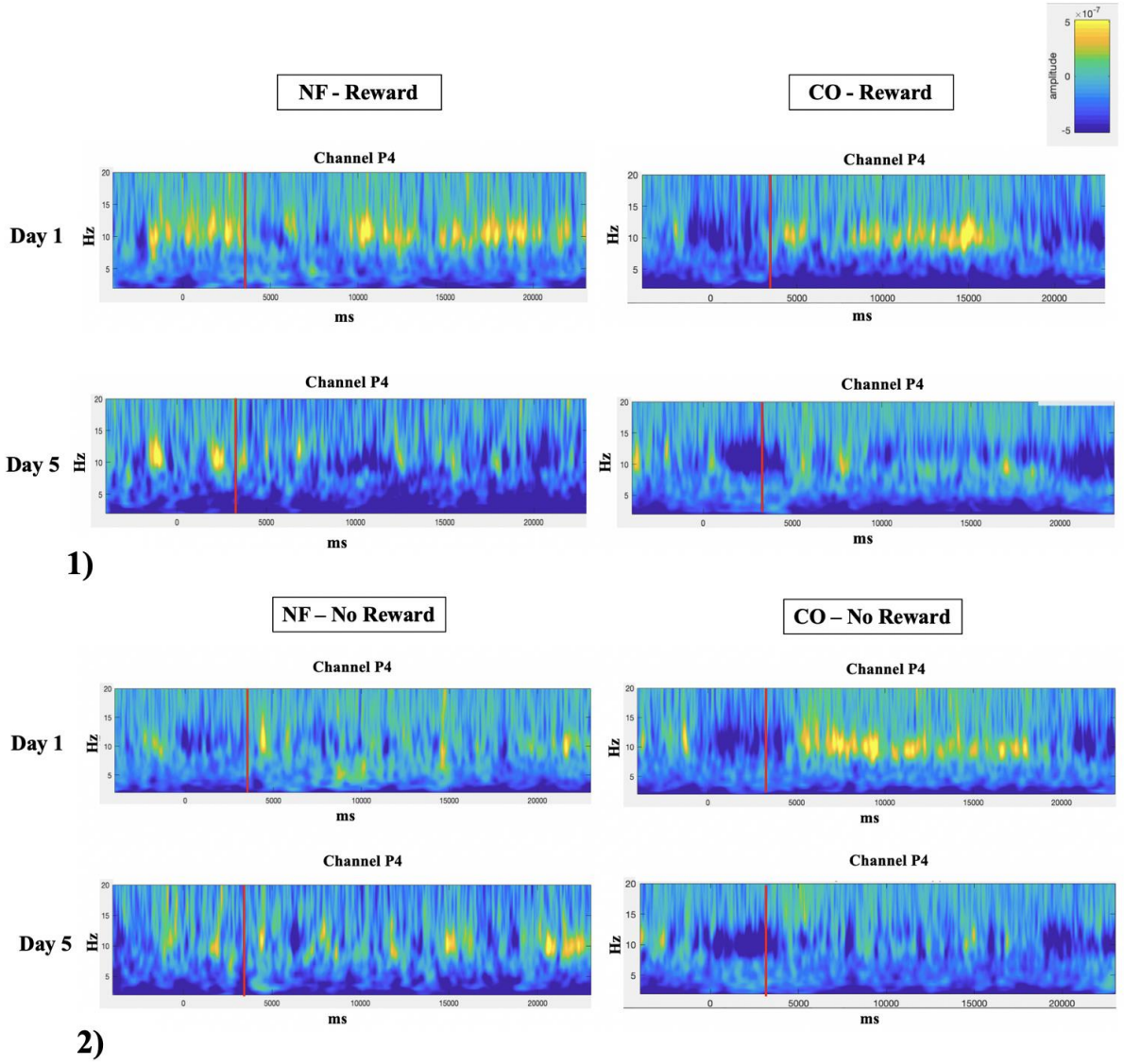

Fig. 8 Representations of the power spectrum in Experiment I. 1) *The power spectrum is presented for the NF-group (left) and CO-group (right). Results of day-1 (top) and day-5 (bottom) are presented for the reward condition and channel location P4. The x-axis indicates the time period from -5000 ms to 23000 ms. The represented time period includes four events (baseline, cue, sample image, and neurofeedback period). The time at 0 ms indicates the presence of the cue (blue or red) predicting the reward condition. The red line represents the start of the neurofeedback time period. The y-axis represents the range of frequencies from 2 to 20 Hz with 0.5 Hz resolution.* ***2)*** *The power spectrum is presented for the NF-group (left) and CO-group (right). Results of day-1 (top) and day-5 (bottom) are presented for the non-reward condition and channel location P4. The x-axis indicates the time period from -5000 ms to 23000 ms. The represented time period includes four events (baseline, cue, sample image, and neurofeedback period). The time at 0 ms indicates the presence of the cue (blue or red) predicting the reward condition. The red line represents the start of the neurofeedback time period. The y-axis represents the range of frequencies from 2 to 20 Hz with 0.5 Hz resolution. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

3.4.3 THETA POWER (4-7 HZ)

The relative power of theta was investigated across 5-days (see Fig. 9). Although a modulation of theta oscillations was observed, power changes across training days were not significant. Thus, a non-significant main effect of "day" ($F_{(4,108)} = 2.271$, $p = .066$, $\eta_p^2 = .078$) was found. In addition, in both groups, a similar trend was observed and no significant differences in theta power were found. Indeed, the main effect of the "group" ($F_{(1,27)} = 2.459$, $p = .129$, $\eta_p^2 = .083$) was not significant. In addition, no significant differences in theta power were found in response to the reward conditions. Hence, a reward-anticipation effect on theta power was not found and the main effect of "reward" ($F_{(1,27)} = .015$, $p = .904$, $\eta_p^2 = .001$) was not significant. However, the type of training received (NF or CO) was effective in modulating the power of theta when a reward was expected. Hence, a significant interaction between group and reward-anticipation ("group*reward": $F_{(1,27)} = 4.881$, $p = .036$, $\eta_p^2 = .153$) was found. The interaction was further investigated with pairwise comparisons. Overall, it was found higher theta suppression in the NF-group (compared to the CO-group), particularly in reward (MD = -.105, SEM = .044, $p = .025$) compared to non-reward (MD = -.023, SEM = .045, $p = .621$) trials. The relative power of theta was also investigated by comparing only day-1 and day-5. Hence, a significant interaction effect between the type of training received (NF or CO) and reward-anticipation across days ("day*reward*group": $F_{(1,27)} = 5.056$, $p = .033$, $\eta_p^2 = .158$) was found. The interaction was further investigated with pairwise comparisons. Results showed an NF-training effect on enhancing theta suppression, mostly observed on day-5 in reward (MD = -.214, SEM = .080, $p = .012$), but not in non-reward (MD = .012, SEM = .067, $p = .860$) trials.

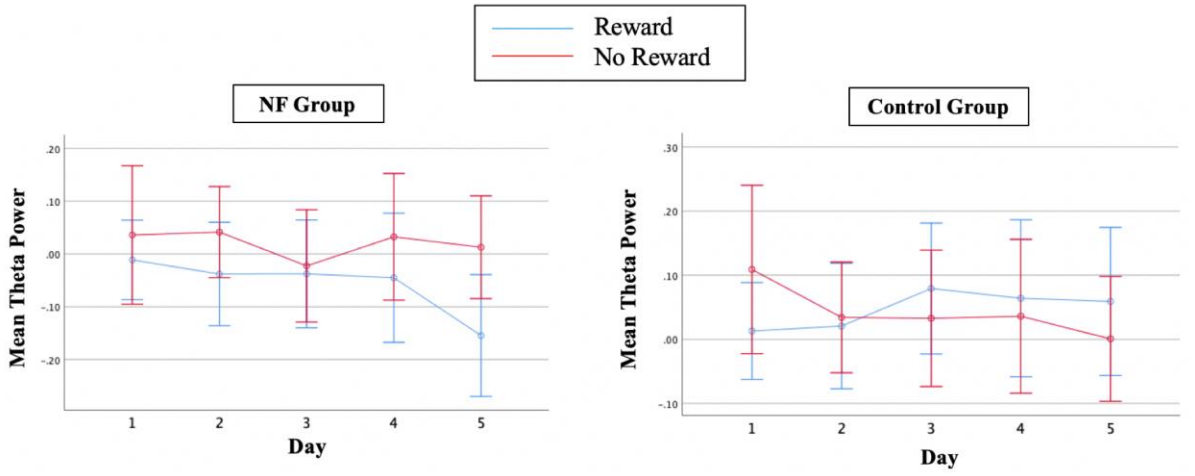

Fig. 9 Results of mean theta power in Experiment I. *The analysis was performed on parietal channel locations P3, Pz, and P4 and the presented signal indicates the grand average across these channel locations. Mean theta power is presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis*

indicates the mean theta power. In both figures, blue lines indicate data from the time-frequency analysis and in response to the reward condition. Red lines indicate data from the time-frequency analysis and in response to the non-reward condition. In both figures, error bars indicate 95% confidence intervals (CI) with covariate gender. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).

3.4.4 LOW-BETA POWER (13-20 HZ)

The relative power of low-beta was investigated across 5-days (see Fig. 10). Beta power decreased across the training and indeed a significant main effect of "day" ($F_{(2.581,69.677)} = 3.775$, $p = .019$, $\eta_p^2 = .123$) was found. The main effect was further investigated with pairwise comparisons showing that the power of beta was lower on day-5 when compared to day-4 (MD = -.083, SEM = .040, $p = .046$), and when compared to day-2 (MD = -.096, SEM = .047, $p = .05$). Nevertheless, no differences in beta power between groups were observed. Hence, the main effect of the "group" ($F_{(1,27)} = 1.710$, $p = .202$, $\eta_p^2 = .060$) was not significant. Moreover, a reward-anticipation effect on beta power was not found and indeed, a main effect of "reward" ($F_{(1,27)} = 1.226$, $p = .270$, $\eta_p^2 = .045$) was not significant. In addition, no differences in beta power were found across training days regarding the interaction between the NF-training and reward-anticipation effects. Indeed, the interaction "group*reward" ($F_{(4,108)} = 1.354$, $p = .255$, $\eta_p^2 = .048$) was found not significant. Furthermore, the relative power of beta was also investigated by comparing only day-1 and day-5. However, neither main nor interaction effects were found significant.

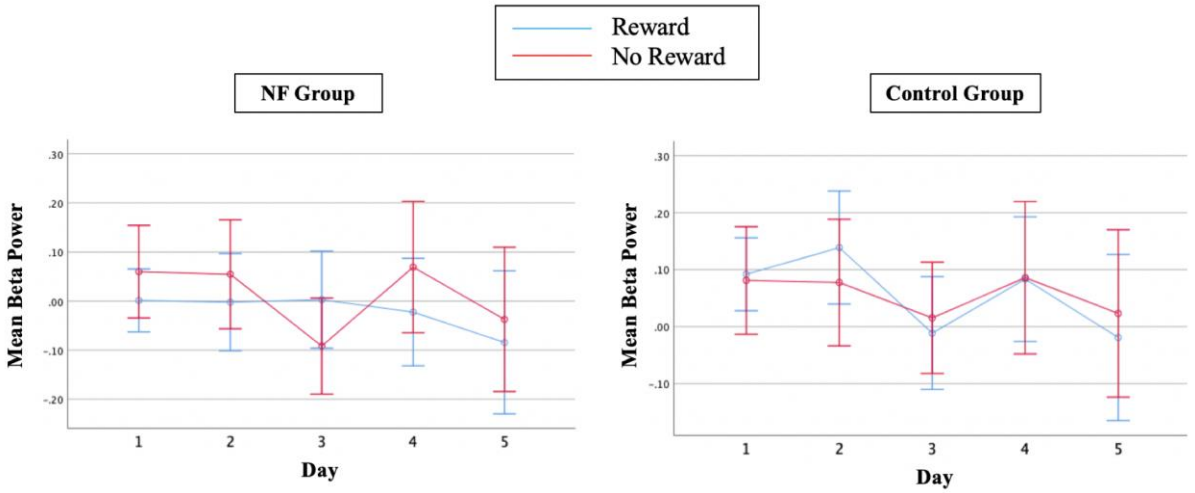

Fig. 10 Results of mean low-beta power in Experiment I. *The analysis was performed on parietal channel locations P3, Pz, and P4 and the presented signal indicates the grand average across these channel locations. Mean low-beta power is presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean low-beta power. In both figures, blue lines indicate data from the time-frequency analysis and in response to the reward condition. Red lines indicate data from the time-frequency analysis and in response to the non-reward condition. In both figures, error bars indicate 95% confidence intervals (CI) with covariate gender. The results presented are this figure is reported by Barbazzeni, Speck and Düzel, (2023).*

3.4.5 TRANSFER EFFECT TASKS

MST

From a between-subject analysis, no significant differences were observed between groups in response to the NF training. Indeed, although a higher MST performance was found in the NF-group when compared to the CO-group, the difference was not significant (pre-training: $U(N_{NF}= 18.53, N_{CO}= 12.47) = 67.000$, $z = -1.888$, $p = .061$; post-training: $U(N_{NF}= 17.83, N_{CO}= 13.17) = 77.500$, $z = -1.452$, $p = .148$). Hence, no transfer effects of NF-training were observed on this cognitive task.

From a within-subject analysis, the NF-group did not show significant improvements in task performance. Indeed, a decrease in performance was observed. In the pre-training assessment, the MST performance was higher (Mdn = 70.6067) than the post-training assessment (Mdn = 68.4460), although the difference was found not significant ($T = 63.00$, $z = -.659$, $p = .510$). Similarly, also the CO-group did not show significant improvements in task performance. However, an increase in performance was observed. In the pre-training assessment, the MST performance was lower (Mdn = 65.1933) than the post-training assessment (Mdn = 65.3753), even though the difference was found not significant ($T = 61.00$, $z = -.057$, $p = .955$).

STROOP TASKS

From a between-subject analysis, no significant differences were observed between groups in response to the NF training. Although a higher Stroop task performance was found in the NF-group when compared to the CO-group, no differences were found (pre-training: $U(N_{NF}= 19.27, N_{CO}= 11.73) = 56.000$, $z = -2.347$, $p = .019$; post-training: $U(N_{NF}= 18.90, N_{CO}= 12.10) = 61.500$, $z = -2.122$, $p = .033$). Thus, this result did not show any significant NF-training effect on this task.

From a within-subject analysis, the NF-group did not show significant improvements in task performance. However, an increase in performance was observed. In the pre-training assessment, the Stroop task performance was lower (Mdn = 96.5007) than the post-training assessment (Mdn = 96.8093), although the difference was not significant ($T = 49.50$, $z = -.825$, $p = .410$). Similarly, the CO-group did not show significant improvements in task performance. Even though Stroop task performance was lower in the pre-training assessment (Mdn =

93.4047) than the post-training assessment (Mdn = 94.7613), the difference was found not significant (T = 73.50, z = -1.319, p = .187).

3.4.6 QUESTIONNAIRE

From the questionnaire results, participants felt overall "good" (NF-group: 46.7%) or "very good" (CO-group: 46.7%) at experiment completion. Participants did find the experiment "absolutely not difficult" (NF-group: 46.7%,) or "not difficult" (CO-group: 40%) to perform. Indeed, participants did consider the experimental instructions "not difficult" (NF-group: 53.3%) or "absolutely not difficult" (CO-group: 66.7%) to understand. Furthermore, when investigating the effect of NF and CT on memory, participants estimated their memory to be "slightly not good" (NF-group: 33.3%, CO-group: 40%) on day-1. Differently, participants estimated their memory to be "good" on day-5 (NF-group: 73.3%, CO-group: 53.3%). In addition, participants reported that it was "very important" to show and to achieve good performances (NF-group: 66.7%, CO-group: 66.7%), and they did find it "not difficult" to remember the images presented during the DMST performance (NF-group: 46.7%, CO-group: 40%). According to the experimental design and the instructions given during maintenance, participants of both groups applied an NF-training strategy (NF-group: "yes", CO-group: "yes") while controlling the movement of the white ball to enhance their alpha suppression by performing a mental calculation. Lastly, all participants did find differences (NF-group: "yes", CO-group: "yes") from day-1 to day-5 of the training (NF-group: 100%, CO-group: 100%). Particularly, participants of both groups reported perceived changes in "concentration" (NF-group: 53.3%, CO-group: 53.3%). Participants did not give any suggestions to improve the experiment (NF-group: "no", CO-group: "no").

3.5 RESULTS: EXPERIMENT II

All the results and related statistics from *Experiment II* and described in this section are reported by Barbazzeni, Speck and Düzel, (2023).

3.5.1 DMST

Accuracy was investigated across 5-days (see Fig. 11.1). A significant main effect of "day" ($F_{(4,112)}$ = 8.991, p = .000, η_p^2 = .243) indicated improved performances through the training. In addition, the improvement in accuracy was influenced by reward-anticipation. Indeed, a significant main effect of "reward" ($F_{(1,28)}$ = 5.313, p = .029, η_p^2 = .159) was found. The main

effect was further investigated with pairwise comparisons showing that performances were indeed higher in reward (MD = 4.156, SEM = 1.803, p = .029) than non-reward trials. Moreover, no differences in accuracy performances were observed between groups. Thus, a non-significant main effect of "group" ($F_{(1,28)}$ = 2.869, p = .101, η_p^2 = .093) was found across 5-days and as indicated by the interaction "day*group" ($F_{(4,112)}$ = .525, p = .717, η_p^2 = .018). Furthermore, improved accuracy was unrelated to either the NF-training or reward-anticipation effects. Between groups, the interactions between NF-training and reward-anticipation ("day*reward*group": $F_{(4,112)}$ = .993, p = .414, η_p^2 = .034) was not significant.

Moreover, RTs were investigated across 5-days (see Fig. 11.2). A significant main effect of "day" ($F_{(2.009,54.241)}$ = 3.183, p = .049, η_p^2 = .105) indicated improved performances through the training. In addition, a significant reward-anticipation effect was found on enhanced RTs performances as indicated by a significant main effect of "reward" ($F_{(1,27)}$ = 4.458, p = .044, η_p^2 = .142). The main effect was further investigated with pairwise comparisons showing that RTs performances were faster in reward (MD = -.018, SEM = .006, p = .005) than non-reward trials. However, RTs performances did not differ between groups. Thus, a non-significant main effect of "group" ($F_{(1,27)}$ = 1.823, p = .188, η_p^2 = .063) was found across 5-days and as indicated by the interaction "day*group" ($F_{(2.009,54.241)}$ = 1.419, p = .251, η_p^2 = .050). Furthermore, faster RTs were unrelated to either the NF-training or reward-anticipation effects. Between groups, the interactions between NF-training and reward-anticipation ("day*reward*group": $F_{(2.831,76.445)}$ = .722, p = .535, η_p^2 = .026) was not significant.

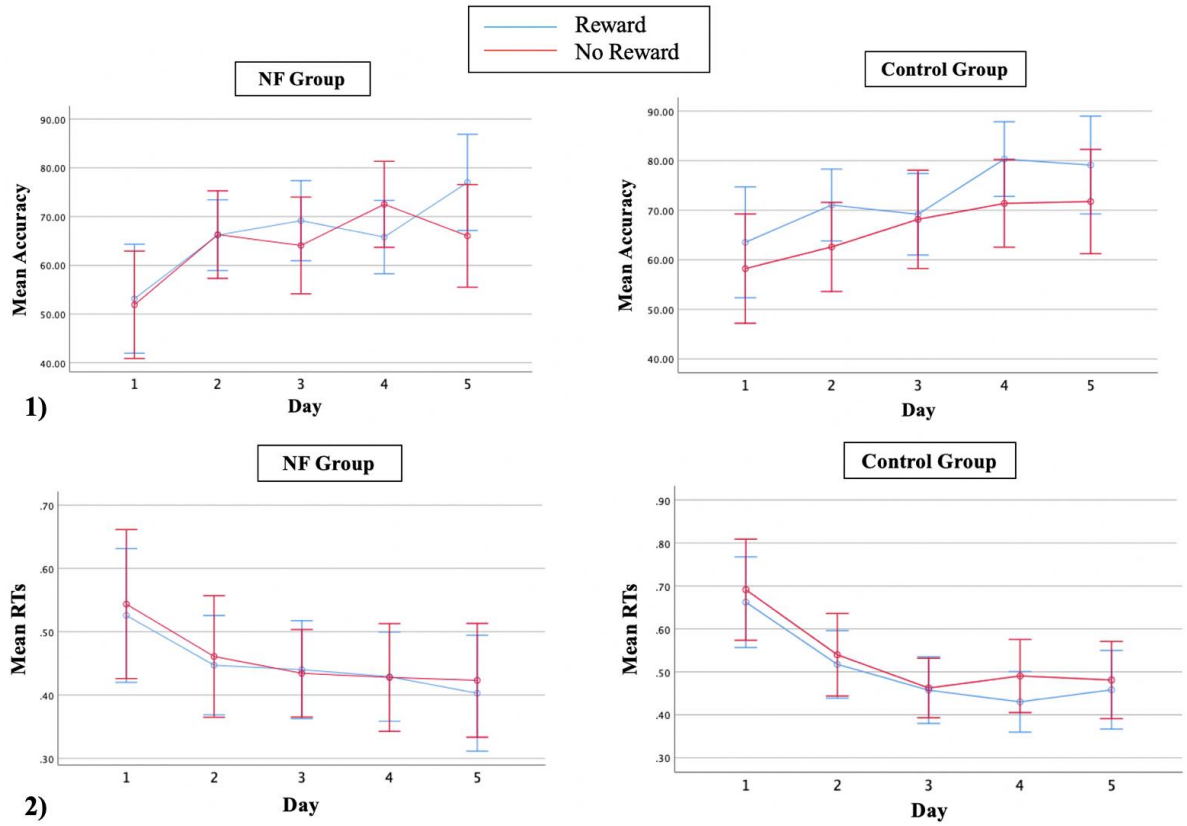

***Fig. 11 Results of mean accuracy and reaction times in Experiment II**. **1)** Mean accuracy is presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean accuracy. **2)** Mean RTs are presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean RTs. In all figures, blue lines indicate behavioral performance in response to the reward condition. Red lines indicate behavioral performance in response to the non-reward condition. Error bars indicate 95% confidence intervals (CI) with covariate gender in all figures. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

3.5.2 ALPHA POWER (7-13 HZ)

The relative power of alpha was investigated across 5-days (see Fig. 12). Although the power of alpha changed in response to the training and across days, differences in power changes were not significant. Thus, a non-significant main effect of "day" ($F_{(2.908,75.602)} = 1.617$, $p = .194$, $\eta_p^2 = .059$) was found. In addition, even though a different pattern was observed between groups, no significant differences in alpha power were found. Indeed, the main effect of "group" ($F_{(1,26)} = .251$, $p = .621$, $\eta_p^2 = .010$) was not significant. Moreover, no significant differences in alpha power were found in response to the reward conditions. Hence, a reward-anticipation effect on alpha power suppression was not found and the main effect of "reward" ($F_{(1,26)} = .339$, $p = .565$ $\eta_p^2 = .013$) was not significant. Furthermore, no differences in alpha power were found across training days in respect to the interaction between the NF-training and reward-anticipation effects. Indeed, the interaction "day*reward*group" ($F_{(3.148,81.860)} = 1.479$, $p = .225$, $\eta_p^2 = .054$)

was found not significant. The relative power of alpha was also investigated by comparing only day-1 and day-5. However, neither main nor interaction effects were found significant.

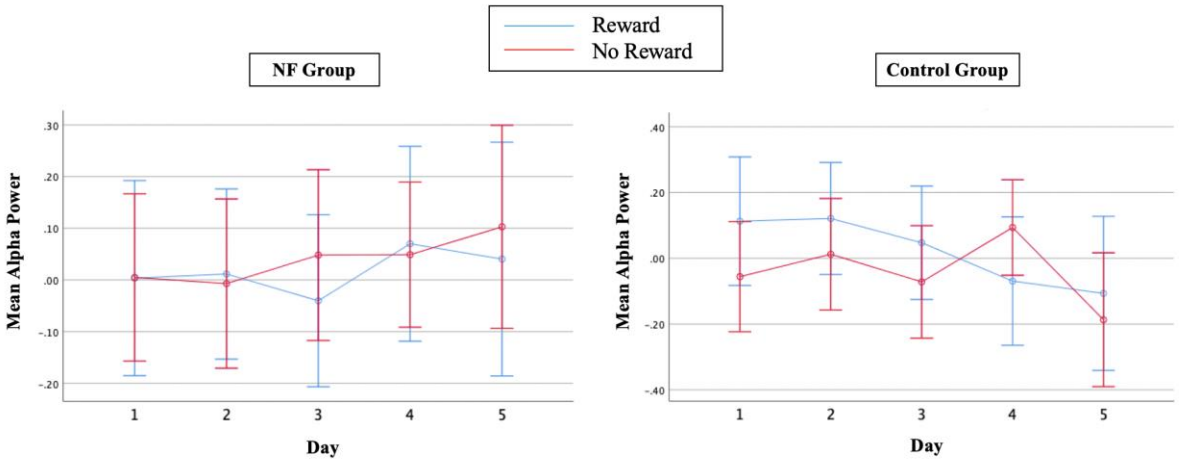

Fig. 12 Results of mean alpha power in Experiment II. *The analysis was performed on parietal channel locations P3, Pz, and P4 and the presented signal indicates the grand average across these channel locations. Mean alpha power is presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean alpha power. In both figures, blue lines indicate data from the time-frequency analysis and in response to the reward condition. Red lines indicate data from the time-frequency analysis and in response to the non-reward condition. In both figures, error bars indicate 95% confidence intervals (CI) with covariate gender. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

3.5.3 THETA POWER (4-7 HZ)

The relative power of theta was investigated across 5-days (see Fig. 13). Although the power of theta changed in response to the training and across days, differences in power changes were not significant. Thus, a non-significant main effect of "day" ($F_{(4,104)} = .719$, $p = .581$, $\eta_p^2 = .027$) was found. In addition, even though a different pattern was observed between groups, no significant differences in theta power were found. Indeed, the main effect of "group" ($F_{(1,26)} = .105$, $p = .748$, $\eta_p^2 = .004$) was not significant. Moreover, no significant differences in theta power were found in response to the reward conditions. Hence, a reward-anticipation effect on theta power was not found and the main effect of "reward" ($F_{(1,26)} = .080$, $p = .779$, $\eta_p^2 = .003$) was not significant. Furthermore, no differences in theta power were found across training days regarding the interaction between the NF-training and reward-anticipation effects. Indeed, the interaction "day*reward*group" ($F_{(4,104)} = .120$, $p = .975$, $\eta_p^2 = .005$) was found not significant. The relative power of theta was also investigated by comparing only day-1 and day-5. However, neither main nor interaction effects were found significant.

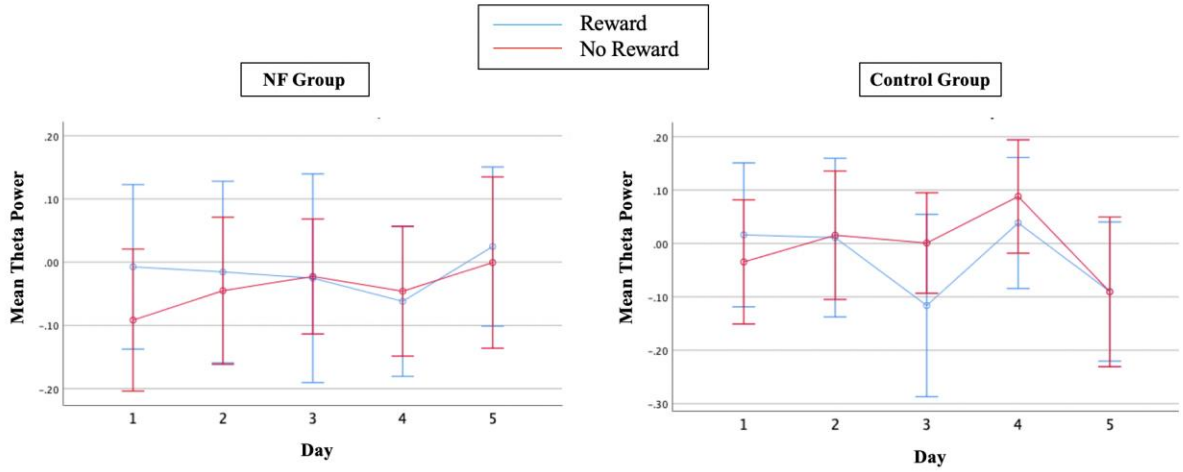

Fig. 13 Results of mean theta power in Experiment II. *The analysis was performed on parietal channel locations P3, Pz, and P4 and the presented signal indicates the grand average across these channel locations. Mean theta power is presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean theta power. In both figures, blue lines indicate data from the time-frequency analysis and in response to the reward condition. Red lines indicate data from the time-frequency analysis and in response to the non-reward condition. In both figures, error bars indicate 95% confidence intervals (CI) with covariate gender. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

3.5.4 LOW-BETA POWER (13-20 HZ)

The relative power of low-beta was investigated across 5-days (see Fig. 14). Although the power of beta changed in response to the training and across days, differences in power changes were not significant. Thus, a non-significant main effect of "day" ($F_{(2.903,75.481)} = .678$, $p = .563$, $\eta_p^2 = .025$) was found. In addition, even though a different pattern was observed between groups, no significant differences in beta power were found. Indeed, the main effect of "group" ($F_{(1,26)} = .249$, $p = .622$, $\eta_p^2 = .009$) was not significant. Moreover, no significant differences in beta power were found in response to the reward conditions. Hence, a reward-anticipation effect on beta power was not found and the main effect of "reward" ($F_{(1,26)} = 2.790$, $p = .107$, $\eta_p^2 = .097$) was not significant. Furthermore, no differences in beta power were found across training days in respect to the interaction between the NF-training and reward-anticipation effects. Indeed, the interaction "day*reward*group" ($F_{(2.720,70.731)} = .469$, $p = .686$, $\eta_p^2 = .018$) was found not significant. The relative power of beta was also investigated by comparing only day-1 and day-5. However, neither main nor interaction effects were found significant.

The power spectrum of *Experiment II* for reward and non-reward conditions are presented in Fig. 15.1 and Fig. 15.2, respectively.

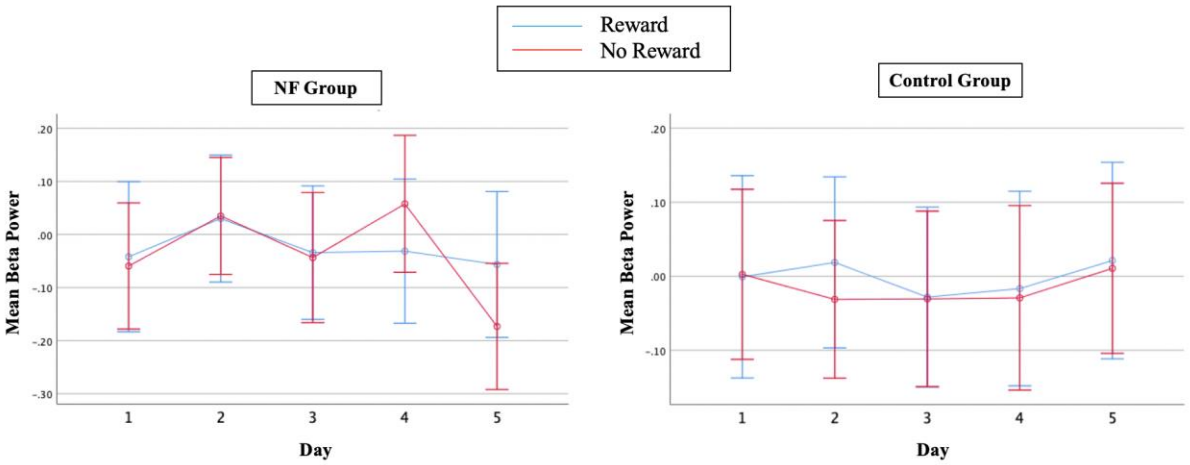

Fig. 14 Results of mean low-beta power in Experiment II. *The analysis was performed on parietal channel locations P3, Pz, and P4 and the presented signal indicates the grand average across these channel locations. Mean low-beta power is presented for the NF-group (left) and CO-group (right). The x-axis indicates training days. The y-axis indicates the mean low-beta power. In both figures, blue indicates data from the time-frequency analysis and in response to the reward condition. Red lines indicate data from the time-frequency analysis and in response to the non-reward condition. In both figures, error bars indicate 95% confidence intervals (CI) with covariate gender. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

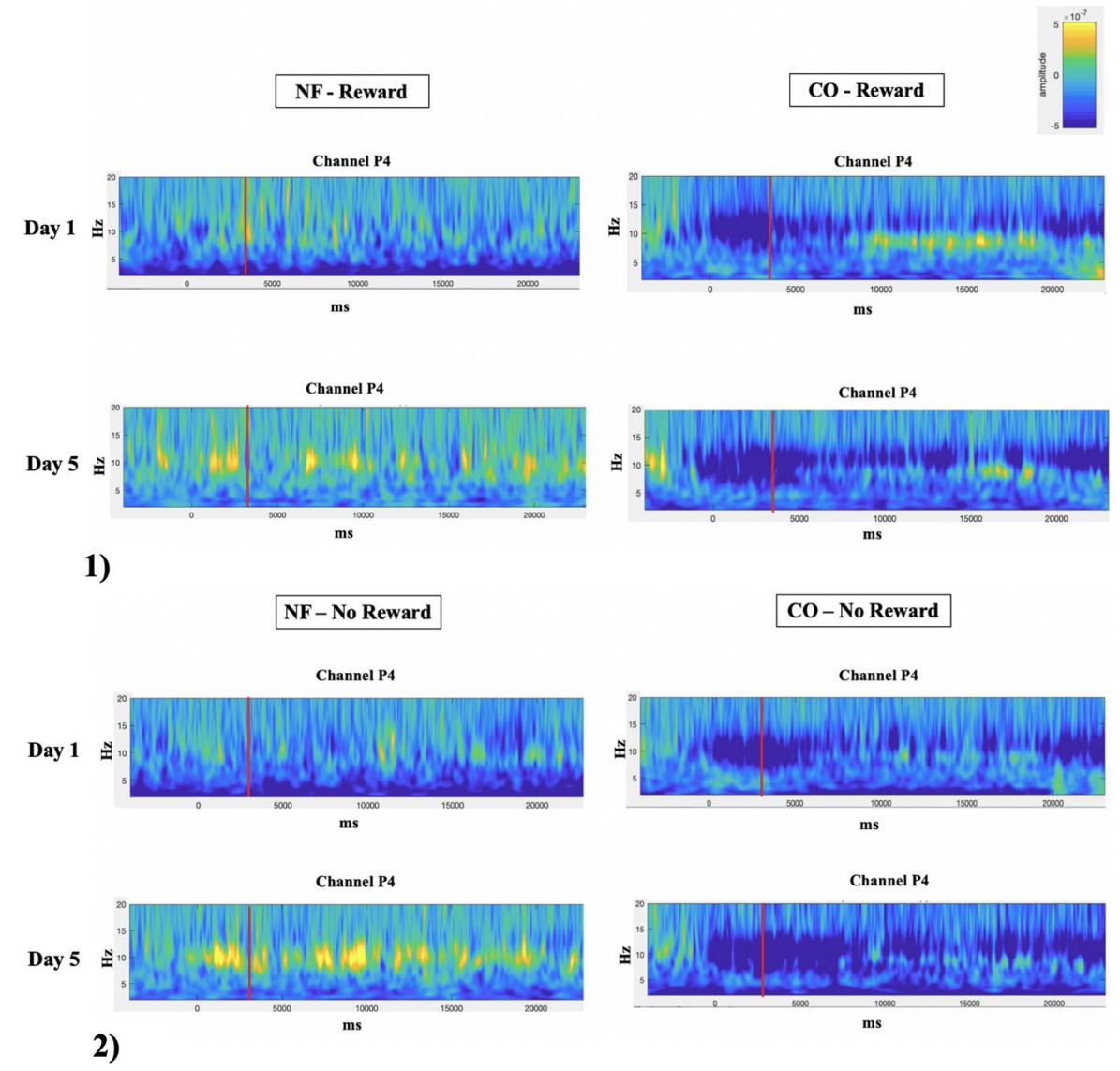

Fig. 15 Representations of the power spectrum in Experiment II. 1) *The power spectrum is presented for the NF-group (left) and CO-group (right). Results of day-1 (top) and day-5 (bottom) are presented for the reward condition and channel location P4. The x-axis indicates the time period from -5000 ms to 23000 ms. The represented time period includes four events (baseline, cue, sample image, and neurofeedback period). The time at 0 ms indicates the presence of the cue (blue or red) predicting the reward condition. The red line represents the start of the neurofeedback time period. The y-axis represents the range of frequencies from 2 to 20 Hz with 0.5 Hz resolution.* ***2)*** *The power spectrum is presented for the NF-group (left) and CO-group (right). Results of day-1 (top) and day-5 (bottom) are presented for the non-reward condition and channel location P4. The x-axis indicates the time period from -5000 ms to 23000 ms. The represented time period includes four events (baseline, cue, sample image, and neurofeedback period). The time at 0 ms indicates the presence of the cue (blue or red) predicting the reward condition. The red line represents the start of the neurofeedback time period. The y-axis represents the range of frequencies from 2 to 20 Hz with 0.5 Hz resolution. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

3.5.5 TRANSFER EFFECT TASKS

MST

From a between-subject analysis, no significant differences were observed between groups in response to the NF training. Indeed, although the MST performance improved in response to the NF-training, when compared to the CO-group the difference in performance was not significant (pre-training: $U(N_{NF}=14.73, N_{CO}=16.27) = 101.000$, $z = -.477$, $p = .653$; post-training: $U(N_{NF}=15.57, N_{CO}=15.43) = 111.500$, $z = -.041$, $p = .967$). Hence, no transfer effects of NF-training were observed on this cognitive task.

