Cyprus University of Technology

Faculty of Health Sciences

Doctoral Dissertation

Gamma-Band Transcranial Magnetic Stimulation in Rehabilitation of Amnestic Mild Cognitive Impairment and Alzheimer's Disease

Artemis G. Traikapi

Limassol, May 2023

CYPRUS UNIVERSITY OF TECHNOLOGY

FACULTY OF HEALTH SCIENCES

DEPARTMENT OF REHABILITATION SCIENCES

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Approval Form

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Limassol, May 2023

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The approval of the dissertation by the Department of Rehabilitation Sciences does not imply necessarily the approval by the Department of the views of the writer.

Acknowledgements

The four years of my PhD have been extraordinary. The number of skills and the knowledge I have gained have helped me to flourish as a person and especially as a neuropsychologist and a scientist. This life-changing experience would not have been possible without the constant support and help I received from many people.

First, I would like to express my deepest appreciation to my supervisor Dr Nikos Konstantinou for providing me the honorable opportunity to work throughout my thesis at the Brain and Science Laboratory at the rehabilitation clinic of Cyprus University of Technology. I am deeply grateful for his consistent guidance but also for creating such an encouraging and supporting working environment which made this journey an absolute pleasure.

I would like to thank all the participants who took part in the several studies of this thesis, particularly the families and patients who participated in the last part of my thesis. Thank you all individually for the time you spent in my research and for the trust you placed in me. You are the core of this work, and I am deeply and honestly grateful.

Many thanks go to my friends and co-PhD travelers at the rehabilitation clinic. It was a pleasure working in such an environment where support, motivation, friendship, and guidance was the foundation.

Finally, my greatest appreciation belongs to my life partner. He has given me strength and encouragement throughout all the challenging moments of completing this thesis. I am truly grateful for his unconditional and endless love, his constant support, motivation and mostly his patience and understanding. Without you this PhD would not have been possible. This thesis is devoted to you!

Abstract

Alzheimer's disease (AD) is a slowly progressive neurodegenerative disorder and the most common cause of dementia worldwide. Many pathogenic mechanisms and hypotheses have been proposed to explain AD pathology, and scientific knowledge has increased enormously over the last decades. However, to date, clinical trials targeting these mechanisms have not succeeded in identifying effective methods to treat or reverse the disease. AD pathogenesis has recently been explored from different perspectives, offering new insights into the potential treatments of AD. Among these, the investigation of gamma oscillations and their potential therapeutic role has signified a new and promising era in AD research.

The aim of this thesis was to combine the most recent scientific findings to develop a novel, gamma-band transcranial magnetic stimulation (TMS) protocol and investigate its efficacy in mitigating cognitive dysfunction in patients with amnestic mild cognitive impairment (MCI) and mild-to-moderate AD. On that basis the thesis is comprised by three main study pillars, being the neurophysiological, normative, and experimental.

Initially, a novel 40 Hz TMS protocol was developed and applied over the motor cortex of healthy participants. Its safety and aftereffects on cortical excitability were evaluated. The results indicated that stimulation was safe, tolerable, and generated a suppressive effect that outlasted the stimulation period. Then, the first standardized Cypriot word pool, a list of 2,850 words, was created and used for the development of alternative and equally difficult neuropsychological tools. Finally, a single-case, randomized, concurrent multiple baseline design across eight cases was employed. Patients received daily 40 Hz TMS treatment sessions for 2 weeks bilaterally to the precuneus. The analyses indicated a significant improvement in all patients' global cognition, while an identical profile of significant improvement was evident in patients' neuropsychiatric symptoms. In general, a wide effect on patients' cognitive function was observed accompanied by a significant improvement in their quality of life. This study offers preliminary evidence regarding the efficacy of gamma-band TMS as an effective and safe non-invasive technique in MCI and AD neurorehabilitation.

Keywords: Alzheimer's Disease, default mode network, episodic memory, transcranial magnetic stimulation, precuneus, 40 Hz gamma brain stimulation

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List of Abbreviations

A+V	Audiovisual
ACE-R	Addenbrooke's cognitive examination-revised
AD	Alzheimer's disease
ADAS-cog	Alzheimer's disease assessment scale-cognitive subscale
AG	Angular gyrus
aMCI	Amnestic mild cognitive impairment
APOE	Apolipoprotein E
B&NPS	Behavioral and neuropsychiatric symptoms
BaCS	Brain and cognitive science laboratory
BADL	Basic activities of daily living
BAI	Beck anxiety inventory
BF	Bayes factor
CBT	Corsi block task
CrQ	Cognitive reserve questionnaire
CSF	Cerebrospinal fluid
CUT	Cyprus university of technology
CWP	Cyprus word pool
Depr	Depression
DLB	Dementia with Lewy bodies
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
EEG	Electroencephalogram
EMG	Electromyography
FDI	First dorsal interosseous muscle
FTD	Frontotemporal dementia
GDS	Global deterioration scale
GDS-30	Geriatric depression scale-30
IADL	Instrumental activities of daily living
LTD	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
MCI	Mild cognitive impairment
MEPs	Motor evoked potentials
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging

MTL	Medial temporal lobe
naMCI	Non-amnestic mild cognitive impairment
NAP	Non-overlap of all pairs
NIA-AA	National institute on aging and Alzheimer's association
NIBS	Non-invasive brain stimulation
NPI	Neuropsychiatric inventory
PC	Precuneus
PCA	Posterior cortical atrophy
PCC	Posterior cingulate gyrus
PCI	Percentage of change index
PEM	percentage of data exceeding the median
PHIP	Parahippocampal gyrus
PND	Percentage of nonoverlapping data
PTI	Post study interview
QoL-AD	Quality of life in Alzheimer's disease
RCT	Randomized control trial
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SAT	Semantic association task
SCM	Single case methodology
SD	Standard deviation
tACS	Transcranial alternating current stimulation
TMS	Transcranial magnetic stimulation
TMT A´	Trail making test A´
TMT B´	Trail making test B´
VaD	Vascular dementia
VC	Visual cortex
W1	Week one
W2	Week two
W3	Week three
W4	Week four
W5	Week five
αβ	Amyloid beta

Chapter 1 Introduction

The concept of dementia has existed for centuries (Pearce, 1985). Dementia is an umbrella term for a collection of symptoms caused by a number of diseases which ultimately affect one's ability to function in everyday life. Several different types of dementia have been identified, some of which are reversible (e.g., dementia due to normal pressure hydrocephalus or vitamin B12 deficiency) and even preventable (e.g., vascular dementia) (Alzheimer's Association, 2020). It was only at the beginning of the 20th century that the clinical syndrome of Alzheimer's disease (AD), a specific type of dementia, and the associative neurophysiological and neuropsychological changes were discovered. In 1907, Alois Alzheimer described the emblematic case of Augusta Deter, a 51-year-old woman who demonstrated severe cognitive and behavioral deficits and died owing to histological changes that were to become the hallmarks of the disease which is named after Alois Alzheimer (Maurer et al., 1997).