From a within-subject analysis, the NF-group did not show significant improvements in task performance. Even though the MST performance was lower in the pre-training assessment (Mdn = 62.2960) than the post-training assessment (Mdn = 62.7307), the difference was found not significant ($T = 44.00$, $z = -.909$, $p = .363$). Similarly, also the CO-group did not show significant improvements in task performance. Indeed, a decrease in performance was observed. In the pre-training assessment, the MST performance was higher (Mdn = 63.6507) than the post-training assessment (Mdn = 60.7473), even though the difference was found not significant ($T = 44.00$, $z = -.909$, $p = .363$).

STROOP TASKS

From a between-subject analysis, no significant differences were observed between groups in response to the NF training. A higher Stroop task performance was found in the CO-group when compared to the NF-group, even though the difference was not significant (pre-training: $U(N_{NF}=14.80, N_{CO}=16.20) = 102.000$, $z = -.437$, $p = .683$; post-training: $U(N_{NF}=14.50, N_{CO}=16.50) = 97.500$, $z = -.623$, $p = .539$). Hence, no transfer effects of NF-training were observed on this cognitive task.

From a within-subject analysis, the NF-group did not show significant improvements in task performance. However, an increase in performance was observed. In the pre-training assessment, the Stroop task performance was lower (Mdn = 94.1187) than the post-training assessment (Mdn = 94.9040), although the difference was found not significant ($T = 56.00$, $z = -1.338$, $p = .181$). Differently, the CO-group did show significant improvements in task performance. Indeed, Stroop task performance was lower in the pre-training assessment (Mdn

= 92.9753) than the post-training assessment (Mdn = 95.0460), and the difference was found significant (T = 77.50, z = -2.238, p = .025).

3.5.6 QUESTIONNAIRE

From the questionnaire results, participants felt overall "good" (NF-group: 46.7%) or "very good" (CO-group: 68.8%) at experiment completion. Participants did find the experiment "slightly not difficult" (NF-group: 40%) or "not difficult" (CO-group: 56.3%) to perform. Indeed, participants did consider the experimental instructions "absolutely not difficult" (NF-group: 46.7%) or "not difficult" (CO-group: 37.5%) to understand. Furthermore, when investigating the effect of NF and cognitive training on memory, participants estimated their memory to be "slightly not good" (NF-group: 40%, CO-group: 50%) on day-1. Differently, participants estimated their memory to be "good" on day-5 (NF-group: 53.3%, CO-group: 43.8%). In addition, participants reported that it was "important" (NF-group: 60%) or "very important" (CO-group: 43.8%) to show and to achieve good performances, and they did find it "not difficult" to remember the images presented during the DMST performance (NF-group: 40%, CO-group: 31.3%). According to the experimental design and the instructions given during maintenance, participants of both groups applied an NF-training strategy (NF-group: "yes", CO-group: "yes") while controlling the movement of the white ball to enhance their alpha suppression by performing mental imagery. Lastly, all participants did find differences (NF-group: "yes," CO-group: "yes") from day-1 to day-5 of the training (NF-group: 100%, CO-group: 100%). Particularly, participants of both groups reported perceived changes in "concentration" (NF-group: 40%, CO-group: 56.3%). Participants did not give any suggestions to improve the experiment (NF-group: "no," CO-group: "no").

3.6 RESULTS: COMBINED ANALYSIS ACROSS EXPERIMENT I AND II

All the results and related statistics from combined analysis across *Experiment I* and *II* described in this section are reported by Barbazzeni, Speck and Düzel, (2023).

3.6.1 ACCURACY

LMM results are reported in Table 1 for the encoding period and Table 2 for the maintenance period. When investigating main effects, improved mean accuracy, observed across 5-days, was found unrelated to any NF-training effects. Indeed, no differences between groups were found, as shown by the negative coefficient (β = -0.93638). Despite higher accuracy

performances observed in the CO-group (M = 68.1400, SD = 17.03148) when compared to the NF-group (M = 67.4615, SD = 17.90666), the difference in performance was found not significant (MD = -.67857, SEM = 1.43965, t_{588} = -.471, p = .638, CI [-3.50605, 2.14892]), and as indicated by the model (p = 0.6). Hence, an NF-training effect on improved performances was not found. However, improved mean accuracy was found significantly related to a reward-anticipation effect as indicated by the positive coefficient (β = 3.3522). Indeed, it was observed that mean accuracy performances were higher in reward (M = 69.4523, SD = 16.49847) than non-reward (M = 66.1377, SD = 18.26908) trials (see Fig. 16.1), and the difference in performance was significant (MD = 3.31468, SEM = 1.43321, t_{588} = 2.313, p = .021, CI [.49984, 6.12952]), as indicated by the model (p = .01). Furthermore, a significant effect of low-beta oscillations on improved mean accuracy was found (see Fig. 16.2). In particular, the effect was observed on the right parietal beta (P4) activity at time window S2 (i.e., from 500 ms to 1000 ms after the onset of the *sample image*). As shown by the positive coefficient (β = 7.6183), the increase in relative power across 5-days was significant (p = 0.001) and positively related to improved performances. When comparing the mean power of low-beta across the 5-days and between the defined time windows (S1 and S2), even though the overall mean power at S2 was higher (M = -.0017, SD = .46163) than at S1 (M = -.0084, SD = .44710), the difference was found not significant (MD = -.00666, SEM = .01619, t_{589} = -.411, p = .681, CI [-.03845, .02514]). When investigating main effects during maintenance, improved mean accuracy was found significantly related to the reward-anticipation (β = 3.2822, p = 0.01) across the 5-days, although no oscillations were found related to improved performances.

From the ML model fit statistic, (full) alternative hypothesis model H_1 was significantly different from null hypothesis model H_0 during encoding ($\chi 2$ (14) = 26.68, p = 0.0211) but not during maintenance ($\chi 2$ (8) = 12.101, p = 0.1467). The Akaike Correction Criteria (AIC) value of the alternative hypothesis model H_1 was indeed lower (4984.3) during encoding but higher in maintenance (4986.9) when compared to the null hypothesis model H_0 (4983). The adjusted R^2 value of the alternative hypothesis model H_1 during encoding (0.1936) and maintenance (0.1840) was generally higher than the null hypothesis model H_0 (0.1740). Hence the (full) alternative hypothesis model H_1 showed a greater model fit only during the encoding period.

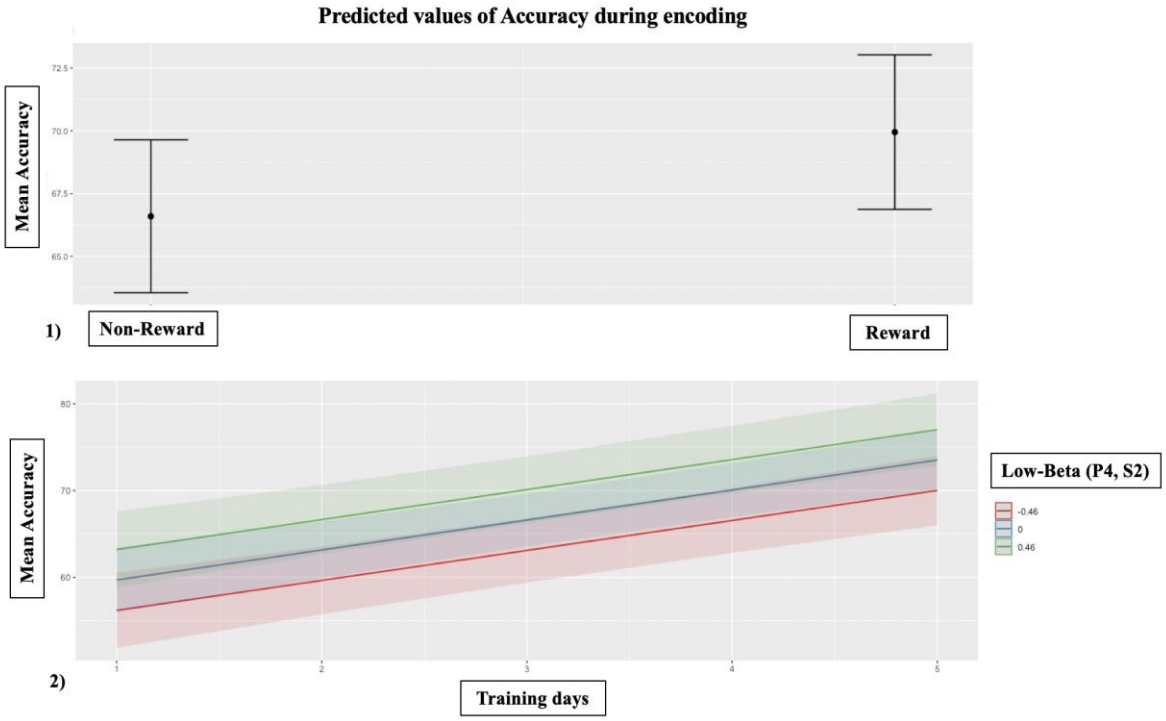

Fig. 16 Representation of predicted accuracy values during the encoding period. 1) *Data values predicted for accuracy are presented in response to the reward (right) and non-reward (left) condition. The x-axis indicates the reward conditions (reward and non-reward). The y-axis indicates mean accuracy. Error bars indicate standard errors.* ***2)*** *Data values predicted for accuracy are presented with respect to the relative power of low-beta frequency measured on channel P4 during the encoding period S2 and across the 5-days of training. The x-axis indicates the relative power of low-beta across 5-days. The y-axis indicates mean accuracy. Confidence interval is based on the standard error. Regarding the relative power of low-beta activities, the green line denotes higher power values, the blue line denotes power values closer to zero, whereas the red line denotes lower power values. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

Table 1. Accuracy results from the linear mixed effect model during encoding. The (full) alternative hypothesis model H_1 was estimated by using the restricted maximum likelihood (REML). Only the initial 1000 ms of the encoding period was analyzed and further divided into two-time windows of 500 ms each (S1: 0-500 ms, S2: 500-1000 ms). Only P4 (right) and P3 (left) parietal channels were considered for this analysis. For each fixed effect coefficient, the related statistics (estimates, *p*-values, lower and upper 95% confidence intervals (CI)) are presented. The results presented in this table are reported by Barbazzeni, Speck and Düzel, (2023).

Linear mixed-effect model for accuracy during encoding

Fixed effect coefficients	Estimate (coefficients)	*p*-value	Lower (95% CI)	Upper (95% CI)
'Intercept'	56.137	0	51.747	60.526
'Group_NF' [1]	-0.93638	0.63793	-4.8425	2.9697
'Reward' [2]	**3.3522**	**0.01034 ****	**0.79302**	**5.9115**
'Day' [3]	**3.4545**	**4.1878e-12 *****	**2.4963**	**4.4126**

'P4_S1_Alpha' [4]	-0.29695	0.89029	-4.5234	3.9295
'P3_S1_Alpha' [5]	2.2286	0.33152	-2.2753	6.7325
'P4_S2_Alpha' [6]	-2.4383	0.25215	-6.6163	1.7396
'P3_S2_Alpha' [7]	0.17891	0.93611	-4.2028	4.5606
'P4_S1_Theta' [8]	-2.7649	0.19333	-6.9349	1.405
'P3_S1_Theta' [9]	1.3674	0.51424	-2.7477	5.4825
'P4_S2_Theta' [10]	3.765	0.08581	-0.53213	8.0621
'P3_S2_Theta' [11]	-3.5677	0.07927	-7.5537	0.41822
'P4_S1_Beta' [12]	-3.2813	0.18691	-8.1588	1.5962
'P3_S1_Beta' [13]	3.1801	0.23433	-2.0664	8.4267
'P4_S2_Beta' [14]	**7.6183**	**0.00198 ****	**2.802**	**12.435**
'P3_S2_Beta' [15]	-3.9588	0.11565	-8.8935	0.97588

[1] Fixed effect "group" including 2 levels: NF-group and CO-group

[2] Fixed effect "reward" including 2 levels: Reward and Non-Reward conditions

[3] Fixed effect "day" including 5 levels: day-1, day-2, day-3, day-4, and day-5

[4] Fixed effect for alpha frequency range. Channel location P4. Encoding period of 0-500 ms

[5] Fixed effect for alpha frequency range. Channel location P3. Encoding period of 0-500 ms

[6] Fixed effect for alpha frequency range. Channel location P4. Encoding period of 500-1000 ms

[7] Fixed effect for alpha frequency range. Channel location P3. Encoding period of 500-1000 ms

[8] Fixed effect for theta frequency range. Channel location P4. Encoding period of 0-500 ms

[9] Fixed effect for theta frequency range. Channel location P3. Encoding period of 0-500 ms

[10] Fixed effect for theta frequency range. Channel location P4. Encoding period of 500-1000 ms

[11] Fixed effect for theta frequency range. Channel location P3. Encoding period of 500-1000 ms

[12] Fixed effect for low-beta frequency range. Channel location P4. Encoding period of 0-500 ms

[13] Fixed effect for low-beta frequency range. Channel location P3. Encoding period of 0-500 ms

[14] Fixed effect for low-beta frequency range. Channel location P4. Encoding period of 500-1000 ms

[15] Fixed effect for low-beta frequency range. Channel location P3. Encoding period of 500-1000 ms

Table 2. Accuracy results from the linear mixed effect model during maintenance. The (full) alternative hypothesis model H_1 was estimated by using the restricted maximum likelihood (REML). The analysis was conducted while considering the entire maintenance period (20 s). Only P4 (right) and P3 (left) parietal channels were considered for this analysis. For each fixed effect coefficient, the related statistics (estimates, *p*-values, lower and upper 95% confidence intervals (CI)) are presented. The results presented in this table are reported by Barbazzeni, Speck and Düzel, (2023).

Linear mixed-effect model for accuracy during maintenance

Fixed effect coefficients	Estimate (coefficients)	P-value	Lower (95% CI)	Upper (95% CI)
'Intercept'	55.584	0	51.064	60.105
'Group_NF'	-0.11841	0.95248	-4.0193	3.7824
'Reward'	**3.2822**	**0.01065 ****	**0.76602**	**5.7984**
'Day'	**3.5565**	**4.174e-12 *****	**2.5699**	**4.5431**
'P4_Alpha' [1]	-7.0532	0.15263	-16.726	2.6194
'P3_Alpha' [2]	2.8494	0.56817	-6.9503	12.649
'P4_Theta' [3]	3.2075	0.45836	-5.2823	11.697
'P3_Theta' [4]	-4.5575	0.22225	-11.883	2.7683
'P4_Beta' [5]	8.0678	0.20412	-4.3961	20.535
'P3_Beta' [6]	-0.57879	0.93406	-14.313	13.155

[1] Fixed effect for alpha frequency range. Channel location P4. Maintenance period of 20 s

[2] Fixed effect for alpha frequency range. Channel location P3. Maintenance period of 20 s

[3] Fixed effect for theta frequency range. Channel location P4. Maintenance period of 20 s

[4] Fixed effect for theta frequency range. Channel location P3. Maintenance period of 20 s

[5] Fixed effect for low-beta frequency range. Channel location P4. Maintenance period of 20 s

[6] Fixed effect for low-beta frequency range. Channel location P3. Maintenance period of 20 s

LMM results from the *post-hoc* analysis and related to the encoding period are reported in Table 3. When investigating interaction effects on improved mean accuracy, a significant interaction (p = 0.02) effect was found between reward-anticipation and the relative power of right parietal low-beta (P4) activity at S2. However, the negative coefficient (β = -6.4747) indicated that slightly lower values of right parietal low-beta power at S2 may positively affect accuracy performances, but only in expectation of reward (see Fig. 17). Overall, the mean low-beta power across the 5-days of training was found to be lower in response to reward (M = -.0216, SD = .47124) than to non-reward (M = .0182, SEM = .45173) trials. Nevertheless, the difference in low-beta power between reward conditions was found not significant (MD = -.03982, SEM = 0.3801, t_{588} = -1.048, p = .295, CI [-.11447, .03483]).

From the ML model fit statistic, the interaction model H_1 was significantly different from the null hypothesis model H_0 during encoding ($\chi 2$ (6) = 18.86, p = 0.0044). Indeed, the AIC value of the interaction model H_1 was lower (4976.1) during encoding than the null hypothesis model H_0. The adjusted R^2 value of the interaction model H_1 (0.1972) was higher than the null hypothesis model H_0. Hence the interaction model H_1 showed a greater model fit during the encoding period.

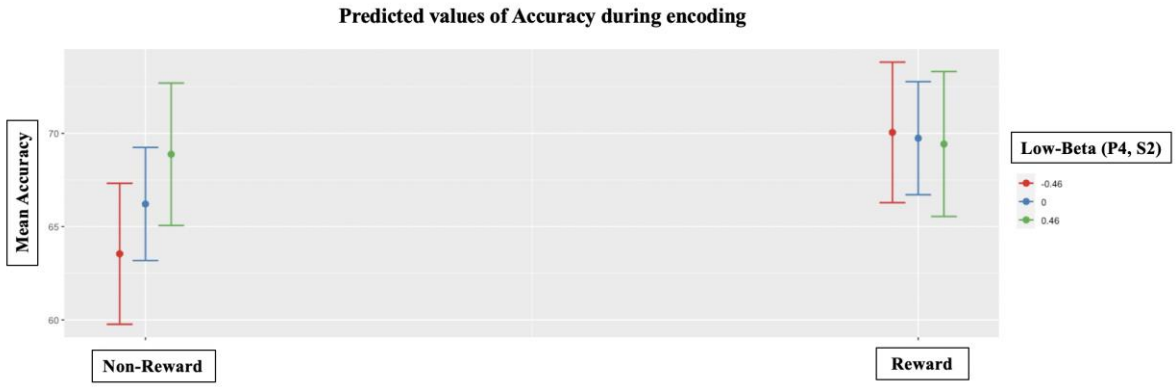

Fig. 17 Representation of predicted accuracy values with interaction effects during encoding. *Data values predicted for accuracy are presented in response to the interaction between (non-)reward condition and the relative power of low-beta frequency (measured on channel P4 during the encoding period S2). The x-axis indicates the reward (right) and non-reward (left) conditions. The y-axis indicates the predicted accuracy values with respect to the interaction between the relative power of low-beta and the (non-)reward condition. Error bars indicate standard errors. Regarding the relative power of low-beta activities, the green line denotes higher power values, the blue line denotes power values closer to zero, whereas the red line denotes lower power values. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

Table 3. Accuracy results from the linear mixed effect model with interaction effects during encoding. Based on a post-hoc analysis, the interaction model H_1 (including main effects and interactions between fixed effect coefficients) was estimated by using the restricted maximum likelihood (REML). Only P4 (right) and P3 (left) parietal channels were considered for this analysis. For each fixed effect coefficient (main effect and interaction) the related statistics (estimates, *p*-values, lower and upper 95% confidence intervals (CI)) are presented. The results presented in this table are reported by Barbazzeni, Speck and Düzel, (2023).

Linear mixed-effect model for accuracy during encoding

Fixed effect coefficients	Estimate (coefficients)	*p*-value	Lower (95% CI)	Upper (95% CI)
'Intercept'	55.649	0	51.168	60.129
'Group_NF' [1]	-0.43387	0.82518	-4.29	3.4223
'Reward' [2]	**3.5267**	**0.0054715 ****	**1.0425**	**6.0108**
'Day' [3]	**3.5209**	**5.2238e-12 *****	**2.5394**	**4.5023**

'P4_S2_Beta' [4]	**8.8588**	**0.028525 ***	**0.93373**	**16.784**
'Group_NF : P4_S2_Beta' [5]	1.896	0.51258	-3.7872	7.5793
'Reward : P4_S2_Beta'[6]	**-6.4747**	**0.023305 ***	**-12.066**	**-0.88352**
Day : P4_S2_Beta'[7]	-1.02	0.29983	-2.9505	0.91052

[1] Fixed effect "group" including 2 levels: NF-group and CO-group

[2] Fixed effect "reward" including 2 levels: Reward and Non-Reward conditions

[3] Fixed effect "day" including 5 levels: day-1, day-2, day-3, day-4, and day-5

[4] Fixed effect for low-beta frequency range. Channel location P4. Encoding period of 500-1000 ms (S2)

[5] Interaction effect between group and low-beta frequency range. Channel location P4. Encoding period at S2

[6] Interaction effect between reward conditions and low-beta frequency range. Channel location P4. Encoding period at S2

[7] Interaction effect between day and low-beta frequency range. Channel location P4. Encoding period at S2

3.6.2 RTS

LMM results are reported in Table 4 during encoding and in Table 5 during maintenance. When investigating main effects, improved mean RTs, observed across 5-days, were found unrelated to any NF-training effects. Indeed, no differences between groups were found, as shown by the negative coefficient (β = -0.03142). Despite faster RTs performances observed in the NF-group (M = .4722, SD = .17491) when compared to the CO-group (M = .5058, SD = .17063), the model showed that the difference in performance was not significant (p = .318). However, a (independent sample) t-test analysis between the groups did show that the difference in RT performances was significant (MD = -.03363, SEM = .01423, t_{588} = -2.363, p = .018, CI [.06158, -.00568]). Hence, even though the (full) alternative hypothesis H_1 model did not find a significant NF-training effect on improving mean RTs across the 5-days, probability due to the weight of the other parameters included in the model, the NF-training might have a potential effect on enhancing RTs (see Fig. 18.1). Furthermore, while investigating the main effects during encoding, theta oscillations' relative power was found to improve mean RTs (see Fig. 18.2). In particular, the effect was observed on the right parietal theta (P4) activity at time window S1 (i.e., from 0 ms to 500 ms after the onset of the *sample image*). As shown by the negative coefficient (β = -0.02738), the increase in relative power across 5-days was significant (p = 0.048) and positively related to faster RTs. When comparing the mean power of theta across the 5-days and between the defined time windows (S1 and S2), even though the overall mean power at S1 was higher (M = -.0120, SD = .51898) than at S2 (M = -.0176, SD = .50695),

the difference in power between these time windows was not significant (MD = .00566, SEM = .01804, t_{589} = .314, p = 754, CI [-.02978, .04110]). Moreover, when investigating the main effects during maintenance, improved mean RTs were found significantly related to the modulation of the relative power of bilateral parietal low-beta oscillations. In particular, the effect observed over the right parietal low-beta at P4 and as shown by the negative coefficient (β = -0.08996) indicated that the increase in relative power across the 5-days was significant (p = 0.031) in improving performances (see Fig. 19.1). On the other hand, the effect observed over the left parietal low-beta at P3 and as shown by the positive coefficient (β = 0.09322) indicated that the increase in relative power across the 5-days was significant (p = 0.045) although demonstrated to slow the RTs performance (see Fig. 19.2). When comparing the mean power of low-beta across the 5-days and between the two-channel locations (P4 and P3), the relative mean power of low-beta at P4 was slightly lower (M = .0014, SD = .24117) than at P3 (M = .0086, SD = .22571). Nevertheless, the difference in relative power between the channel locations was not significant (MD = -.00712, SEM = .00523, t_{589} = -1.360, p = .174, CI [-.01740, .00316]).

From the ML model fit statistic, the (full) alternative hypothesis model H_1 was not significantly different from the null hypothesis model H_0 during the encoding period ($\chi 2$ (14) = 15.888, p = 0.3202) but it differed during maintenance ($\chi 2$ (8) = 18.241, p = 0.0194). Indeed, the AIC value of the alternative hypothesis model H_1 was higher (-833.27) during encoding but lower in maintenance (-847.63) than the null hypothesis model H_0 (-845.38). The adjusted R^2 value of the alternative hypothesis model H_1 during the encoding (0.7304) and maintenance (0.7359) periods was higher than the null hypothesis model H_0 (0.7283). Hence the (full) alternative hypothesis model H_1 showed a greater model fit only during the maintenance period.

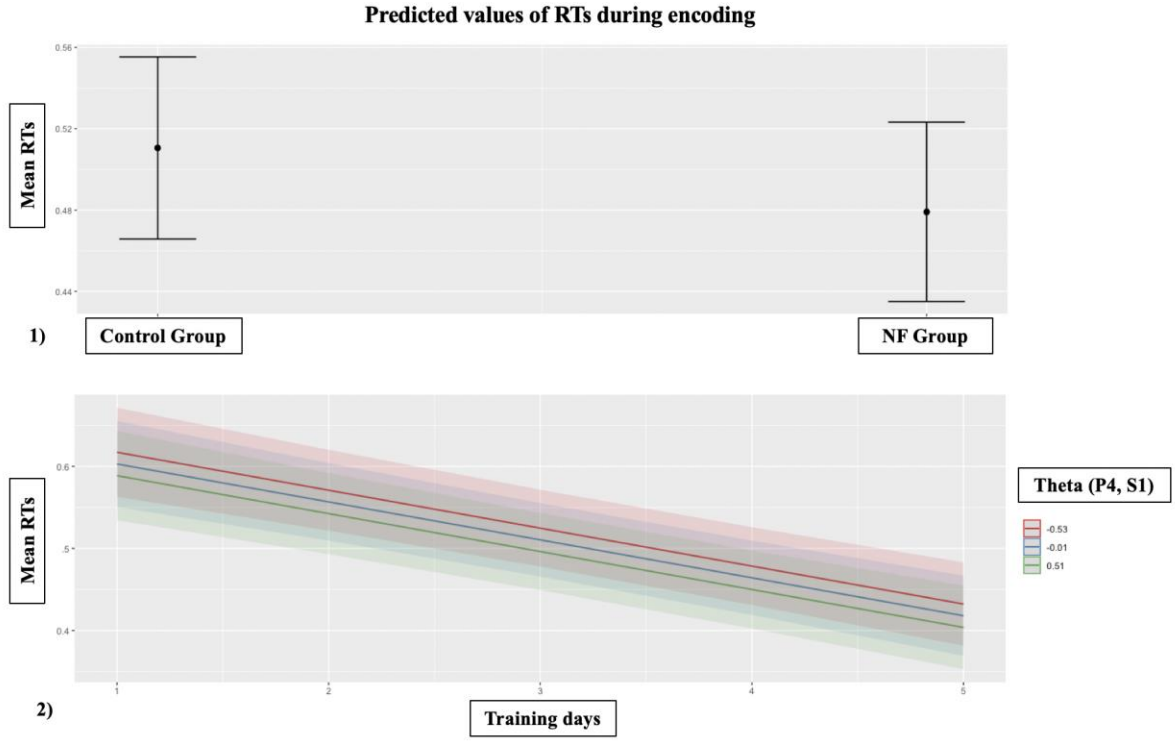

Fig. 18 Representation of predicted RTs values during the encoding period. 1) *Data values predicted for RTs are presented in relation to the NF-group (right) and CO-group (left). The x-axis indicates the two groups (NF and CO). The y-axis indicates mean RTs. Error bars indicate standard errors.* ***2)*** *Data values predicted for RTs are presented with respect to the relative power of theta frequency measured on channel P4 during the encoding period S1 and across the 5-days of training. The x-axis indicates the relative power of theta across 5-days. The y-axis indicates mean RTs. Confidence interval is based on the standard error. Regarding the relative power of theta activities, the green line denotes higher power values, the blue line denotes power values closer to zero, whereas the red line denotes lower power values. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

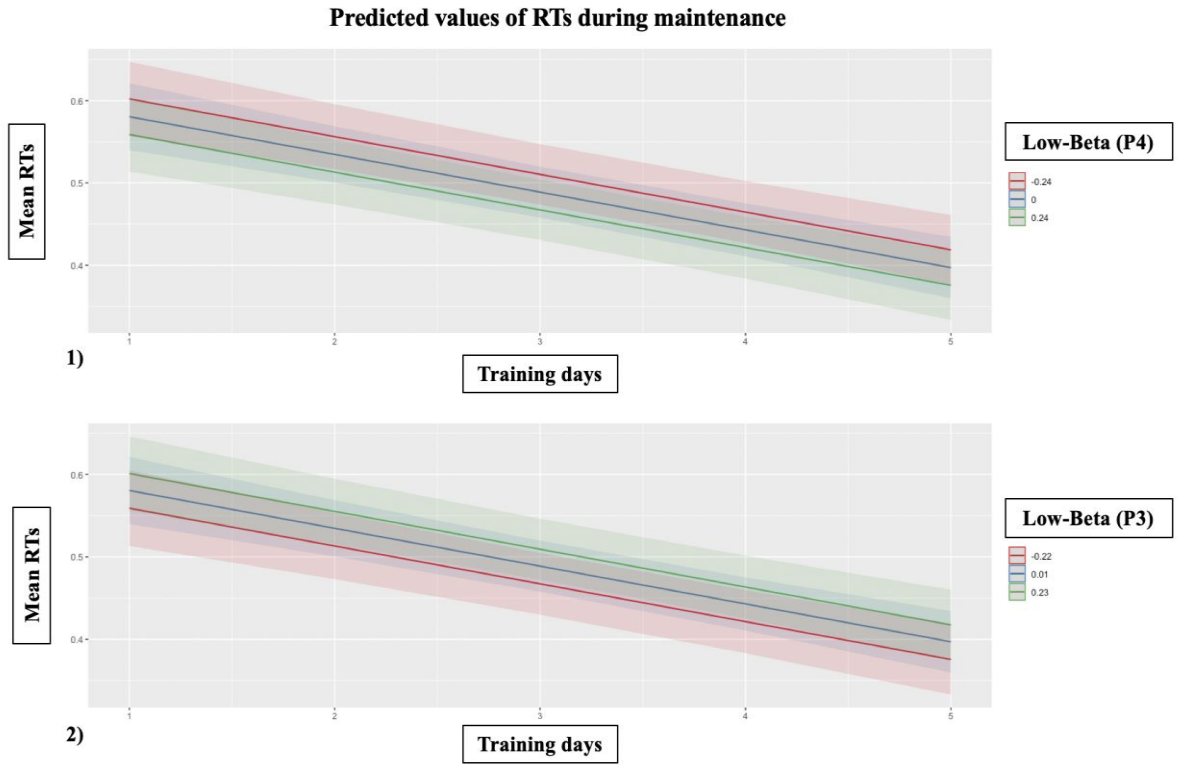

Fig. 19 Representation of predicted RTs values during maintenance. 1) *Data values predicted for RTs are presented with respect to the relative power of low-beta frequency measured on channel P4 and across the 5-days of training. The x-axis indicates the relative power of low-beta at P4 across 5-days. The y-axis indicates mean RTs. Confidence interval is based on the standard error. Regarding the relative power of low-beta activities at P4, the green line denotes higher power values, the blue line denotes power values closer to zero, whereas the red line denotes lower power values.* ***2)*** *Data values predicted for RTs are presented with respect to the relative power of low-beta frequency measured on channel P3 and across the 5-days of training. The x-axis indicates the relative power of low-beta at P3 across 5-days. The y-axis indicates mean RTs. Confidence interval is based on the standard error. Regarding the relative power of low-beta activities at P3, the green line denotes higher power values, the blue line denotes power values closer to zero, whereas the red line denotes lower power values. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

Table 4. RTs result from the linear mixed effect model during encoding. The (full) alternative hypothesis model H_1 was estimated by using the restricted maximum likelihood (REML). Only the initial 1000 ms of the encoding period was analyzed and further divided into two-time windows of 500 ms each (S1: 0-500 ms, S2: 500-1000 ms). Only P4 (right) and P3 (left) parietal channels were considered for this analysis. For each fixed effect coefficient, the related statistics (estimates, *p*-values, lower and upper 95% confidence intervals (CI)) are presented. The results presented in this table are reported by Barbazzeni, Speck and Düzel, (2023).

Linear mixed-effect model for RTs during encoding

Fixed effect coefficients	Estimate (coefficients)	*p*-value	Lower (95% CI)	Upper (95% CI)
'Intercept'	0.64949	0	0.58983	0.70917
'Group_NF'	-0.03142	0.31852	-0.09324	0.03039
'Reward'	-0.01174	0.14214	-0.02744	0.00394

'Day'	**-0.04623**	**9.9032e-14 *****	**-0.05814**	**-0.03433**
'P4_S1_Alpha'	-0.01059	0.45378	-0.03835	0.01716
'P3_S1_Alpha'	0.00375	0.79914	-0.02522	0.03273
'P4_S2_Alpha'	0.01955	0.16865	-0.00830	0.04741
'P3_S2_Alpha'	-0.01761	0.22544	-0.04613	0.01089
'P4_S1_Theta'	**-0.02738**	**0.04818 ***	**-0.05455**	**-0.00021**
'P3_S1_Theta'	0.01868	0.17813	-0.00853	0.04590
'P4_S2_Theta'	0.00802	0.57443	-0.02002	0.03606
'P3_S2_Theta'	-0.00359	0.7913	-0.03023	0.02304
'P4_S1_Beta'	-0.01251	0.44115	-0.04441	0.01937
'P3_S1_Beta'	0.01866	0.2914	-0.01605	0.05338
'P4_S2_Beta'	-0.01792	0.27006	-0.04981	0.01395
'P3_S2_Beta'	0.00569	0.72904	-0.02658	0.03798

Table 5. RTs result from the linear mixed effect model during maintenance. The (full) alternative hypothesis model H_1 was estimated by using the restricted maximum likelihood (REML). The analysis was conducted while considering the entire maintenance period (20 s). Only P4 (right) and P3 (left) parietal channels were considered for this analysis. For each fixed effect coefficient, the related statistics (estimates, p-values, lower and upper 95% confidence intervals (CI)) are presented. The results presented in this table are reported by Barbazzeni, Speck and Düzel, (2023).

Linear mixed-effect model for RTs during maintenance

Fixed effect coefficients	Estimate (coefficients)	P-value	Lower (95% CI)	Upper (95% CI)
'Intercept'	0.64791	0	0.58883	0.70699
'Group_NF'	-0.03491	0.26923	-0.09691	0.02709
'Reward'	-0.01115	0.1499	-0.02635	0.00404
'Day'	**-0.04586**	**1.4744e-13 *****	**-0.05776**	**-0.03396**
'P4_Alpha'	0.01460	0.67175	-0.05306	0.08227
'P3_Alpha'	0.02065	0.54877	-0.04695	0.08826

'P4_Theta'	-0.04588	0.10875	-0.10199	0.01022
'P3_Theta'	-0.02420	0.3202	-0.07198	0.02357
'P4_Beta'	**-0.08996**	**0.03132 ***	**-0.17183**	**-0.00809**
'P3_Beta'	**0.09322**	**0.04578 ***	**0.00175**	**0.18469**

LMM results from the *post-hoc* investigation during the encoding period are reported in Table 6. When investigating interaction effects on improved mean RTs, a significant interaction (p = 0.02) was found between the effect of group and the relative power of right parietal theta at S1. However, the positive coefficient (β = 0.05065) indicated that higher right parietal theta power at S1 would affect RT performances, particularly in response to the NF-training (see Fig. 20). Thus, an NF-training effect on RTs performances was found across the training while modulating theta oscillations. Overall, the mean theta power across the 5-days of training was found to be higher in the NF-group (M = -.0004, SD= .53714) than the CO-group (M = -.0239, SD = .51104). Nevertheless, the difference in theta power between groups was not significant (MD = .02342, SEM = 0.4276, t_{588} = .548, p = .584, CI [-.06056, .10741]). Furthermore, when investigating mean RTs during maintenance, no significant interactions between factors were found from the *post-hoc* analysis (see Table 7).

From the ML model fit statistic, the interaction model H_1 was significantly different from the null hypothesis model H_0 during the encoding ($\chi 2$ (5) = 15.887, p = 0.0071) period but not during maintenance ($\chi 2$ (9) = 15.316, p = 0.0826). Indeed, the AIC value of the interaction model H_1 was lower (-851.27) during encoding but higher in maintenance (-842.7) than the null hypothesis model H_0. The adjusted R^2 value of the interaction model H_1 during the encoding (0.7339) and maintenance (0.7347) periods was higher than the null hypothesis model H_0. Hence the interaction model H_1 showed a greater model fit only during the encoding period.

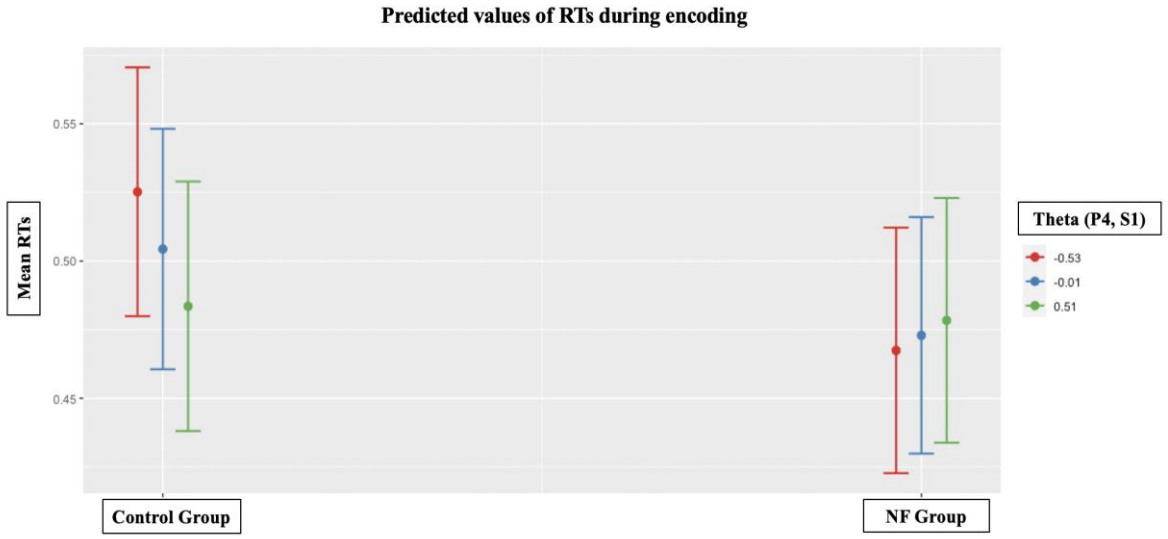

Fig. 20 Representation of predicted RTs values with interaction effects during encoding. *Data values predicted for RTs are presented in response to the interaction between groups and the relative power of the theta (measured on channel P4 during the encoding period S1). The x-axis indicates the NF-group (right) and CO-group (left). The y-axis indicates the predicted RTs values with respect to the interaction between the relative power of theta and (NF and CO) groups. Error bars indicate standard errors. Regarding the relative power of theta activities, the green line denotes higher power values, the blue line denotes power values closer to zero, whereas the red line denotes lower power values. The results presented in this figure are reported by Barbazzeni, Speck and Düzel, (2023).*

Table 6. RTs result from the linear mixed effect model with interaction effects during encoding. Based on a post-hoc analysis, the interaction model H_1 (including main effects and interactions between fixed effect coefficients) was estimated by using the restricted maximum likelihood (REML). Only P4 (right) and P3 (left) parietal channels were considered for this analysis. For each fixed effect coefficient (main effect and interaction) the related statistics (estimates, *p*-values, lower and upper 95% confidence intervals (CI)) are presented. The results presented in this table are reported by Barbazzeni, Speck and Düzel, (2023).