The understanding of dementia's cognitive and behavioral manifestation and their relationship to brain pathology has increased substantially over the last 50 years. This is mostly because mortality rates have fallen and life expectancy has increased significantly (Bondi et al., 2017). Longevity makes age-related diseases more prevalent, a trend which is aggravated by lifestyle and behavioral changes that predispose towards them (Martin Prince et al., 2015).

Dementia due to AD is a devastating disorder associated with dramatic cognitive, emotional, and social consequences for the patients. It can also be overwhelming for carers and families. The impact on the families and carers can be emotional, physical, and financial which, all together cause excessive distress and, in many cases, psychological disorders, such as depression (Borsje et al., 2016; Cheng et al., 2019; Givens et al., 2014). Furthermore, AD has a remarkable impact on the global economy in terms of medical and social care (World Health Organization, 2020). The field of AD research has made great steps in understanding the underlying pathology and finding possible therapies. However, there are currently no effective treatments available.

1.1 Alzheimer's Disease: Epidemiology and Etiology

AD is a slowly progressive neurodegenerative disorder and the most common cause of dementia, counting for 60-80% of the total dementia cases worldwide (Alzheimer's Association, 2020). Every three seconds someone in the world is diagnosed with dementia, which translates to more than 10 million new cases every year. At the same time, it is estimated that these numbers will have tripled by 2050 when 152 million people will be living with dementia (World Health Organization, 2018). The alarming rise of AD imposes a mounting social and financial burden all over the world making the need for development of effective intervention strategies for preventing, delaying, or improving the symptoms paramount (Cummings et al., 2014).

The clinical representation of AD has an insidious onset, including memory loss followed by cognitive decline, beyond what is considered a consequence of normal ageing, as well as behavioral malfunctions which together lead to failure to sustain independence in everyday function (Scheltens et al., 2016). Individuals that develop AD, progress from normal cognition to a transitional phase called Mild Cognitive Impairment (MCI), followed by mild to severe sporadic dementia. The average survival time is approximately eight years for those diagnosed at the age of 65. AD can be sporadic with late onset or familial with early onset. Age is the most important risk factor in sporadic AD, which principally is considered a disorder of the elderly, with most cases appearing after the age of 65 and representing the late-life onset of the disease. Cases that occur earlier in life (< 65 years) are classified as early onset AD or familial AD (Chen & Mobley, 2019). In most of these early onset cases, but not all, there is a family history of dementia which is considered substantially or even entirely genetically determined, associated with mutations in three genes: amyloid precursor protein (APP), prosenilin 1 (PS1) and prosenilin 2 (PS2; for a review see Dai et al., 2018). Sporadic AD has no known cause and presents no obvious inheritance pattern. However, even though a specific gene has not been identified as a cause, the Apolipoprotein E (APOE) gene appears to be a strong risk factor leading to the development of AD later in life (Roses, 1996; Tsai et al., 1994).

Even though the pathological changes observed in AD brains are well known (Braak & Braak, 1991; Förstl et al., 1996; Terry et al., 1991) the exact etiology remain unclear.

AD is thought of as a complex disease resulting from the complicated interactions among various factors, such as environment, education, age, and genetics. The early onset of the disease indicates that genetic factors may play an essential role in the development of the disease (Dai et al., 2018). However, over 50% of these cases and most of the sporadic cases cannot be explained by genetics (Janssen et al., 2003; Wingo et al., 2012). The pathological hallmarks are remarkably similar in both sporadic and familial AD, with the difference being that individuals with the gene mutations (i.e., APP, PS1 & PS2) will develop clinical symptoms earlier in life (Kim et al., 2018).

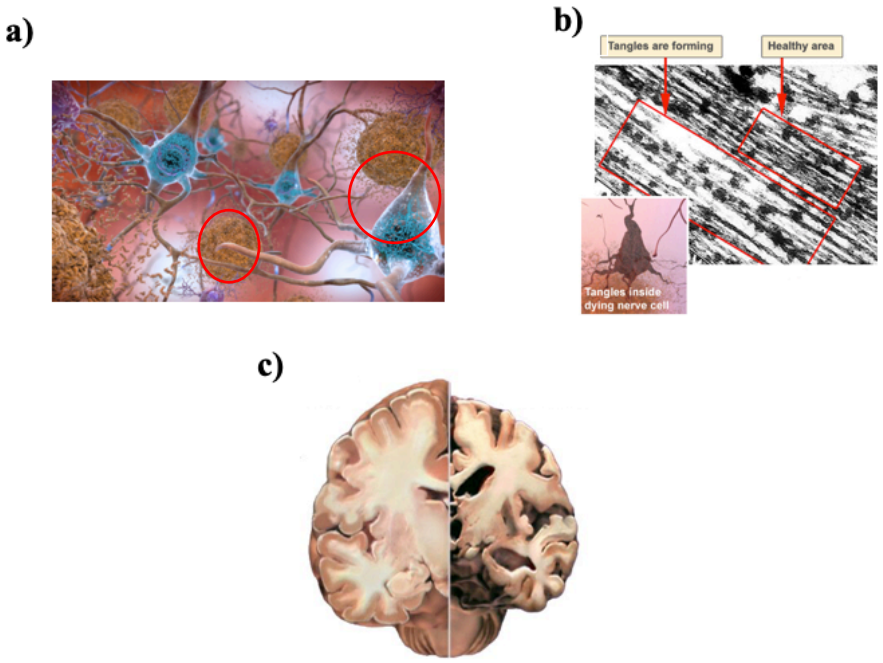
1.2 The Histological Hallmarks of Alzheimer's Disease

The neuropathology of AD includes a broad variety of neurotoxic cascades, including mitochondria dysfunction, inflammation, oxidative stress in the brain, reduced synthesis of neurotransmitters and an abnormal protein aggregation (Kim et al., 2018). Among them, the major hallmark and the most dominant paradigm of AD is the proteinaceous aggregation of amyloid plaques and neurofibrillary tangles (Bloom, 2014). Amyloid plaques are extracellular deposits consisting of amyloid beta peptide (Aβ) originated through abnormal proteolysis from the APP (Figure 1.1). APP is a protein found in cell membranes that normally plays an important role in neuronal growth and repair. An abnormally increased production of Aβ leads to the accumulation of amyloid plaques. Specifically, when the Aβ is secreted in the extracellular space, it spontaneously transforms into neurotoxic fibrils (amyloid plaques), which in turn damage neuronal cells and synapses (Hardy & Higgins, 1992). In turn, the accumulation of Aβ stimulates microglia cells—responsible for destroying waste and toxins in the brain—causing them to become overactive, producing large amounts of cytokines. However, instead of fighting the pathogens, cytokines damage healthy neurons which in turn further activate microglia cells, thus increasing further the inflammatory mediators' production. These observed sustained inflammatory responses in AD patients are considered to play a fundamental role in the progression of the pathological changes observed in AD (Kinney et al., 2018; Newcombe et al., 2018).

The second histopathological hallmark of AD is the intracellular aggregation of tau protein. Tau proteins are predominantly found in brain cells and hold multiple roles

necessary for proper cell function. In healthy neurons, tau binds to and stabilizes microtubules, structures that help guide nutrients and molecules from the cell body to the axon and dendrites (Barbier et al., 2019; Weingarten et al., 1975). In AD, abnormal chemical changes trigger tau to detach from microtubules and bond to other tau molecules, forming neurofibrillary tangles. These tangles eventually lead to microtubule breakdown, disrupting the nerve cell's transportation mechanism and causing degeneration and cell death. The abnormal accumulation of Aβ plaques and neurofibrillary tangles causes cell degeneration and death leading to dramatic brain shrinkage and cell loss (Goedert, 1993).

Figure 1.1 Neuropathological hallmarks of Alzheimer's disease



Note: a) Extracellular accumulation of amyloid plaques, consisting of Aβ protein, originated through abnormal proteolysis from the amyloid precursor protein (APP). The Aβ protein, which is the breakdown of APP, instead of being cleaned, as happens in healthy brains by the microglia neurons, bind together, forming the amyloid plaques. Consequently, the neuronal communication is interrupted leading to cell death. Picture retrieved from: Georgia Institute of Technology; b) Intracellular aggregation of neurofibrillary tangles formed by hyperphosphorylation of microtubule associated tau protein, leading to cell degeneration and death. As more tangles are formed more neurons are lost. Picture retrieved from: neurofibrillary tangles; c) A healthy brain is depicted on the left, whereas on the right is a brain with severe AD. The AD brain has suffered a dramatic shrinkage due to the disease's pathology.

The neuroanatomical location of amyloid plaques and neurofibrillary tangles has been well investigated. Therefore, it is known that they tend to be formed in stereotypic and rather a predictable pattern (Braak & Braak, 1997; Thal et al., 2002). Amyloid plaques are observed in the neocortex early in the disease, expanding to the allocortex and subcortical nuclei (e.g., striatum) as the disease progresses. At the final stages, amyloid plaques are being widely expanded in the brain, including the brainstem and the cerebellum (Thal et al., 2002). The formation of neurofibrillary tangles is observed in the neurons of the medial temporal structures, such as the entorhinal cortex, the CAI and subicular regions of the hippocampus formation and the parahippocampal gyrus, early in the course of the disease (Deture & Dickson, 2019; Perl, 2010). In addition, the episodic memory deficits observed early in AD are well correlated with the distribution of the neurofibrillary tangles within the medial temporal structures and MRI volumetric loss of the hippocampus, suggesting that the tangles may substrate for memory loss in AD (Deweer et al., 1995; Guillozet et al., 2003). As the disease progresses, tangles are widely distributed within the brain, including several limbic system regions (e.g., thalamus, striatum, amygdala). At the final stage of the disease the neocortex is devastatingly affected (Braak & Braak, 1991).

All in all, the major hallmarks of AD include the abnormal accumulation of amyloid plaques and neurofibrillary tangles which cause a loss of cortical neurons and synapses, together with the presence of chronic inflammation which further elicit brain neurodegeneration. The neurodegeneration is progressive, hence, the clinical representation follows well defined stages according to the aggregate of histopathological changes (Braak & Braak, 1991).

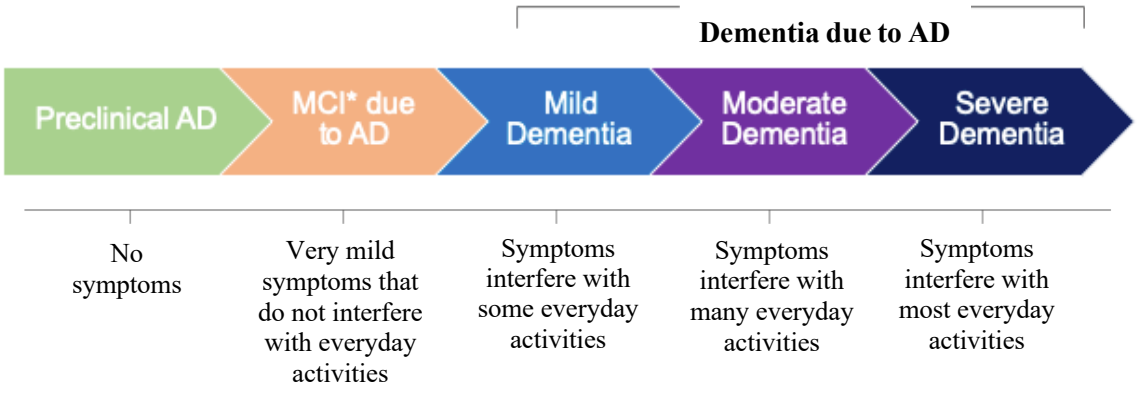
1.3 Stages of Alzheimer's Disease

The progress of AD from unnoticeable brain and behavioral changes to severe brain deterioration and cognitive and emotional deficits that eventually lead to physical disability is called the AD continuum (Figure 1.2). The continuum of AD includes several preclinical and clinical stages which differentiate the severity of AD according to the extent of AD pathology's accumulation.