Linear mixed-effect model for RTs during encoding

Fixed effect coefficients	Estimate (coefficients)	*p*-value	Lower (95% CI)	Upper (95% CI)
'Intercept'	0.6479	0	0.59003	0.70576
'Group_NF'	-0.03093	0.31429	-0.09125	0.02939
'Reward'	-0.01222	0.1114	-0.02729	0.00283
'Day'	**-0.04594**	**2.82e-14 *****	**-0.05750**	**-0.03437**
'P4_S1_Theta'[1]	**-0.04024**	**0.04662 ***	**-0.07987**	**-0.00060**
'Group_NF : P4_S1_Theta'[2]	**0.05065**	**0.00193 ****	**0.01870**	**0.08260**
Day : P4_S1_Theta'[3]	4.2859e-05	0.99414	-0.01141	0.01149

[1] Fixed effect for theta frequency range. Channel location P4. Encoding period of 0-500 ms (S1)

[2] Interaction effect between group and theta frequency range. Channel location P4. Encoding period S1

[3] Interaction effect between day and theta frequency range. Channel location P4. Encoding period S1

Table 7. RTs result from the linear mixed effect model with interaction effects during maintenance. Based on a post-hoc analysis, the interaction model H_1 (including main effects and interactions between fixed effect coefficients) was estimated by using the restricted maximum likelihood (REML). Only P4 (right) and P3 (left) parietal channels were considered for this analysis. For each fixed effect coefficient (main effect and interaction) the related statistics (estimates, *p*-values, lower and upper 95% confidence intervals (CI)) are presented. The results presented in this table are reported by Barbazzeni, Speck and Düzel, (2023).

Linear mixed-effect model for RTs during maintenance

Fixed effect coefficients	Estimate (coefficients)	P-value	Lower (95% CI)	Upper (95% CI)
'Intercept'	0.64842	0	0.58926	0.70758
'Group_NF'	-0.03305	0.28875	-0.09405	0.02804
'Reward'	-0.01002	0.1917	-0.02509	0.00504
'Day'	**-0.04520**	**4.2788e-13 *****	**-0.05718**	**-0.03323**
'P4_Beta'[1]	**-0.26277**	**0.00736 ****	**-0.45468**	**-0.07086**
'P3_Beta'[3]	**0.22721**	**0.03270 ***	**0.018762**	**0.43565**
'Group_NF : P4_Beta'[4]	0.10527	0.14403	-0.03606	0.24661
'Group_NF : P3_Beta'[5]	-0.09771	0.21942	-0.25381	0.05839
'Day : P4_Beta'[6]	0.03569	0.17937	-0.01645	0.08784
'Day : P3_Beta'[7]	-0.02727	0.35987	-0.08574	0.03118
'P4_Beta : P3_Beta'[7]	-0.05758	0.28995	-0.16435	0.04919

[1] Fixed effect for low-beta frequency range. Channel location P4. Maintenance period of 20 s

[2] Fixed effect coefficient for low-beta frequency range. Channel location P3. Maintenance period of 20 s

[3] Interaction effect between group and low-beta frequency range. Channel location P4. Maintenance period of 20 s

[4] Interaction effect between group and low-beta frequency range. Channel location P3. Maintenance period of 20 s

[5] Interaction effect between day and low-beta frequency range. Channel location P4. Maintenance period of 20 s

[6] Interaction effect between day and low-beta frequency range. Channel location P3. Maintenance period of 20 s

[7] Interaction effect between low-beta frequency range. Channel locations P4 and P3. Maintenance period 20 s

3.7 DISCUSSION

The current research work by Barbazzeni, Speck and Düzel (2023) was aimed to improve WM by combining CT with EEG-NF under high and low motivational expectancies of monetary reward. Hence, the study focused on specific oscillatory activities, known as suppression of alpha oscillations, demonstrated to be involved in attention mechanisms under WM processes and modulated by reward anticipation. In a double-blind study design, participants were trained across 5-days to suppress alpha power by receiving real-time NF or CO feedback of their ongoing relative alpha power. It was investigated whether the developed NF-training method would have enhanced alpha power suppression, particularly observed when a reward was expected. Consequently, it was investigated whether an NF-training and reward-anticipation effect would have improved WM performances. Moreover, the study investigated whether the proposed NF-training method would have facilitated the performance of untrained and unrelated cognitive tasks by transfer effects but also it investigated the effect of training on neighboring frequencies bands such as theta and beta oscillations. A second experiment was also conducted to validate the developed NF method and according to inter-individual NF learning mechanisms to investigate and compare the effect of implementing different mental strategies on modulating alpha suppression and, consequently, WM. Thus, based on the same study design, two experiments were conducted that differed by the instructions given during maintenance. In *Experiment I*, participants were instructed to perform an MC task cognitively unrelated to the DMST. In *Experiment II*, participants were instructed to perform a MI task while rehearsing the sample image, and thus related to the DMST. In both experiments, mental strategies were applied while controlling the alpha level and independently of whether it was a real-time or a control NF. Lastly, by combining both experiments, an exploratory analysis was performed to investigate further whether observed WM improvements were related to any oscillatory activities changes across the 5-days of training. Besides alpha oscillations, the neighboring theta and beta activities were also analyzed due to their implication in memory formation. Hence, the overall effect of cognitive training and related oscillatory activities was explored during the encoding and maintenance periods.

A significant improvement in WM was found concerning the DMST performance when investigating *Experiment I*. Indeed, increased accuracy and faster RTs were observed across training days, particularly when a reward was expected. Thus, a reward-anticipation effect was found to influence motivational expectancies and, consequently performances. However,

having observed no performance differences between groups, WM enhancements were not related to an NF-training effect but generally related to the effect of CT. Moreover, an increased alpha suppression was observed across training days, although the overall decrease in power was neither significant nor related to the NF-training. In fact, in both groups, a decreased alpha power was found. Despite the observed decrease in power, the effect was not related to reward-anticipation. Indeed, no significant differences in alpha power were found in response to reward and non-reward trials. Barbazzeni, Speck and Düzel (2023) explained the lack of an NF-training effect on alpha suppression as a consequence of the fact that the CO-group was also encouraged to apply a mental strategy while controlling the alpha-level through the control feedback signal. This would justify the likewise decrease in power due to the dynamic engagement while performing the task. Indeed, the CO-group has been treated as an *active control* group. Thus, possible placebo effects (Raz & Harris, 2016) may have biased the observed results as already demonstrated by previous experimental studies (Thibault & Raz, 2016). In addition, by comparing day-1 with day-5, the interaction "day*reward*channel" was found to be significant. The interaction effect indicated a decreased alpha power over the last training day and across the parietal channel locations with a reward-anticipation effect. In contrast to the findings by Barbazzeni, Speck and Düzel (2023), different results were found in the study of Pornpattananangkul and Nusslock (2016), who demonstrated a positive effect of anticipatory reward on alpha power suppression, and also differently from Malecki, et al. (2009), who found a significant effect of enhanced alpha suppression on improving WM performances in a DMST. Furthermore, when investigating the power of theta, a significant NF-training effect was observed on enhancing theta suppression across the training. Thus, NF-training of alpha suppression was found to transfer its effect on modulating a neighbor frequency band such as theta oscillations during maintenance, and the effect was found to be enhanced over days (Barbazzeni, Speck, & Düzel, 2023). According to the literature, Brzezicka et al. (2019) investigated theta power changes relative to memory load during maintenance. They found a significant decrease in theta power over the dorsolateral prefrontal cortex (DLPFC) during memory retention, where the decrease was proportional to memory load. In addition, the decrease in power was a predictor of the subject's RTs, revealing that theta power over the DLPFC can explain individual differences in WM performance. Moreover, in parallel to an NF-training effect on theta suppression during maintenance, a reward-anticipation effect was also found on decreasing the power (Barbazzeni, Speck, & Düzel, 2023). Previous studies have already related theta oscillations to the brain's reward system. Indeed, these studies found how theta activities are involved in learning processes (Begus & Bonawitz, 2020), and how the

process of learning and memory formation are closely influenced by a reward expectation (Cohen et al., 2012; Gruber et al., 2013). Nevertheless, other findings are also in contrast with the results obtained by Barbazzeni, Speck and Düzel (2023), finding instead an increase of theta power during maintenance. The study of Bahramisharif et al. (2018) demonstrated that a consistent decrease of alpha/theta power was observed at encoding, although this event was followed by a rapid increase in power during maintenance and related with the serial representation of items in a WM task. Based on previous results, also the study of Khader et al. (2010) aimed at investigating oscillatory activities related to WM maintenance and long-term memory (LTM). Indeed, the study explored how neural activities measured during the maintenance period of a DMST predict LTM encoding. According to the assumption that an increase of alpha and theta power is associated with higher WM load and successful encoding, the study did show that increased activity of these oscillations over occipital and parietal regions was indeed related with subsequently remember stimuli, demonstrating that increased alpha and theta activity is involved in LTM encoding processes. Moreover, while investigating training effects on beta oscillations, an overall decrease in beta power during maintenance was found across days and possibly implicated in enhancing WM performances (Barbazzeni, Speck & Düzel, 2023). Nevertheless, the decrease in power was found unrelated to either an NF-training effect or a reward-anticipation effect. Similarly, Hanslmayr et al. (2012), investigated the role of alpha and beta bands desynchronization during encoding and retrieval processes. They demonstrated that increased alpha and beta power desynchronization correlates with successful memory encoding in a subsequent memory (SM) or difference memory (DM) paradigm, but also with the retrieval of episodic memories in an old/new recognition paradigm. Despite the fact that the experimental stimuli used in the study were visual words (and not visual objects), their results supported the finding that alpha and beta suppressions are responsible for storing the amount of information encoded into memories. In addition to these results, the study of Proskovec et al. (2018) involved a whole-brain approach to relate oscillatory activities with SWM performances finding that decreased alpha and beta power over the parietal regions were related to SWM performances, underling attentive mechanisms during encoding and maintenance. Moreover, other studies have also associated beta power suppression with motor-cortical activities and related to successful learning mechanisms and enhanced RTs performances (Pollok et al., 2014; Hervault et al., 2021).

When investigating *Experiment II*, results were in contrast with the research hypothesis tested by Barbazzeni, Speck and Düzel (2023). Even though WM improvements were found across

the training, with a significant reward-anticipation effect, enhanced accuracies and RTs were observed in both groups. Thus, an NF-training effect on improving WM was not found. In addition, no significant effects of either NF-training or reward-anticipation were observed on alpha suppression, theta, or beta oscillations. Differently from *Experiment I*, the opposite pattern was found. Indeed, when compared to the CO-group, the NF-group did show increased power activities and generally observed across all the investigated frequency bands. Thus, while investigating the reasons how MI was not more effective than MC, as a strategy to modulate oscillations during maintenance, a few explanations were considered by the authors. In *Experiment I*, participants were instructed to perform an MC task during maintenance (Kawabata, 1974; Lin et al., 2012; Magosso et al., 2019), a mental strategy implemented to stimulate alpha power suppression by increasing concentration during task performance. This additional task would have stimulated participants while involving multitasking and divided attention (e.g., cognitively unrelated to the DMST). Differently, in *Experiment II*, participants were instructed to implement a MI strategy to visually rehearse the *sample image*. It may be possible that this strategy (e.g., cognitively related to the DMST) did not require enough attention, thus leading to a loss of concentration. Nevertheless, it is not possible to conclude that MC requires more effort than MI because it has not been investigated how participants perceived the difficulty of implementing one or the other mental strategy. Therefore, the reason why MC demonstrated to be more successful cannot be explained yet. Moreover, differently from previous findings, even when targeting the lower or upper alpha frequencies during NF (e.g., NF training based on the individual alpha range) did not improve performances (Barbazzeni, Speck & Düzel, 2023). Indeed, the results presented in this research work differ from Hanslmayer et al. (2005), who showed that NF enhanced upper alpha power with a positive effect on cognitive performance and from, Zoefel et al. (2011) who suggested that cognitive performance can be improved by enhancing the upper frequencies of the alpha range. Furthermore, more researches (Hanslmayr et al., 2012; Klimesch et al., 1996; Klimesch et al., 1997; Klimesch, 1999, Klimesch et al., 2006), did find that alpha power suppression is associated with different cognitive processes: upper alpha frequencies responsible to sustain semantic memory, whereas lower-alpha frequencies in support of attentional processes. In this regard, the study of Klimesch et al. (1996) investigated the event-related shifts between the two alpha bands and how this shift can be a predictor of recall performances. Indeed, Klimesch et al. found that good performers showed larger alpha suppression in the lower frequencies, whereas bad performers in the upper alpha frequencies. This phenomenon, called the *"Dm effect"* to represent differences due to memory, was shown to be robust over parietal regions

and explained by the fact that bad performers were less attentive or alert during encoding, thus leading to reduced lower-alpha suppression. Based on these findings, a clear investigation of the underlying neural oscillation would improve associated cognitive processes.

Furthermore, when investigating transfer effects on unrelated cognitive tasks due to NF-training, no NF-training effect was found by Barbazzeni, Speck and Düzel (2023) in both tasks and experiments. Therefore, an effective transfer effect of untrained cognitive tasks was not found, and clear NF-training facilitation processes cannot be considered. In conclusion to the experiment, participants were presented with a questionnaire to investigate their feelings, perception, and opinions about the current research. From the frequency distribution analysis, both groups reported feeling overall good after the experiment, finding the execution and the understanding of the experimental instructions effortless. Lastly, better memory and concentration were perceived in both groups and experiments after the training.

An exploratory analysis based on an LMM was also conducted to investigate ensued WM results and whether observed performances may relate to particular oscillatory change activities measured during encoding and maintenance across training days (Barbazzeni, Speck & Düzel, 2023). Thus, an investigation across *Experiment I* and *Experiment II* was conducted.

When investigating main effects during encoding, improved mean accuracy was found related to a significant increase of parietal beta activities. In particular, the overall increase of beta was observed at time window S2, indicating that the involvement of beta activity during encoding appears around 500 ms after stimulus onset. Moreover, a reward-anticipation effect was also found to improve accuracies across the training. A significant interaction effect was also observed between beta activities and reward-anticipation, indicating that for lower beta values, accuracy performances tended to be higher, but only when a reward was expected. Thus, the authors concluded that possible reward-anticipation effects on beta power suppression may influence accuracy performance. Moreover, as found by Steiger and Bunzeck (2017), improved mean RTs were found related to a significant increase of parietal theta (Barbazzeni, Speck & Düzel, 2023). The overall increase of theta power was observed at time period S1, indicating that theta activities may appear within 500 ms after stimulus onset (i.e., sample image) and a predictor of successful memory encoding. Similarly, the study of Kleberg et al. (2014) demonstrated that in a remember/know task, pre- and post-stimulus theta oscillations were associated with preparatory mechanisms underlying encoding and episodic memory formation. Likewise, the study of Osipova et al., (2006), besides the involvement of gamma activity, found

that increased theta activity was related to later remembered items in line with the "subsequent memory effect", but also with recognized items and in line with the "old/new effect." The increase of theta activities was found over parietal and temporal areas, suggesting that these oscillations were implicated with synaptic plasticity processes while facilitating memory encoding. Nevertheless, from the model fit comparison analysis, this finding by Barbazzeni, Speck and Düzel (2023) was not fully supported and further investigations are needed to explore the model and the outcome of the related factors. Furthermore, when investigating interaction effects, the post-hoc analysis did show that an NF-training effect modulating the power of theta oscillations was significant in predicting RTs performances. Indeed, the NF-group was found to show faster RTs performances. Besides, overall lower values of theta power were mostly related to better performances. Thus, the significance of this interaction may indicate that possible NF-training effects on modulating theta oscillations are effective in improving RTs. Indeed, decreased theta activities were also related to encoding processes (Greenberg, et al., 2015; Crespo-García et al., 2016; Fellner, et al., 2016).

When investigating maintenance, although a reward-anticipation effect was found significantly related to improved mean accuracies, no oscillatory activities were found related to enhanced accuracy performances (Barbazzeni, Speck & Düzel, 2023). However, parietal low-beta activities observed over both hemispheres were found related to improved mean RTs, although their involvement was differently related to performance enhancements. Indeed, the authors showed that the increase of right parietal beta was related to faster RTs, whereas the increase of left parietal beta was associated with slower RTs performances. Moreover, no significant interaction effects were observed from a post-hoc analysis. Although the role of beta oscillations in supporting WM processes remains unclear, by comparing the obtained results with previous research works, the study of Deiber et al. (2007) found that beta oscillations increase over the parietal regions as memory load increases; suggesting the relevance of beta activity in retaining and maintaining items for further task requirements, even though other studies found a decrease in power (Pesonen, Hamalainen, & Krause, 2007; Bocková et al., 2007). Moreover, Zanto and Gazzaley (2009) proposed another view of beta oscillation correlating it with higher WM performances and enabling effective filtering of irrelevant information. In a further study, Chen and Huang (2015) aimed to investigate the process of maintaining and manipulating encoded information in WM during the performance of a visual N-back WM task, and which neural oscillations were associated with WM load. They found that while accuracy decreases and RTs increase with increasing WM load, alpha power

decreases and beta power increases with increasing temporal WM load, advancing the hypothesis that decreased alpha oscillations would reflect a mechanism of task-related cortical activity, whereas beta oscillations to a mechanism of maintenance. Moreover, Proskovec et al. (2019), investigated the relationship between load-related differences in oscillations and behavioral performance in an SWM study. Results showed that during the encoding and maintenance period, alpha activity decreased in the left inferior frontal gyrus (IFG) and right superior temporal sulcus (STS), as well as, beta activity decreased in right superior parietal regions during maintenance in high- compared to low-load SWM trials, suggesting that alpha and beta oscillations are essential to establish the increased demands of high-load SWM processing. The top-down control of spatial attention and maintenance of features have been mostly related to parietal regions, suggesting the hypothesis that these particular areas are responsible for retaining information with increased WM load. Furthermore, it was observed that RTs improvements were related to the beta activity (Barbazzeni, Speck & Düzel, 2023); similarly, the study of Senkowski et al. (2006) while investigating neural processes underlying RT facilitations, beta activity (13-30 Hz) was related to sensory-motor processing when implementing multisensory stimuli. Evoked beta responses and RTs were recorded during a simple task where participants were instructed to classify, by pressing a button, the appearance of different stimuli presented in a stream of auditory, visual, or multi-sensory modalities. Senkowski et al. found that beta oscillations correlated negatively with RT measures among all stimulus types and that these negative correlations were mostly localized over the frontal, occipital, and sensory-motor scalp regions. Based on these results, they concluded that the relationship between increased beta activity and multisensory processing might be linked to the effect of RT speed improvements. In conclusion, from the LMM analysis reported by Barbazzeni, Speck and Düzel (2023), the interaction between oscillations and reward was found impactful on enhancing WM, advancing the hypothesis that WM capacity varies among participants and is influenced by motivational factors. Although it is still unclear which reward-related oscillatory activities facilitate the performance of WM, this relationship was investigated by Kawasaki and Yamaguchi (2013). In their study, a time-frequency analysis was conducted during a monetary-rewarded delayed-response task in which the position of colored disks was required to be memorized while comparing WM capacity under low- and high-reward trials. The authors found that the amplitude of frontal theta tended to increase during the delay periods and positively correlated with visual WM performance, whereas frontal beta oscillations were identified as reward-related activities; indeed, during the delay period, beta amplitudes were correlated with enhanced WM performance between high-reward and no-

reward trials. Based on these results, with the proposed study, a link between WM-related theta and reward-beta oscillations over the frontal regions was defined, and playing these oscillations a dominant role in enhancing visual WM capacity. Moreover, additional results associated with reward-related performance come from the study of Steiger and Bunzeck (2017). Indeed, their study investigated the impact of the structural decline of the dopaminergic system during aging and its effect on motivation. To address this issue, they analyzed the EEG signal in a reward-learning paradigm where scene images were initially encoded and combined with cues predicting monetary reward (high vs. low). Successively, recognition memory for scenes has been tested. Results showed faster RTs during encoding when images were predictive of high reward and particularly, the high reward was associated with increased theta power over occipito-parietal and frontocentral sites. Even though these results were confirmed in the young participant's group but not in the elderly, the authors claimed a relationship between reward-based processes, theta oscillations, and age-dependent changes of the dopaminergic system.

Despite the lack of an NF-training effect targeting alpha suppression on improving WM, the findings from the LMM analysis described by Barbazzeni, Speck and Düzel (2023) were promising. Indeed, across 300 distinct EEG sessions it was possible to demonstrate how WM performances enhancements were associated with a parallel modulation of oscillatory activities during the training. In particular, it was explored how improved accuracy and RTs were the results of underlying increased beta and theta oscillations during encoding and maintenance, finding that right parietal beta oscillations might be a potential target for improving WM accuracy. (Barbazzeni, Speck & Düzel, 2023).

3.8 CONCLUSION

Supporting information processes, executive functioning, and the maintenance of information for goal-oriented behavior, WM acquires a prominent role in our daily life. Previous findings have found that the maintenance of information is supported by the change in the activity of alpha oscillations (Malecki et al., 2009; Klimesch, 2012), and where a desynchronization was found related to successful performance in a discrimination task (Ergenoglu et al., 2004; Hanslmayr et al., 2005; Hanslmayr, et al., 2005) and cognitive load (Kardan et al., 2020). Moreover, reward anticipation was also found to modulate the amplitude of sustained neural activity while improving performances in a DMST (Malecki et al., 2009) and how cognitive performances were related to enhanced suppression of alpha power while expecting a reward (Pornpattananangkul & Nusslock, 2016). Thus, NF-training of alpha power was proposed to

improve cognition by regulating underlying oscillatory activities (Biswas & Ray, 2019; Zoefel, Huster, & Herrmann, 2011; Hanslmayr et al., 2005).

Therefore, the work of this thesis aimed to improve WM. A novel paradigm was established by Barbazzeni, Speck and Düzel, (2023) to enhance performances by combining CT with NF-training of alpha suppression while performing a monetary rewarded DMST across 5-days of training. Thus, it was investigated whether NF-training and monetary reward would have enhanced alpha suppression and whether NF-training would have facilitated the performance of untrained tasks by transfer effects. Moreover, two experiments were conducted to investigate the effect of different metal strategies to modulate the alpha-level during maintenance, consequently WM performances. Lastly, the overall effect of training on neural oscillations was investigated in a combined-study analysis to explore any relationships between ensued WM performances and oscillatory changes across training days.

Results from *Experiment I* and *Experiment II* (Barbazzeni, Speck & Düzel, 2023) showed a significant effect of CT in improving WM across training days. The effect was mostly observed in anticipation of a reward, supporting the notion that motivational factors can influence behavioral performances in high compared to low expectancies of reward. However, WM enhancements were observed in both groups where a significant difference in performance was not found. Thus, WM results were unrelated to the effect of NF-training. Overall, although NF-training did show to modulate ongoing alpha and neighboring theta and beta oscillations, the effect was not significant. However, results from *Experiment I* did show a significant NF-training effect on enhancing theta suppression across the training with a significant reward-anticipation effect. In addition, an increase of beta suppression was also found across days, even though unrelated to the effect of an NF-training. Moreover, no significant NF-training effects were found on transfer tasks in both experiments. Hence, it cannot be concluded that NF-training can potentially facilitate the performance of unrelated and untrained cognitive tasks by transfer effects. Contrary to the research hypothesis, the engagement of participants in a MI task during maintenance did not provide the expected results on enhancing alpha suppression. Indeed, when analyzing the power of alpha during maintenance, the opposite pattern was observed between *Experiment I* and *Experiment II*, characterized by an overall decrease and increase in alpha power, respectively. Thus, engaging participants in an MC task while controlling the alpha level demonstrated to be a better mental strategy aimed at enhancing alpha suppression. Nevertheless, despite a lack of a significant NF-training effect on alpha

suppression and WM, results from the post-NF-training reported that participants perceived a better memory after the training, accompanied by a better concentration. Thus, the developed method may have a potential capability in stimulating attention and concentration, as perceived by the majority of participants.

In conclusion, an exploratory analysis was conducted by combining both experiments to examine any relationships between ensued WM performances and oscillatory activities during the encoding. The LMM analysis did show that improved mean accuracy was related to increased beta oscillations over the right parietal regions, with a significant reward-anticipation effect. In addition, an interaction effect did show how reward expectancies may influence accuracy performances when modulating the power of beta across training days. Moreover, the increase of right parietal theta was found associated with improved mean RTs, and where an interaction effect was found indicating that an NF-training effect on modulating the power of theta may be responsible for RTs performances. Differently, when investigating the maintenance period, the LMM analysis did show that while improved accuracy was positively associated with reward expectancy, the modulation of beta oscillations was differently related to RT performances. Indeed, it was observed that the increase of right parietal beta was related to faster RTs, whereas the increase of left parietal beta was found to slow RTs performances. Therefore, the authors found how the variation in WM performances across training days was related to an analog change in neural oscillations, observed during encoding and maintenance, and this result was consistent in a large dataset of 300 EEG sessions.

Finally, based on the results presented by Barbazzeni, Speck and Düzel (2023), in the following chapter, a research protocol based on the developed NF method was proposed to regulate dysfunctional alpha and theta suppression in pAD patients when compared to age-matched healthy controls. The proposed research protocol and experimental design were adapted to foster the understanding of cognitive decline, related brain oscillations in healthy aging and in a clinical population such as pAD.

3.9 CLOSING REMARKS

In this chapter, the main research study conducted by Barbazzeni, Speck and Düzel (2023) and reported in this thesis was described. The introduction gave an overview of the scientific objective and research hypothesis, whereas the method covered the experimental procedures

and analysis. Furthermore, results were discussed and compared with previous studies, followed by a general conclusion concerning the main findings.

Considering the importance of WM in supporting information processing, learning, and executive functioning, the investigation of underlying oscillatory activities was explored. The study aimed to test whether the developed NF-training method would have enhanced alpha suppression while performing a WM task in a high and low condition of reward expectancies. Transfer effects on unrelated cognitive tasks were also explored and the implementation of different mental strategies that were compared to test interindividual differences in NF learning and their effect on enhancing alpha suppression during maintenance. Thus, two experiments were conducted and compared to investigate the developed method and experimental procedures.

Results showed improved behavioral performances with a consistent reward-anticipation effect, although the observed WM enhancements could not be attributed to an NF-training effect. Moreover, despite a modulation in alpha power across training days, a significant effect of NF-training was not found, and neither was a reward-anticipation effect on enhancing alpha suppression. However, in *Experiment I, an* NF-training effect on enhancing theta suppression with a reward-anticipation effect was found. This result was followed by observed enhanced beta suppression across days, although unrelated to the effect of NF-training or reward. Thus, the lack of significant NF-training results in *Experiment II* forced to conclude the inefficacy of the developed method to enhance alpha suppression or modulate neighboring frequency bands. In addition, no consistent transfer effects were found in response to the NF training. Nevertheless, an exploratory analysis based on an LMM and conducted across both experiments was aimed to explore any relationship between enhanced WM performances and neural oscillations. Hence, it was found that during encoding, improved mean accuracy was related to increased beta oscillations and with a significant reward-anticipation effect modulating underlying beta activities. Whereas faster mean RTs were related to increased theta power with a significant NF-training effect. Differently, during maintenance, improved accuracy was found positively associated with reward expectancies although unrelated to the activity of specific oscillations. Furthermore, improved mean RTs were found related to the activity of bilateral beta oscillations, where the increase over the right parietal region contributed to faster RTs, whereas the increase over the left parietal region contributed to slower RTs.

Lastly, this research study aims to contribute to the field of cognitive neuroscience. Although the proposed NF-training method was not able to support evidence of its efficacy in enhancing alpha suppression and WM, the findings obtained from the LMM analysis were indeed capable to demonstrate and explain how the WM enhancement across training days was associated with a parallel change in neural oscillations, during encoding and maintenance, but also how reward is a motivating factor to improve learning. Further studies interested in WM enhancement and related oscillatory activities might benefit from this research study that was demonstrated over a large dataset.

CHAPTER 4:

NEUROFEEDBACK BASED ON EEG TO MODULATE ALPHA OSCILLATIONS IN PRECLINICAL ALZHEIMER'S DISEASE: A RESEARCH PROTOCOL

4.1 CHAPTER OVERVIEW

Chapter 4 represents the second project of this thesis work. This chapter will describe a proposal for a research protocol designed for pAD patients. The proposal was developed based on the knowledge and experience previously acquired from the study involving healthy volunteers, as reported in *Chapter 3*. The introduction will give an overview of the scientific objective and research hypotheses. Moreover, the method will cover the experimental design, the NF-training method, and analysis adapted for this research protocol.

4.2 INTRODUCTION AND SCIENTIFIC OBJECTIVE

In *Chapter 2*, effective and innovative methods to delay cognitive decline while exploiting cognitive reserve and neuroplasticity were presented (Herrera et al., 2012). Thus, CT was proposed to enhance cognitive functioning in several domains (Kallio et al., 2017, Gates, et al. 2020, Al-Thaqib et al. 2018), as well as, its combination with NF did show promising results in improving memory and other cognitive functions by regulating underlying neural patterns (Luijmes et al., 2016). Indeed, several studies (Jirayucharoensak et al., 2019; Marlats et al. 2020, Reis et al. 2016; Gomez-Pilar et al. 2016) demonstrated the positive effect of implementing different NF-training protocols to ameliorate cognitive functioning and corresponding neural oscillations. In addition, despite the common application of NF in healthy volunteers, these studies have demonstrated the effectiveness of this method not only in healthy aging but also in early AD stages.

Therefore, the experience mastered in implementing the developed NF-training method, applied in healthy volunteers, raised the motivation to propose an alternative NF-training protocol to regulate impaired oscillatory activities in a group of pAD. Previous studies investigating prominent biomarkers during the early stage of the disease hypothesized that alpha and theta oscillations would be dysfunctional compared to age-matched healthy controls and lead to severe cognitive impairments such as memory and attentional deficits. In this regard, the protocol was proposed to investigate whether the application of the NF-training

method, described in *Chapter 2 Subsection 2.5.1*, would have been capable of enhancing alpha power suppression in a single training session and whether the regulation of alpha oscillations would have transferred its effect on increasing theta suppression. Due to the Covid-19 pandemic which affected the global population in several ways and in particular also research works, the proposed protocol couldn't be executed in this type of sample involving pAD patients and old individuals. Nevertheless, the protocol was planned as follows. A group of pAD would be compared with a group of age-matched healthy controls to test this hypothesis. Furthermore, the proposed NF protocol was aimed to provide a structured and methodological procedure, ready to be applied. Indeed, this NF protocol would represent a valuable and customizable method to be tested and further improved by future studies while contributing to developing research in the field of dementia.

In the context of cognitive neuroscience, the proposed research protocol was designed to extend the understanding of those mechanisms behind the cognitive decline associated with neurodegenerative diseases. By proposing an alternative NF-training method, it would be possible to investigate dysfunctional neural and cognitive mechanisms while augmenting the potential of cognitive reserve and neuroplasticity. Lastly, future development of NF as a novel and personalized tool for pAD would also be expected. Thus, aimed at regulating underlying neural activities related to cognitive decline, consequently improving cognitive functioning and the quality of a patient's life.

4.3 METHOD

4.3.1 METHOD VALIDATION: A COMPARISON WITH PREVIOUS STUDIES

In *Chapter 3*, NF-training of alpha suppression was applied in healthy volunteers and across two experiments. Results from *Experiment I* demonstrated that although a decrease in alpha power was observed, a significant effect of NF-training was not found. However, the NF-training had an effect on increasing theta suppression. Indeed, when analyzing the power of theta during maintenance an enhancement of theta suppression was found in response to NF, and when a reward was expected. Nevertheless, in contrast to the research hypothesis, these results were not replicated in *Experiment II*, questioning how to properly design an NF-training method to suppress alpha power.

Albeit these debatable results, the protocol described in this chapter was aimed to differ from previous NF procedures (Jirayucharoensak et al., 2019; Gomez-Pilar et al., 2016; Luijmes et al., 2016; Marlats et al., 2020; Reis et al., 2016; Surmeli et al., 2016). Thus, differences were i) the application of the method targeting very earlier stages of AD (such as pAD), ii) the implementation of open-source OpenBCI hardware (affordable and portable) to acquire data with high-quality resolution, iii) NF specifically tuned to alpha power suppression, iv) the placement of 10 channel locations (including the reference and ground electrode) over the central, parietal and temporal regions, v) the inclusion of reward to reinforce motivation, and vi) the replicability and simple execution of the proposed protocol within one single training session.

This NF-training protocol might represent a novelty compared to previous applications; feasible, effective and replicable; these are the three main characteristics that the protocol aims to achieve when including a clinical population such as pAD. Nevertheless, to design a standard and effective procedure in regulating dysfunctional neural patterns, the suggested protocol is expected to be further improved, leading to identifying the optimal number of channel locations, the number of training sessions, and the target of specific neural oscillation.

4.3.2. PARTICIPANTS

During the study, all recommendations of the World Medical Association (Revised Declaration of Helsinki, 1989) are obeyed. The Ethics Committee of the University Hospital Magdeburg approved the study (approval number 108/20). Before signing the consent form, the experimental protocol procedure should be explained in detail to all participants, and withdrawal from the study is possible at any time. Participant confidentiality must be guaranteed throughout the study in which anonymous codes are assigned to all participants. Data acquired during the study is used for research purposes only. Inclusion and exclusion criteria are also established. Inclusion criteria regard participants of 60-85 years old who underwent a previous Positron Emission Tomography–Magnetic Resonance Imaging (PET/MRI) evaluation. The diagnosis of pAD would be made in accordance with the National Institute on Aging (NIA) and Alzheimer's Association (AA) workgroup criteria (Knopman et al., 2012; Jack et al., 2012; Sperling et al., 2011), such as (1) abnormal level of amyloid-plagues (stage 1), (2) abnormal level of amyloid-plagues and brain atrophy (stage 2), (3) feature of stage 2 with emerging cognitive impairments (stage 3), and (4) not demented. Moreover,

exclusion criteria regard any neurological disorder, history of epilepsy, chronic abuse (e.g., alcohol, drugs, analgesics, or other substances), participation in other clinical trials, severe visual and auditory disorders, and claustrophobia.

4.3.3 EXPERIMENTAL DESIGN

Twenty-five pAD patients (pAD-group) and twenty-five healthy old volunteers (HE-group) undergo a single NF-training session. Before starting the experiment, a familiarization session precedes the experiment in which participants are explained the procedure, the NF-training method, and how to perform the training task through a short practice. In accordance with the NF-training protocol and before starting each NF-training run, an individual's alpha range is identified during an eyes-open baseline of 2 min, in which participants are asked to observe a fixation cross displayed on a computer screen. Successively, 4 NF-training runs (6 min each) are performed to investigate the effectiveness of this method on increasing alpha (during training) and theta (analyzed after the alpha training) power suppression. Each NF-training run consists of 12 trials, with a total of 48 trials across the four runs. At each trial, alpha power is assessed through the NF signal displayed for 20 seconds. To reinforce motivation while performing the NF and the execution of the task, at the end of each trial a reward is presented for 2 seconds. Thus, a smiling face is displayed for a positive alpha suppression enhancement, whereas for an insufficient alpha suppression enhancement, a neutral face is displayed. Successively, differences in alpha power suppression are compared between groups and theta power suppression in the post-training analysis. Lastly, a questionnaire is given to all participants to collect their feelings and opinions about the current training at experiment completion.

4.3.4 EEG RECORDING AND NEUROFEEDBACK

The method implemented to record the EEG activity and generate the NF signal as described in *Chapter 2 Subsection 2.5.1*. Below method adaptations designed for this research protocol are presented.

The individual’s alpha range is estimated on three possible ranges by applying an FFT: from 4 to 8 Hz, from 6 to 9 Hz, and from 7 to 10 Hz. The shift toward lower frequencies was considered due to tonic changes affecting alpha oscillations during aging and particularly in neurodegenerative disorders, such as dementia (Klimesch, 1999). Thus, the frequency range

that would show the highest frequency power is selected as the individual's alpha range and implemented for the NF-training.

Unlike the study described in *Chapter 3,* which involved healthy volunteers, in this protocol proposal, participants of both groups are trained to increase alpha suppression by receiving a real-time NF related to the ongoing alpha activities. Thus, the control group would be represented by age-matched healthy individuals. In addition, based on the described EEG recording setup, some channel locations can be modified. Instead of placing the in-Ear EEG electrode, another scalp location (i.e., Cz) can be implemented. And similarly, earlobes can be used as suitable references instead of the mastoids.

All the codes (i.e., Python and Matlab) of the developed NF-training method and related explanation can be found at: https://github.com/BeatriceBarbazzeni/NF-protocol-method.