1.3.1 Preclinical Stage of AD

The preclinical stage of AD is considered the earliest stage in the AD continuum. Extensive research from both genetically at-risk cohorts and clinically normal older individuals indicates that the pathological cascade of AD begins several years or even decades before the onset of clinically evident deficits (Dubois et al., 2016). It is well accepted therefore, that AD starts with a long asymptomatic period during which the pathology is being developed, and that individuals with evident AD pathophysiology are at increased risk of progressing to dementia due to AD (Caselli & Reiman, 2013; Dubois et al., 2016; Morris, 2005). In recent years, using neuroimaging techniques, cerebrospinal fluid (CSF) assays and other biomarkers, scientists have developed the ability to detect the AD-related pathophysiology in vivo, including the presence of amyloid plaques and neurofibrillary tangles (Khoury & Ghossoub, 2019; Leuzy et al., 2018). In addition, studies suggest that very subtle cognitive changes can be detectable years before someone meets the MCI criteria. Therefore, these changes can predict the progression to AD. The pitfall, however, stands in that not all the older adults who have the pathophysiological processes of AD will manifest symptoms in their lifetime given that it is recognized that the presence of amyloid plaques can also be evident in normal ageing (Dayan, 1970; Price & Morris, 1999; Sperling et al., 2011).

Figure 1.2 Alzheimer's disease continuum



Note: This figure is retrieved from Alzheimer's Association (2020). *Mild Cognitive Impairment.

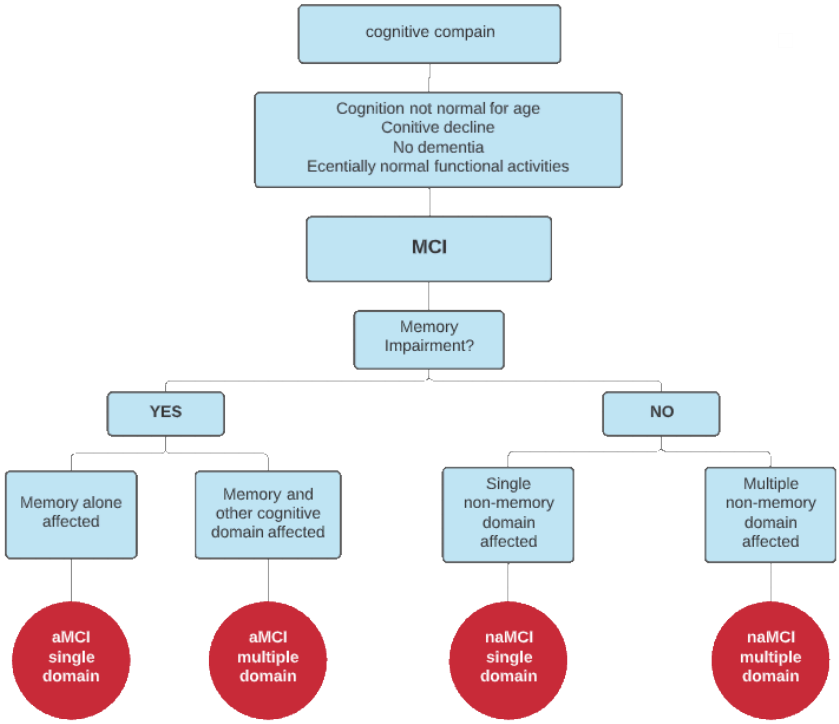
All in all, there are several biomarkers associated with the risk of developing AD later in life (Caselli & Reiman, 2013). The extent to which these biomarkers predict the subsequent clinical course of cognitively normal individuals is yet to be identified. Hence, it remains critical to better define the preclinical stage of AD and to uncover the exact biomarker profile that best predicts the individuals most likely to benefit from very early interventions (Sperling et al., 2011). It is widely acknowledged that symptoms do not need to be observed for a disease to be diagnosed (e.g., type II diabetes, renal insufficiency, hypertension). Therefore, it is likely that in the future people will be diagnosed with AD preclinically based on the presence of specific evidence of pathological processes and be treated before the onset of the symptoms (Sperling et al., 2011).

1.3.2 Mild Cognitive Impairment due to Alzheimer's Disease

The neurodegenerative changes in the brain owing to AD are accumulated during the preclinical phase. When a threshold is crossed, the clinical deficits start to become apparent. The patient then enters the MCI stage, which is considered a transition between normal ageing and dementia. Over the last 20 years there has been a substantial increase in the literature concerning the construct of MCI (Gauthier et al., 2006; Petersen et al., 2001). Its main purpose as a diagnostic entity is to identify the earliest futures of different types of dementia, such as AD, and hence, to provide clinicians with the opportunity to intervene in the prodromal stages. However, even though, conceptually, its entity is reasonable, the diagnosis often poses difficulties in clinical practice (Petersen, 2004). On this ground, diagnostic criteria have been developed and are being revised to account for recent scientific acknowledgements. The most recently revised diagnostic criteria (Petersen et al., 2009; Petersen, 2016) describe two MCI phenotypes: (1) the amnestic MCI (aMCI) and (2) the non-amnestic MCI (naMCI) both of which are further divided to single or multiple domain subtypes (Figure 1.3).

According to these criteria, MCI diagnosis requires: (1) complaints of changes in cognition in relation to previous level of performance, preferably collaborated by an informant; (2) objective cognitive decline, documented by standardized neuropsychological measures, to one or more domains; (3) fairly reserved cognitive abilities for age; (4) absence of dementia, and (5) relatively maintained dependency in everyday activities (Petersen, 2004).

Figure 1.3 Flow chart of decision process for diagnosis of MCI and its subtypes



Note: From "Mild Cognitive Impairment: Ten Years Later", by R. C. Petersen et al., 2009, *Archives of Neurology, 66*(12), Criteria section, Figure 2 (https://doi.org/10.1001).

After the identification of the MCI phenotype, the diagnostic process follows the combination of the specific phenotype with the assumed causes (Figure 1.4). This step allows for the recognition that AD is not the only etiology of MCI, which can result from a variety of diseases (Petersen, 2004). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013) includes MCI as a diagnostic entity under the of name of Mild Neurocognitive Disorder, requiring however, the clinician to specify the underlying cause (e.g., due to AD, Lewy body disease, vascular disease).

Figure 1.4 Presumed outcome of subtypes of MCI when combined with presumed pathogenesis

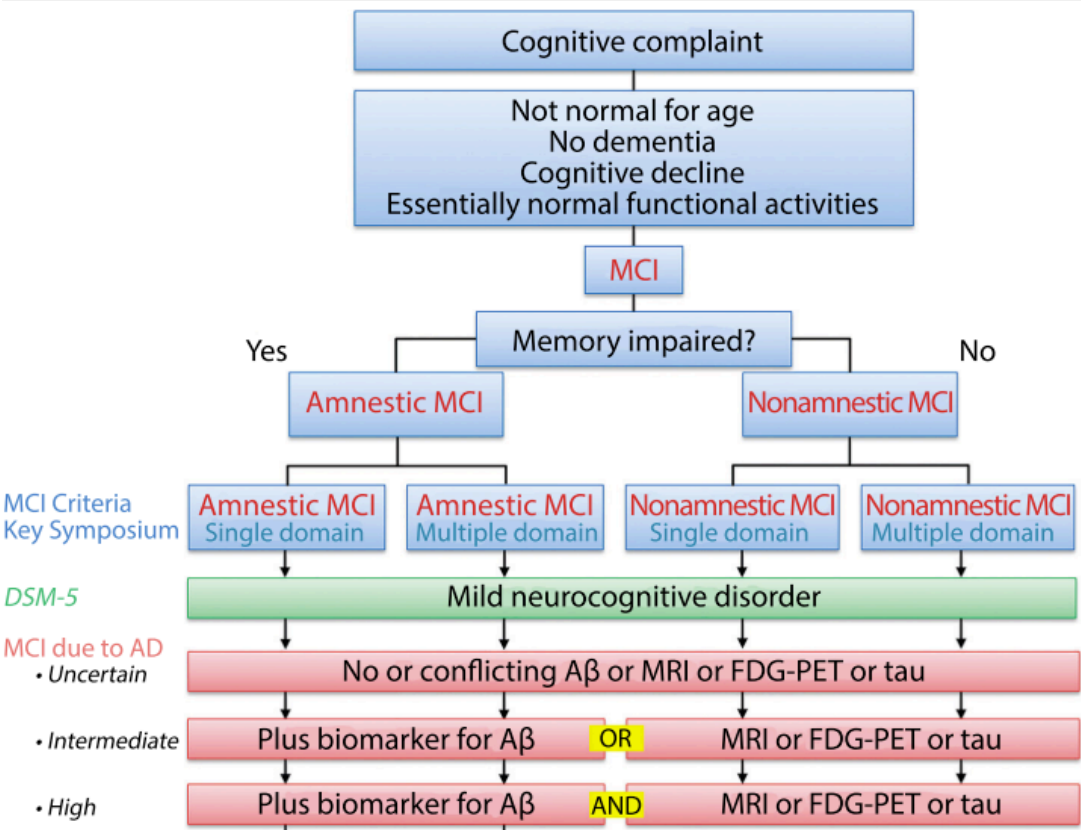
		Pathogenesis			
		Degenerative	Vascular	Psychiatric	Medical Conditions
Amnestic MCI	Single domain	AD		Depr	
	Multiple domain	AD	VaD	Depr	
Non-amnestic MCI	Single domain	FTD			
	Multiple domain	DLB	VaD		

Note: It is evident for example, that a multiple domain amnestic MCI can be a result of Alzheimer's Disease but can also be caused by vascular dementia or depression. Depr: Depression; VaD: vascular dementia; FTD: frontotemporal dementia; DLB: dementia with Lewy bodies. Figure adopted from "Mild Cognitive Impairment as a Diagnostic Entity", by R. C. Petersen, 2004, *Journal of International Medicine, 256*(3), Diagnosis of dementia and Alzheimer's Disease section, Figure 4 (https://doi.org/10.1111/j.1365-2796.2004.01388.x).

Traditionally, the aMCI is considered to be the prodromal stage of AD, as memory deficits are the hallmark of AD. However, over the course of the years it became evident that other phenotypes (i.e., logopenic aphasia, posterior cortical atrophy) can also lead to this type of dementia (Petersen, 2016) or that some individuals with MCI revert to normal cognition or remain stable (Koepsell & Monsell, 2012; Shimada et al., 2019). For this reason, the National Institute on Aging and the Alzheimer's Association developed the criteria for MCI caused by AD, known as the NIA-AA criteria (Albert et al., 2011; Dubois et al., 2014, 2016). These criteria have been enriched with biomarkers for underlying AD pathophysiology. The NIA-AA criteria support the diagnosis of prodromal AD in asymptomatic individuals based on the presence of related biomarkers (Figure 1.5). The diagnostic framework provides three levels of likelihood that the MCI

is due to AD (unlikely, intermediate, and high). The advantage is that the framework is applicable when there are no supportive biomarkers, minimizing however, the diagnostic specificity (Dubois et al., 2016).

Figure 1.5 Flow chart of diagnosis of MCI due to Alzheimer's Disease



Note: With conflicting or no biomarker measures it is uncertain whether the MCI is caused by the AD. If one biomarker is evident (Aβ, tau or metabolic abnormalities through neuroimaging methods) there is an intermediate likelihood of MCI due to AD. There is a high likelihood of MCI due to AD if two biomarkers are evident. The biomarkers of Aβ and tau protein can be obtained from CSF or from positron emission tomography to accompany the MCI clinical syndromes. FDG-PET: fluorodeoxyglucose positron emission tomography; MRI: magnetic resonance imaging; tau: microtubule associated protein. From "Mild Cognitive Impairment", by R. C. Petersen, 2016, *Continuum (Minneap Minn) (22)*2, Multiple Terminologies section, Figure 2-1 (https://doi.org/10.1212%2).

The core diagnostic criterion for aMCI due to AD is early, subjective, and objective episodic memory impairment. It is well known that 86-94% of AD patients present with an amnestic profile that appears as an episodic memory deficit (Galton et al., 2000;

Lopez et al., 2000; Morris, 2006), and therefore, individuals' performance in episodic memory tasks can be the strongest predictor for progressing to AD (Tierney et al., 1996), consistent with the underlying brain pathology (Guillozet et al., 2003). The neuropsychological evaluation of episodic memory by a word learning list provides sensitivity and specificity estimates of 93% and 99%, respectively, for the differentiation of healthy adults from early AD patients (Buschke et al., 1997). It is important to state that in most cases, the MCI stage is characterized by cognitive impairment further to episodic memory decline (Economou et al., 2007). Finally, the presence of several biomarkers such as: atrophy of medial temporal structures on magnetic resonance imaging (MRI), the abnormal cerebrospinal fluid markers and specific metabolic patterns evident with molecular neuroimaging methods, will indicate the likelihood that the MCI is due to AD (Dubois et al., 2016). Finally, it is important to state that there are several atypical presentations of AD (approximately 11% of cases) which vary from the typical amnestic type (e.g., a posterior variant of AD, a logopenic variant of AD and a frontal variant of AD). The criteria have also been revised for atypical cases (Dubois et al., 2016).