4.3.5 EEG PRE-PROCESSING AND SPECTRAL ANALYSIS

The general pre-processing and analysis procedure was described in *Chapter 2, Subchapter 2.5.2.* Analysis adaptations based on the current study and experimental design are described below.

For each NF-training run, pre-processed data are epoched, differentiating those trials that received a smiling face (reward) and those trials that received a neutral face (non-reward). Each epoch would include all event information which consists of a time period (i.e., epoch length) of 28 s.

After performing the artifact correction and the Morlet Wavelets analysis, averaged epochs are baseline normalized by applying the decibel log-ratio formula (Cohen, 2014).

This analysis is computed for the frequency band of interest (i.e., alpha and theta), single subject, selected channel location, reward condition (smiling face outcome), and NF-training run. Lastly, a grand average between participants is performed to investigate alpha and theta power for each NF-training run, reward condition, channel location, and group. While considering tonic changes influencing alpha oscillations and determining a shift toward lower frequencies (Klimesch, 1999), in the current analysis, alpha power is set in the range of 5-10 Hz, whereas theta power is in the range of 2-7 Hz (Rondina et al., 2019).

4.3.6 NEUROFEEDBACK TRAINING TASK

All stimuli can be presented on a computer screen of size = 1680x1050 pixels, width = 47.5 cm, luminosity = 80, contrast = 80, visual angle = 10° 25' 0.36".

The experimental task (see Fig. 21) is designed to be performed in a daily NF-training session. For each NF-training run, task instructions are displayed for 6 s. These instructions are given in the German language (or any other language e.g., English for further experiments). The first instructional text is “Jetzt sehen Sie eine weiße Kugel, die sich bewegt“ (“now you will see a white moving ball”), followed by the second instructional text “Versuchen Sie, die Bewegung des Balls nach oben zu steuern“ (“try to control the movement of the ball toward the top”). After these instructions, for each trial, a fixation cross is displayed (6 s) while recording alpha activities at baseline. Afterward, the NF-training period appears for the 20 s and is displayed as a white ball moving in real-time. Participants are instructed to modulate and control the movement of the white ball toward the top of the screen. The capability to move the white ball toward the top of the computer screen would represent an increase in alpha suppression. In contrast, the movement of the white ball at the level of the baseline line would represent an insufficient alpha suppression. Both groups (pAD and HE) are encouraged to enhance alpha suppression while receiving a real-time NF based on their ongoing alpha power. After the NF, a reward image is displayed for 2 s. Hence, a smiling face would appear at each trial in which participants are increasing alpha suppression, whereas a neutral face would appear when participants are decreasing alpha suppression. Participants are encouraged and motivated to focus on the NF period to receive as many smiles as possible. Based on the protocol procedure, each NF-training run consists of 12 trials (28 s each), for a total of 48 trials.

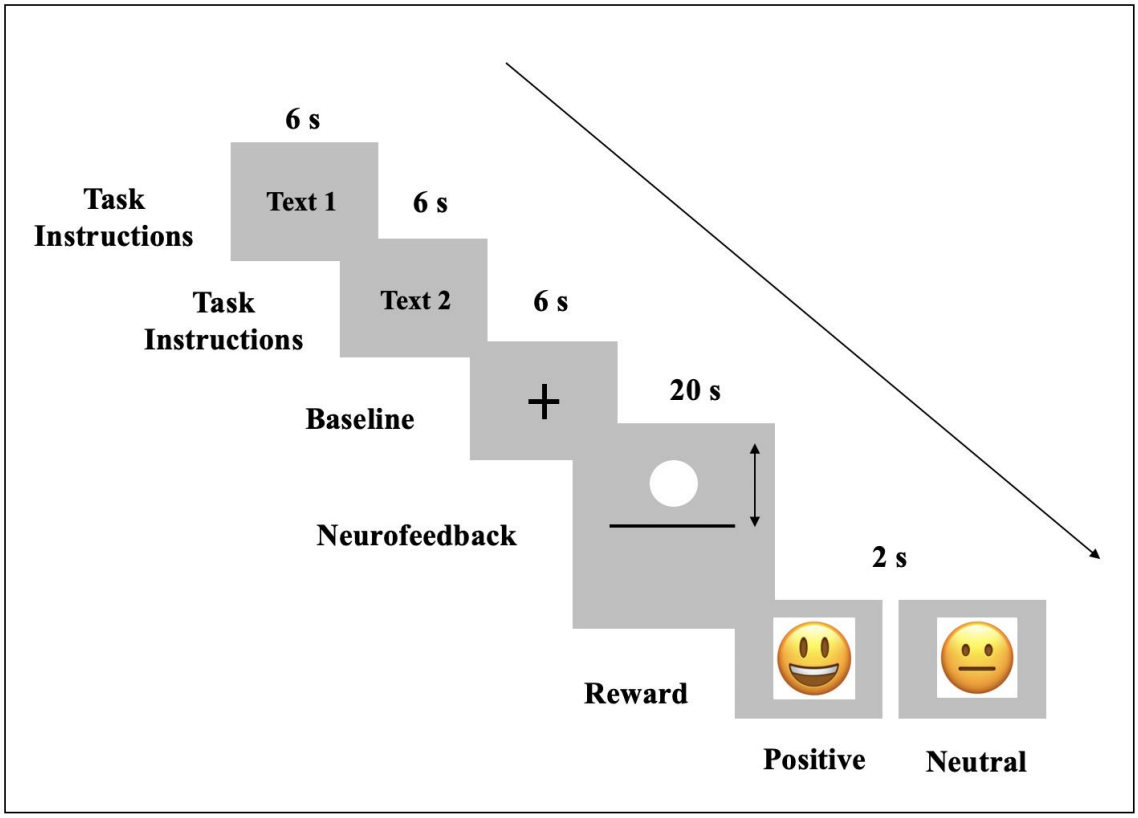

Fig. 21 Representation of one single trial of the Neurofeedback task in the pAD NF-training protocol. *At the beginning of each block, instructions will be displayed for 6 s in each text (Text 1 and Text 2). Afterward, a fixation cross (baseline) will be displayed for each trial lasting for 6 s followed by the NF (20 s). The NF will be displayed as a white moving ball where a horizontal line represents the trial-by-trial baseline. During this period, participants will be instructed to move and to control the white ball toward the top of the screen. Successively, a reward image will be displayed for 2 s. Depending on the participant's performance, a smiling face will be displayed when increasing alpha suppression, whereas a neutral face will be displayed when decreasing alpha suppression. The single daily session will consist of 4 NF training blocks. Each NF block will consist of 12 trials (28 s each).*

4.3.7 QUESTIONNAIRE POST NF TRAINING

A questionnaire is given to participants at the end of the entire NF training session. The questionnaire is given in the German language (or any other language e.g., English for further experiments). Eleven questions are asked in a customized 6-points Likert scale, where:

- 1 = "absolutely not good" \ "überhaupt nicht gut"
- 2 = "not good" \ "nicht gut"
- 3 = "slightly not good" \ "ein bisschen nicht gut"
- 4 = slightly good" \ "ein bisschen gut"
- 5 = "good" \ "gut"
- 6 = "very good" \ "sehr gut"

or from:

- 1 = “absolutely not difficult” \ “überhaupt nicht anstrengend”
- 2 = “not difficult” \ “nicht anstrengend”,
- 3 = slightly not difficult” \ “ein bisschen nicht anstrengend”
- 4 = “slightly difficult” \ “ein bisschen anstrengend”
- 5 = “difficult” \ “anstrengend”
- 6 = “very difficult” \ “sehr anstrengend”

and in a “yes” \ “ja” and “no” \ “nein” scale. The eleven questions are reported in *Appendix B.*

4.3.8 STATISTICAL ANALYSIS

To statistically investigate the results from the time-frequency analysis, a two-way mixed repetitive measures ANOVAs is suggested. The within-subjects factors are “NF-training run” and “channel location”. The between-subjects factor is “group” with factor “gender” as a covariate on the mean distribution. In this NF protocol, the difference between reward conditions will not be considered, while the difference in alpha and theta power across training blocks, channel locations, and groups is investigated.

However, to investigate any difference between reward conditions and in response to alpha and theta oscillations, a non-parametric statistic can be applied due to the possible unbalanced number of trials. Thus, the Mann-Whitney U test, as a between-subject analysis, can be applied to test differences in alpha and theta power between groups (pAD versus HE) and in response to the reward condition (smiling face versus neutral face).

Lastly, the questionnaire answers are suggested to be statistically investigated based on the frequency distributions. The frequencies are computed based on the median distribution. In particular, the percentage value corresponding to the most frequent answers is considered.

4.4 CLOSING REMARKS

In this chapter, an NF-training protocol proposal designed for pAD patients was described.

Several studies tried to detect specific biomarkers of AD and early disease onset; besides amyloid-plaques and NFT accumulation, abnormal neural oscillations were identified. The lack of effective pharmacological treatments aimed at the development of alternative approaches to delay cognitive decline while regulating underlying neural activities; thus, findings of CT and NF were described in *Chapter 1* and *Chapter 2*. Based on this background and acquired experience with the developed NF-training method, a protocol aimed to potentially regulate dysfunctional alpha and theta oscillations in a group of pAD was suggested. The introduction gave an overview of the scientific objective and research hypothesis, whereas the method covered the proposed experimental procedures and analysis. While contributing to research development, the proposed protocol tries to address the understanding of cognitive decline in pAD by providing a structured and customizable method to exploit cognitive reserve and applicable for others working in the field of dementia and EEG-neurofeedback. This valuable procedure aims to be tested and improved in further studies, leading to the identification of the appropriate number of training sessions, channels and scalp locations, selected frequency range, and motivational mechanisms under reward expectancies. Although more data is needed to confirm the capability of NF training, it would be expected that in a few years, besides CT and current treatments, NF training may be developed as an alternative method to regulate impaired oscillations and cognitive dysfunctions in early dementia.

CHAPTER 5:

GENERAL CONCLUSIONS

5.1 SUMMARY

The findings of this thesis add to the understanding of the mechanisms underlying WM functioning and how enhanced performances are related to the modulation of specific oscillatory activities measured at different stages of memory formation. Based on the central role of the WM process in supporting daily living tasks and its progressive decline observed in aging and in neurodegenerative diseases such as AD, the importance of preserving WM functioning has been longly investigated. Thus, in *Chapter 2*, innovative approaches to enhance WM functioning were proposed to target the neural substrate of cognitive reserves. CT was found to ameliorate global cognition by training-specific tasks. Indeed, while stimulating neuroplasticity, CT was effective in generating long-term effects on cognition in healthy young adults and patients affected by mild and more advanced AD. Moreover, NF-training was suggested as an alternative method aimed at self-regulating neural oscillations based on real-time feedback of brain signals. Among neuroimaging techniques, NF based on EEG was the most suitable to train and regulate oscillatory patterns underlying cognitive and behavioral processes. Hence, the effects of NF-training were explored in healthy young adults and also in elders and patients with cognitive disorders. Different training protocols were proposed to improve WM by targeting neural activities related to memory processes such as theta, alpha, or beta oscillations. However, the variability of results and the lack of standardized protocols lead to the need for a better understanding of the mechanisms behind NF-training, particularly in the context of clinical research on cognitive decline. Hence, in *Chapter 3*, an innovative NF-training method based on EEG and combined with CT was proposed to improve WM in healthy volunteers (Barbazzeni, Speck & Düzel, 2023). A few factors known to interact with WM functioning were considered to investigate WM processes. Indeed, WM was already found to be influenced by motivational components, such as reward expectancy, which in turn was found to modulate specific neural activities, namely suppression of alpha oscillations. Thus, to enhance WM, the developed NF-training method aimed at enhancing alpha suppression in high and low expectancies of reward while performing a DMST. To test the efficacy of the developed method on WM and alpha activities, participants were randomly assigned to two groups. They were trained to enhance alpha suppression over 5-days by receiving a real-time

NF or control feedback. Implementing mental strategies during NF training also gained control in self-regulating oscillatory activities. Thus, two experiments were conducted to explore the effect of implementing different mental strategies on enhancing alpha suppression during the NF-training and manipulating their relatedness with the ongoing memory task. In addition, due to the specificity of CT in training a particular cognitive domain, the importance of transferring training effects on unrelated and untrained tasks would represent an advantage, particularly in elders in which cognitive decline tends to be widespread. Thus, transfer effects of NF-training on two different tasks were also investigated. Lastly, due to the complex involvement of different neural oscillations in memory processes, the overall effect of cognitive and NF-training on WM was further explored in neighboring frequencies such as theta and beta oscillations. Findings from both experiments did show a significant reward-anticipation effect on improving WM across the training, although the developed NF-training method was not effective in enhancing alpha suppression. Besides, no reward-anticipation effects were found to influence alpha oscillations. Nevertheless, it was found that the type of mental strategy implemented to control the alpha level was relevant and capable of modulating the oscillations in different directions. Indeed, engaging participants in a mental calculation task had a significant effect on modulating the power of theta and beta oscillations during maintenance. The effect of NF-training was found to transfer by enhancing theta suppression across days with a significant reward-anticipation effect. A potential effect of NF on increasing beta suppression was also observed, even though more data are needed to support this finding. Furthermore, no significant transfer effects were observed on unrelated and untrained cognitive tasks in response to the NF-training. Despite the findings from the developed NF-training method did not match the expected results on WM, an exploratory analysis was conducted to further investigate any relationship between ensued behavioral performances and related changes in oscillatory activities across training days. Indeed, results demonstrated how improved accuracies were predicted by increased right parietal beta oscillations during encoding, and how the reward expectancies may modulate these oscillations, which in turn influence performances. Furthermore, improved RTs were predicted by increased right parietal theta oscillations, where a significant NF-training effect on theta oscillations was found, and consequently had an effect on RTs. During maintenance, despite a lack of significant oscillatory activities related to accuracy improvements, RTs performances were found related to the activity of bilateral parietal beta oscillations. However, faster RTs were found related to increased beta activities over the right hemisphere, whereas slower RTs were found related to increased beta activities over the left hemisphere. Thus, in *Chapter 3*, WM mechanisms were

explored in relation to 300 distinct EEG recording sessions finding how the modulation of beta and theta oscillations, observed at different stages of memory formation, may predict behavioral performances across training days. In addition, having observed a potential transfer effect of NF-training on theta suppression, combined with reward expectancies, in *Chapter 4* a proposal for an NF-training protocol was presented to improve alpha and theta suppression in a group of pAD. Previous studies have found that dysfunctional alpha and theta oscillations are characteristic biomarkers of early disease onset, consequently responsible for memory and attentional deficits. Hence, the scientific objective and method were described with the aim to be easily tested and replicated. In response to previously implemented NF-training protocols, the designed method aimed to differ by targeting the very early stage of AD while increasing the probability of a positive training outcome, the implementation of a newly designed open-source hardware to record data, the specificity of the target NF-training frequency band activity, the small number of electrode locations and training sessions, and the inclusion of a reward factor to enhance engagement during task performance. Due to the lack of standardized procedures leading to high variability in NF-training outcomes, the protocol aimed to represent a customizable method to be further tested and improved by future studies in the field of neurofeedback and dementia. Furthermore, to meet clinical and physiological changes of pAD and healthy old individuals, an adaptation of the NF-training method applied in *Chapter 3* was described. Finally, the proposed research protocol represented a novelty and was designed to foster the understanding of those mechanisms associated with cognitive decline while augmenting the potential for neural and cognitive interventions by targeting the substrate of cognitive reserve and neural plasticity.

5.2 GENERAL DISCUSSION AND FUTURE PERSPECTIVES

5.2.1 THE EFFECT OF NEUROFEEDBACK TRAINING AND WORKING MEMORY

In *Chapter 2*, innovative methods to improve cognitive functions and related neural mechanisms were described. Cognitive training was proposed to improve global cognition by training specific tasks (Kallio et al., 2017, Gates, et al. 2020, Al-Thaqib et al. 2018), finding its application particularly promising in the context of age-related cognitive decline (Herrera et al., 2012; van Heugten et al., 2016). Besides the enhancement of the target cognitive abilities, CT was found to transfer its effect on other cognitive domains (Katz, Shah & Meyer 2018) paving the way toward an innovative approach potentially capable of stimulating neuroplasticity (Park & Bischof, 2013). However, the modulation of underlying neural patterns

is a secondary effect of the primary cognitive enhancements. Therefore, NF-training, particularly based on EEG (Kamiya, 1962; Kamiya, 2011), was proposed to target and regulate specific neural signals based on real-time feedback of the same activities to consequently improve cognitive and behavioral functions (Taya et al., 2015; da Paz & Tomaz, 2020). By the time, besides the enhancement of neural oscillations to improve cognition (Vernon, 2005; Engelbregt et al., 2016; Rogala et al., 2016), NF-training represented an alternative method to clinical applications (Strerman, & Egner, 2006; Butnik, 2005) and in aging (Becerra et al., 2012; Michalczyk, 2020; Reis et al., 2016) by regulating dysfunctional patterns and related cognitive processes. WM received particular attention due to its involvement in learning, information processing, executive function, highly supporting even simpler daily living tasks (Cowan, 2014). Moreover, WM was also found to be primarily affected by cognitive decline and AD (Stern, 2002; Summers and Saunders, 2012), thus preserving its functioning has been for a long time the goal of several studies in cognitive neuroscience. Nevertheless, the variability of results among studies and the different NF-training protocols implemented led to a lack of standard procedures (Marzbani et al., 2016) and the need for further research. In *Chapter 3*, the scientific objective of this thesis in improving WM in healthy volunteers was fostered. Hence, an innovative method based on the combination of CT with EEG-NF was developed and analyzed (Barbazzeni, Speck & Düzel, 2023). Previous findings found a selective and sustained alpha oscillatory activity while maintaining encoded items in WM (Malecki, et al., 2009; Klimesch, 2012). Moreover, increased alpha suppression was associated with a WM task's cognitive effort (Kardan et al., 2020), particularly while expecting a reward (Pornpattananganguki and Nusslock, 2016). Hence, the modulation of sustained alpha activity had the effect of orienting attention (Klimesch, 2012) and improving cognitive performances on delayed memory (Malecki, et al., 2009). Furthermore, other studies explored the potential effect of NF-training of alpha power to foster cognitive performances (Biswas et al., 2019; Hanslmayr et al., 2005; Zoefel et al., 2011). However, different results were found showing how an increase (Escolano et al., 2011; Hsueh et al., 2016; Wei et al., 2017) or a decrease (Hanslmayr et al., 2012; Klimesch et al., 1996; Klimesch et al., 1997; Klimesch, 1999) in the alpha activity was related to better performances. In addition, inter-individual differences in learning to control brain activities were found to predict the success of NF-training outcomes. Indeed, 10-50% of individuals fail to control NF signals across training sessions (Blankertz et al., 2010; Kober et al., 2013; Khodakarami & Firoozabadi, 2020). Hence, investigating which mental strategy would be more effective to enhance NF learning should be considered when predicting training trajectories (Khodakarami & Firoozabadi, 2020). Positive thinking and

positive thoughts were found successful strategies on training alpha oscillations (Nan et al., 2012; Angelakis et al., 2007), but also mental arithmetic (Magosso et al., 2019; Lin et al., 2012) was found effective in decreasing alpha power due to the high cognitive load required. Findings from *Chapter 3* did show how alpha activity can be differently modulated when participants are instructed to engage in different mental strategies. Overall, while investigating the NF-training group, MC was found to increase alpha suppression, whereas MI generally increases alpha power even though the effects were not significant. Based on the "near" versus "far" effect approach (Chan, Mueller, & Masson, 2019) and in relation to the trained DMST, this was a surprising result, considering MC a task generating "far" effects and MI "near" effects. Overall, the developed NF-training method did not significantly enhance alpha suppression through the training, independently of the mental strategies implemented during maintenance. Moreover, even though in *Experiment I,* a potential reward-anticipation effect on alpha suppression was observed, the overall effect was not significant. Neither WM improvements were found related to the NF-training. In fact, in contrast to previous studies (Zoefel et al., 2011; Hanslmayer et al., 2005; Klimesch, 1999; Klimesch, Doppelmayr, & Hanslmayer, 2006), even when targeting either the upper or the lower frequencies of alpha (e.g., NF training based on the individual alpha range) did not show training effects on WM performances. Moreover, despite a lack of effective NF-training on alpha suppression, *Experiment I* showed an NF-training transfer on enhancing theta suppression with a significant reward-anticipation effect. According to previous studies, theta power was found to decrease with increased memory load during maintenance and predictor of WM performances (Brzezicka et al., 2019). Besides, the role of theta power in learning processes is known (Begus & Bonawitz, 2020) and how its activity is closely related to reward anticipation (Cohen et al., 2012; Gruber et al., 2013). Furthermore, in *Experiment I,* beta power was also found to decrease, although not specifically related to an NF-training effect. Alpha and beta power decreases were already found to correlate with successful memory encoding and retrieval of episodic memories in an "old/new" recognition task (Hanslmayr et al. 2012) and enhance SWM performances (Proskovec et al., 2018). In addition, a motor-cortical activity of beta suppression supporting learning and enhanced RTs was also demonstrated (Pollok et al., 2014; Hervault et al., 2021). Altogether, findings from *Chapter 3* did show a potential effect of NF-training in transferring its effect on neighboring frequency bands. However, the type of mental strategy implemented might have played a central role in determining the observed results. Lastly, besides DMST performances, the widespread effect of NF-training in transferring its effect on untrained tasks was also explored. However, no significant NF training effects on transfer tasks were found in both

experiments. Accordingly, a previous study (Gordon et al., 2020) has demonstrated that transfer effects are rare and mostly short-lasting. Indeed, a combined approach based on an NF and WM training task found no significant differences in transfer task performances compared to a control group. Rather, strong near transfer effects were mostly observed when implementing only a specific WM training approach (Linares et al., 2019; Soveri et al., 2017b).

In summary, for a successful NF-training outcome, different factors should be considered. Oscillatory activities and cognitive processes are closely related. Thus, the importance of targeting the right frequency band would lead to better insight concerning the process under investigation. Hence, a deeper investigation on the selected alpha frequency range should be considered when exploring attentional or higher cognitive processes. Reward expectancy was found to improve WM, even though a potential effect on enhancing alpha suppression was observed but not significant. However, due to the complexity and the length of the experiment, the lack of alpha suppression in response to reward anticipation may be related to disengagement from reward expectancy and a redirected focus toward the dual-task performance during maintenance. In addition, the maintenance period was relatively long, and possible fatigue effects may have canceled the expected results. Indeed, the capability of suppressing alpha power in response to NF was mostly observed at the beginning of the maintenance period. Nevertheless, observing similar alpha activity trends in the CO-group raised the discussion concerning placebo effects when including an active control group. From the questionnaire, both groups reported that it was important to reach and to show a good performance. Thus, during task performance, the type and modality of instructions given to a control group should also be evaluated. At the same time, the experiment did show how mental strategies differently influence the modulation of alpha activities, consequently predicting the variability in NF learning. Lastly, when investigating transfer effects on unrelated and untrained tasks, NF-training effects are possible, although more effective results would be expected only when implementing a separate CT approach.

5.2.2 THETA AND BETA OSCILLATIONS UNDERLYING WORKING MEMORY PROCESSES AND MEMORY FORMATION

Findings from *Chapter 3* demonstrated enhanced WM performances across training days, even though unrelated to a significant NF-training effect (Barbazzeni, Speck & Düzel, 2023). From an exploratory analysis based on an LMM approach, WM improvements were investigated in relation to the manipulation of different experimental conditions and oscillatory changes

measured across training days. During encoding, enhanced mean accuracy was found to be positively related to the increase of relative mean power of low-beta observed over the right parietal region. In addition, the activity of beta on item encoding (i.e., sample image) was found to appear after 500 ms from stimulus onset. The importance of beta activities during encoding is already known (Waldhauser, Johansson, & Hanslmayr, 2012) and is associated with the "subsequent memory effect" (Scholz, Schneider, & Rose, 2017), independently of stimulus modality. A pre-stimulus low-beta activity was found as a mechanism to inhibit competing sources of information while preparing the integration of new inputs into memory, and where the increase in power was found as a predictor of successful encoding for later remembered information (Scholz, Schneider, & Rose, 2017). The increase of beta activity was also found within a time frame of 200 ms from stimulus onset and associated with the detection of target stimuli in a visual oddball paradigm (Güntekin et al., 2013), but also later-onset beta activities (between 200 and 500 ms) were found in an attention task and correlated with higher performances (Palacios-García et al., 2021) reflecting a top-down and "attentional control" (Eysenck et al., 2007) mechanism of ongoing cognitive processing. Even though results from *Chapter 3* found a rather later-onset activity of low-beta, the increase in power was positively associated with improved accuracies observed across the training, indicating successful encoding and attentive mechanisms of inhibition from distracting information. A reward-anticipation effect was also found on performances while interacting with the power of low-beta. Indeed, when considering the relative mean beta power, lower activity values were found to be higher predictors of accuracy performances, but only when a reward was expected. Hence, motivational factors may lead to performance variability among individuals even though how reward expectancy relates to beta oscillations has been poorly investigated. The study by Kawasaki and Yamaguchi (2013) investigated the response of oscillatory activities under high and low-reward conditions during a delayed-response task. While the increase of theta oscillations was found during maintenance and related to WM performances, the increase of beta activities was mostly related to high reward expectancies. Thus, the effect of reward was demonstrated on WM performances but also on modulating the power of oscillatory activities across days. Moreover, improved mean RTs were found related to the increase of mean theta activity over the right parietal region. During encoding, the increase of relative theta power was also observed within 500 ms from stimulus onset (i.e., sample image), indicating a rather early response activity of theta than expected (Osipova et al., 2006; Kleberg et al., 2014; Guderian et al., 2009). The finding of an overall theta power increase across the training and in response to RTs relates to previous studies (Steiger and Bunzeck, 2017). Preparatory

mechanisms of theta activity were associated with its pre-and post-stimulus onset activity anticipating successful encoding and memory formation (Kleberg et al., 2014). Similarly, the "subsequent memory effect" as well as the "old/new effect" have been related to enhanced theta in response to later remembered and recognized items (Osipova et al., 2006). In addition, a significant NF-training effect on relative theta power was found to predict RT performances across the training. Indeed, when considering mean theta power across days, lower values were mostly associated with enhanced performances. Thus, a possible transfer of NF-training effects on theta might have been observed, where indeed previous findings have already demonstrated that decreased theta activity is a predictor of successful encoding (Greenberg, et al., 2015; Crespo-García et al., 2016; Fellner, et al., 2016). During maintenance, despite a reward-anticipations effect, no specific oscillations were found related to mean accuracy improvements. However, improved mean RTs were found related to the mean activity of beta localized at the bilateral parietal regions. Despite a lack of difference in the relative power of low-beta between the two opposite parietal regions, their activity contributed differently to RTs. Hence, the increased relative power of low-beta over the right parietal channel was a predictor of faster RT performances, whereas slower performances were predicted by the increased relative power of low-beta over the left parietal channel. Nevertheless, from a posthoc investigation, no significant interactions between the specific beta oscillatory activity with other experimental factors were found on mean RTs. Previous studies have already explored the role of beta oscillation in underlying WM maintenance processes. However, the contribution of beta oscillations to memory formation is still unclear due to the variability in results across studies, where either an increase or a decrease in power was associated with WM processes. In resonance with the results from *Chapter 3*, previous findings found that an increase of parietal beta activity was proportional to the increase of memory capacity (Deiber et al., 2007). In particular, the higher WM memory load, lower accuracies, and slower RTs were indeed found related to increased beta and decreased alpha power (Chen and Huang, 2015) while representing predominant processes of maintaining and manipulating encoded items during task performance. In addition, another view of beta oscillations was also suggested as an active and attentive filter of irrelevant information during task performance (Zanto and Gazzaley, 2009). Moreover, the negative correlation between the sensory-motor mechanism of beta oscillations and RT facilitations was previously confirmed by Senkowski et al. (2006), finding that increased evoked beta activities were followed by faster RTs in response to different stimulus types. Thus, a multisensory mechanism of processing information has been associated with beta activities. Meanwhile, other studies have observed that a decrease in beta

power was related to active maintenance of items during WM processes (Pesonen, Hamalainen, & Krause, 2007; Bocková et al., 2007). Furthermore, *Chapter 3* highlighted the active role of parietal regions when associated with WM capacity as a mechanism of top-down control of spatial attention and maintenance of selected information. Accordingly, the SWM study of Proskovec et al. (2019), investigating the effect of memory load and related oscillatory activities, found decreased beta activities over the parietal regions and was accompanied by a decreased alpha activity in the IFG and STS areas. Observing these results during encoding and maintenance, the involvement of alpha and beta oscillation was consequently coupled with cognitive effort and higher demand when processing information in WM.

In summary, results from *Chapter 3* demonstrated that despite improved WM performances, in terms of accuracy and RTs, were found in response to CT, an NF-training effect based on alpha suppression was not found on WM. Nevertheless, findings from the LMM analysis were promising in explaining ensued WM performances. Indeed, it was possible to demonstrate how cognitive enhancements were associated with a parallel modulation of oscillatory activities across training days. In particular, this exploratory analysis highlighted how improved accuracy and RTs were the results of the underlying increase of beta and theta oscillatory activities measured during encoding and maintenance and how the anticipation of reward interacts with oscillations to influence WM performances. Thus, the findings presented in this thesis, based on a large dataset of 300 EEG recording sessions, may contribute to the understanding of WM processes and underlying neural mechanisms for successful memory formation (Barbazzeni, Speck & Düzel, 2023).

5.2.3 THE IMPORTANCE OF STANDARDIZED PROTOCOLS TO ENHANCE THE EFFECTIVENESS OF NF IN THE CONTEXT OF PRECLINICAL ALZHEIMER'S DISEASE

Chapter 1 introduced the global concern of increased life expectancy (Baltes & Lindenberger, 1997) while projecting aging to become one of the highest risk factors for the development of age-related diseases such as AD. Indeed, AD represents 60-80% of dementia cases, and the rate is estimated to rapidly increase in the coming years (Alzheimer's Association, 2017). Due to the progressive evolution of cognitive and physiological symptoms, this event translates into social and public health concerns while affecting the global economy and the need for better healthcare delivery and caregiver support. Hence, fostering the detection of early disease onset before any irreversible damage would represent a step forward for AD and dementia treatment. Therefore, to approach the disease with effective actions, *Chapter 1* discussed the importance

of detecting biomarkers characteristics of early disease onset and progression. Among different biomarkers, dysfunctional neural oscillations would be an indicator of early-onset disease and easily detected by the implementation of EEG (Hamm et al., 2015). Despite the variability across findings, a general increase of the relative power of slow oscillations such as delta and theta, besides a decrease of fast oscillations such as alpha, beta, and gamma, was typically observed in MCI and AD patients (Moretti et al., 2004; Osipova et al., 2005; Hsiao et al., 2013), particularly when compared to healthy aging individuals (Moretti et al., 2010; Czigler et al., 2008; van der Hiele et al., 2007). However, the lack of effective pharmacological treatments to delay or even stop disease progression aimed the need for innovative intervention methods. Hence, *Chapter 2* discussed alternative non-invasive approaches to cope with cognitive decline and underlying dysfunctional neural patterns. Besides CT (Kallio et al., 2017, Gates, et al. 2020, Al-Thaqib et al. 2018), aimed to exploit cognitive reserves and neuroplasticity in response to age-related cognitive decline and dementia (Yong, 2016; Scarmeas et al., 2003; Herrera et al., 2012), NF-training was also proposed to investigate those mechanisms supporting cognitive and behavioral processes while paving the way toward its clinical applications. Nevertheless, despite successful results from applying NF in enhancing oscillatory activities and cognitive functions, the variety of NF-training protocols (Marzbani et al., 2016), and a few study limitations often encountered in previous works highlight the importance of identifying and establishing standard procedures in the context of AD and dementia. In *Chapter 2*, different experiments were described in healthy old but also in early-stage and more advanced AD patients. Indeed, the combination of CT with NF did show promising results in improving memory but also related oscillatory activities (Luijmes et al., 2016; Jirayucharoensak et al., 2019; Marlats et al. 2020, Reis et al. 2016; Gomez-Pilar et al. 2016) while rising an optimistic perspective toward AD and dementia. However, among clinical applications, the implemented NF-training protocols differed when considering the selected frequency range, the location of electrodes, the type of montage, the EEG recording in different modality states, or the software implemented (Marzbani et al., 2016). In addition, previous protocols differed in relation to the sample sizes and control groups, the number and the length of the training session, or the cognitive task involved. Besides, a lack of double-blind experimental designs and control groups may even affect the reliability and replicability of results, even though needed when designing standard procedures. Likewise, the importance of considering psychological and social variables influencing cognitive reserve and consequently the effectiveness of NF-training should also be considered. In *Chapter 2,* the NF protocols were implemented across different disease groups such as MND, MCI, VD, and AD.

The number of participants undergoing the NF training varied from 5 to 58 (Berman & Friederick, 2009; Luijmes et al., 2016; Surmeli et al., 2016; Jirayucharoensak et al., 2019; Marlats et al., 2020; Jang et al., 2019, Lavy et al., 2019; Li et al., 2020), or even one participant (Kaufmann et al., 2019). Moreover, the number of NF-training sessions varied from a minimum of 10 to a maximum of 96 with a variable duration of 30-75 min each session. Moreover, the specific NF-training protocol varied from an individual qEEG measurement, alpha, beta/alpha ratio, SMR/theta, beta, SMR, and AA. Moreover, the electrode locations varied from AF3, AF4, Cz, Pz, F6, or individualized based on a qEEG. And lastly, the cognitive assessments were based on the performance of different tests such as MMSE, MoCA, CANTAB, WAIS-IV, and CAMOG. Despite the variability of NF protocols and procedures, positive results were found on improving cognitive functions and target neural oscillations. However, several studies suffered from a few study limitations, such as the lack of a control group, small sample size, or lack of blindness in the design. Meanwhile, due to the variability of NF protocols and their effectiveness, besides inter-individual differences in NF learning (Khodakarami & Firoozabadi, 2020), the probability of a successful and effective training might expect to be higher when targeting preclinical stages of AD, and where the detection of biomarkers based on EEG would show dysfunctional oscillations predictor of progressive cognitive decline. In fact, depending on the severity of symptoms, around 20% of MCI patients were found to recover (Koepsell & Monsell, 2012), even though the probability of recovery can be even higher when considering pAD patients (Schultz et al., 2015).

Thus, the experience from the work described in *Chapter 3* stimulated a proposal for a research protocol designed for pAD patients and presented in *Chapter 4*. In the protocol, the proposed NF-training method was an adapted version from the approach implemented in *Chapter 3*. With respect to the findings reported in *Chapter 3* and based on the hypothesis, reported in *Chapter 1*, that dysfunctional alpha and theta oscillation are responsible for progressive cognitive impairments, typically observed in later AD stages, the proposed NF protocol aims at regulating these oscillations in a group of pAD patients when compared to age-matched healthy controls. Moreover, the protocol provided a structure and methodological procedures ready to be tested, customized, and improved while augmenting the possibility of transforming the proposed protocol into a standard procedure to enhance the effectiveness, reproducibility, and validity of results. The experimental procedure described in *Chapter 4* includes 25 patients with a diagnosis of pAD according to NIA and AA criteria and 25 age-matched healthy volunteers. Based on an individual alpha rage, both groups undergo a single session of 4 NF-

training runs (each lasting 6 min) targeting alpha suppression. Besides, the possible transfer of NF-training effect on theta suppression is also investigated. In addition, a reward is also used to engage participants while performing the task. Lastly, the novel, portable, OpenBCI open-source hardware is used to record the signal from 8 channels distributed across the temporal, parietal, and central regions. Therefore, the proposed NF-training protocol aims to represent an initial method to be tested and further developed to meet the clinical features and needs of pAD. Thus, once the proper number of training sessions, channel locations, and type of NF-training signal is established, the method can be translated into a standardized procedure for more effective NF-training results.

In summary, the demographic shift toward the aging population and the increasing rate of AD and dementia raised the need for innovative approaches to improve cognitive functions and related neural oscillations. CT and NF-training demonstrated to be promising methods in response to cognitive decline across different disease stages. However, the variability of NF protocols and experimental designs may affect the effectiveness of NF. Hence, a proposal for an NF protocol was developed to provide an initial method to be tested and further improved with the goal to establish a standard procedure in the context of pAD.

5.3 FINAL REMARKS

Aging is a progressive decline in maintaining physiological and cognitive functioning and a high-risk factor for disease development such as AD (WHO, 2018). However, the incidence of AD cases is forecasted to increase in the coming years, becoming a significant social concern while affecting the global economy and healthcare system. Moreover, the lack of effective treatments to delay the progression of the disease acknowledged the need for innovative approaches not only to detect characteristic biomarkers of early disease-onset but also in response to cognitive decline and related neural dysfunctions. Non-invasive methods such as CT and NF-training have demonstrated promising results in improving cognitive functions and underlying neural oscillations. Even though the majority of applications were encountered in healthy young volunteers, positive results were also observed in early and moderate AD stages. Moreover, the variability among NF protocols may affect the effectiveness of NF and the reproducibility of results. Overall, among cognitive functions, WM attracted attention due to its importance in our daily lives and primarily affected by AD. Besides, alpha oscillations were also found related to WM processes and severely affected during aging and in parallel with

neighboring frequency bands. Thus, this thesis aimed at developing a novel NF-training paradigm to improve WM in healthy young volunteers while targeting alpha oscillations. Moreover, the method has been further extended in an NF protocol proposal applied in pAD to primarily regulate alpha and secondary neighboring frequencies.