1.3.3 Dementia due to Alzheimer's Disease

AD dementia is defined as the dementia triggered by the AD pathophysiology and comprises the mildest to most severe stages. In the recent past, AD was always diagnosed postmortem, however, today, the neuropathological changes that outline the disease can be defined in vivo by well-established biomarkers (Jack et al., 2018). In the most recently revised research framework for AD, three groups of biomarkers were recognized: (1) aggregated amyloid plaques, (2) aggregated neurofibrillary tangles, and (3) neurodegeneration or neuronal injury, all of which can be identified through neuroimaging and CSF measures (Jack et al., 2018). Although biomarkers can increase substantially the certainty that the basis of a given dementia is the AD pathophysiology it is recommended to be used only for research purposes and not for routine diagnostic purposes. One reason for this is that the core criteria for the diagnosis of AD provide very good diagnostic accuracy. Another reason is that access to biomarkers is limited in clinical settings. Finally, a third reason is that more research is needed to ensure that the criteria of the biomarkers have been appropriately designed (McKhann et al., 2011).

The diagnosis of AD can be classified into three categories: (1) *Probable* dementia due to AD, (2) *Possible* dementia due to AD, which refers to atypical or etiologically mixed presentations, and (3) *Possible* dementia due to AD with evidence of biomarkers. The first two diagnoses are proposed for application in clinical settings while the third one is intended for research purposes. Patients are diagnosed with Probable AD if they meet the core criteria. Firstly, the presence of dementia must be established through neuropsychological evaluation using well standardized measures (for a review on all-cause dementia's core clinical criteria see McKhann et al., 2011). In addition, patients' cognitive impairments must be clearly progressive over months or years, based on neuropsychological evaluations or detailed history. The cognitive appearance of the disease can be either amnestic or non-amnestic. The amnestic presentation, which is the most common, involves both episodic memory decline, such as learning and recall of new information impairment, as well as dysfunction in at least one more cognitive domain. The less common non-amnestic presentation can involve language, visuospatial or executive dysfunctions. Finally, there must be an absence of any other disease capable of generating a dementia syndrome or core features of other dementias (McKhann et al., 2011).

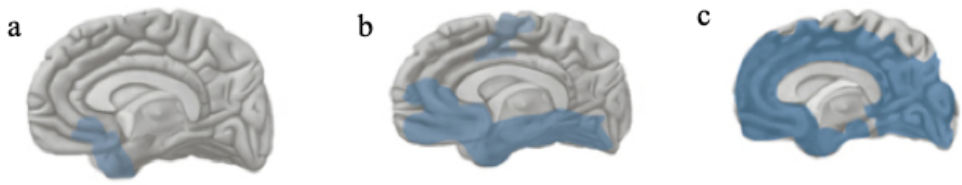
The borderline between MCI and AD dementia lies in the ability to function properly in everyday life. While in MCI the underlying deficits do not intervene in one's everyday function, when dementia's pathophysiology threshold is crossed, patients' ability to function is impaired. Individuals experience noticeable memory, behavioral or thinking symptoms that deteriorate over time. The symptoms reflect the underlying damage of brain cells due to the accumulated pathology (Jack et al., 2018).

AD is separated into three stages of severity: mild, moderate, and severe. In mild AD individuals may still be able to live independently, work, participate in activities, or drive. However, they will experience cognitive deficits that are noticeable to family and close friends and may require assistance to maximize independence. Moderate AD typically is the longest stage which can last even for years. At that point, symptoms are more pronounced, and individuals may need a greater level of care. Patients experience cognitive deficits which prevent them from communicating and performing everyday living activities, such as bathing, dressing, or eating. In addition, personality, and behavioral changes, such as agitation and suspicion, increase the need for more intensive care. The last stage is the most detrimental as patients suffer substantial brain

shrinkage (Figure 1.6). Therefore, the effect of AD on individuals' physical and mental health became remarkably apparent. Patients lose their ability to respond to their environment or to conduct a conversation. In addition, brain areas involved in movement are damaged, and therefore they lose their ability to control movement. At this stage, patients fall into a vegetative state until death (Alzheimer's Association, 2020).

The exact pace at which symptoms advance from one stage to another varies from person to person with several aspects, such as cognitive reserve, contributing to this. The effect of AD on lifespan depends crucially on the age of the diagnosis. A median life expectancy is estimated from seven to ten years for those diagnosed in their 60s or 70s, to only about three years for those diagnosed in their 90s (Brookmeyer et al., 2002; Joling et al., 2020).

Figure 1.6 Histological changes in different stages of Alzheimer's disease



Note: a) During the asymptomatic period, lesions (blue) are observed on the medial temporal structures. These structures engage in episodic memory, deficits on which is the most common presentation of typical AD; b) Lesions expand to temporal, frontal and parietal lobe; c) Cortical and subcortical brain areas are severely affected, and patients lose most of their cognitive and physical abilities. Picture retrieved from: Alzheimer's Disease.

Overall, the AD continuum includes several preclinical and clinical stages. Diagnostic criteria have been developed and expanded over recent years to distinguish between different stages on the wide spectrum of AD, from the asymptomatic to the most severe stage. In addition, several biomarkers have enriched the diagnostic criteria, hence, the neuropathological changes that outline the disease can be defined in vivo. Consequently, the dementia syndrome can be attributed to AD with high specificity. Although biomarkers are proposed to be used only for research purposes, the ultimate aim is to define the earliest boundary of AD and the exact correlated biomarkers which

will distinguish with certainty individuals that will progress to AD dementia from the ones that will not.

1.4 Neuropsychological Profile of Alzheimer's Disease

1.4.1 Memory Related Impairment

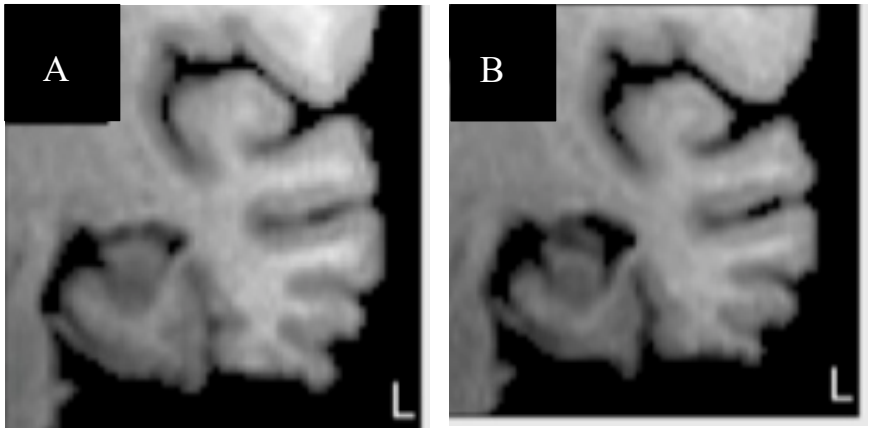
The most common clinical syndrome resulting from AD pathophysiology is the typical amnesia predominant dementia syndrome, which is most likely to begin as an aMCI. As a matter of fact, this presentation of AD is so common that for almost two decades the diagnostic criteria required memory impairment for the diagnosis (McKhann et al., 1984). However, over the last few years it has been recognized that AD is a heterogeneous disease that also includes atypical clinical phenotypes (Galton et al., 2000; Price et al., 1993), such as posterior cortical atrophy (PCA) or a frontal and dysexecutive variant in which memory is relatively preserved (Meyer & Hudock, 2018; Ossenkoppele et al., 2015). Nonetheless, the typical amnestic presentation involves approximately 86% to 94% of the total AD cases and follows a specific deterioration and neuropsychological pattern (Dubois et al., 2014). For the purposes of this paper, the discussion henceforth will be focused only on the typical phenotype of AD.

The neuropathological changes, resulting from the aggregation of neurofibrillary tangles, in AD start from the entorhinal cortex and hippocampal formations from the preclinical stage of AD, causing neuronal loss and atrophy in key memory areas and networks. Brain atrophy is normal in healthy ageing. However, while in normal ageing approximately only 0.2% to 0.4% of brain volume vanishes every year, in AD the rate is tenfold and becomes more devastating in key memory areas, such as in the hippocampus, where 10% of the volume is suppressed per year (Figure 1.7; Jahn, 2013).

The aforementioned structures of MTL and their interconnections with the cortex are well known to be critical in memory functions and explain the amnestic manifestation of AD. The memory systems affected by AD have been well researched and understood (Iachini et al., 2010; Spaan, 2016; White & Ruske, 2002). Among the major memory systems, episodic memory disruptions represent the earliest signs and symptoms. Episodic memory is defined as the neurocognitive system that allows the conscious recollection of events (episodes) that were previously experienced as well as acquiring

new facts or episodes (Gallagher & Koh, 2011). In AD, episodic memory dysfunction impedes individuals' ability to learn and recall new information (i.e., anterograde amnesia). Therefore, early in the disease, even during the aMCI stage, episodic memory deficits are manifested as misplacing the keys, missing appointments, forgetting to have dinner with a friend or not paying the bills. Patients and their loved ones may attribute these events to fatigue or to distraction. However, episodic memory is the key system for remembering more crucial events, such as taking medication or whether the oven has been turned off. Potentially dangerous incidents alarm the family and precipitate the initial visit to the doctor where the diagnosis of Probable AD will be made.

Figure 1.7 Hippocampus atrophy in an AD patient



Note: Coronal view of the left hippocampus at (A) baseline, gray matter volume = 5.3±0.4 mL, and (B) 4 years later, gray matter volume = 3.5±0.2 mL. The average reduction is 0.2 mL/year (-12%). From "Memory Loss in Alzheimer's Disease," by H. Jahn, 2013, *Dialogues in Clinical Neuroscience*, *15*(4), Atrophy in Alzheimer's Disease section, Figure 1B (https://doi.org/10.3188)

Episodic memory decline remains one of the most meaningful functional barriers as patients progress from mild to moderate AD (Gold & Budson, 2008). These disruptions in episodic memory follow Ribot's law (Ribot, 1881), indicating that the most recent memories are the ones to be lost first, before the more remote ones. Consequently, as the disease progresses, memories from the distant past are better remembered than the ones that occurred after or shortly before the onset of AD (Sagar et al., 1988).

As discussed earlier, episodic memory system is the most affected by AD pathophysiology and the major function burden in AD, however, other systems are impaired too. For instance, AD patients exhibit a progressive decline in semantic

memory including word finding and picture naming (Rogers et al., 2006; Tippett et al., 2007). Furthermore, individuals cannot take advantage of semantic relations between words (Buschke et al., 1997; Spaan et al., 2005). More specifically, patients exhibit difficulty in their ability to appraise semantic relations—they are no longer able to discriminate between two related concepts (e.g., rose-flower)—most likely because the underlying attributed knowledge that discriminates these two concepts has vanished (Spaan, 2016). Deficits in semantic memory are attributed to histological changes in the anterior and inferolateral temporal lobes as well as to the frontal lobes where the amyloid pathology is evident (Davies et al., 2004; Starr et al., 2005). Finally, studies indicate dysfunctions in working memory (Belleville et al., 2007), visuospatial memory (Quental et al., 2009) and in several forms of classical conditioning, including the amygdala-based fear conditioning (Hamann et al., 2002), all of which can be evident in the beginning of the disease and gradually further deteriorate as the disease progresses.

To summarize, AD is known as an amnesia predominant syndrome that manifests with episodic memory dysfunctions which constitutes the major everyday function burden. Accordingly, AD patients exhibit difficulties in learning and recalling information which occur after the onset of the disease. Memory deficits are often expanding, early on in the disease, to other systems implicating the function of semantic, working, and visuospatial memory (Gold & Budson, 2008).

1.4.2 Non-memory Related Cognitive Dysfunction

The clinical diagnosis of AD is made when memory loss accelerates and several other cognitive and behavioral deficits emerge, reaching the criteria for dementia. As the AD pathology progresses from the MTL to other neocortical regions, such as the frontal and parietal lobes, additional behavioral and cognitive symptoms appear and the full AD syndrome becomes evident (Braak & Braak, 1996; Jack et al., 2000). Wide research has indicated that significant deficits in executive function (e.g., problem-solving, mental manipulation of information), attention and processing speed are evident in MCI patients compared to healthy age-matched adults (Clément et al., 2013; Economou et al., 2007; Kochan et al., 2011; Summers & Saunders, 2012). While these deficits may not interfere with everyday activities at the MCI stage, they are substantially impaired in relation to normal ageing and are reliable predictors of progression to AD, especially

when accompanied with episodic memory decline (Saunders & Summers, 2011; Storandt et al., 2006).

Additionally, AD patients demonstrate affected performance in verbal fluency, especially on category fluency (generating words from a given category, e.g., animals; Henry et al., 2004; Mueller et al., 2015). The reduced ability of AD patients to efficiently generate words from given categories, a task that requires integrity of semantic memory, is explained by the loss of knowledge of the attributes and associations that define a particular semantic category. This fact supports the notion that AD patients have a deterioration in the structure and organization of semantic memory (Rohrer et al., 1999; Weintraub et al., 2012). Finally, it has also been suggested that deficits in visuospatial abilities, evident in visuoconstructional tasks and tasks that require visual orientation and visuoperceptual abilities, may be apparent from preclinical stages. It is evident that the preclinical stage of AD is characterized by a broad cognitive impairment (Economou et al., 2007) even though memory difficulties are usually most evident and affect patients' function (Gold & Budson, 2008).