In *Chapter 1*, an introduction on aging and AD was reported. Particularly, a deeper understanding of differentiating healthy aging from dysfunctional processes typically observed in age-related diseases was discussed. Hence, the need for innovative and effective approaches to treating AD was brought to *Chapter 2*. Alternative methods such as CT and NF were developed and supported by a variety of studies. Indeed, this chapter gave a detailed overview and insight about CT and EEG-NF in enhancing cognitive performances in the young population, in healthy aging and also in AD. These two chapters were indeed needed to prepare the reader before diving into the main research work described in this thesis. Moreover, *Chapter 3* the main research concerning this thesis, included the scientific rationale, the experimental procedure, the results, and their final discussion. Furthermore, based on the experience developed from the research work met in this thesis, in *Chapter 4*, an additional research protocol was proposed to regulate dysfunctional neural oscillations in preclinical AD patients. This protocol aimed to represent a customizable method to further improve and test in future studies. Lastly, in *Chapter 5*, a summary and a general discussion of the main findings were given with an outlook on study contribution and future perspectives.

REFERENCES

Abdul Kadir, L., Stacey, M., and Barrett-Jolley, R. (2018). Emerging Roles of the Membrane Potential: Action Beyond the Action Potential. *Frontiers in Physiology*, 9. doi:10.3389/fphys.2018.01661

Aguirre, E., Woods, R. T., Spector, A., & Orrell, M. (2013). Cognitive stimulation for dementia: A systematic review of the evidence of effectiveness from randomized controlled trials. *Ageing Research Review*, *12*, 253–262

Ahmad, I., Ansari, F., & Dey, U. K. (2012). A Review of EEG Recording Techniques. *International Journal of Electronics and Communication Engineering and Technology*, *3*, 177–186.

Aiken and West (1991). *Multiple Regression: Testing and Interpreting Interactions.*

Alavash, M., Tune, S., and Obleser, J. (2021). Dynamic large-scale connectivity of intrinsic cortical oscillations supports adaptive listening in challenging conditions. *PLoS Bioogy.,* 19(10): e3001410. https://doi.org/10.1371/journal.pbio.3001410

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association,* 7(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008

Alsharif, A. H., Salleh, N., Baharun, R. B., & Safaei, M. (2020). Neuromarketing Approach: An Overview and Future Research Directions. *Journal of Theoretical and Applied Information Technology,* 98, 991–1001.

Al-Thaqib, A., Al-Sultan, F., Al-Zahrani, A., Al-Kahtani, F., Al-Regaiey, K., Iqbal, M., & Bashir, S. (2018). Brain training games enhance cognitive function in healthy subjects. *Medical Science Monitor Basic Research*, *24*, 63–69. https://doi.org/10.12659/msmbr.909022

Alzheimer's Association. (2014). Alzheimer's disease facts and figures. *Alzheimers Dement*, 2014102e47-e92. [PubMed: 24818261]

Alzheimer's Association. (2017). 2017 Alzheimer's disease facts and figures. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*(4), 325–373. https://doi.org/10.1016/j.jalz.2017.02.001

Angelakis, E., Stathopoulou, S., Frymiare, J. L., Green, D. L., Lubar, J. F., & Kounios, J. (2007). EEG neurofeedback: a brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly. *The Clinical Neuropsychologist*, *21*(1), 110–129. https://doi.org/10.1080/13854040600744839

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., Kong, E., Larraburo, Y., Rolle, C., Johnston, E., & Gazzaley, A. (2013). Video game training enhances cognitive control in older adults. *Nature*, *501*(7465), 97–101. https://doi.org/10.1038/nature12486

Arns, M., Batail, J.-M., Bioulac, S., Congedo, M., Daudet, C., Drapier, D., Fovet, T., Jardri, R., Le-Van-Quyen, M., Lotte, F., Mehler, D., Micoulaud-Franchi, J.-A., Purper-Ouakil, D., Vialatte, F., & NExT group. (2017). Neurofeedback: One of today's techniques in psychiatry? *L'Encephale*, *43*(2), 135–145. https://doi.org/10.1016/j.encep.2016.11.003

Au, J., Sheehan, E., Tsai, N., Duncan, G. J., Buschkuehl, M., & Jaeggi, S. M. (2015). Improving fluid intelligence with training on working memory: a meta-analysis. *Psychonomic Bulletin & Review*, *22*(2), 366–377. https://doi.org/10.3758/s13423-014-0699-x

Au, J., Buschkuehl, M., Duncan, G. J., & Jaeggi, S. M. (2016). There is no convincing evidence that working memory training is NOT effective: A reply to Melby-Lervåg and Hulme (2015). *Psychonomic Bulletin & Review*, *23*(1), 331–337. https://doi.org/10.3758/s13423-015-0967-4

Aurlien, H., Gjerde, I. O., Aarseth, J. H., Eldøen, G., Karlsen, B., Skeidsvoll, H., & Gilhus, N. E. (2004). EEG background activity described by a large computerized database. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *115*(3), 665–673. https://doi.org/10.1016/j.clinph.2003.10.019

Aviyente, S., Bernat, E. M., Evans, W. S., & Sponheim, S. R. (2011). A phase synchrony measure for quantifying dynamic functional integration in the brain. *Human Brain Mapping*, *32*(1), 80–93. https://doi.org/10.1002/hbm.21000

Babiloni, C., Binetti, G., Cassarino, A., Dal Forno, G., Del Percio, C., Ferreri, F., Ferri, R., Frisoni, G., Galderisi, S., Hirata, K., Lanuzza, B., Miniussi, C., Mucci, A., Nobili, F., Rodriguez, G., Luca Romani, G., & Rossini, P. M. (2006). Sources of cortical rhythms in adults during physiological aging: a multicentric EEG study. *Human Brain Mapping*, *27*(2), 162–172. https://doi.org/10.1002/hbm.20175

Babiloni, C., Del Percio, C., Boccardi, M., Lizio, R., Lopez, S., Carducci, F., Marzano, N., Soricelli, A., Ferri, R., Triggiani, A. I., Prestia, A., Salinari, S., Rasser, P. E., Basar, E., Famà, F., Nobili, F., Yener, G., Emek-Savaş, D. D., Gesualdo, L., … Frisoni, G. B. (2015). Occipital sources of resting-state alpha rhythms are related to local gray matter density in subjects with amnesic mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, *36*(2), 556–570. https://doi.org/10.1016/j.neurobiolaging.2014.09.011

Bäckman, L., & Small, B. J. (1998). Influences of cognitive support on episodic remembering: tracing the process of loss from normal aging to Alzheimer's disease. *Psychology and Aging*, *13*(2), 267–276. https://doi.org/10.1037//0882-7974.13.2.267

Baddeley, A. D., & Hitch, G. J. (2000). Development of working memory: should the Pascual-Leone and the Baddeley and Hitch models be merged? *Journal of Experimental Child Psychology*, *77*(2), 128–137. https://doi.org/10.1006/jecp.2000.2592

Baddeley, A. D. (2001). Is working memory still working? *The American Psychologist*, *56*(11), 851–864. https://doi.org/10.1037/0003-066x.56.11.851

Baddeley, A. D., Baddeley, H. A., Bucks, R. S., & Wilcock, G. K. (2001). Attentional control in Alzheimer's disease. *Brain: A Journal of Neurology*, *124*(Pt 8), 1492–1508. https://doi.org/10.1093/brain/124.8.1492

Bahar-Fuchs, A., Clare, L., & Woods, B. (2013). Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *Cochrane Database of Systematic Reviews*, *6*, CD003260. https://doi.org/10.1002/14651858.CD003260.pub2

Bahramisharif, A., Jensen, O., Jacobs, J., & Lisman, J. (2018). Serial representation of items during working memory maintenance at letter-selective cortical sites. *PLoS Biology*, *16*(8), e2003805. https://doi.org/10.1371/journal.pbio.2003805

Baker, S. N. (2007). Oscillatory interactions between sensorimotor cortex and the periphery. *Current Opinion in Neurobiology*, *17*(6), 649–655. https://doi.org/10.1016/j.conb.2008.01.007

Baldauf, D., and Desimone, R. (2014). Neural mechanisms of object-based attention. *Science*, 344 (6182): 424–7. https://www.science.org/doi/10.1126/science.1247003

Baldwin, C. L., & Penaranda, B. N. (2012). Adaptive training using an artificial neural network and EEG metrics for within- and cross-task workload classification. *NeuroImage*, *59*(1), 48–56. https://doi.org/10.1016/j.neuroimage.2011.07.047

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet*, *377*(9770), 1019–1031. https://doi.org/10.1016/s0140-6736(10)61349-9

Baltes, P. B., Sowarka, D., & Kliegl, R. (1989). Cognitive training research on fluid intelligence in old age: What can older adults achieve by themselves? *Psychology and Aging*, *4*(2), 217–221. https://doi.org/10.1037/0882-7974.4.2.217

Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychology and Aging*, *12*(1), 12–21. https://doi.org/10.1037//0882-7974.12.1.12

Baniqued, P. L., Kranz, M. B., Voss, M. W., Lee, H., Cosman, J. D., Severson, J., & Kramer, A. F. (2014). Corrigendum: Cognitive training with casual video games: points to consider. *Frontiers in Psychology*, *5*, 234. https://doi.org/10.3389/fpsyg.2014.00234

Barbazzeni B., Speck O., Düzel E., (2023). Cognitive training, but not EEG-neurofeedback, improves working memory in healthy volunteers, Brain Communications; Volume 5, Issue 2, fcad101, https://doi.org/10.1093/braincomms/fcad101

Başar, E., Başar-Eroglu, C., Karakaş, S., & Schürmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *39*(2–3), 241–248. https://doi.org/10.1016/s0167-8760(00)00145-8

Bauer, R. H. (1976). Short-term memory: EEG alpha correlates and the effect of increased alpha. *Behavioral Biology*, *17*(4), 90793–90798. https://doi.org/10.1016/S0091-6773

Bauer, M., Kluge, C., Bach, D., Bradbury, D., Heinze, H. J., Dolan, R. J., & Driver, J. (2012). Cholinergic enhancement of visual attention and neural oscillations in the human brain. *Current Biology*: CB, 22(5), 397–402. https://doi.org/10.1016/j.cub.2012.01.022

Bateman, R. J., Aisen, P. S., De Strooper, B., Fox, N. C., Lemere, C. A., Ringman, J. M., Salloway, S., Sperling, R. A., Windisch, M., & Xiong, C. (2011). Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimer's Research & Therapy*, *3*(1), 1. https://doi.org/10.1186/alzrt59

Bearden, T. S., Cassisi, J. E., & Pineda, M. (2003). Neurofeedback training for a patient with thalamic and cortical infarctions. *Applied Psychophysiology and Biofeedback*, *28*(3), 241–253. https://doi.org/10.1023/a:1024689315563

Beatty, J. (1971). Effects of initial alpha waves abundance and operant training procedures on occipital alpha and beta wave activity. *Psychonomic Science*, *23*, 197–199.

Beatty, J. (1972). Similar effects of feedback signals and instructional information on EEG activity. *Physiology & Behavior*, *9*(2), 151–154. https://doi.org/10.1016/0031-9384(72)90227-2

Becerra, J., Fernández, T., Roca-Stappung, M., Díaz-Comas, L., Galán, L., Bosch, J., Espino, M., Moreno, A. J., & Harmony, T. (2012). Neurofeedback in healthy elderly human subjects with electroencephalographic risk for cognitive disorder. *Journal of Alzheimer's Disease: JAD*, *28*(2), 357–367. https://doi.org/10.3233/JAD-2011-111055

Begus, K., & Bonawitz, E. (2020). The rhythm of learning: Theta oscillations as an index of active learning in infancy. *Developmental Cognitive Neuroscience*, *45*, 100810. https://doi.org/10.1016/j.dcn.2020.100810

Belham, F. S., Satler, C., Garcia, A., Tomaz, C., Gasbarri, A., & Rego, A. (2013). Aged-related differences in cortical activity during visuo-spatial working memory task with facial stimuli. *PLoS One*, *8*, 1–8.

Belluscio, M. A., Mizuseki, K., Schmidt, R., Kempter, R., & Buzsaki, G. (2012). Cross-frequency phase-phase coupling between theta and gamma oscillations in the hippocampus. *Journal of Neuroscience*, *32*, 423–435.

Beres, A. M. (2017). Time is of the essence: A review of electroencephalography (EEG) and event-related brain potentials (ERPs) in language research. *Applied Psychophysiology and Biofeedback*, *42*(4), 247–255. https://doi.org/10.1007/s10484-017-9371-3

Berger, H. (1929). Über das Elektrenkephalogramm des Menschen (On the human electroencephalogram). *Archiv Für Psychiatrie Und Nervenkrankheiten*, *87*, 527–570.

Berger, H. (1938) Das Elektrenkephalogramm des Menschen. Geschäftsstelle der Deutschen Akademie der Naturforscher, Halle

Berman, M. H., & Frederick, J. A. (2009). P4-265: Efficacy of neurofeedback for executive and memory function in dementia. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *5*(4S_Part_17), e8–e8. https://doi.org/10.1016/j.jalz.2009.07.046

Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., & Becic, E. (2008). Transfer effects in task-set cost and dual-task cost after dual-task training in older and younger adults: further evidence for cognitive plasticity in attentional control in late adulthood. *Experimental Aging Research*, *34*(3), 188–219. https://doi.org/10.1080/03610730802070068

Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., & Becic, E. (2005). Training effects on dual-task performance: are there age-related differences in plasticity of attentional control? *Psychology and Aging*, *20*(4), 695–709. https://doi.org/10.1037/0882-7974.20.4.695

Bielas, J., & Michalczyk, Ł. (2021). Beta neurofeedback training improves attentional control in the elderly. *Psychological Reports*, *124*(1), 54–69. https://doi.org/10.1177/0033294119900348

Biswas, A., & Ray, S. (2019). Alpha neurofeedback has a positive effect for participants who are unable to sustain their alpha activity. *ENeuro*, *6*(4), ENEURO.0498-18.2019. https://doi.org/10.1523/eneuro.0498-18.2019

Blankertz, B., Sannelli, C., Halder, S., Hammer, E. M., Kübler, A., & Müller, K.-R. (2010). Neurophysiological predictor of SMR-based BCI performance. *NeuroImage*, *51*(4), 1303–1309. https://doi.org/10.1016/j.neuroimage.2010.03.022

Bleichner, M. G., Lundbeck, M., Selisky, M., Minow, F., Jäger, M., Emkes, R., Debener, S., & De Vos, M. (2015). Exploring miniaturized EEG electrodes for brain-computer interfaces. An EEG you do not see? *Physiological Reports*, *3*(4), e12362. https://doi.org/10.14814/phy2.12362

Bocková, M., Chládek, J., Jurák, P., Halámek, J., & Rektor, I. (2007). Executive functions processed in the frontal and lateral temporal cortices: intracerebral study. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *118*(12), 2625–2636. https://doi.org/10.1016/j.clinph.2007.07.025

Bollimunta, A., Mo, J., Schroeder, C. E., and Ding, M. (2011). Neuronal mechanisms and attentional modulation of corticothalamic α oscillations. *The Journal of Neuroscience*, 31 (13): 4935–43. doi:10.1523/JNEUROSCI.5580-10.2011

Bonnefond, M., & Jensen, O. (2012). Alpha oscillations serve to protect working memory maintenance against anticipated distracters. *Current Biology: CB*, *22*(20), 1969–1974. https://doi.org/10.1016/j.cub.2012.08.029

Bonsanquet, N. (2001). The socioeconomic impact of Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *16*, 249–253.

Boyle, P. A., Wilson, R. S., Yu, L., Barr, A. M., Honer, W. G., Schneider, J. A., & Bennett, D. A. (2013a). Much of late life cognitive decline is not due to common neurodegenerative pathologies: Cognitive Decline. *Annals of Neurology*, *74*(3), 478–489. https://doi.org/10.1002/ana.23964

Boyle, P. A., Yu, L., Wilson, R. S., Schneider, J. A., & Bennett, D. A. (2013b). Relation of neuropathology with cognitive decline among older persons without dementia. *Frontiers in Aging Neuroscience*, *5*, 50. https://doi.org/10.3389/fnagi.2013.00050

Braak, H., & Braak, E. (1997). Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiology of Aging*, *18*(4), 351–357. https://doi.org/10.1016/s0197-4580(97)00056-0

Bragin, A., Jando, G., Nadasdy, Z., Hetke, J., Wise, K., & Buzsaki, G. (1995). Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *15*(1), 47–60.https://doi.org/10.1523/jneurosci.15-01-00047.1995

Bressler, S. L. (1996). Interareal synchronization in the visual cortex. *Behavioral Brain Research*, 76:37–49

Brookes, M. J., Hale, J. R., Zumer, J. M., Stevenson, C. M., Francis, S. T., Barnes, G. R., Owen, J. P., Morris, P. G., & Nagarajan, S. S. (2011). Measuring functional connectivity using MEG: methodology and comparison with fcMRI. *NeuroImage*, *56*(3), 1082–1104. https://doi.org/10.1016/j.neuroimage.2011.02.054

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *3*(3), 186–191. https://doi.org/10.1016/j.jalz.2007.04.381

Brown, E. N., Kass, R. E., & Mitra, P. P. (2004). Multiple neural spike train data analysis: state-of-the-art and future challenges. Nature Neuroscience, 7(5), 456–461. https://doi.org/10.1038/nn1228

Bruce, A. (2014). Molecular biology of the cell (Sixth ed.). New York, NY. ISBN 9780815344322

Brzezicka, A., Kamiński, J., Reed, C. M., Chung, J. M., Mamelak, A. N., & Rutishauser, U. (2019). Working memory load-related theta power decreases in dorsolateral prefrontal cortex predict individual differences in performance. *Journal of Cognitive Neuroscience*, *31*(9), 1290–1307. https://doi.org/10.1162/jocn_a_01417

Buldú, J. M., Bajo, R., Maestú, F., Castellanos, N., Leyva, I., Gil, P., Sendiña-Nadal, I., Almendral, J. A., Nevado, A., del-Pozo, F., & Boccaletti, S. (2011). Reorganization of functional networks in mild cognitive impairment. *PloS One*, *6*(5), e19584. https://doi.org/10.1371/journal.pone.0019584

Budzynski, T. H. (1996). Brain brightening: Can neurofeedback improve cognitive process? *Biofeedback*, *24*, 14–17.

Buffalo, E. A., Fries, P., Landman, R., Buschman, T. J., & Desimone, R. (2011). Laminar differences in gamma and alpha coherence in the ventral stream. *Proceedings of the National Academy of Sciences of the United States of America*, 108(27), 11262–11267. https://doi.org/10.1073/pnas.1011284108

Burgess, A. P., & Gruzelier, J. H. (1997). Short duration synchronization of human theta rhythm during recognition memory. *Neuroreport*, *8*(4), 1039–1042. https://doi.org/10.1097/00001756-199703030-00044

Burgess, R. C. (2014). Filters, Analog/Digital. In *Encyclopedia of the Neurological Sciences*(pp. 299–307). Elsevier.

Burrow, T. (1943). The neurodynamics of behavior. A phylobiological foreword. *Philosophy of Science*, 10 (4): 271–288. doi:10.1086/286819

Busch, N. A., Dubois, J., and VanRullen, R. (2009). The phase of ongoing EEG oscillations predicts visual perception. *The Journal of Neuroscience*, 29 (24): 7869–76. doi:10.1523/jneurosci.0113-09.2009

Butnik, S. M. (2005). Neurofeedback in adolescents and adults with attention deficit hyperactivity disorders. *Clinical Psychology*, *61*, 621–625. https://doi.org/10.1002/jclp.20124

Buzsáki, G. (2006) Rhythms of the brain. Oxford University Press, Oxford

Campos da Paz, V. K., Garcia, A., Campos da Paz Neto, A., & Tomaz, C. (2018). SMR neurofeedback training facilitates working memory performance in healthy older adults: A behavioral and EEG study. *Frontiers in Behavioral Neuroscience*, *12*, 321. https://doi.org/10.3389/fnbeh.2018.00321

Campos Da Paz, V. K., & Tomaz, C. (2020). *Neurofeedback Training on Aging: Prospects on Maintaining Cognitive Reserve*

Cannatà, A. P., Alberoni, M., Franceschi, M., & Mariani, C. (2002). Frontal impairment in subcortical ischemic vascular dementia in comparison to Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *13*(2), 101–111. https://doi.org/10.1159/000048641

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., Berger, M. S., Barbaro, N. M., & Knight, R. T. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science (New York, N.Y.), 313*(5793), 1626–1628. https://doi.org/10.1126/science.1128115

Canolty, Ryan T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences*, *14*(11), 506–515. https://doi.org/10.1016/j.tics.2010.09.001

Cardin, J. A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., et al. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature*, 459 (7247): 663–7. doi:10.1038/nature08002

Carlesimo, G. A., Mauri, M., Graceffa, A. M., Fadda, L., Loasses, A., Lorusso, S., & Caltagirone, C. (1998). Memory performances in young, elderly, and very old healthy individuals versus patients with Alzheimer's disease: evidence for discontinuity between normal and pathological aging. *Journal of Clinical and Experimental Neuropsychology*, *20*(1), 14–29. https://doi.org/10.1076/jcen.20.1.14.1482

Casey, D. A., Antimisiaris, D., & O'Brien, J. (2010). Drugs for Alzheimer's disease: are they effective? *P & T: A Peer-Reviewed Journal for Formulary Management*, *35*(4), 208–211

Cassani, R., Estarellas, M., San-Martin, R., Fraga, F. J., & Falk, T. H. (2018). Systematic review on resting-state EEG for Alzheimer's disease diagnosis and progression assessment. *Disease Markers*, *2018*, 5174815. https://doi.org/10.1155/2018/5174815

Chan, S., Mueller, U., & Masson, M. E. J. (2019). Far-transfer effects of strategy-based working memory training. *Frontiers in Psychology*, *10*, 1285. https://doi.org/10.3389/fpsyg.2019.01285

Chein, J. M., & Morrison, A. B. (2010). Expanding the mind's workspace: training and transfer effects with a complex working memory span task. *Psychonomic Bulletin & Review, 17*(2), 193–199. https://doi.org/10.3758/PBR.17.2.193

Chen, Y., & Huang, X. (2015). Modulation of Alpha and Beta Oscillations during an n-back Task with Varying Temporal Memory Load. *Frontiers in Psychology, 6*, 2031. https://doi.org/10.3389/fpsyg.2015.02031

Cherry, K. E., Simmons, S. S., and Camp, C. J. (1999). Spaced retrieval enhances memory in older adults with probable Alzheimer's disease. *Journal of Clinical Geropsychology*, 5, 159–175

Choi, J., & Twamley, E. W. (2013). Cognitive rehabilitation therapies for Alzheimer's disease: a review of methods to improve treatment engagement and self-efficacy. *Neuropsychology Review, 23*(1), 48–62. https://doi.org/10.1007/s11065-013-9227-4

Christiansen, H., Reh, V., Schmidt, M. H., & Rief, W. (2014). Slow cortical potential neurofeedback and self-management training in outpatient care for children with ADHA: Study protocol and first preliminary results of a randomized controlled trial. *Frontiers Human Neuroscience*, *8*. https://doi.org/10.3389/fnhu,.2014.00943

Christof, K., Massimini, C. M., Boly, M., & Tononi, G. (2016). Neural correlates of consciousness: progress and problems. *Nature Reviews Neuroscience, 17,* 307–321

Chudasama, Y. (2010). Delayed (Non)Match-to-Sample Task. Encyclopedia of Psychopharmacology. *Encyclopedia of Psychopharmacology. I. P. Stolerman. Berlin*, 372–372

Churchland, P., S., Koch, C., and Sejnowski, T. J. (1993). What is computational neuroscience? In Eric L. Schwartz (ed.). Computational Neuroscience. MIT Press. pp. 46–55

Clare, L., & Woods, R. T. (2004). Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: A review. *Neuropsychological Rehabilitation*, *14*(4), 385–401. https://doi.org/10.1080/09602010443000074

Cohen, L. Time–Frequency Analysis. Prentice-Hall, New York, 1995. ISBN 978-0135945322

Cohen, M. X., Axmacher, N., Lenartz, D., Elger, C. E., Sturm, V., & Schlaepfer, T. E. (2009). Good vibrations: cross-frequency coupling in the human nucleus accumbens during reward processing. *Journal of Cognitive Neuroscience*, 21(5), 875–889. https://doi.org/10.1162/jocn.2009.21062

Cohen, M. X., Bour, L., Mantione, M., Figee, M., Vink, M., Tijssen, M. A. J., van Rootselaar, A.-F., van den Munckhof, P., Schuurman, P. R., & Denys, D. (2012). Top-down-directed synchrony from medial frontal cortex to nucleus accumbens during reward anticipation. *Human Brain Mapping*, *33*(1), 246–252. https://doi.org/10.1002/hbm.21195

Cohen, M. X. (2014). *Analyzing neural time series data: theory and practice*. The MIT Press.

Colgin, L. L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M.-B., & Moser, E. I. (2009). Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature*, *462*(7271), 353–357. https://doi.org/10.1038/nature08573

Colgin, L. L. (2011). Oscillations and hippocampal-prefrontal synchrony. *Current Opinion in Neurobiology*, *21*(3), 467–474. https://doi.org/10.1016/j.conb.2011.04.006

Collette, F., Van Der Linden, M., Becht, S., Belleville, S., & Salmon, E. (1997). Working Memory Deficits in Alzheimer's Disease. *Brain and Cognition*, *37*, 147–149.

Collette, F., Van der Linden, M., & Salmon, E. (1999). Executive dysfunction in Alzheimer's disease. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *35*(1), 57–72. https://doi.org/10.1016/s0010-9452(08)70785-8

Collura, T. F., Guan, J., Tarrant, J., Bailey, J., & Starr, F. (2010). EEG biofeedback case studies using live Z-score training and a normative database. *Journal of Neurotherapy*, *14*(1), 22–46. https://doi.org/10.1080/10874200903543963

Colović, M. B., Krstić, D. Z., Lazarević-Pašti, T. D., Bondžić, A. M., & Vasić, V. M. (2013). Acetylcholinesterase inhibitors: pharmacology and toxicology. *Current Neuropharmacology*, *11*(3), 315–335. https://doi.org/10.2174/1570159X11311030006

Corrada, M. M., Brookmeyer, R., Berlau, D., Paganini-Hill, A., & Kawas, C. H. (2008). Prevalence of dementia after age 90: results from the 90+ study. *Neurology*, *71*(5), 337–343. https://doi.org/10.1212/01.wnl.0000310773.65918.cd

Corrada, M. M., Brookmeyer, R., Paganini-Hill, A., Berlau, D., & Kawas, C. H. (2010). Dementia incidence continues to increase with age in the oldest old: the 90+ study. *Annals of Neurology*, *67*(1), 114–121. https://doi.org/10.1002/ana.21915

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L., & Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science (New York, N.Y.)*, *261*(5123), 921–923. https://doi.org/10.1126/science.8346443

Cowan, N. (2014). Working memory underpins cognitive development, learning, and education. *Educational Psychology Review*, *26*(2), 197–223. https://doi.org/10.1007/s10648-013-9246-y

Craig, D., Mirakhur, A., Hart, D. J., McIlroy, S. P., & Passmore, A. P. (2005). A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *13*(6), 460–468. https://doi.org/10.1097/00019442-200506000-00004

Crespo-García, M., Zeiller, M., Leupold, C., Kreiselmeyer, G., Rampp, S., Hamer, H. M., & Dalal, S. S. (2016). Slow-theta power decreases during item-place encoding predict spatial accuracy of subsequent context recall. *NeuroImage*, *142*, 533–543. https://doi.org/10.1016/j.neuroimage.2016.08.021

Critchley, M. (1984). And all the daughters of musick shall be brought low. Language function in the elderly. *Archives of Neurology*, *41*(11), 1135–1139. https://doi.org/10.1001/archneur.1984.04050220029009

Cummings, J. L. (2000). Cognitive and behavioral heterogeneity in Alzheimer's disease: seeking the neurobiological basis. *Neurobiology of Aging*, *21*(6), 845–861. https://doi.org/10.1016/s0197-4580(00)00183-4

Czigler, B., Csikós, D., Hidasi, Z., Anna Gaál, Z., Csibri, E., Kiss, E., Salacz, P., & Molnár, M. (2008). Quantitative EEG in early Alzheimer's disease patients - power spectrum and complexity features. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *68*(1), 75–80. https://doi.org/10.1016/j.ijpsycho.2007.11.002

David, O., Kilner, J. M., and Friston, K. J. (2006). Mechanisms of evoked and induced responses in MEG/EEG. *NeuroImage*, 31(4), 1580–1591. https://doi.org/10.1016/j.neuroimage.2006.02.034

Davis, R. N., Massman, P. J., & Doody, R. S. (2001). Cognitive intervention in Alzheimer's disease: a randomized placebo-controlled study. *Alzheimer Disease and Associated Disorders*, *15*, 1–9.

Dayan P., and Abbott, L. F. (2001). Theoretical neuroscience: computational and mathematical modeling of neural systems. Cambridge, Mass: MIT Press. ISBN 978-0-262-04199-7

Debener, S., Herrmann, C. S., Kranczioch, C., Gembris, D., & Engel, A. K. (2003). Top-down attentional processing enhances auditory evoked gamma band activity. *Neuroreport, 14*, 683–686. https://doi.org/10.1097/01.wnr.0000064987.96259.5c

de Cheveigné, A., & Nelken, I. (2019). Filters: When, why, and how (not) to use them. *Neuron, 102*(2), 280–293. https://doi.org/10.1016/j.neuron.2019.02.039

Deiber, M.-P., Missonnier, P., Bertrand, O., Gold, G., Fazio-Costa, L., Ibañez, V., & Giannakopoulos, P. (2007). Distinction between perceptual and attentional processing in working memory tasks: a study of phase-locked and induced oscillatory brain dynamics. *Journal of Cognitive Neuroscience*, *19*(1), 158–172. https://doi.org/10.1162/jocn.2007.19.1.158

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

De Vreese, L. P., & Neri, M. (1998). Ecological impact of combined cognitive training programs (CTP) and drug treatment (ChE-I) in AD. *International Psychogeriatrics*, 11.

De Vreese, L. P., Verlato, C., Emiliani, S., Schioppa, S., Belloi, L., & Salvioli, G. (1998). Effect size of a three-month drug treatment in AD when combined with individual cognitive retraining: preliminary results of a pilot study. *European Archives of Psychiatry and Clinical Neuroscience, 248*, 41–42.

De Vreese, L. P., Neri, M., Fioravanti, M., Belloi, L., & Zanetti, O. (2001). Memory rehabilitation in Alzheimer's disease: a review of progress. *International Journal of Geriatric Psychiatry, 16*(8), 794–809. https://doi.org/10.1002/gps.428.abs

Diagnostic and Statistical Manual of Mental Disorders (2013). *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edn. Washington, DC: American Psychiatric Association.

Dias, A. M., Van Deusen, A. M., Oda, E., & Bonfim, M. R. (2012). Clinical efficacy of a new automated hemoencephalographic neurofeedback protocol. *The Spanish Journal of Psychology*, *15*(3), 930–941. https://doi.org/10.5209/rev_sjop.2012.v15.n3.39385

Di Flumeri, G., Aricò, P., Borghini, G., Sciaraffa, N., Di Florio, A., & Babiloni, F. (2019). The dry revolution: Evaluation of three different EEG dry electrode types in terms of signal spectral features, mental states classification and usability. *Sensors (Basel, Switzerland)*, *19*(6), 1365. https://doi.org/10.3390/s19061365

Drachman, D. A., O'Donnell, B. F., Lew, R. A., & Swearer, J. M. (1990). The prognosis in Alzheimer's disease. "How far" rather than "how fast" best predicts the course. *Archives of Neurology*, *47*(8), 851–856. https://doi.org/10.1001/archneur.1990.00530080033007

Dux, P. E., Tombu, M. N., Harrison, S., Rogers, B. P., Tong, F., & Marois, R. (2009). Training improves multitasking performance by increasing the speed of information processing in human prefrontal cortex. *Neuron*, *63*(1), 127–138. https://doi.org/10.1016/j.neuron.2009.06.005

Ebner, A., Sciarretta, G., Epstein, C. M., and Newer, M. EEG instrumentation (Chapter 1.2) Recommendations for the practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Physiology (EEG Suppl. 52). Editors: G. Deuschl and A. Eisen. 1999 International Federation of Clinical Neurophysiology. All rights reserved. Published by Elsevier Science B.V.

Edmonds, W. A., & Tenenbaum, G. (2011). *Case studies in applied psychophysiology: Neurofeedback and biofeedback treatments for advances in human performance*. New Jersey, John Wiley & Sons.

Engel, A. K., Fries, P., & Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. *Nature Reviews. Neuroscience*, *2*(10), 704–716. https://doi.org/10.1038/35094565

Engel, A. K., & Singer, W. (2001). Temporal binding and the neural correlates of sensory awareness. *Trends in Cognitive Sciences*, 5(1), 16–25. https://doi.org/10.1016/s1364-6613(00)01568-0

Engel, A. K., & Fries, P. (2010). Beta-band oscillations-signalling the status quo? *Current Opinion in Neurobiology*, *20*, 156–165

Engelbregt, H. J., Keeser, D., van Eijk, L., Suiker, E. M., Eichhorn, D., Karch, S., Deijen, J. B., & Pogarell, O. (2016). Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *127*(4), 1931–1937. https://doi.org/10.1016/j.clinph.2016.01.004

Enriquez-Geppert, S., Huster, R. J., Figge, C., & Herrmann, C. S. (2014). Self-regulation of frontal-midline theta facilitates memory updating and mental set shifting. *Frontiers in Behavioral Neuroscience, 8*. https://doi.org/10.3389/fn-beh.2014.00420

Enriquez-Geppert, S., Huster, R. J., & Herrmann, C. S. (2017). EEG-neurofeedback as a tool to modulate cognition and behavior: A review tutorial. *Frontiers in Human Neuroscience, 11*, 51. https://doi.org/10.3389/fnhum.2017.00051

Enzinger, C., Fazekas, F., Matthews, P. M., Ropele, S., Schmidt, H., Smith, S., & Schmidt, R. (2005). Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. *Neurology*, *64*(10), 1704–1711. https://doi.org/10.1212/01.WNL.0000161871.83614.BB

Ergenoglu, T., Demiralp, T., Bayraktaroglu, Z., Ergen, M., Beydagi, H., & Uresin, Y. (2004). Alpha rhythm of the EEG modulates visual detection performance in humans. *Brain*

Research. Cognitive Brain Research, *20*(3), 376–383. https://doi.org/10.1016/j.cogbrainres.2004.03.009

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108

Escolano, C., Aguilar, M., & Minguez, J. (2011). EEG-based upper alpha neurofeedback training improves working memory performance. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*, *2011*, 2327–2330. https://doi.org/10.1109/IEMBS.2011.6090651

Evans, D. A., Funkenstein, H. H., Albert, M. S., Scherr, P. A., Cook, N. R., Chown, M. J., Hebert, L. E., Hennekens, C. H., & Taylor, J. O. (1989). Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA: The Journal of the American Medical Association*, *262*(18), 2551–2556. https://doi.org/10.1001/jama.262.18.2551

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion (Washington, D.C.)*, *7*(2), 336–353. https://doi.org/10.1037/1528-3542.7.2.336

Ewers, M., Sperling, R. A., Klunk, W. E., Weiner, M. W., & Hampel, H. (2011). Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. *Trends in Neurosciences*, *34*(8), 430–442. https://doi.org/10.1016/j.tins.2011.05.005

Farina, E., Fioravanti, R., Chiavari, L., Imbornone, E., Alberoni, M., Pomati, S., Pinardi, G., Pignatti, R., & Mariani, C. (2002). Comparing two programs of cognitive training

in Alzheimer's disease: a pilot study. *Acta Neurologica Scandinavica*, *105*(5), 365–371. https://doi.org/10.1034/j.1600-0404.2002.01086.x

Farnia, S., Abedi-Darzi, S., Fattahi, S., Charati, J. Y., Motamedi, M. R., Bakhshian, F., & Mansoori, P. (2017). The effect of Beta and Alpha Neurofeedback on Memory: A Randomized, Double-blind, Sham-Controlled, Clinical Trial. *Clinical Trial. Iranian Journal of Psychiatry and Behavioral Sciences*, *11*(2). https://doi.org/10.5812/jpbs.7431

Feinberg, I., & Campbell, I. G. (2013). Longitudinal sleep EEG trajectories indicate complex patterns of adolescent brain maturation. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *304*(4), R296-303. https://doi.org/10.1152/ajpregu.00422.2012

Fell, J., and Axmacher, N. (2011). The role of phase synchronization in memory processes. *Nature Reviews Neuroscience*, 12(2), 105–118. https://doi.org/10.1038/nrn2979

Fellner, M.-C., Volberg, G., Wimber, M., Goldhacker, M., Greenlee, M. W., & Hanslmayr, S. (2016). Spatial mnemonic encoding: Theta power decreases and medial temporal lobe BOLD increases co-occur during the usage of the method of loci. *ENeuro*, *3*(6). https://doi.org/10.1523/ENEURO.0184-16.2016

Fernandez, T., Becerra, J., Roca, M., Espino, M., Bahlke, M. Y., Har- Mony, T., Fernandez-Bouza, A., Belmont, H., & Diaz-Comas, L. (2008). Neurofeedback in healthy elderly humans with electroencephalographic risk of cognitive impairment. *Frontiers in Human Neuroscience. Conference Abstract*. https://doi.org/10.3389/conf.neuro.09.2009.01.173

Fiedler, L., Obleser, J., Lunner, T., & Graversen, C. (2016). Ear-EEG allows extraction of neural responses in challenging listening scenarios - A future technology for hearing aids? *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual*

International Conference, *2016*, 5697–5700. https://doi.org/10.1109/EMBC.2016.7592020

Fingelkurts, An. A., and Fingelkurts, Al. A. (2004). Making complexity simpler: Multivariability and metastability in the brain. *International Journal of Neuroscience*, 114 (7), 843–862. doi:10.1080/00207450490450046

Fingelkurts, An.A., and Fingelkurts, Al. A., and Kähkönen, S. A. (2005). Functional connectivity in the brain – is it an elusive concept? *Neuroscience & Biobehavioral Reviews*, 28 (8), 827–836. doi:10.1016/j.neubiorev.2004.10.009

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., and Wiebe, S. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, 55 (4), 475–82. doi:10.1111/epi.12550

Fjell, A. M., Mcevoy, L., Holland, D., Dale, A. M., & Walhovd, K. B. (2014). Alzheimer's Disease Neuroimaging Initiative. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Progress in Neurobiology*, 201411720–201411740.

Forsberg, A., Fellman, D., Laine, M., Johnson, W., & Logie, R. H. (2020). Strategy mediation in working memory training in younger and older adults. *Quarterly Journal of Experimental Psychology (2006)*, *73*(8), 1206–1226. https://doi.org/10.1177/1747021820915107

Foster, J. J., Sutterer, D. W., Serences, J. T., Vogel, E. K., and Awh, E. (2017). Alpha-Band Oscillations Enable Spatially and Temporally Resolved Tracking of Covert Spatial Attention. *Psychological Science*, 28 (7), 929–941. doi:10.1177/0956797617699167

Foxe, J. J., & Snyder, A. C. (2011). The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Frontiers in Psychology*, *2*, 154. https://doi.org/10.3389/fpsyg.2011.00154

Frank, D. L., Khorshid, L., Kiffer, J. F., Moravec, C. S., & McKee, M. G. (2010). Biofeedback in medicine: who, when, why and how? *Mental Health in Family Medicine*, *7*(2), 85–91.

Freyer, F., Aquino, K., Robinson, P. A., Ritter, P., and Breakspear, M. (2009). Bistability and non-Gaussian fluctuations in spontaneous cortical activity. *The Journal of Neuroscience*, 29 (26): 8512–24. doi:10.1523/JNEUROSCI.0754-09.2009

Fries, P., Reynolds, J. H., Rorie, A. E., & Desimone, R. (2001). Modulation of oscillatory neuronal synchronization by selective visual attention. *Science*, *291*, 1560–1563. https://doi.org/10.1126/science.291.5508.1560

Fries, P. (2005). A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, 9(10), 474–480. https://doi.org/10.1016/j.tics.2005.08.011

Galante, E., Venturini, G., & Fiaccadori, C. (2007). Computer-based cognitive intervention for dementia: preliminary results of a randomized clinical trial. *Giornale Italiano Di Medicina Del Lavoro Ed Ergonomia*, *29*(3 Suppl B), B26-32.

Garcés, P., Angel Pineda-Pardo, J., Canuet, L., Aurtenetxe, S., López, M. E., Marcos, A., Yus, M., Llanero-Luque, M., Del-Pozo, F., Sancho, M., & Maestú, F. (2014). The Default Mode Network is functionally and structurally disrupted in amnestic mild cognitive impairment - a bimodal MEG-DTI study. *NeuroImage. Clinical*, *6*, 214–221. https://doi.org/10.1016/j.nicl.2014.09.004

Garn, H., Waser, M., Deistler, M., Schmidt, R., Dal-Bianco, P., Ransmayr, G., Zeitlhofer, J., Schmidt, H., Seiler, S., Sanin, G., Caravias, G., Santer, P., Grossegger, D.,

Fruehwirt, W., & Benke, T. (2014). Quantitative EEG in Alzheimer's disease: cognitive state, resting state and association with disease severity. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *93*(3), 390–397. https://doi.org/10.1016/j.ijpsycho.2014.06.003

Gates, N. J., Rutjes, A. W., Di Nisio, M., Karim, S., Chong, L.-Y., March, E., Martínez, G., & Vernooij, R. W. (2020). Computerised cognitive training for 12 or more weeks for maintaining cognitive function in cognitively healthy people in late life. *Cochrane Database of Systematic Reviews*, *2*(2), CD012277. https://doi.org/10.1002/14651858.CD012277.pub3

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., Belleville, S., Brodaty, H., Bennett, D., Chertkow, H., Cummings, J. L., de Leon, M., Feldman, H., Ganguli, M., Hampel, H., Scheltens, P., Tierney, M. C., Whitehouse, P., Winblad, B., & International Psychogeriatric Association Expert Conference on mild cognitive impairment. (2006). Mild cognitive impairment. *Lancet*, *367*(9518), 1262–1270. https://doi.org/10.1016/S0140-6736(06)68542-5

Germano, C., & Kinsella, G. J. (2005). Working memory and learning in early Alzheimer's disease. *Neuropsychology Review*, *15*(1), 1–10. https://doi.org/10.1007/s11065-005-3583-7

Gerstner, W., Kistler, W., Naud, R., and Paninski, L. (2014). Neuronal Dynamics. Cambridge, UK: Cambridge University Press. ISBN 9781107447615

Gevins, A., & Smith, M. E. (2000). Neurophysiological measures of working memory and individual differences in cognitive ability and cognitive style. *Cerebral Cortex (New York, N.Y.: 1991)*, *10*(9), 829–839. https://doi.org/10.1093/cercor/10.9.829

Ghosh, S., Sinha, J. K., Khan, T., Devaraju, K. S., Singh, P., Vaibhav, K., and Gaur, P. (2021). Pharmacological and Therapeutic Approaches in the Treatment of Epilepsy. *Biomedicines*, 9(5):470. doi: 10.3390/biomedicines9050470

Gomez-Pilar, J., Corralejo, R., Nicolas-Alonso, L. F., Álvarez, D., & Hornero, R. (2016). Neurofeedback training with a motor imagery-based BCI: neurocognitive improvements and EEG changes in the elderly. *Medical & Biological Engineering & Computing*, *54*(11), 1655–1666. https://doi.org/10.1007/s11517-016-1454-4

Gomez-Ramirez, M., Kelly, S. P., Molholm, S., Sehatpour, P., Schwartz, T. H., & Foxe, J. J. (2011). Oscillatory sensory selection mechanisms during intersensory attention to rhythmic auditory and visual inputs: a human electrocorticographic investigation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *31*(50), 18556–18567. https://doi.org/10.1523/JNEUROSCI.2164-11.2011

Gordon, S., Todder, D., Deutsch, I., Garbi, D., Alkobi, O., Shriki, O., Shkedy-Rabani, A., Shahar, N., & Meiran, N. (2020). Effects of neurofeedback and working memory-combined training on executive functions in healthy young adults. *Psychological Research*, *84*(6), 1586–1609. https://doi.org/10.1007/s00426-019-01170-w

Goutagny, R., Gu, N., Cavanagh, C., Jackson, J., Chabot, J.-G., Quirion, R., Krantic, S., & Williams, S. (2013). Alterations in hippocampal network oscillations and theta-gamma coupling arise before Aβ overproduction in a mouse model of Alzheimer's disease. *The European Journal of Neuroscience*, *37*(12), 1896–1902. https://doi.org/10.1111/ejn.12233

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L., & Hämäläinen, M. (2013). MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience*, *7*, 267. https://doi.org/10.3389/fnins.2013.00267

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Parkkonen, L., & Hämäläinen, M. S. (2014). MNE software for processing MEG and EEG data. *NeuroImage*, *86*, 446–460. https://doi.org/10.1016/j.neuroimage.2013.10.027

Gray, C. M., König, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature*, 338(6213), 334–337. https://doi.org/10.1038/338334a0

Green, C. S., & Bavelier, D. (2003). Action video game modifies visual selective attention. *Nature*, *423*(6939), 534–537. https://doi.org/10.1038/nature01647

Greenberg, J. A., Burke, J. F., Haque, R., Kahana, M. J., & Zaghloul, K. A. (2015). Decreases in theta and increases in high frequency activity underlie associative memory encoding. *NeuroImage*, *114*, 257–263. https://doi.org/10.1016/j.neuroimage.2015.03.077

Grober, E., & Kawas, C. (1997). Learning and retention in preclinical and early Alzheimer's disease. *Psychology and Aging*, *12*(1), 183–188. https://doi.org/10.1037//0882-7974.12.1.183

Gross, J., Baillet, S., Barnes, G. R., Henson, R. N., Hillebrand, A., Jensen, O., Jerbi, K., Litvak, V., Maess, B., Oostenveld, R., Parkkonen, L., Taylor, J. R., van Wassenhove, V., Wibral, M., & Schoffelen, J.-M. (2013). Good practice for conducting and reporting MEG research. *NeuroImage*, 65, 349–363. https://doi.org/10.1016/j.neuroimage.2012.10.001

Grossberg, G. T., & Desai, A. K. (2003). Management of Alzheimer's disease. The journals of gerontology. *Series A, Biological Sciences and Medical Sciences*, *58*, 331–353.

Gruber, T., Müller, M. M., Keil, A., & Elbert, T. (1999). Selective visual-spatial attention alters induced gamma band responses in the human EEG. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, 110(12), 2074–2085. https://doi.org/10.1016/s1388-2457(99)00176-5

Gruber, M. J., Watrous, A. J., Ekstrom, A. D., Ranganath, C., & Otten, L. J. (2013). Expected reward modulates encoding-related theta activity before an event. *NeuroImage*, *64*, 68–74. https://doi.org/10.1016/j.neuroimage.2012.07.064

Gruzelier, J., & Egner, T. (2004). Physiological self-regulation: Biofeedback and neurofeedback. In A. Williamon (Ed.), *Musical Excellence: Strategies and Techniques to Enhance Performance* (pp. 197–219). Oxford University Press.

Gruzelier, J., Egner, T., & Vernon, D. (2006). Validating the efficacy of neurofeedback for optimising performance. *Progress in Brain Research*, *159*, 421–431. https://doi.org/10.1016/S0079-6123(06)59027-2

Guderian, S., Schott, B. H., Richardson-Klavehn, A., & Düzel, E. (2009). Medial temporal theta state before an event predicts episodic encoding success in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(13), 5365–5370. https://doi.org/10.1073/pnas.0900289106

Guertin, P. A. (2019). Central pattern generators in the brainstem and spinal cord: an overview of basic principles, similarities and differences. *Reviews in the Neurosciences*, 30 (2): 107–164. doi:10.1515/revneuro-2017-0102

Güntekin, B., Emek-Savaş, D. D., Kurt, P., Yener, G. G., & Başar, E. (2013). Beta oscillatory responses in healthy subjects and subjects with mild cognitive impairment. *NeuroImage. Clinical*, *3*, 39–46. https://doi.org/10.1016/j.nicl.2013.07.003

GVB-geliMED. Retrieved July 20, 2022, from https://www.gvb-gelimed.de

Hall, C. B., Derby, C., LeValley, A., Katz, M. J., Verghese, J., & Lipton, R. B. (2007). Education delays accelerated decline on a memory test in persons who develop dementia. *Neurology*, *69*(17), 1657–1664. https://doi.org/10.1212/01.wnl.0000278163.82636.30

Haegens, S., Nácher, V., Hernández, A., Luna, R., Jensen, O., & Romo, R. (2011). Beta oscillations in the monkey sensorimotor network reflect somatosensory decision making. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(26), 10708–10713. https://doi.org/10.1073/pnas.1107297108

Haegens, S., Luther, L., & Jensen, O. (2012). Somatosensory anticipatory alpha activity increases to suppress distracting input. *Journal of Cognitive Neuroscience*, *24*(3), 677–685. https://doi.org/10.1162/jocn_a_00164

Haken, H. (1996). Principles of brain functioning. Springer. ISBN 978-3-540-58967-9

Handel, B., Lutzenberger, W., Their, P., & Haarmeier, T. (2007). Opposite dependencies on visual motion coherence in human area MT + and early visual cortex. *Cerebral Cortex*, *17*, 1542–1549

Händel, B., & Haarmeier, T. (2009). Cross-frequency coupling of brain oscillations indicates the success in visual motion discrimination. *NeuroImage*, *45*(3), 1040–1046. https://doi.org/10.1016/j.neuroimage.2008.12.013

Hanslmayr, S., Klimesch, W., Sauseng, P., Gruber, W., Doppelmayr, M., Freunberger, R., & Pecherstorfer, T. (2005). Visual discrimination performance is related to decreased alpha amplitude but increased phase locking. *Neuroscience Letters*, *375*(1), 64–68. https://doi.org/10.1016/j.neulet.2004.10.092

Hanslmayr, S., Sauseng, P., Doppelmayr, M., Schabus, M., & Klimesch, W. (2005). Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. *Applied Psychophysiology and Biofeedback*, *30*(1), 1–10. https://doi.org/10.1007/s10484-005-2169-8

Hanslmayr, S., Staudigl, T., & Fellner, M.-C. (2012). Oscillatory power decreases and long-term memory: the information via desynchronization hypothesis. *Frontiers in Human Neuroscience*, *6*, 74. https://doi.org/10.3389/fnhum.2012.00074

Hameed, M. Q., Dhamne, S. C., Gersner, R., Kaye, H. L., Oberman, L. M., Pascual-Leone, A., & Rotenberg, A. (2017). Transcranial magnetic and direct current stimulation in children. *Current Neurology and Neuroscience Reports*, *17*(2). https://doi.org/10.1007/s11910-017-0719-0

Hamm, V., Héraud, C., Cassel, J.-C., Mathis, C., & Goutagny, R. (2015). Precocious alterations of brain oscillatory activity in Alzheimer's disease: A window of opportunity for early diagnosis and treatment. *Frontiers in Cellular Neuroscience*, *9*, 491. https://doi.org/10.3389/fncel.2015.00491

Hammond, D. C. (2005). Neurofeedback treatment of depression and anxiety. *Journal of Adult Development*, *12*(2–3), 131–137. https://doi.org/10.1007/s10804-005-7029-5

Hammond, D. C., Bodenhamer-Davis, G., Gluck, G., Stokes, D., Hunt Harper, S., Trudeau, D., Macdonald, M., Lunt, J., & Kirk, L. (2010). Standards of Practice for Neurofeedback and Neurotherapy: A Position Paper of the International Society for Neurofeedback & Research. *Journal of Neurotherapy*, *15*, 54–64. https://doi.org/10.1080/10874208.2010.54760

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science (New York, N.Y.)*, *297*(5580), 353–356. https://doi.org/10.1126/science.1072994

Hartmann, T., Schulz, H., & Weisz, N. (2011). Probing of brain states in real-time: Introducing the ConSole environment. *Frontiers in Psychology*, *2*, 36. https://doi.org/10.3389/fpsyg.2011.00036

He, W., Goodkind, D., & Kowal, P. (2016). *An Aging World: 2015*.Suitland, MD: United States Census Bureau.

Heiss, W. D., Kessler, J., Slansky, I., Mielke, R., Szelies, B., & Herholz, K. (1993). Activation PET as an instrument to determine therapeutic efficacy in Alzheimer's diseasea.

Annals of the New York Academy of Sciences, *695*(1), 327–331. https://doi.org/10.1111/j.1749-6632.1993.tb23078.x

Herrera, C., Chambon, C., Michel, B. F., Paban, V., & Alescio-Lautier, B. (2012). Positive effects of computer-based cognitive training in adults with mild cognitive impairment. *Neuropsychologia*, *50*(8), 1871–1881. https://doi.org/10.1016/j.neuropsychologia.2012.04.012

Herrmann, C. S., Lenz, D., Junge, S., Busch, N. A., & Maess, B. (2004a). Memory-matches evoke human gamma-responses. *BMC Neuroscience*, *5*, 13. https://doi.org/10.1186/1471-2202-5-13

Herrmann, C. S., Munk, M. H. J., & Engel, A. K. (2004b). Cognitive functions of gamma-band activity: memory match and utilization. *Trends in Cognitive Sciences*, *8*(8), 347–355. https://doi.org/10.1016/j.tics.2004.06.006

Herrmann, C. S., & Demiralp, T. (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *116*(12), 2719–2733. https://doi.org/10.1016/j.clinph.2005.07.007

Hervault, M., Zanone, P.-G., Buisson, J.-C., & Huys, R. (2021). Cortical sensorimotor activity in the execution and suppression of discrete and rhythmic movements. *Scientific Reports*, *11*(1), 22364. https://doi.org/10.1038/s41598-021-01368-2

Hinterberger, T., Kübler, A., Kaiser, J., Neumann, N., & Birbaumer, N. (2003). A brain-computer interface (BCI) for the locked-in: comparison of different EEG classifications for the thought translation device. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *114*(3), 416–425. https://doi.org/10.1016/s1388-2457(02)00411-x

Hipp, J. F., Hawellek, D. J., Corbetta, M., Siegel, M., & Engel, A. K. (2012). Large-scale cortical correlation structure of spontaneous oscillatory activity. *Nature Neuroscience*, *15*(6), 884–890. https://doi.org/10.1038/nn.3101

Hodgkin, A. L., and Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology*, 117 (4), 500–44. doi:10.1113/jphysiol.1952.sp004764

Hsiao, F.-J., Wang, Y.-J., Yan, S.-H., Chen, W.-T., & Lin, Y.-Y. (2013). Altered oscillation and synchronization of default-mode network activity in mild Alzheimer's disease compared to mild cognitive impairment: an electrophysiological study. *PloS One*, *8*(7), e68792. https://doi.org/10.1371/journal.pone.0068792

Hsueh, J.-J., Chen, T.-S., Chen, J.-J., & Shaw, F.-Z. (2016). Neurofeedback training of EEG alpha rhythm enhances episodic and working memory: Alpha Neurofeedback on Memory. *Human Brain Mapping*, *37*(7), 2662–2675. https://doi.org/10.1002/hbm.23201

Hyafil, A., Giraud, A.-L., Fontolan, L., & Gutkin, B. (2015). Neural cross-frequency coupling: Connecting architectures, mechanisms, and functions. *Trends in Neurosciences*, 38(11), 725–740. https://doi.org/10.1016/j.tins.2015.09.001

Hyman, B. T., & Trojanowski, J. Q. (1997). Editorial on consensus recommendations for the postmortem diagnosis of Alzheimer disease from the national institute on aging and the Reagan institute working group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *Journal of Neuropathology and Experimental Neurology*, *56*(10), 1095–1097. https://doi.org/10.1097/00005072-199710000-00002

Hodges, J. R. (2000). Memory in the dementias. In: Tulving, E., and Craik, F. I. M. (eds.), *The Oxford Handbook of Memory*, Oxford University Press, Oxford, pp. 441–459.

Hofmann, M., Hock, C., Kühler, A., & Müller-Spahn, F. (1996). Interactive computer-based cognitive training in patients with Alzheimer's disease. *Journal of Psychiatric Research*, *30*(6), 493–501. https://doi.org/10.1016/s0022-3956(96)00036-2

Husseini, F., Damirchi, A., and Babaei, P. (2016). Effect of brain training on cognitive performance in elderly women diagnosed with mild cognitive impairment. *Caspian Journal of Neurological Sciences*, *2*(7), 25–31. https://doi.org/10.18869/acadpub.cjns.2.7.25

Hrishikesan, S. (2018). Advantages, Disadvantages and Applications of EEG. Electronicsandcommunications.Com. Retrieved May 4, 2022, from https://www.electronicsandcommunications.com/2018/08/advantages-disadvantages-applications-of-eeg.html

Hurt, E., Arnold, L. E., & Lofthouse, N. (2014). Quantitative EEG neurofeedback for the treatment of pediatric attention-deficit/hyperactivity disorder, autism spectrum disorders, learning disorders, and epilepsy. *Child and Adolescent Psychiatric Clinics of North America*, *23*(3), 465–486. https://doi.org/10.1016/j.chc.2014.02.001

IBM Corp. Released 2018. IBM SPSS Statistics for Macintosh, Version 26.0.

Ieracitano, C., Mammone, N., Hussain, A., & Morabito, F. C. (2020). A novel multi-modal machine learning based approach for automatic classification of EEG recordings in dementia. *Neural Networks: The Official Journal of the International Neural Network Society*, *123*, 176–190. https://doi.org/10.1016/j.neunet.2019.12.006

Irwin, K., Sexton, C., Daniel, T., Lawlor, B., & Naci, L. (2018). Healthy aging and dementia: Two roads diverging in midlife? *Frontiers in Aging Neuroscience*, *10*, 275. https://doi.org/10.3389/fnagi.2018.00275

Ishii, R., Canuet, L., Aoki, Y., Hata, M., Iwase, M., Ikeda, S., Nishida, K., & Ikeda, M. (2017). Healthy and pathological brain aging: From the perspective of oscillations, functional connectivity, and signal complexity. *Neuropsychobiology*, *75*(4), 151–161. https://doi.org/10.1159/000486870

Izhikevich, E. M. (2007). Dynamical systems in neuroscience. Cambridge, Massachusetts: The MIT Press

Jack, C. R., Lowe, V. J., Weigand, S. D., Wiste, H. J., Senjem, M. L., & Knopman, D. S. (2009). Serial PIB and MRI in normal, mild cognitive impairment and Alzheimers disease: implications for sequence of pathological events in Alzheimers disease. *Brain*, *132*, 1355–1365. https://doi.org/10.1093/brain/awp062

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(19), 6829–6833. https://doi.org/10.1073/pnas.0801268105

Jaeggi, S. M., Studer-Luethi, B., Buschkuehl, M., Su, Y., Jonides, J., & Perrig, W. J. (2010). The relationship between n-back performance and matrix reasoning-implications for training and transfer. *Intelligence*, *38*, 625–635.

Jang, J.-H., Kim, J., Park, G., Kim, H., Jung, E.-S., Cha, J.-Y., Kim, C.-Y., Kim, S., Lee, J.-H., & Yoo, H. (2019). Beta wave enhancement neurofeedback improves cognitive functions in patients with mild cognitive impairment: A preliminary pilot study: A preliminary pilot study. *Medicine*, *98*(50), e18357. https://doi.org/10.1097/MD.0000000000018357

Jas, M., Engemann, D., Raimondo, F., Bekhti, Y., & Gramfort, A. (2016). Automated rejection and repair of bad trials in MEG/EEG. *2016 International Workshop on Pattern Recognition in Neuroimaging (PRNI)*.

Jas, M., Engemann, D. A., Bekhti, Y., Raimondo, F., & Gramfort, A. (2017). Autoreject: Automated artifact rejection for MEG and EEG data. *NeuroImage*, *159*, 417–429. https://doi.org/10.1016/j.neuroimage.2017.06.030

Jensen, O., Gelfand, J., Kounios, J., & Lisman, J. (1999). 10-12 Hz oscillations increase with memory load in a short-term memory task. *NeuroImage*, *9*.

Jensen, Ole, & Tesche, C. D. (2002). Frontal theta activity in humans increases with memory load in a working memory task: Frontal theta increases with memory load. *The European Journal of Neuroscience*, *15*(8), 1395–1399. https://doi.org/10.1046/j.1460-9568.2002.01975.x

Jensen, O., Kaiser, J., & Lachaux, J.-P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences*, *30*(7), 317–324. https://doi.org/10.1016/j.tins.2007.05.001

Jensen, O., and Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: Gating by inhibition. *Frontiers in Human Neuroscience*, 4. https://doi.org/10.3389/fnhum.2010.00186

Jensen, O., Spaak, E., Zumer, J.M. (2019). Human Brain Oscillations: From Physiological Mechanisms to Analysis and Cognition. In: Supek, S., Aine, C. (eds) Magnetoencephalography. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-319-62657-4_17-1

Jelic, V., Johansson, S.-E., Almkvist, O., Shigeta, M., Julin, P., Nordberg, A., Winblad, B., & Wahlund, L.-O. (2000). Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. *Neurobiology of Aging*, *21*(4), 533–540. https://doi.org/10.1016/s0197-4580(00)00153-6

Jiang, Y., Abiri, R., & Zhao, X. (2017). Tuning up the old brain with new tricks: Attention training via neurofeedback. *Frontiers in Aging Neuroscience*, *9*, 52. https://doi.org/10.3389/fnagi.2017.00052

Jirayucharoensak, S., Israsena, P., Pan-Ngum, S., Hemrungrojn, S., & Maes, M. (2019). A game-based neurofeedback training system to enhance cognitive performance in healthy elderly subjects and in patients with amnestic mild cognitive impairment. *Clinical Interventions in Aging*, *14*, 347–360. https://doi.org/10.2147/CIA.S189047

Johnson, K. O. (2000). Neural coding. Neuron, 26(3), 563–566. https://doi.org/10.1016/S0896-6273(00)81193-9J

Johnston, S. J., Boehm, S. G., Healy, D., Goebel, R., & Linden, D. E. J. (2010). Neurofeedback: A promising tool for the self-regulation of emotion networks. *NeuroImage*, *49*(1), 1066–1072. https://doi.org/10.1016/j.neuroimage.2009.07.056

Jones, M. W., & Wilson, M. A. (2005). Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biology*, *3*(12), e402. https://doi.org/10.1371/journal.pbio.0030402

Kai, T., Asai, Y., Sakuma, K., Koeda, T., & Nakashima, K. (2005). Quantitative electroencephalogram analysis in dementia with Lewy bodies and Alzheimer's disease. *Journal of the Neurological Sciences*, *237*(1–2), 89–95. https://doi.org/10.1016/j.jns.2005.05.017

Kallio, E.-L., Öhman, H., Kautiainen, H., Hietanen, M., & Pitkälä, K. (2017). Cognitive training interventions for patients with Alzheimer's disease: A systematic review. *Journal of Alzheimer's Disease: JAD*, *56*(4), 1349–1372. https://doi.org/10.3233/JAD-160810

Kamiya, J. (1962). Conditioned discrimination of the EEG alpha rhythm in humans. In *Proceedings of the Western Psychological Association*. San Francisco, CA.

Kamiya, J. (2011). The first communications about operant conditioning of the EEG. *Journal of Neurotherapy*, *15*(1), 65–73. https://doi.org/10.1080/10874208.2011.545764

Kanda, P. A. de M., Anghinah, R., Smidth, M. T., & Silva, J. M. (2009). The clinical use of quantitative EEG in cognitive disorders. *Dementia & Neuropsychologia*, *3*(3), 195–203. https://doi.org/10.1590/S1980-57642009DN30300004

Kappel, S. L. (2016). *Development and Characterization of Ear-EEG for Real-Life Brain-Monitoring.* Ph.D. thesis. Aarhus University. DOI:10.7146/aul.260.183

Kappel, S. L., & Kidmose, P. (2018). Real-life dry-contact ear-EEG. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*, *2018*, 5470–5474. https://doi.org/10.1109/EMBC.2018.8513532

Kappel, S. L., Makeig, S., & Kidmose, P. (2019). Ear-EEG forward models: Improved head-models for ear-EEG. *Frontiers in Neuroscience*, *13*, 943. https://doi.org/10.3389/fnins.2019.00943

Karbach, J., & Verhaeghen, P. (2014). Making working memory work: a meta-analysis of executive-control and working memory training in older adults: A meta-analysis of executive-control and working memory training in older adults. *Psychological Science*, *25*(11), 2027–2037. https://doi.org/10.1177/0956797614548725

Kardan, O., Adam, K. C. S., Mance, I., Churchill, N. W., Vogel, E. K., & Berman, M. G. (2020). Distinguishing cognitive effort and working memory load using scale-invariance and alpha suppression in EEG. *NeuroImage*, *211*(116622), 116622. https://doi.org/10.1016/j.neuroimage.2020.116622

Kawabata, N. (1974). Dynamics of the electroencephalogram during performance of a mental task. *Kybernetik*, *15*(4), 237–242. https://doi.org/10.1007/bf00277499

Katz, B., Shah, P., & Meyer, D. E. (2018). How to play 20 questions with nature and lose: Reflections on 100 years of brain-training research. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(40), 9897–9904. https://doi.org/10.1073/pnas.1617102114

Kaufmann, L., Wood, G., Robertson, M., Marksteiner, J., & Kober, S. E. (2019). EEG-neurofeedback as a training method for cognitive and non-cognitive functions in early dementia: A case report. *Lernen und Lernstörungen*, *8*(3), 179–189. https://doi.org/10.1024/2235-0977/a000274

Kawasaki, M., & Yamaguchi, Y. (2013). Frontal theta and beta synchronizations for monetary reward increase visual working memory capacity. *Social Cognitive and Affective Neuroscience*, *8*(5), 523–530. https://doi.org/10.1093/scan/nss027

Kayser, J., & Tenke, C. E. (2006). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *117*(2), 369–380. https://doi.org/10.1016/j.clinph.2005.08.033

Keizer, A. W., Verment, R. S., & Hommel, B. (2010). Enhancing cognitive control through neurofeedback: a role of gamma-band activity in managing episodic retrieval. *NeuroImage*, *49*(4), 3404–3413. https://doi.org/10.1016/j.neuroimage.2009.11.023

Khader, P. H., Jost, K., Ranganath, C., & Rösler, F. (2010). Theta and alpha oscillations during working-memory maintenance predict successful long-term memory encoding. *Neuroscience Letters*, *468*(3), 339–343. https://doi.org/10.1016/j.neulet.2009.11.028

Khodakarami, Z., & Firoozabadi, M. (2020). Psychological, neurophysiological, and mental factors associated with gamma-enhancing neurofeedback success. *Basic and Clinical Neuroscience*, *11*(5), 701–714. https://doi.org/10.32598/bcn.11.5.1878.1

Kilner, J. M., Baker, S. N., Salenius, S., Hari, R., & Lemon, R. N. (2000). Human cortical muscle coherence is directly related to specific motor parameters. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *20*(23), 8838–8845. https://doi.org/10.1523/jneurosci.20-23-08838.2000

Kim, J., & Shin, W. (2014). How to do random allocation (randomization). *Clinics in Orthopedic Surgery*, *6*(1), 103–109. https://doi.org/10.4055/cios.2014.6.1.103

Kleberg, F. I., Kitajo, K., Kawasaki, M., & Yamaguchi, Y. (2014). Ongoing theta oscillations predict encoding of subjective memory type. *Neuroscience Research*, *83*, 69–80. https://doi.org/10.1016/j.neures.2014.02.010

Klimesch, W. (1994). Episodic and semantic memory: an analysis in the EEG-theta and alpha band. *Electroencephalography and Clinical Neurophysiology*, *91*, 428–441.

Klimesch, W., Schmike, H., Doppelmayr, M., Ripper, J., Schwaiger, J., & Pfurtscheller, G. (1996). Event-related desynchronization (ERD) and the Dm-effect: Does alpha desynchronization during encoding predict later recall performance? *International Journal of Psychophysiology*, *24*, 47–60.

Klimesh, W. (1997). EEG-alpha rhythms and memory processes. *International, Journal of Psychophysiology*, *24*, 39–46.

Klimesch, W., Russegger, H., Doppelmayr, M., & Pachinger, T. (1998). Induced and evoked band power changes in an oddball task. *Electroencephalography and Clinical Neurophysiology*, *108*, 123–130.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., & Schwaiger, J. (1998). Induced alpha band power changes in the human EEG and attention. *Neuroscience Letters*, *244*(2), 73–76. https://doi.org/10.1016/s0304-3940(98)00122-0

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Research. Brain Research Reviews*, *29*(2–3), 169–195. https://doi.org/10.1016/s0165-0173(98)00056-3

Klimesch, W., Vogt, F., & Doppelmayr, M. (1999). Interindividual differences in alpha and theta power reflect memory performance. *Intelligence*, *27*(4), 347–362. https://doi.org/10.1016/s0160-2896(99)00027-6

Klimesch, W., Doppelmayr, M., Schwaiger, J., Auinger, P., & Winkler, T. (1999). "Paradoxical" alpha synchronization in a memory task. *Brain Research. Cognitive Brain Research*, *7*(4), 493–501.

Klimesch, W., Schack, B., & Sauseng, P. (2005). The functional significance of thêta and upper alpha oscillations for working memory: A review. *Experimental Psychology*, *52*, 99–108.

Klimesch, W., Doppelmayr, M., & Hanslmayr, S. (2006). Upper alpha ERD and absolute power: their meaning for memory performance. *Progress in Brain Research*, *159*, 151–165. https://doi.org/10.1016/S0079-6123(06)59010-7

Klimesch, Wolfgang, Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Klimesh, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences*, *16*, 1–12.

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Training of working memory in children with ADHD. *Journal of Clinical and Experimental Neuropsychology*, *24*(6), 781–791. https://doi.org/10.1076/jcen.24.6.781.8395

Knopman, D. S., Jack, C. R., Jr, Wiste, H. J., Weigand, S. D., Vemuri, P., Lowe, V., Kantarci, K., Gunter, J. L., Senjem, M. L., Ivnik, R. J., Roberts, R. O., Boeve, B. F., & Petersen, R. C. (2012). Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. *Neurology*, *78*(20), 1576–1582. https://doi.org/10.1212/WNL.0b013e3182563bbe

Knyazev, G. G., Slobodskoj-Plusnin, J. Y., & Bocharov, A. V. (2009). Event-related delta and theta synchronization during explicit and implicit emotion processing. *Neuroscience*, *164*(4), 1588–1600. https://doi.org/10.1016/j.neuroscience.2009.09.057

Knyazev, Gennady G. (2012). EEG delta oscillations as a correlate of basic homeostatic and motivational processes. *Neuroscience and Biobehavioral Reviews*, *36*(1), 677–695. https://doi.org/10.1016/j.neubiorev.2011.10.002

Kober, S. E., Witte, M., Ninaus, M., Neuper, C., & Wood, G. (2013). Learning to modulate one's own brain activity: the effect of spontaneous mental strategies. *Frontiers in Human Neuroscience*, *7*, 695. https://doi.org/10.3389/fnhum.2013.00695

Koelewijn, L., Bompas, A., Tales, A., Brookes, M. J., Muthukumaraswamy, S. D., Bayer, A., & Singh, K. D. (2017). Alzheimer's disease disrupts alpha and beta-band resting-state oscillatory network connectivity. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *128*(11), 2347–2357. https://doi.org/10.1016/j.clinph.2017.04.018

Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L. O., John, E. R., & Jelic, V. (2005). Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging*, *26*(2), 165–171. https://doi.org/10.1016/j.neurobiolaging.2004.03.008

Koepsell, T. D., & Monsell, S. E. (2012). Reversion from mild cognitive impairment to normal or near-normal cognition: risk factors and prognosis. *Neurology*, *79*(15), 1591–1598. https://doi.org/10.1212/WNL.0b013e31826e26b7

LabStreamingLayer. LabStreamingLayer Super Repository Comprising Submodules for LSL and Associated Apps. Retrieved July 20, 2022, from https://github.com/sccn/labstreaminglayer

Laine, M., Fellman, D., Waris, O., & Nyman, T. J. (2018). The early effects of external and internal strategies on working memory updating training. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-22396-5

Lakatos, P., Karmos, G., Mehta, A. D., Ulbert, I., & Schroeder, C. E. (2008). Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science (New York, N.Y.)*, *320*(5872), 110–113. https://doi.org/10.1126/science.1154735

Lapborisuth, P., Zhang, X., Noah, A., & Hirsch, J. (2017). Neurofeedback-based functional near-infrared spectroscopy upregulates motor cortex activity in imagined motor tasks. *Neurophotonics*, *4*(2), 021107. https://doi.org/10.1117/1.NPh.4.2.021107

Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A., and Kleinschmidt, A. (2003). Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proceedings of the National Academy of Sciences of the United States of America*, 100 (19): 11053–8. doi:10.1073/pnas.1831638100. PMC 196925

Lauritzen, I., Pardossi-Piquard, R., Bauer, C., Brigham, E., Abraham, J.-D., Ranaldi, S., Fraser, P., St-George-Hyslop, P., Le Thuc, O., Espin, V., Chami, L., Dunys, J., & Checler, F. (2012). The β-secretase-derived C-terminal fragment of βAPP, C99, but not Aβ, is a key contributor to early intraneuronal lesions in triple-transgenic mouse hippocampus. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *32*(46), 16243–1655a. https://doi.org/10.1523/JNEUROSCI.2775-12.2012

Lavy, Y., Dwolatzky, T., Kaplan, Z., Guez, J., & Todder, D. (2019). Neurofeedback improves memory and peak alpha frequency in individuals with mild cognitive impairment. *Applied Psychophysiology and Biofeedback*, *44*(1), 41–49. https://doi.org/10.1007/s10484-018-9418-0

Lecomte, G., & Juhel, J. (2011). The effects of neurofeedback training on memory performance in elderly subjects. *Psychology (Irvine, Calif.)*, *02*(08), 846–852. https://doi.org/10.4236/psych.2011.28129

Leong, R. L. F., Lo, J. C., Sim, S. K. Y., Zheng, H., Tandi, J., Zhou, J., & Chee, M. W. L. (2017). Longitudinal brain structure and cognitive changes over 8 years in an East Asian cohort. *NeuroImage*, *147*, 852–860. https://doi.org/10.1016/j.neuroimage.2016.10.016

Lévesque, J., Beauregard, M., & Mensour, B. (2006). Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. *Neuroscience Letters*, *394*(3), 216–221. https://doi.org/10.1016/j.neulet.2005.10.100

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment* (5th ed.). Oxford University Press.

Li, X., Zhang, J., Li, X.-D., Cui, W., & Su, R. (2020). Neurofeedback training for brain functional connectivity improvement in mild cognitive impairment. *Journal of Medical and Biological Engineering*, *40*(4), 484–495. https://doi.org/10.1007/s40846-020-00531-w

Liebe, S., Hoerzer, G. M., Logothetis, N. K., & Rainer, G. (2012). Theta coupling between V4 and prefrontal cortex predicts visual short-term memory performance. *Nature Neuroscience*, *15*(3), 456–462, S1-2. https://doi.org/10.1038/nn.3038

Lin, C.-L., Jung, M., Wu, Y. C., Lin, C.-T., & She, H.-C. (2012). Brain dynamics of mathematical problem solving. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*, *2012*, 4768–4771. https://doi.org/10.1109/EMBC.2012.6347033

Linares, R., Borella, E., Lechuga, M. T., Carretti, B., & Pelegrina, S. (2019). Nearest transfer effects of working memory training: A comparison of two programs focused on working memory updating. *PloS One*, *14*(2), e0211321. https://doi.org/10.1371/journal.pone.0211321

Lindholm, E., & Lowry, S. (1978). Alpha production in humans under conditions of false feedback. *Bulletin of the Psychonomic Society*, *11*(2), 106–108. https://doi.org/10.3758/bf03336779

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. *NeuroImage*, *193*, 75–92. https://doi.org/10.1016/j.neuroimage.2019.03.011

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., … Mukadam, N. (2017). Dementia prevention, intervention, and care. *Lancet*, *390*(10113), 2673–2734. https://doi.org/10.1016/s0140-6736(17)31363-6

Lizio, R., Vecchio, F., Frisoni, G. B., Ferri, R., Rodriguez, G., & Babiloni, C. (2011). Electroencephalographic rhythms in Alzheimer's disease. *International Journal of Alzheimer's Disease*, *2011*, 927573. https://doi.org/10.4061/2011/927573

Llinás, R., and Yarom, Y. (1986). Oscillatory properties of guinea-pig inferior olivary neurones and their pharmacological modulation: an in vitro study. *The Journal of Physiology*, 376: 163–82. doi:10.1113/jphysiol.1986.sp016147

Llinás, R. R. (2014). Intrinsic electrical properties of mammalian neurons and CNS function: a historical perspective. *Frontiers in Cellular Neuroscience*, 8: 320. doi:10.3389/fncel.2014.00320

Loewenstein, D. A., Acevedo, A., Czaja, S. J., & Duara, R. (2004). Cognitive rehabilitation of mildly impaired Alzheimer's disease patients on cholinesterase inhibitors. *American Journal of Geriatric Psychiatry, 12*, 395–402.

LoGiudice, D., & Watson, R. (2014). Dementia in older people: an update: Dementia - an update. *Internal Medicine Journal*, *44*(11), 1066–1073. https://doi.org/10.1111/imj.12572

Luijmes, R. E., Pouwels, S., & Boonman, J. (2016). The effectiveness of neurofeedback on cognitive functioning in patients with Alzheimer's disease: Preliminary results. *Neurophysiologie Clinique [Clinical Neurophysiology]*, *46*(3), 179–187. https://doi.org/10.1016/j.neucli.2016.05.069

Lyketsos, C. G., & Lee, H. B. (2004). Diagnosis and treatment of depression in Alzheimer's disease. A practical update for the clinician. *Dementia and Geriatric Cognitive Disorders*, *17*(1–2), 55–64. https://doi.org/10.1159/000074277

Lynch, J. J., & Paskewitz, D. A. (1971). On the mechanisms of the feedback control of human brain wave activity. *The Journal of Nervous and Mental Disease*, *153*(3), 205–217. https://doi.org/10.1097/00005053-197109000-00005

Lynch, J. J., Paskewitz, D. A., & Orne, M. T. (1974). Some factors in the feedback control of human alpha rhythm. *Psychosomatic Medicine*, *36*(5), 399–410. https://doi.org/10.1097/00006842-197409000-00003

Lotte, F., Bougrain, L., Cichocki, A., Clerc, M., Congedo, M., Rakotomamonjy, A., & Yger, F. (2018). A review of classification algorithms for EEG-based brain-computer

interfaces: a 10 year update. *Journal of Neural Engineering*, *15*(3), 031005. https://doi.org/10.1088/1741-2552/aab2f2

Mably, A. J., Gereke, B. J., Jones, D. T., & Colgin, L. L. (2017). Impairments in spatial representations and rhythmic coordination of place cells in the 3xTg mouse model of Alzheimer's disease: impaired place fields and rhythms in AD mice. *Hippocampus*, *27*(4), 378–392. https://doi.org/10.1002/hipo.22697

Mably, A. J., & Colgin, L. L. (2018). Gamma oscillations in cognitive disorders. *Current Opinion in Neurobiology*, *52*, 182–187. https://doi.org/10.1016/j.conb.2018.07.009

Magezi, D. A. (2015). Linear mixed-effects models for within-participant psychology experiments: an introductory tutorial and free, graphical user interface (LMMgui). *Frontiers in Psychology, 6*, 2. https://doi.org/10.3389/fpsyg.2015.00002

Magosso, E., De Crescenzio, F., Ricci, G., Piastra, S., & Ursino, M. (2019). EEG alpha power is modulated by attentional changes during cognitive tasks and Virtual Reality immersion. *Computational Intelligence and Neuroscience*, *2019*, 7051079. https://doi.org/10.1155/2019/7051079

Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., Wood, R. A., Joyce, N. M., Boniske, T., Atkins, S. M., & Merzenich, M. M. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(33), 12523–12528. https://doi.org/10.1073/pnas.0605194103

Makeig, S., Westerfield, M., Jung, T. P., Enghoff, S., Townsend, J., Courchesne, E., and Sejnowski, T. J. (2002). Dynamic brain sources of visual evoked responses. *Science*. 295 (5555): 690–4. doi:10.1126/science.1066168

Mäkinen, V., Tiitinen, H., and May, P. (2005). Auditory event-related responses are generated independently of ongoing brain activity. *NeuroImage*, 24 (4): 961–8. doi:10.1016/j.neuroimage.2004.10.020

Malecki, U., Stallforth, S., Heipertz, D., Lavie, N., & Duezel E (2009). Neural generators of sustained activity differ of stimulus-encoding and delay maintenance. *European Journal of Neuroscience, 30*, 924–933.

Marlats, F., Bao, G., Chevallier, S., Boubaya, M., Djabelkhir-Jemmi, L., Wu, Y.-H., Lenoir, H., Rigaud, A.-S., & Azabou, E. (2020). SMR/theta neurofeedback training improves cognitive performance and EEG activity in elderly with mild cognitive impairment: A pilot study. *Frontiers in Aging Neuroscience*, *12*, 147. https://doi.org/10.3389/fnagi.2020.00147

Marzbani, H., Marateb, H. R., & Mansourian, M. (2016). Neurofeedback: A comprehensive review on system design, methodology and clinical applications. *Basic and Clinical Neuroscience, 7*(2), 143–158. https://doi.org/10.15412/J.BCN.03070208

Mathewson, K. E., Gratton, G., Fabiani, M., Beck, D. M., and Ro, T. (2009). To see or not to see: prestimulus alpha phase predicts visual awareness. *The Journal of Neuroscience*, 29 (9): 2725–32. doi:10.1523/JNEUROSCI.3963-08.2009

Mathewson, K. E., Basak, C., Maclin, E. L., Low, K. A., Boot, W. R., Kramer, A. F., Fabiani, M., & Gratton, G. (2012). Different slopes for different folks: alpha and delta EEG power predict subsequent video game learning rate and improvements in cognitive control tasks: Electrophysiological predictors of learning rate. *Psychophysiology*, *49*(12), 1558–1570. https://doi.org/10.1111/j.1469-8986.2012.01474.x

Mayo Clinic (2020). *EEG (electroencephalogram)*. Mayoclinic.Org. Retrieved May 5, 2022, from https://www.mayoclinic.org/tests-procedures/eeg/about/pac-20393875

McNamara, D. S., & Scott, J. L. (2001). Working memory capacity and strategy use. *Memory & Cognition*, *29*(1), 10–17. https://doi.org/10.3758/bf03195736

Mehler, D. M. A., & Kording, K. P. (2018). *The lure of misleading causal statements in functional connectivity research. arXiv*. 1812.03363

Melby-Lervåg, M., & Hulme, C. (2013). Is working memory training effective? A meta-analytic review. *Developmental Psychology*, *49*(2), 270–291. https://doi.org/10.1037/a0028228

Melby-Lervåg, M., Redick, T. S., & Hulme, C. (2016). Working memory training does not improve performance on measures of intelligence or other measures of "far transfer": Evidence from a meta-analytic review: Evidence from a meta-analytic review. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, *11*(4), 512–534. https://doi.org/10.1177/1745691616635612

Micoulaud-Franchi, J.-A., Batail, J.-M., Fovet, T., Philip, P., Cermolacce, M., Jaumard-Hakoun, A., & Vialatte, F. (2019). Towards a pragmatic approach to a psychophysiological unit of analysis for mental and brain disorders: An EEG-Copeia for neurofeedback. *Applied Psychophysiology and Biofeedback*, *44*(3), 151–172. https://doi.org/10.1007/s10484-019-09440-4

Middaugh, S. J., & Pawlick, K. (2002). Biofeedback and behavioral treatment of persistent pain in the older adult: a review and a study. *Applied Psychophysiology and Biofeedback*, *27*(3), 185–202. https://doi.org/10.1023/a:1016208128254

Mikulca, J. A., Nguyen, V., Gajdosik, D. A., Teklu, S. G., Giunta, E. A., Lessa, E. A., Tran, C. H., Terak, E. C., & Raffa, R. B. (2014). Potential novel targets for Alzheimer pharmacotherapy: II. Update on secretase inhibitors and related approaches. *Journal of Clinical Pharmacy and Therapeutics*, *39*(1), 25–37. https://doi.org/10.1111/jcpt.12112

Mirmiran, M., van Someren, E. J., & Swaab, D. F. (1996). Is brain plasticity preserved during aging and in Alzheimer's disease? *Behavioural Brain Research*, *78*(1), 43–48. https://doi.org/10.1016/0166-4328(95)00217-0

Mitchell, D. J., McNaughton, N., Flanagan, D., & Kirk, I. J. (2008). Frontal-midline theta from the perspective of hippocampal "theta." Progress in Neurobiology, 86(3), 156–185. https://doi.org/10.1016/j.pneurobio.2008.09.005

Mitra, P. P., & Pesaran, B. (1999). Analysis of dynamic brain imaging data. Biophysical Journal, 76(2), 691–708. https://doi.org/10.1016/S0006-3495(99)77236-X

Molin, C. (2013). *The relationship between EEG data, cognitive functioning and neuropsychiatric symptoms in elderly patients with Alzheimer's disease. Master's thesis Medical Psychology*. Department of Cognitive Neuropsychology, University of Tilburg, Netherlands.

Moretti, D. V., Babiloni, C., Binetti, G., Cassetta, E., Dal Forno, G., Ferreric, F., Ferri, R., Lanuzza, B., Miniussi, C., Nobili, F., Rodriguez, G., Salinari, S., & Rossini, P. M. (2004). Individual analysis of EEG frequency and band power in mild Alzheimer's disease. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *115*(2), 299–308. https://doi.org/10.1016/s1388-2457(03)00345-6

Moretti, D. V., Pievani, M., Geroldi, C., Binetti, G., Zanetti, O., Rossini, P. M., & Frisoni, G. B. (2010). EEG markers discriminate among different subgroup of patients with mild cognitive impairment. *American Journal of Alzheimer's Disease and Other Dementias*, *25*(1), 58–73. https://doi.org/10.1177/1533317508329814

Morris, J. C., & Price, J. L. (2001). Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *Journal of Molecular Neuroscience: MN*, *17*(2), 101–118. https://doi.org/10.1385/jmn:17:2:101

Morrison, A. B., & Chein, J. M. (2011). Does working memory training work? The promise and challenges of enhancing cognition by training working memory. *Psychonomic Bulletin & Review*, *18*(1), 46–60. https://doi.org/10.3758/s13423-010-0034-0

Mortamais, M., Ash, J. A., Harrison, J., Kaye, J., Kramer, J., Randolph, C., Pose, C., Albala, B., Ropacki, M., Ritchie, C. W., & Ritchie, K. (2017). Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*(4), 468–492. https://doi.org/10.1016/j.jalz.2016.06.2365

Mrazek, M. D., Franklin, M. S., Phillips, D. T., Baird, B., & Schooler, J. W. (2013). Mindfulness training improves working memory capacity and GRE performance while reducing mind wandering. *Psychological Science*, *24*(5), 776–781. https://doi.org/10.1177/0956797612459659

Mulholland, T. (2012). Objective EEG Methods for Studying Covert Shifts of Visual Attention. In McGuigan, F. J.; Schoonover, R. A. (eds.). *The Psychophysiology of Thinking: Studies of Covert Processes*, pp. 109–5. ISBN 978-0-323-14700-2

Müller, N., & Weisz, N. (2012). Lateralized auditory cortical alpha band activity and inter-regional connectivity pattern reflect anticipation of target sounds. *Cerebral Cortex*, *22*, 1604–1613

Munia, T. T. K., & Aviyente, S. (2019). Time-frequency based phase-amplitude coupling measure for neuronal oscillations. Scientific Reports, 9(1), 12441. https://doi.org/10.1038/s41598-019-48870-2

Mureşan, R. C., Jurjuţ, O. F., Moca, V. V., Singer, W., and Nikolić, D. (2008). The oscillation score: an efficient method for estimating oscillation strength in neuronal activity. *Journal of Neurophysiology*, 99 (3): 1333–53. doi:10.1152/jn.00772.2007

Murman, D. L. (2015). The impact of age on cognition. *Seminars in Hearing*, *36*(3), 111–121. https://doi.org/10.1055/s-0035-1555115

Muthuswamy, J., and Thakor, N. V. (1998) Spectral analysis methods for neurological signals. *Journal of Neuroscience Methods*, 83:1–14

Nan, W., Rodrigues, J. P., Ma, J., Qu, X., Wan, F., Mak, P.-I., Mak, P. U., Vai, M. I., & Rosa, A. (2012). Individual alpha neurofeedback training effect on short term memory. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *86*(1), 83–87. https://doi.org/10.1016/j.ijpsycho.2012.07.182

Neely, A. S., Vikstrom, S., & Josephsson, S. (2009). Collaborative memory intervention in dementia: caregiver participation matters. *Neuropsychological Rehabilitation*, *19*(5), 696–715. https://doi.org/10.1080/09602010902719105

Nenert, R., Viswanathan, S., Dubuc, D. M., & Visscher, K. M. (2012). Modulations of ongoing alpha oscillations predict successful short-term visual memory encoding. *Frontiers in Human Neuroscience, 6*, 127. https://doi.org/10.3389/fnhum.2012.00127

Newson, J. J. (2018, September 2). *The remarkable inconsistency of EEG frequency band definitions - sapien labs*. Sapien Labs | Neuroscience | Human Brain Diversity Project. Retrieved July 16, 202, from https://sapienlabs.org/the-remarkable-inconsistency-of-frequency-band-definitions

Nhat, P., Tuan, D., Zohreh, R., Taeho, K., Nam, B., Phuc, N., Hoang, T., Farnoush, B., Ann, H., Thang, D., & Tam, V. (2020). WAKE: a behind-the-ear wearable system for microsleep detection. In *Proceedings of the 18th International Conference on Mobile Systems, Applications, and Services. MobiSys '20* (pp. 404–418). Association for Computing Machinery.

Niedermeyer, E., & Dasilva, F. L. (2004). *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*. Lippincott Williams & Wilkins.

Nousia, A., Siokas, V., Aretouli, E., Messinis, L., Aloizou, A.-M., Martzoukou, M., Karala, M., Koumpoulis, C., Nasios, G., & Dardiotis, E. (2018). Beneficial effect of multidomain cognitive training on the neuropsychological performance of patients with early-stage Alzheimer's disease. *Neural Plasticity*, *2018*, 1–9. https://doi.org/10.1155/2018/2845176

ONESTEP-EEG-Gel - H+H Medizinprodukte. Eeg-gel.de. Retrieved July 20, 2022, from https://eeg-gel.de/en/produkte.php

Open source tools for neuroscience. Openbci.com. Retrieved July 20, 2022, from http://www.openbci.com/

Osipova, D., Ahveninen, J., Jensen, O., Ylikoski, A., & Pekkonen, E. (2005). Altered generation of spontaneous oscillations in Alzheimer's disease. *NeuroImage*, *27*(4), 835–841. https://doi.org/10.1016/j.neuroimage.2005.05.011

Osipova, D., Takashima, A., Oostenveld, R., Fernández, G., Maris, E., & Jensen, O. (2006). Theta and gamma oscillations predict encoding and retrieval of declarative memory. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *26*(28), 7523–7531. https://doi.org/10.1523/JNEUROSCI.1948-06.2006

Palacios-García, I., Silva, J., Villena-González, M., Campos-Arteaga, G., Artigas-Vergara, C., Luarte, N., Rodríguez, E., & Bosman, C. A. (2021). Increase in beta power reflects attentional top-down modulation after psychosocial stress induction. *Frontiers in Human Neuroscience*, *15*, 630813. https://doi.org/10.3389/fnhum.2021.630813

Palop, J. J., & Mucke, L. (2010). Amyloid-β induced neuronal dysfunction in alzheimer's disease: from synapses toward neural networks. *Nature Neuroscience*, *13*, 812–818

Palva, J. M., Palva, S., & Kaila, K. (2005). Phase synchrony among neuronal oscillations in the human cortex. *The Journal of Neuroscience: The Official Journal of the Society for*

Neuroscience, 25(15), 3962–3972. https://doi.org/10.1523/JNEUROSCI.4250-04.2005

Palva, S., & Palva, J. M. (2007). New vistas for alpha-frequency band oscillations. *Trends in Neurosciences*, *30*(4), 150–158. https://doi.org/10.1016/j.tins.2007.02.001

Park, D. C., & Bischof, G. N. (2013). The aging mind: neuroplasticity in response to cognitive training. *Dialogues in Clinical Neuroscience*, *15*(1), 109–119. https://doi.org/10.31887/dcns.2013.15.1/dpark

Pascual-Marqui, R. D., Michel, C. M., & Lehmann, D. (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *18*(1), 49–65. https://doi.org/10.1016/0167-8760(84)90014-x

Pasquier, F., Grymonprez, L., Lebert, F., & Van der Linden, M. (2001). Memory impairment differs in frontotemporal dementia and Alzheimer's disease. *Neurocase*, *7*(2), 161–171. https://doi.org/10.1093/neucas/7.2.161

Peirce, J., Gray, J. R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., Kastman, E., & Lindeløv, J. K. (2019). PsychoPy2: Experiments in behavior made easy. *Behavior Research Methods*, *51*(1), 195–203. https://doi.org/10.3758/s13428-018-01193-y

Pesonen, M., Hämäläinen, H., & Krause, C. M. (2007). Brain oscillatory 4–30 Hz responses during a visual n-back memory task with varying memory load. *Brain Research*, *1138*, 171–177. https://doi.org/10.1016/j.brainres.2006.12.076

Petersen, R. C. (2009). Early diagnosis of Alzheimer's disease: is MCI too late? *Current Alzheimer Research*, *6*(4), 324–330. https://doi.org/10.2174/156720509788929237

Peyrache, A., Dehghani, N., Eskandar, E. N., Madsen, J. R., Anderson, W. S., Donoghue, J. A., and Destexhe, A. (2012). Spatiotemporal dynamics of neocortical excitation and inhibition during human sleep. *Proceedings of the National Academy of Sciences*, 109 (5): 1731–1736. doi:10.1073/pnas.1109895109

Pfurtscheller, G., Zalaudek, K., & Neuper, C. (1998). Event-related beta synchronization after wrist, finger and thumb movement. *Electroencephalography and Clinical Neurophysiology*, *109*(2), 154–160. https://doi.org/10.1016/s0924-980x(97)00070-2

Pfurtscheller, G., and Lopes da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clinical Neurophysiology*, 110 (11): 1842–57. doi:10.1016/S1388-2457(99)00141-8

Piaceri, I., Nacmias, B., & Sorbi, S. (2013). Genetics of familial and sporadic Alzheimer s disease. *Frontiers in Bioscience (Elite Edition)*, *E5*(1), 167–177. https://doi.org/10.2741/e605

Pikovsky, A., Rosenblum, M., and Kurths, J. (2001). Synchronization: a universal concept in nonlinear sciences. Cambridge University Press. ISBN 978-0-521-53352-2

Pillai, J. A., Hall, C. B., Dickson, D. W., Buschke, H., Lipton, R. B., & Verghese, J. (2011). Association of crossword puzzle participation with memory decline in persons who develop dementia. *Journal of the International Neuropsychological Society: JINS*, *17*(6), 1006–1013. https://doi.org/10.1017/S1355617711001111

Pillai, J. A., Bonner-Jackson, A., Walker, E., Mourany, L., & Cummings, J. L. (2014). Higher working memory predicts slower functional decline in autopsy-confirmed Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *38*(3–4), 224–233. https://doi.org/10.1159/000362715

Pinherio, J. C., & Bates, D. M. (2004). Mixed-Effects Models in S and S-PLUS. *Statistics and Computing Series.*

Plotkin, W. P., & Rice, K. M. (1981). Biofeedback as a placebo: anxiety reduction facilitated by training in either suppression or enhancement of alpha brainwaves. *Journal of Consulting and Clinical Psychology*, *49*(4), 590–596. https://doi.org/10.1037//0022-006x.49.4.590

Prichep, L. S., John, E. R., Ferris, S. H., Rausch, L., Fang, Z., Cancro, R., Torossian, C., & Reisberg, B. (2006). Prediction of longitudinal cognitive decline in normal elderly with subjective complaints using electrophysiological imaging. *Neurobiology of Aging*, *27*(3), 471–481. https://doi.org/10.1016/j.neurobiolaging.2005.07.021

Prichep, L. S. (2007). Quantitative EEG and electromagnetic brain imaging in aging and in the evolution of dementia. *Annals of the New York Academy of Sciences*, *1097*(1), 156–167. https://doi.org/10.1196/annals.1379.008

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *9*(1), 63-75.e2. https://doi.org/10.1016/j.jalz.2012.11.007

Prince, M. J., Wu, F., Guo, Y., Gutierrez Robledo, L. M., O'Donnell, M., Sullivan, R., & Yusuf, S. (2015). The burden of disease in older people and implications for health policy and practice. *Lancet*, *385*(9967), 549–562. https://doi.org/10.1016/S0140-6736(14)61347-7

Proskovec, A. L., Wiesman, A. I., Heinrichs-Graham, E., & Wilson, T. W. (2018). Beta oscillatory dynamics in the prefrontal and superior temporal cortices predict spatial working memory performance. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-26863-x

Proskovec, A. L., Wiesman, A. I., Heinrichs-Graham, E., & Wilson, T. W. (2019). Load effects on spatial working memory performance are linked to distributed alpha and beta oscillations. *Human Brain Mapping*, *40*(12), 3682–3689. https://doi.org/10.1002/hbm.24625

Pollok, B., Latz, D., Krause, V., Butz, M., & Schnitzler, A. (2014). Changes of motor-cortical oscillations associated with motor learning. *Neuroscience*, *275*, 47–53. https://doi.org/10.1016/j.neuroscience.2014.06.008

Pornpattananangkul, N., & Nusslock, R. (2016). Willing to wait: Elevated-reward processing EEG activity associated with a greater preference for larger-but-delayed rewards. *Neuropsychologia*, *91*, 141–162.

Portugal, A. M., Ferreira, D. S., Reis, J. S., Pinho, F., & Dias, N. S. (2013). Cognitive intervention protocol for age-related memory impairments. *2013 IEEE 2nd International Conference on Serious Games and Applications for Health (SeGAH)*.

Quayhagen, M. P., Quayhagen, M., Corbeil, R. R., Roth, P. A., & Rodgers, J. A. (1995). A dyadic remediation program for care recipients with dementia. *Nursing Research*, *44*(3), 153–159. https://doi.org/10.1097/00006199-199505000-00005

Quayhagen, M. P., & Quayhagen, M. (2001). Testing of a cognitive stimulation intervention for dementia caregiving dyads. *Neuropsychological Rehabilitation*, *11*(3–4), 319–332. https://doi.org/10.1080/09602010042000024

R Core Team. R: A Language and Environment for Statistical ## Computing. R Foundation for Statistical Computing; 2017. https://www.R-project.org/

Ranganath, C., & Paller, K. A. (1999). Frontal brain potentials during recognition are modulated by requirements to retrieve perceptual detail. *Neuron*, *22*(3), 605–613. https://doi.org/10.1016/s0896-6273(00)80714-x

Rasey, H., Lubar, J. F., McIntyre, A., Zoffuto, A., & Abbott, P. L. (1995). EEG biofeedback for the enhancement of attentional processing in normal college students. *Journal of Neurotherapy*, *1*(3), 15–21. https://doi.org/10.1300/j184v01n03_03

Raz, A., & Harris, C. (Eds.). (2016). *Placebo Talks: Modern perspectives on placebos in society*. Oxford University Press

Redick, T. S., Shipstead, Z., Wiemers, E. A., Melby-Lervåg, M., & Hulme, C. (2015). What's working in working memory training? An educational perspective. *Educational Psychology Review*, *27*(4), 617–633. https://doi.org/10.1007/s10648-015-9314-6

Reif, F. (1965). Fundamentals of Statistical and Thermal Physics (International student ed.). Boston: McGraw-Hill. p. 2. ISBN 007-051800-9

Reiner, M., Rozengurt, R., & Barnea, A. (2014). Better than sleep: Theta neurofeedback training accelerates memory consolidation. *Biological Psychology*, *95*, 45–53. https://doi.org/10.1016/j.biopsycho.2013.10.010

Reis, J., Portugal, A. M., Fernandes, L., Afonso, N., Pereira, M., Sousa, N., & Dias, N. S. (2016). An Alpha and Theta Intensive and Short Neurofeedback Protocol for Healthy Aging Working-Memory Training. *Frontiers in Aging Neuroscience*, *8*. https://doi.org/10.3389/fnagi.2016.0015

Rice, K. M., & Blanchard, E. B. (1982). Biofeedback in the treatment of anxiety disorders. *Clinical Psychology Review*, *2*(4), 557–577. https://doi.org/10.1016/0272-7358(82)90030-7

Ripley, B. D. (2001). The R project in statistical computing. *MSOR Connections*, *1*(1), 23–25. https://doi.org/10.11120/msor.2001.01010023

Ritchie, K., Ritchie, C. W., Yaffe, K., Skoog, I., & Scarmeas, N. (2015). Is late-onset Alzheimer's disease really a disease of midlife? *Alzheimer's & Dementia (New York, N. Y.)*, *1*(2), 122–130. https://doi.org/10.1016/j.trci.2015.06.004

Ritchie, K., Carrière, I., Su, L., O'Brien, J. T., Lovestone, S., Wells, K., & Ritchie, C. W. (2017). The midlife cognitive profiles of adults at high risk of late-onset Alzheimer's disease: The PREVENT study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*(10), 1089–1097. https://doi.org/10.1016/j.jalz.2017.02.008

Roberts, R., & Knopman, D. S. (2013). Classification and epidemiology of MCI. *Clinics in Geriatric Medicine*, *29*(4), 753–772. https://doi.org/10.1016/j.cger.2013.07.003

Rocha, A. F. (2020). Toward a comprehensive understanding of EEG and its analyses. In *bioRxiv*. https://doi.org/10.1101/2020.02.14.948968

Rogala, J., Jurewicz, K., Paluch, K., Kublik, E., Cetnarski, R., & Wróbel, A. (2016). The do's and don'ts of neurofeedback training: A review of the controlled studies using healthy adults. *Frontiers in Human Neuroscience*, *10*. https://doi.org/10.3389/fnhum.2016.00301

Rondina Ii, R., Olsen, R. K., Li, L., Meltzer, J. A., & Ryan, J. D. (2019). Age-related changes to oscillatory dynamics during maintenance and retrieval in a relational memory task. PloS one, 14(2), e0211851. https://doi.org/10.1371/journal.pone.0211851

Ros, T., Théberge, J., Frewen, P. A., Kluetsch, R., Densmore, M., Calhoun, V. D., & Lanius, R. A. (2013). Mind over chatter: Plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. *NeuroImage*, *65*, 324–335. https://doi.org/10.1016/j.neuroimage.2012.09.046

Ros, T., Enriquez-Geppert, S., Zotev, V., Young, K. D., Wood, G., Whitfield-Gabrieli, S., Wan, F., Vuilleumier, P., Vialatte, F., Van De Ville, D., Todder, D., Surmeli, T., Sulzer,

J. S., Strehl, U., Sterman, M. B., Steiner, N. J., Sorger, B., Soekadar, S. R., Sitaram, R., … Thibault, R. T. (2020). Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist). *Brain: A Journal of Neurology*, *143*(6), 1674–1685. https://doi.org/10.1093/brain/awaa009

Roy, D. S., Arons, A., Mitchell, T. I., Pignatelli, M., Ryan, T. J., & Tonegawa, S. (2016). Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. *Nature*, *531*(7595), 508–512. https://doi.org/10.1038/nature17172

Rund, B. R., Barder, H. E., Evensen, J., Haahr, U., ten Velden Hegelstad, W., Joa, I., Johannessen, J. O., Langeveld, J., Larsen, T. K., Melle, I., Opjordsmoen, S., Røssberg, J. I., Simonsen, E., Sundet, K., Vaglum, P., McGlashan, T., & Friis, S. (2016). Neurocognition and duration of psychosis: A 10-year follow-up of first-episode patients. *Schizophrenia Bulletin*, *42*(1), 87–95. https://doi.org/10.1093/schbul/sbv083

Sacuiu, S. F. (2016). Dementias. *Handbook of Clinical Neurology*, *138*, 123–151. https://doi.org/10.1016/B978-0-12-802973-2.00008-2

Sauseng, P., & Klimesch, W. (2008). What does phase information of oscillatory brain activity tell us about cognitive processes? *Neuroscience and Biobehavioral Reviews*, *32*(5), 1001–1013. https://doi.org/10.1016/j.neubiorev.2008.03.014

Sauseng, P., Klimesch, W., Gerloff, C., & Hummel, F. C. (2009). Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. *Neuropsychologia*, *47*(1), 284–288. https://doi.org/10.1016/j.neuropsychologia.2008.07.021

Sauseng, P., Griesmayr, B., Freunberger, R., & Klimesch, W. (2010). Control mechanisms in working memory: a possible function of EEG theta oscillations. *Neuroscience and Biobehavioral Reviews*, *34*(7), 1015–1022. https://doi.org/10.1016/j.neubiorev.2009.12.006

Savulich, G., Thorp, E., Piercy, T., Peterson, K. A., Pickard, J. D., & Sahakian, B. J. (2019). Improvements in attention following Cognitive Training with the novel "Decoder" game on an iPad. *Frontiers in Behavioral Neuroscience*, *13*, 2. https://doi.org/10.3389/fnbeh.2019.00002

Sazgar, M., & Young, M. G. (2019). EEG Artifacts. In *Absolute Epilepsy and EEG Rotation Review* (pp. 149–162). Springer International Publishing.

Scarmeas, N., & Stern, Y. (2003). Cognitive reserve and lifestyle. *Journal of Clinical and Experimental Neuropsychology*, *25*(5), 625–633. https://doi.org/10.1076/jcen.25.5.625.14576

Scheeringa, R., Petersson, K. M., Oostenveld, R., Norris, D. G., Hagoort, P., & Bastiaansen, M. C. (2009). Trial- by-trial coupling between EEG and BOLD identifies networks related to alpha and theta EEG power increases during working memory maintenance. *NeuroImage*, *44*, 1224–1238

Schestatsky, P., Morales-Quezada, L., & Fregni, F. (2013). Simultaneous EEG monitoring during transcranial direct current stimulation. *Journal of Visualized Experiments: JoVE*, *76*. https://doi.org/10.3791/50426

Schmidt, C., Wolff, M., Weitz, M., Bartlau, T., Korth, C., & Zerr, I. (2011). Rapidly progressive Alzheimer disease. *Archives of Neurology*, *68*(9), 1124–1130. https://doi.org/10.1001/archneurol.2011.189

Schnitzler, A., and Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nature Reviews Neuroscience*, 6(4), 285–296. https://doi.org/10.1038/nrn1650

Scholz, S., Schneider, S. L., & Rose, M. (2017). Differential effects of ongoing EEG beta and theta power on memory formation. *PloS One*, *12*(2), e0171913. https://doi.org/10.1371/journal.pone.0171913

Schulz, K. F., Altman, D. G., Moher, D., & CONSORT Group. (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Annals of Internal Medicine*, *152*(11), 726–732. https://doi.org/10.7326/0003-4819-152-11-201006010-00232

Schultz, S. A., Larson, J., Oh, J., Koscik, R., Dowling, M. N., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Bendlin, B. B., Asthana, S., Hermann, B. P., Johnson, S. C., Sager, M., LaRue, A., & Okonkwo, O. C. (2015). Participation in cognitively-stimulating activities is associated with brain structure and cognitive function in preclinical Alzheimer's disease. *Brain Imaging and Behavior*, *9*(4), 729–736. https://doi.org/10.1007/s11682-014-9329-5

Schwaighofer, M., Fischer, F., & Bühner, M. (2015). Does working memory training transfer? A meta-analysis including training conditions as moderators. *Educational Psychologist*, *50*(2), 138–166. https://doi.org/10.1080/00461520.2015.1036274

Scott, W. C., Kaiser, D., Othmer, S., & Sideroff, S. I. (2005). Effects of an EEG biofeedback protocol on a mixed substance abusing population. *The American Journal of Drug and Alcohol Abuse*, *31*(3), 455–469. https://doi.org/10.1081/ada-200056807

Sejdić, E., Djurović, I., and Jiang, J. (2009). Time-frequency feature representation using energy concentration: An overview of recent advances. *Digital Signal Processing*, vol. 19, no. 1, pp. 153-183

Senkowski, D., Molholm, S., Gomez-Ramirez, M., & Foxe, J. J. (2006). Oscillatory beta activity predicts response speed during a multisensory audiovisual reaction time task: a high-density electrical mapping study. *Cerebral Cortex (New York, N.Y.: 1991)*, *16*(11), 1556–1565. https://doi.org/10.1093/cercor/bhj091

Senkowski, D., Schneider, T. R., Foxe, J. J., & Engel, A. K. (2008). Crossmodal binding through neural coherence: implications for multisensory processing. Trends in Neurosciences, 31(8), 401–409. https://doi.org/10.1016/j.tins.2008.05.002

Sereno, S. C., Rayner, K., & Posner, M. I. (1998). Establishing a time-line of word recognition: evidence from eye movements and event-related potentials. *Neuroreport*, *9*(10), 2195–2200. https://doi.org/10.1097/00001756-199807130-00009

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, *1*(1), a006189. https://doi.org/10.1101/cshperspect.a006189

Shaw, C. A., Lanius, R. A., & Vandendoel, K. (1994). The origin of synaptic neuroplasticity - Crucial molecules or a dynamical cascade. *Brain Research Reviews*, *19*, 241–263

Shaw, J. C. (2003). The Brain's alpha rhythms and the mind: a review of classical and modern studies of the alpha rhythm component of the electroencephalogram with commentaries on associated neuroscience and neuropsychology. Elsevier, Amsterdam

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Siapas, A. G., Lubenov, E. V., & Wilson, M. A. (2005). Prefrontal phase locking to hippocampal theta oscillations. *Neuron*, *46*(1), 141–151. https://doi.org/10.1016/j.neuron.2005.02.028

Siegel, M., Donner, T. H., Oostenveld, R., Fries, P., & Engel, A. K. (2008). Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. *Neuron*, 60(4), 709–719. https://doi.org/10.1016/j.neuron.2008.09.010

Simons, D. J., Boot, W. R., Charness, N., Gathercole, S. E., Chabris, C. F., Hambrik, D. Z., & Stine-Morrow, E. A. (2016). Do "Brain-Training" Programs Work? Psychological science in the public interest. *American Psychological Society*, *17*, 103–186.

Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., Weiskopf, N., Blefari, M. L., Rana, M., Oblak, E., Birbaumer, N., & Sulzer, J. (2017). Closed-

loop brain training: the science of neurofeedback. *Nature Reviews. Neuroscience*, *18*(2), 86–100. https://doi.org/10.1038/nrn.2016.164

Sitzer, D. I., Twamley, E. W., & Jeste, D. V. (2006). Cognitive training in Alzheimer's disease: a meta-analysis of the literature. *Acta Psychiatrica Scandinavica*, *114*(2), 75–90. https://doi.org/10.1111/j.1600-0447.2006.00789.x

Smailovic, U., & Jelic, V. (2019). Neurophysiological markers of Alzheimer's disease: Quantitative EEG approach. *Neurology and Therapy*, *8*(Suppl 2), 37–55. https://doi.org/10.1007/s40120-019-00169-0

Smith, S. J. M. (2005). EEG in the diagnosis, classification, and management of patients with epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76 Suppl 2*(suppl_2), ii2-7. https://doi.org/10.1136/jnnp.2005.069245

Soler, A., Muñoz-Gutiérrez, P. A., Bueno-López, M., Giraldo, E., & Molinas, M. (2020). Low-density EEG for neural activity reconstruction using multivariate empirical mode decomposition. *Frontiers in Neuroscience*, *14*, 175. https://doi.org/10.3389/fnins.2020.00175

Solomon, E. P., Berg, L. R., and Martin, D. W. (2002), Biology (6th ed.), Brooks/Cole, ISBN 0-534-39175-3

Sommers, M. S. (1997). Speech perception in older adults: the importance of speech-specific cognitive abilities. *Journal of the American Geriatrics Society*, *45*(5), 633–637. https://doi.org/10.1111/j.1532-5415.1997.tb03101.x

Soveri, A., Antfolk, J., Karlsson, L., Salo, B., & Laine, M. (2017a). Working memory training revisited: A multi-level meta-analysis of n-back training studies. *Psychonomic Bulletin & Review*, *24*(4), 1077–1096. https://doi.org/10.3758/s13423-016-1217-0

Soveri, A., Karlsson, E. P. A., Waris, O., Grönholm-Nyman, P., & Laine, M. (2017b). Pattern of near transfer effects following working memory training with a dual N-back task. *Experimental Psychology*, *64*(4), 240–252. https://doi.org/10.1027/1618-3169/a000370

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, *6*(3), 309–315. https://doi.org/10.1038/nn1008

Spaak, E., Fonken, Y., Jensen, O., & de Lange, F. P. (2016). The neural mechanisms of prediction in visual search. *Cerebral Cortex (New York, N.Y.: 1991)*, *26*(11), 4327–4336. https://doi.org/10.1093/cercor/bhv210

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R., Jr, Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003

Spitzer, B., Wacker, E., & Blankenburg, F. (2010). Oscillatory correlates of vibrotactile frequency processing in human working memory. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(12), 4496–4502. https://doi.org/10.1523/JNEUROSCI.6041-09.2010

Stam, C. J. (2014). Modern network science of neurological disorders. *Nature Reviews. Neuroscience*, *15*(10), 683–695. https://doi.org/10.1038/nrn3801

Stark, S. M., Yassa, M. A., Lacy, J. W., & Stark, C. E. L. (2013). A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive

impairment. *Neuropsychologia*, *51*(12), 2442–2449. https://doi.org/10.1016/j.neuropsychologia.2012.12.014

Steffens, D. C., Maytan, M., Helms, M. J., & Plassman, B. L. (2005). Prevalence and clinical correlates of neuropsychiatric symptoms in dementia. *American Journal of Alzheimer's Disease and Other Dementias*, *20*(6), 367–373. https://doi.org/10.1177/153331750502000611

Steiger, T. K., & Bunzeck, N. (2017). Reward dependent invigoration relates to theta oscillations and is predicted by dopaminergic midbrain integrity in healthy elderly. *Frontiers in Aging Neuroscience*, *9*, 1. https://doi.org/10.3389/fnagi.2017.00001

Sterman, M. B., & Egner, T. (2006). Foundation and practice of neurofeedback for the treatment of epilepsy. *Applied Psychophysiology and Biofeedback*, *31*(1), 21–35. https://doi.org/10.1007/s10484-006-9002-x

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society: JINS*, *8*(3), 448–460. https://doi.org/10.1017/s1355617702813248

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, 47, 2015-2028.

Stern, Y. (2012). Cognitive reserve in aging and Alzheimer's Disease. *The Lancet Neurology*, *11*, 1006–1012.

Storey, E., Slavin, M. J., & Kinsella, G. J. (2002). Patterns of cognitive impairment in Alzheimer's disease: assessment and differential diagnosis. *Frontiers in Bioscience*, *7*(1–3), e155-84. https://doi.org/10.2741/A914

Stoyell, S. M., Wilmskoetter, J., Dobrota, M.-A., Chinappen, D. M., Bonilha, L., Mintz, M., Brinkmann, B. H., Herman, S. T., Peters, J. M., Vulliemoz, S., Seeck, M., Hämäläinen, M. S., & Chu, C. J. (2021). High-density EEG in current clinical

practice and opportunities for the future. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society*, *38*(2), 112–123. https://doi.org/10.1097/WNP.0000000000000807

Stratmann, K., Heinsen, H., Korf, H., Del Turco, D., Ghebremedhin, E., & Seidel, K. (2016). Precortical phases of Alzheimer's Disease (AD)-Related Tau Cytoskeletal Pathology. *Brain Pathology*, *26*, 371–386.

Strayer, F., Scott, W. B., & Baken, P. (1973). A re-examination of alpha feedback training: operant conditioning or perceptual differentiation? *Canadian Journal of Psychology*, *27*(3), 247–253. https://doi.org/10.1037/h0082475

Stroth, S., Hille, K., Spitzer, M., & Reinhardt, R. (2009). Aerobic endurance exercise benefits memory and affect in young adults. *Neuropsychological Rehabilitation*, *19*(2), 223–243. https://doi.org/10.1080/09602010802091183

Suffczynski, P., Kalitzin, S., Pfurtscheller, G., and Lopes da Silva, F. H. (2001). Computational model of thalamo-cortical networks: dynamical control of alpha rhythms in relation to focal attention. *International Journal of Psychophysiology*, 43(1): 25–40. doi:10.1016/S0167-8760(01)00177-5

Summers, M. J., & Saunders, N. L. J. (2012). Neuropsychological measures predict decline to Alzheimer's dementia from mild cognitive impairment. *Neuropsychology*, *26*(4), 498–508. https://doi.org/10.1037/a0028576

Surmeli, T., Eralp, E., Mustafazade, I., Kos, H., Özer, G. E., & Surmeli, O. H. (2016). Quantitative EEG neurometric analysis–guided neurofeedback treatment in dementia: 20 Cases. How neurometric analysis is important for the treatment of dementia and as a biomarker? *Clinical EEG and Neuroscience: Official Journal of the EEG and Clinical Neuroscience Society (ENCS)*, *47*(2), 118–133. https://doi.org/10.1177/1550059415590750

Sveinbjornsdottir, S. (2016). The clinical symptoms of Parkinson's disease. *Journal of Neurochemistry*, 139 (Suppl 1): 318–324. doi:10.1111/jnc.13691

Tallon-Baudry, C., and Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Sciences*, 3 (4): 151–162. doi:10.1016/S1364-6613(99)01299-1

Tamayev, R., Matsuda, S., Arancio, O., & D'Adamio, L. (2012). β- but not γ-secretase proteolysis of APP causes synaptic and memory deficits in a mouse model of dementia: SAPPβ/β-CTF and not Aβ cause memory deficits. *EMBO Molecular Medicine*, *4*(3), 171–179. https://doi.org/10.1002/emmm.201100195

Tass, P. A. (2007). Phase resetting in medicine and biology: stochastic modelling and data analysis. Berlin Heidelberg: Springer-Verlag. ISBN 978-3-540-65697-5

Taya, F., Sun, Y., Babiloni, F., Thakor, N., & Bezerianos, A. (2015). Brain enhancement through cognitive training: a new insight from brain connectome. *Frontiers in Systems Neuroscience*, *9*, 44. https://doi.org/10.3389/fnsys.2015.00044

Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement Science Review*, *2*(2).

Thibault, R. T., Lifshitz, M., Birbaumer, N., & Raz, A. (2015). Neurofeedback, self-regulation, and brain imaging: Clinical science and fad in the service of mental disorders. *Psychotherapy and Psychosomatics*, *84*(4), 193–207. https://doi.org/10.1159/000371714

Thibault, R. T., & Raz, A. (2016). When can neurofeedback join the clinical armamentarium? *The Lancet. Psychiatry*, *3*(6), 497–498. https://doi.org/10.1016/S2215-0366(16)30040-2

Thibault, R. T., & Raz, A. (2017). The psychology of neurofeedback: Clinical intervention even if applied placebo. *The American Psychologist*, *72*(7), 679–688. https://doi.org/10.1037/amp0000118

Thibault, R. T., MacPherson, A., Lifshitz, M., Roth, R. R., & Raz, A. (2018). Neurofeedback with fMRI: A critical systematic review. *NeuroImage*, *172*, 786–807. https://doi.org/10.1016/j.neuroimage.2017.12.071

Tiesinga, P. H. E., Fellous, J.-M., Salinas, E., José, J. V., & Sejnowski, T. J. (2004). Synchronization as a mechanism for attentional gain modulation. *Neurocomputing*, 58–60, 641–646. https://doi.org/10.1016/j.neucom.2004.01.108

Trappenberg, T. P. (2010). Fundamentals of Computational Neuroscience. United States: Oxford University Press Inc. pp. 2. ISBN 978-0-19-851582-1

Traub, R. D., Jefferys, J. G. R., and Whittington, M. A. (1999) Fast oscillations in cortical circuits. MIT Press, Cambridge

Torgerson, D. J., & Roberts, C. (1999). Understanding controlled trials. Randomisation methods: concealment. *BMJ (Clinical Research Ed.)*, *319*(7206), 375–376. https://doi.org/10.1136/bmj.319.7206.375

Toscano, G., Carboni, M., Rubega, M., Spinelli, L., Pittau, F., Bartoli, A., Momjian, S., Manni, R., Terzaghi, M., Vulliemoz, S., & Seeck, M. (2020). Visual analysis of high density EEG: As good as electrical source imaging? *Clinical Neurophysiology Practice*, *5*, 16–22. https://doi.org/10.1016/j.cnp.2019.09.002

van der Hiele, K., Vein, A. A., van der Welle, A., van der Grond, J., Westendorp, R. G. J., Bollen, E. L. E. M., van Buchem, M. A., van Dijk, J. G., & Middelkoop, H. A. M. (2007). EEG and MRI correlates of mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, *28*(9), 1322–1329. https://doi.org/10.1016/j.neurobiolaging.2006.06.006

van Dijk, H., Schoffelen, J. M., Oostenveld, R., and Jensen, O. (2008). Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. *The Journal of Neuroscience*, 28 (8): 1816–23. doi:10.1523/jneurosci.1853-07.2008

van Ede, F., de Lange, F., Jensen, O., & Maris, E. (2011). Orienting attention to an upcoming tactile event involves a spatially and temporally specific modulation of sensorimotor alpha- and beta-band oscillations. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *31*(6), 2016–2024. https://doi.org/10.1523/JNEUROSCI.5630-10.2011

van Elswijk, G., Maij, F., Schoffelen, J.-M., Overeem, S., Stegeman, D. F., & Fries, P. (2010). Corticospinal beta-band synchronization entails rhythmic gain modulation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(12), 4481–4488. https://doi.org/10.1523/JNEUROSCI.2794-09.2010

van Heugten, C. M., Ponds, R. W. H. M., & Kessels, R. P. C. (2016). Brain training: hype or hope? *Neuropsychological Rehabilitation*, *26*(5–6), 639–644. https://doi.org/10.1080/09602011.2016.1186101

Vaz Portugal Silva, A. M. Theta and Alpha Neurofeedback for Age-Related Cognitive Deficits. Master Thesis. University of Minho, Escola de Ciências da Saúde. 2013.

Verde, M. F., Macmillan, N. A., and Rotello, C. M. (2006). Measures of sensitivity based on a single trial hit rate and false alarm rate: The accuracy, precision, and robustness of d', A_z and A'. *Perception & Psychophysics,* 68, 643-654

van Elswijk, G., Maij, F., Schoffelen, J.-M., Overeem, S., Stegeman, D. F., & Fries, P. (2010). Corticospinal beta-band synchronization entails rhythmic gain modulation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(12), 4481–4488. https://doi.org/10.1523/JNEUROSCI.2794-09.2010

Vernon, David, Egner, T., Cooper, N., Compton, T., Neilands, C., Sheri, A., & Gruzelier, J. (2003). The effect of training distinct neurofeedback protocols on aspects of cognitive performance. *International Journal of Psychophysiology: Official*

Journal of the International Organization of Psychophysiology, *47*(1), 75–85. https://doi.org/10.1016/s0167-8760(02)00091-0

Vernon, D. J. (2005). Can neurofeedback training enhance performance? An evaluation of the evidence with implications for future research. *Applied Psychophysiology and Biofeedback*, *30*(4), 347–364. https://doi.org/10.1007/s10484-005-8421-4

Vernon, D., Dempster, T., Bazanova, O., Rutterford, N., Pasqualini, M., & Andersen, S. (2009). Alpha neurofeedback training for performance enhancement: Reviewing the methodology. *Journal of Neurotherapy*, *13*(4), 214–227. https://doi.org/10.1080/10874200903334397

Voytek, B., Secundo, L., Bidet-Caulet, A., Scabini, D., Stiver, S. I., Gean, A. D., Manley, G. T., & Knight, R. T. (2010). Hemicraniectomy: a new model for human electrophysiology with high spatio-temporal resolution. *Journal of Cognitive Neuroscience*, 22(11), 2491–2502. https://doi.org/10.1162/jocn.2009.21384

Waldhauser, G. T., Johansson, M., & Hanslmayr, S. (2012). Alpha/beta oscillations indicate inhibition of interfering visual memories. *The Journal of Neuroscience*, *32*(6).

Walker, E. A., Redfern, A., & Oleson, J. J. (2019). Linear mixed-model analysis to examine longitudinal trajectories in vocabulary depth and breadth in children who are hard of hearing. *Journal of Speech, Language, and Hearing Research: JSLHR*, *62*(3), 525–542. https://doi.org/10.1044/2018_JSLHR-L-ASTM-18-0250

Wan, F., da Cruz, J. N., Nan, W., Wong, C. M., Vai, M. I., & Rosa, A. (2016). Alpha neurofeedback training improves SSVEP-based BCI performance. *Journal of Neural Engineering*, *13*(3), 036019. https://doi.org/10.1088/1741-2560/13/3/036019

Wang, X. J. (2010). Neurophysiological and computational principles of cortical rhythms in cognition. *Physiological Reviews*, 90 (3): 1195–268. doi:10.1152/physrev.00035.2008

Wang, J.-R., & Hsieh, S. (2013). Neurofeedback training improves attention and working memory performance. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *124*(12), 2406–2420. https://doi.org/10.1016/j.clinph.2013.05.020

Wang, Y., Yan, J., Wen, J., Yu, T., & Li, X. (2016). An intracranial electroencephalography (iEEG) Brain Function Mapping tool with an application to epilepsy surgery evaluation. *Frontiers in Neuroinformatics*, *10*, 15. https://doi.org/10.3389/fninf.2016.00015

Wei, T.-Y., Chang, D.-W., Liu, Y.-D., Liu, C.-W., Young, C.-P., Liang, S.-F., & Shaw, F.-Z. (2017). Portable wireless neurofeedback system of EEG alpha rhythm enhances memory. *Biomedical Engineering Online*, *16*(1). https://doi.org/10.1186/s12938-017-0418-8

Weisz, N., Hartmann, T., Müller, N., Lorenz, I., & Obleser, J. (2011). Alpha rhythms in audition: cognitive and clinical perspectives. *Frontiers in Psychology*, *2*, 73. https://doi.org/10.3389/fpsyg.2011.00073

Willem, M., Tahirovic, S., Busche, M. A., Ovsepian, S. V., Chafai, M., Kootar, S., Hornburg, D., Evans, L. D. B., Moore, S., Daria, A., Hampel, H., Müller, V., Giudici, C., Nuscher, B., Wenninger-Weinzierl, A., Kremmer, E., Heneka, M. T., Thal, D. R., Giedraitis, V., … Haass, C. (2015). η-Secretase processing of APP inhibits neuronal activity in the hippocampus. *Nature*, *526*(7573), 443–447. https://doi.org/10.1038/nature14864

Wilson, R. S., Bacon, L. D., Fox, J. H., & Kaszniak, A. W. (1983). Primary memory and secondary memory in dementia of the Alzheimer type. *Journal of Clinical Neuropsychology*, *5*(4), 337–344. https://doi.org/10.1080/01688638308401181

Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., & Fries, P. (2007). Modulation of neuronal interactions through neuronal synchronization. *Science (New York, N.Y.)*, *316*(5831), 1609–1612. https://doi.org/10.1126/science.1139597

World Health Organization, WHO (2018).. *Ageing and health*. Retrieved May 5, 2022, from https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

Yong, E. (2016, October 3). *The weak evidence behind brain-training games*. The Atlantic. https://www.theatlantic.com/science/archive/2016/10/the-weak-evidence-behind-brain-training-games/502559/

Yuki, O., Yul-Wan, K., & Seiji, S. (2019). A linear mixed-effect model analysis of the effect of schizotypal personality traits on confidence in reality monitoring. *Tohuku Psychologica Folia*, *77*, 83–90.

Zander, T. O., & Kothe, C. (2011). Towards passive brain–computer interfaces: applying brain–computer interface technology to human–machine systems in general. *Journal of Neural Engineering*, *8*(2), 025005. https://doi.org/10.1088/1741-2560/8/2/025005

Zanto, T. P., & Gazzaley, A. (2009). Neural suppression of irrelevant information underlies optimal working memory performance. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *29*(10), 3059–3066. https://doi.org/10.1523/JNEUROSCI.4621-08.2009

Zhao, Q., Zhou, B., Ding, D., Teramukai, S., Guo, Q., Fukushima, M., & Hong, Z. (2014). Cognitive decline in patients with Alzheimer's disease and its related factors in a memory clinic setting, Shanghai, China. *PloS One*, *9*(4), e95755. https://doi.org/10.1371/journal.pone.0095755

Zhao, X., Chen, L., & Maes, J. H. R. (2018). Training and transfer effects of response inhibition training in children and adults. *Developmental Science*, *21*(1), e12511. https://doi.org/10.1111/desc.12511

Zhao, X., Fu, J., & Maes, J. H. R. (2019). Prospective memory training in young adults enhances trained-task but not transfer-task performance. *Memory (Hove, England)*, *27*(7), 1018–1023. https://doi.org/10.1080/09658211.2019.1613435

Zhou, X., Li, Q., Kilsgaard, S., Moradi, F., Kappel, S. L., & Kidmose, P. (2016). A wearable ear-EEG recording system based on dry-contact active electrodes. *2016 IEEE Symposium on VLSI Circuits (VLSI-Circuits)*.

Zoefel, B., Huster, R. J., & Herrmann, C. S. (2011). Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. *NeuroImage*, *54*(2), 1427–1431. https://doi.org/10.1016/j.neuroimage.2010.08.078

LIST OF FIGURES

Fig. 1 EEG recording setup 51

Fig. 2 OpenBCI Cyton Board (8-channels) and USB Dongle 52

Fig. 3 Detection of the individual's alpha range 53

Fig. 4 Schematic representation of the real-time neurofeedback 53

Fig. 5 Single-trial representation of the monetary-rewarded DMST 64

Fig. 6 Results of mean accuracy and reaction times in Experiment I 72

Fig. 7 Results of mean alpha power in Experiment I 73

Fig. 8 Representations of the power spectrum in Experiment I. 74

Fig. 9 Results of mean theta power in Experiment I 75

Fig. 10 Results of mean low-beta power in Experiment I 76

Fig. 11 Results of mean accuracy and reaction times in Experiment II 80

Fig. 12 Results of mean alpha power in Experiment II 81

Fig. 13 Results of mean theta power in Experiment II. 82

Fig. 14 Results of mean low-beta power in Experiment II. 83

Fig. 15 Representations of the power spectrum in Experiment II 84

Fig. 16 Representation of predicted accuracy values during the encoding period 88

Fig. 17 Representation of predicted accuracy values with interaction effects during encoding 91

Fig. 18 Representation of predicted RTs values during the encoding period. 94

Fig. 19 Representation of predicted RTs values during maintenance 95

Fig. 20 Representation of predicted RTs values with interaction effects during encoding. 98

Fig. 21 Representation of one single trial of the Neurofeedback task in the pAD NF-training protocol. 119

LIST OF TABLES

Table 1. Accuracy results from the linear mixed effect model during encoding 88

Table 2. Accuracy results from the linear mixed effect model during maintenance 89

Table 3. Accuracy results from the linear mixed effect model with interaction effects during encoding 91

Table 4. RTs result from the linear mixed effect model during encoding..... 95

Table 5. RTs result from the linear mixed effect model during maintenance 96

Table 6. RTs result from the linear mixed effect model with interaction effects during encoding..... 98

Table 7. RTs result from the linear mixed effect model with interaction effects during maintenance. ..... .99

Supplementary Table 1. Additional DMST results from the ANOVA in Experiment I. VI

Supplementary Table 2. Additional Alpha power results from the ANOVA in Experiment I. VI

Supplementary Table 3. Additional Theta power results from the ANOVA in Experiment I. VIII

Supplementary Table 4. Additional Low-Beta power results from the ANOVA in Experiment I. ...IX

Supplementary Table 5. Additional DMST results from the ANOVA in Experiment II. X

Supplementary Table 6. Additional Alpha power results from the ANOVA in Experiment II. XI

Supplementary Table 7. Additional Theta power results from the ANOVA in Experiment II. XII

Supplementary Table 8. Additional Low-Beta power results from the ANOVA in Experiment II. XIII

Appendix A. Questionnaire post-NF-training in German and English language presented in *Experiment I* and *Experiment II*. XV

Appendix B. Questionnaire post-NF-training in German and English language presented for the NF protocol proposal designed for pAD. XVI

LIST OF ABBREVIATIONS

A

Akaike Correction Criteria
AIC
alpha asymmetry
AA
Alzheimer's Association
AA
Alzheimer's disease
AD
amnestic MCI
aMCI
Analysis of Variance
ANOVA

B

Bluetooth Low Energy
BLE
Boston Naming Test
BNT,
brain-computer interfaces
BCI

C

Cambridge Cognitive Examination
CAMCOG
Cambridge Neuropsychological Test Automated Battery
CANTAB
Cambridge Neuropsychological Test Automated Battery Rapid Visual Information processing
CANTAB RVP
care as usual
CAU
Central Nervous System Vital Signs
CNSVS
Clinical Dementia Rating Scale-Global
CDR-SG
Clinical Dementia Rating Scale-Sum of Boxes
CDR-SB
Clinical Global Impression
CGI
clock-drawing test
CDT
Cognitive rehabilitation
CR
Cognitive stimulation
CS
cognitive training
CT
Confidence Intervals
CI
control group
CO

D

default mode network
DMN
delayed match-to-sample task
DMST
Diagnostic and Statistical Manual of Mental Disorders
DSM-5
difference memory
DM
digit span backward
DSB
digit span forward
DSF
dorsolateral prefrontal cortex
DLPFC

E

electroencephalographic
EEG
electroencephalography
EEG
event-related potentials
ERPs

F

False Alarm Rates
FARs
Fast Fourier Transform
FFT
finite impulse response
FIR
functional magnetic resonance imaging
fMRI

functional Near-Infrared Spectroscopy
fNIRS

G

Goldberg Anxiety Scale
GAS
Groninger Intelligentie Test
GIT

H

healthy old volunteers
HE
hemoencephalography
HEG
Hertz
Hz
Hit Rates
HR

I

individual alpha means peak frequency
IAF
inferior frontal gyrus
IFG
instrumental activities of daily living
IADL
intelligence quotient
IQ
intracranial electrodes
iEEG

L

Lab streaming layer
LSL
Linear Mixed-Effect Model
LMM
long-term memory
LTM
low-resolution electromagnetic tomography
LORETA

M

magnetoencephalography
MEG
maximum likelihood
ML
Mean
M
Mean Difference
MD
Median
Mdn
mental calculation
MC
mental imagery
MI
microVolts
µV
mild cognitive impairment
MCI
milliseconds
ms
Mini-mental State Examination
MMSE
minutes
min
Mnemonic Similarity Test
MST
Montreal Cognitive Assessment
MoCA
motor imagery-based BCI
MI-BCI
multidomain cognitive training
MCT

N

National Alzheimer's Coordinating Center
NACC
National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NINCDS-ADRDA
National Institute on Aging
NIA
neurocognitive disorders
MND
neurofeedback
NF
neurofeedback based on EEG
EEG-NF
neurofibrillary tangles
NFT

P

peak alpha frequency
PAF

phase-amplitude coupling
PAC
Positron Emission Tomography–Magnetic Resonance Imaging
PET/MRI
power spectral density
PSD
preclinical Alzheimer's Disease
pAD

Q

quantitative EEG
qEEG

R

randomized controlled trials
RCTs
reaction times
RTs
reliable change index
RCI
restricted maximum likelihood
REML

S

seconds
s
semantic fluency
SF
sensorimotor rhythm
SMR
slow cortical potential NF
SCP-NF
spatial span CANTAB
SSP CANTAB
spatial working memory
SWM
Standard Error of the Mean
SEM
subsequent memory
SM
success ratio
SR
superior temporal sulcus
STS

T

time-frequency representation
TFR
Trail Making Test
TMT
trail-making test A
TMT A
trail-making test B
TMT B
transcranial direct current stimulation
tDCS
transcranial magnetic stimulation
TMS

V

vascular dementia
VD
volts
V

W

Wechsler Adult Intelligence Scale-IV
WAIS-IV
Wechsler memory scale
WMS-R
working memory
WM
World Health Organisation
WHO

* The location of scalp electrodes is in reference to the 10-20 International System.

APPENDICES

The following tables were reported in the research work by Barbazzeni, Speck and Düzel (2023).

Supplementary Table 1. Additional DMST results from the ANOVA in Experiment I.

DMST - Accuracy					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
reward*group	Sphericity	.047	1	28	.830
day*reward	Sphericity	1.761	4	112	.142

DMST - RTs					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
gender	Sphericity	.368	1	27	.549
day*gender	Greenhouse-Geisser	1.224	2.800	75.601	.306
reward*gender	Sphericity	10.019	1	27	.004
reward*group	Sphericity	.047	1	27	.830
day*reward	Sphericity	.875	4	108	482
day*reward*gender	Sphericity	.736	4	108	.570

Supplementary Table 2. Additional Alpha power results from the ANOVA in Experiment I.

Alpha (7-13 Hz)					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
gender	Sphericity	2.779	1	27	.107

channel	Sphericity	.615	2	54	.545
day*gender	Greenhouse-Geisser	1.278	2.543	68.672	.288
day*group	Greenhouse-Geisser	.443	2.543	68.672	.691
reward*gender	Sphericity	.454	1	27	.506
reward*group	Sphericity	.900	1	27	.351
channel*gender	Sphericity	.895	2	54	.415
channel*group	Sphericity	.359	2	54	.700
day*reward	Greenhouse-Geisser	.936	2.617	70.668	.418
day*reward*gender	Greenhouse-Geisser	.530	2.617	70.668	.639
day*channel	Greenhouse-Geisser	1.148	4.628	124.950	.338
day*channel*gender	Greenhouse-Geisser	1.211	4.628	124.950	.309
day*channel*group	Greenhouse-Geisser	.978	4.628	124.950	.430
reward*channel	Sphericity	.470	2	54	.628
reward*channel*gender	Sphericity	.447	2	54	.642
reward*channel*group	Sphericity	2.001	2	54	.145
day*reward*channel	Greenhouse-Geisser	2.156	4.569	123.365	.069
day*reward*channel*gender	Greenhouse-Geisser	1.862	4.569	123.365	.112

day*reward*channel*group	Greenhouse-Geisser	.229	4.569	123.365	.939

Supplementary Table 3. Additional Theta power results from the ANOVA in Experiment I.

Theta (4-7 Hz)					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
gender	Sphericity	2.243	1	27	.146
channel	Sphericity	.783	2	54	.462
day*gender	Sphericity	2.196	4	108	.074
day*group	Sphericity	.369	4	108	.830
reward*gender	Sphericity	.241	1	27	.627
channel*gender	Sphericity	.656	2	54	.523
channel*group	Sphericity	2.465	2	54	.094
day*reward	Sphericity	.390	4	108	.816
day*reward*gender	Sphericity	.422	4	108	.793
day*reward*group	Sphericity	1.311	4	108	.271
day*channel	Greenhouse-Geisser	.730	4.535	122.446	.590
day*channel*gender	Greenhouse-Geisser	.769	4.535	122.446	.563
day*channel*group	Greenhouse-Geisser	.277	4.535	122.446	.911
reward*channel	Huynh-Feldt	2.551	1.866	50.391	.092

reward*channel*gender	Huynh-Feldt	1.495	1.866	50.391	.234
reward*channel*group	Huynh-Feldt	.227	1.866	50.391	.782
day*reward*channel	Greenhouse-Geisser	.445	4.614	124.573	.802
day*reward*channel*gender	Greenhouse-Geisser	.529	4.614	124.573	.740
day*reward*channel*group	Greenhouse-Geisser	.505	4.614	124.573	.758

Supplementary Table 4. Additional Low-Beta power results from the ANOVA in Experiment I.

Low-beta (13-20 Hz)					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
gender	Sphericity	2.606	1	27	.118
channel	Huynh-Feldt	.836	1.843	49.757	.431
day*gender	Greenhouse-Geisser	2.809	2.581	69.677	.054
day*group	Greenhouse-Geisser	.068	2.581	69.677	.965
reward*gender	Sphericity	.908	1	27	.349
reward*group	Sphericity	.524	1	27	.475
channel*gender	Huynh-Feldt	.712	1.843	49.757	.485
channel*group	Huynh-Feldt	2.544	1.843	49.757	.093
day*reward	Greenhouse-Geisser	1.405	3.259	87.997	.245
day*reward*gen	Greenhouse-	1.009	3.259	87.997	.397

der	Geisser				
day*channel	Greenhouse-Geisser	.344	5.303	143.169	.894
day*channel*gender	Greenhouse-Geisser	.484	1.316	35.545	.798
day*channel*group	Greenhouse-Geisser	1.662	1.316	35.545	.143
reward*channel	Greenhouse-Geisser	.021	1.316	35.545	.934
reward*channel*gender	Greenhouse-Geisser	.073	1.316	35.545	.854
reward*channel*group	Greenhouse-Geisser	.392	1.316	35.545	.592
day*reward*channel	Greenhouse-Geisser	1.056	4.386	118.417	.384
day*reward*channel*gender	Greenhouse-Geisser	.947	4.386	118.417	.445
day*reward*channel*group	Greenhouse-Geisser	.927	4.386	118.417	.457

Supplementary Table 5. Additional DMST results from the ANOVA in Experiment II.

DMST - Accuracy					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
reward*group	Sphericity	1.150	1	28	.293
day*reward	Sphericity	.499	4	112	.736

DMST - RTs					
Effect	**Correction**	**F**	**df1**	**df2**	***p***

gender	Sphericity	.193	1	27	.664
day*gender	Greenhouse-Geisser	.485	2.009	54.241	.619
reward*gender	Sphericity	1.394	1	27	.248
reward*group	Sphericity	2.359	1	27	.136
day*reward	Greenhouse-Geisser	.715	2.831	76.445	.539
day*reward*gender	Greenhouse-Geisser	.432	2.831	76.445	.720

Supplementary Table 6. Additional Alpha power results from the ANOVA in Experiment II.

Alpha (7-13 Hz)					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
gender	Sphericity	.018	1	26	.896
channel	Sphericity	.561	2	52	.574
day*gender	Greenhouse-Geisser	1.592	2.908	75.602	.200
day*group	Greenhouse-Geisser	1.839	2.908	75.602	.149
reward*gender	Sphericity	.680	1	26	.417
reward*group	Sphericity	1.552	1	26	.224
channel*gender	Sphericity	.862	2	52	.428
channel*group	Sphericity	.118	2	52	.889
day*reward	Greenhouse-Geisser	.958	3.148	81.860	.420

day*reward*gender	Greenhouse-Geisser	1.205	3.148	81.860	.314
day*channel	Greenhouse-Geisser	.610	2.804	72.902	.600
day*channel*gender	Greenhouse-Geisser	.552	2.804	72.902	.637
day*channel*group	Greenhouse-Geisser	1.276	2.804	72.902	.289
reward*channel	Huynh-Feldt	.271	1.769	45.984	.737
reward*channel*gender	Huynh-Feldt	.181	1.769	45.984	.809
reward*channel*group	Huynh-Feldt	3.078	1.769	45.984	.062
day*reward*channel	Greenhouse-Geisser	1.695	3.123	81.188	.173
day*reward*channel*gender	Greenhouse-Geisser	1.347	3.123	81.188	.264
day*reward*channel*group	Greenhouse-Geisser	.659	3.123	81.188	.585

Supplementary Table 7. Additional Theta power results from the ANOVA in Experiment II.

Theta (4-7 Hz)					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
gender	Sphericity	1.849	1	26	.186
channel	Greenhouse-Geisser	.224	1.174	30.533	.679
day*gender	Sphericity	.494	4	104	.740
day*group	Sphericity	2.055	4	104	.092

reward*gender	Sphericity	.091	1	26	.766
reward*group	Sphericity	.513	1	26	.480
channel*gender	Greenhouse-Geisser	.316	1.174	30.533	.614
channel*group	Greenhouse-Geisser	.674	1.174	30.533	.441
day*reward	Sphericity	1.284	4	104	.281
day*reward*gender	Sphericity	1.070	4	104	.375
day*channel	Greenhouse-Geisser	1.341	1.317	34.235	.265
day*channel*gender	Greenhouse-Geisser	.748	1.317	34.235	.428
day*channel*group	Greenhouse-Geisser	1.930	1.317	34.235	.171
reward*channel	Greenhouse-Geisser	.921	1.192	30.990	.362
reward*channel*gender	Greenhouse-Geisser	.658	1.192	30.990	.449
reward*channel*group	Greenhouse-Geisser	1.682	1.192	30.990	.206
day*reward*channel	Greenhouse-Geisser	1.777	1.378	35.841	.191
day*reward*channel*gender	Greenhouse-Geisser	1.051	1.378	35.841	.336
day*reward*channel*group	Greenhouse-Geisser	1.219	1.378	35.841	.293

Supplementary Table 8. Additional Low-Beta power results from the ANOVA in Experiment II.

Low-Beta (13-20 Hz)					
Effect	**Correction**	**F**	**df1**	**df2**	***p***
gender	Sphericity	.301	1	26	.588
channel	Sphericity	.041	2	52	.960
day*gender	Greenhouse-Geisser	.528	2.903	75.481	.658
day*group	Greenhouse-Geisser	1.904	2.903	75.481	.138
reward*gender	Sphericity	3.990	1	26	.056
reward*group	Sphericity	.014	1	26	.905
channel*gender	Sphericity	.245	2	52	.784
channel*group	Sphericity	.544	2	52	.583
day*reward	Greenhouse-Geisser	.498	2.720	70.731	.667
day*reward*gender	Greenhouse-Geisser	.447	2.720	70.731	.701
day*channel	Greenhouse-Geisser	.936	3.378	87.839	.435
day*channel*gender	Greenhouse-Geisser	.764	3.378	87.839	.532
day*channel*group	Greenhouse-Geisser	.748	3.378	87.839	.541
reward*channel	Sphericity	.143	2	52	.867
reward*channel*gender	Sphericity	.731	2	52	.486
reward*channel*group	Sphericity	1.309	2	52	.279

day*reward*channel	Greenhouse-Geisser	.868	3.565	92.684	.476
day*reward*channel*gender	Greenhouse-Geisser	.537	3.565	92.684	.689
day*reward*channel*group	Greenhouse-Geisser	.717	3.565	92.684	.567

Appendix A. Questionnaire post-NF-training in German and English language presented in *Experiment I* and *Experiment II* (Barbazzeni, Speck & Düzel, 2023).

German Language	English Language
Wie gut fühlen Sie sich heute allgemein?	How do you feel today?
Wie anstrengend fanden Sie das Experiment?	How difficult was the experiment?
Wie fanden Sie Ihr Gedächtnis an Tag 1?	How do you estimate your memory on day 1?
Wie fanden Sie Ihr Gedächtnis an Tag 5?	How do you estimate your memory on day 5?
Fanden Sie es schwierig, die Aufgabenstellungen zu verstehen (z.B. das Neurofeedback zu kontrollieren oder sich an die Bilder zu erinnern)?	Did you find it difficult to understand the experimental instructions (e.g., to control the neurofeedback or to remember the images)?
Wie wichtig war es Ihnen, eine gute Leistung bei den Aufgaben zu zeigen?	How important was it for you, to show and to reach a good performance?

Fanden Sie es schwierig, sich an die Bilder zu erinnern?	Did you find it difficult to remember the images?
Haben Sie eine bestimmte Strategie für das Neurofeedback verwendet?	Did you use a specific strategy to perform the neurofeedback?
Wenn ja, welche?	If yes, which one?
Sind Ihnen Unterschiede von Tag 1 bis Tag 5 aufgefallen (z.B. Stimmung, Gedächtnis, Konzentration…)?	Did you find differences between day 1 and day 5 (e.g., concentration, memory, mood…)?
Haben Sie Verbesserungsvorschläge für dieses Experiment?	Do you have some suggestions to improve this experiment?

Appendix B. Questionnaire post-NF-training in German and English language presented for the NF protocol proposal designed for pAD.

German Language	English Language
Wie gut fühlen Sie sich heute allgemein?	How do you feel today?
Wie anstrengend fanden Sie das Experiment?	How difficult was the Experiment?
Wie schätzen Sie Ihre Fähigkeit ein, die Ballbewegung in den ersten Blöcken zu modulieren?	How difficult was it to control the movement of the ball in the first block?
	How difficult was it to control the movement of the ball in the last block?

Wie schätzen Sie Ihre Fähigkeit ein, die Ballbewegung in den letzten Blöcken zu modulieren?	
Fanden Sie es schwierig, die Aufgabenstellungen zu verstehen (z.B. das Neurofeedback zu kontrollieren)?	Did you find difficult to understand the experimental instructions (i.e., to control NF)
Wie wichtig war es Ihnen, eine gute Leistung bei den Aufgaben zu zeigen?	How important was it for you, to show and to reach a good performance?
Fanden Sie es schwierig, die Ballbewegung zu kontrollieren?	Did you find it difficult to control the movement of the ball?
Woran dachten Sie, bei der Durchführung des Neurofeedbacks? Erzählen Sie uns gern mehr, falls Ihnen dazu noch etwas einfällt.	Did you use a specific strategy to perform the Neurofeedback? If yes, which one?
Haben Sie Unterschiede zwischen den ersten und den letzten Blöcken bemerkt (z.B. Stimmung, Gedächtnis, Konzentration…)? Wenn ja, welche?	Did you find any difference between the first and the last block? (e.g., mood, concentration, memory…)?
Haben Sie Verbesserungsvorschläge für dieses Experiment?	Do you have any suggestions to improve the experiment?
Wenn ja, welche?	If yes, which one?

Ehrenerklärung

Ich versichere hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; verwendete fremde und eigene Quellen sind als solche kenntlich gemacht.

Ich habe insbesondere nicht wissentlich:

• Ergebnisse erfunden oder widersprüchlich Ergebnisse verschwiegen,

• statistische Verfahren absichtlich missbraucht, um Daten in ungerechtfertigter Weise zu interpretieren,

• fremde Ergebnisse oder Veröffentlichungen plagiiert,

• fremde Forschungsergebnisse verzerrt wiedergegeben.

Mir ist bekannt, dass Verstöße gegen das Urheberrecht Unterlassungs- und Schadensersatz-ansprüche des Urhebers sowie eine strafrechtliche Ahndung durch die Strafverfolgungsbe- hörden begründen kann.

Ich erkläre mich damit einverstanden, dass die Arbeit ggf. mit Mitteln der elektronischen Datenverarbeitung auf Plagiate überprüft werden kann.

Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form als Dissertation eingereicht und ist als Ganzes auch noch nicht veröffentlicht.

(O r t, D a t u m) (Unterschrift)