1.4.3 Neuropsychiatric Symptoms

The exhibited cognitive deficits resulting from the underlying pathophysiology of AD are devastating. However, the AD clinical presentation is also well associated with severe behavioral and neuropsychiatric symptoms (B&NPS) from the early onset of the disease (Fernández et al., 2010). These symptoms are believed to represent clinical features of AD and are considered as confounding variables that induce noticeable impairment while accelerating cognitive decline and having a negative effect on patients' and carers' quality of life (Serra et al., 2010). The estimated prevalence of the B&NPS ranges from 25% to 80%, expressed in varying degrees throughout the course of the disease (Finkel et al., 1996). The presence of B&NPS from the MCI stage may have a prognostic value for the progression to AD while they are predictive indices of more accelerated deterioration of cognitive function (Li et al., 2014), loss of independence and institutionalization (Zahodne et al., 2015), and shorter survival (Vilalta-Franch et al., 2013).

The most frequently observed B&NPS involve delusions, apathy, anxiety, depression, sleep disturbances and agitation (Senanarong et al., 2004). Symptoms such as:

wandering, psychosis, aggression, hallucinations, disinhibition, and disturbances in eating behaviors are evident, however, less frequent (Assal & Cummings, 2002; Ropacki & Jeste, 2005). Considering the prodromal stages of AD, depressive symptoms, anxiety, apathy, and irritability are the first to be observed (Craig et al., 2005) while the other symptoms, such as psychosis and wandering, are more typical in advanced AD (Piccininni et al., 2005). Whether the B&NPS are the expression of patients' psychological reaction to cognitive dysfunction or reflect specific brain pathological changes due to AD is a debatable matter (Serra et al., 2010). However, neuroimaging studies have reported a link between brain atrophy or other structural and/or functional abnormalities and the presence and severity of specific B&NPS (Aalten et al., 2007; Craig et al., 1996). This suggests that neuropsychiatric symptoms might be a part of AD clinical representation (Serra et al., 2010). Regardless, symptoms like sleep disturbances, depression, anxiety, apathy, or agitation are recognized as core AD symptoms and are of high importance for diagnosis as they can be partly treated with medication and hence prolong patients' quality of life (Fernández et al., 2010).

Overall, AD should not be thought of as solely a memory syndrome but rather a disorder that progressively affects every aspect of cognition and behavior. In addition, even though episodic memory impairments are the first to be observed and disrupt patients' ability to function, several non-memory deficits and neuropsychiatric symptoms accompany the onset of the disease.

1.5 Alzheimer's Disease as a Disconnection Syndrome

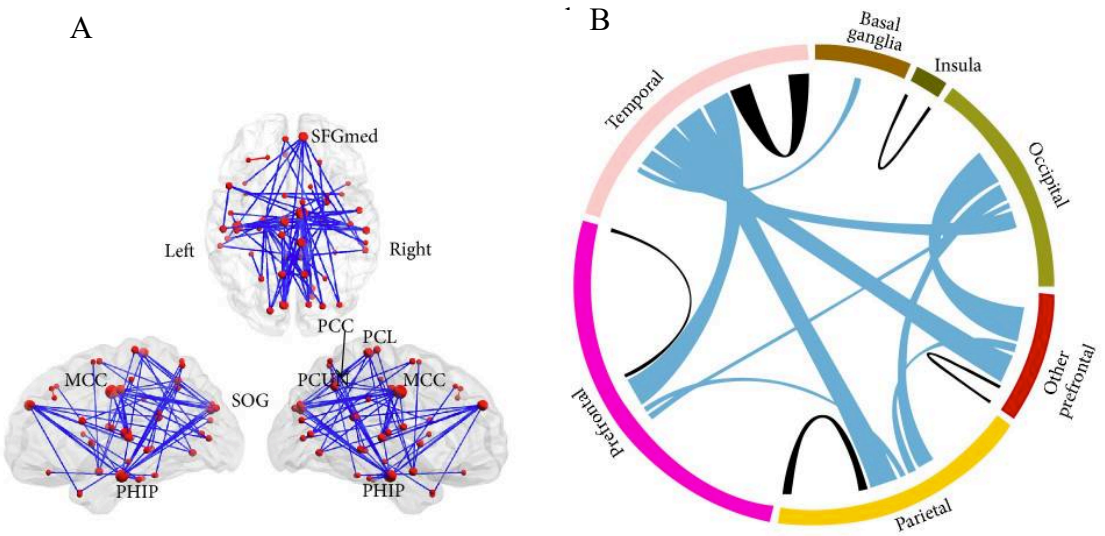
The past decade has witnessed a rapid progress in neuroimaging techniques which have helped to see AD from a different perspective. A wide range of studies (i.e., pathophysiological, electrophysiological, neuroimaging) have suggested that AD pathophysiology causes loss of brain cells and synapses in key cortical layers which serve as gateways of neuronal projection between the hippocampus and the rest of the brain (Allen et al., 2007; Hyman et al., 1986). Further research has identified alterations in the connection between specific brain regions or networks in MCI and AD (Chen et al., 2011; Wang et al., 2007; Yao et al., 2013). In addition, the impaired functional connectivity has been significantly correlated with patients' cognitive abilities and the large-scale interconnectivity patterns between several brain areas can differentiate AD

and MCI patients from healthy subjects (Chen et al., 2011). Finally, it is evident that the AD severity is related to the long-distance connectivity loss (Liu et al., 2014). Therefore, convergent evidence suggests that AD can be better explained by the disturbance of the interactions between different brain areas, hence, AD can be thought of as a disconnection syndrome (Bajo et al., 2010; Delbeuck et al., 2003, 2007).

In a recent whole-brain functional connectivity study, Zhou et al. (2015) demonstrated widespread impaired functional connectivity patterns (Figure 1.8), including several important nodes of the default mode network (DMN), such as the precuneus (PC), the posterior cingulate gyrus (PCC) and the parahippocampal gyrus (PHIP). These changes were positively correlated with patients' impaired cognitive abilities. These findings, consistent with previous studies (Greicius et al., 2004; Rombouts et al., 2005), illustrate that the DMN is the most affected network in MCI and AD (Figure 1.9 & 1.10), and abnormal changes may represent a potential imaging-based biomarker for the early identification of AD.

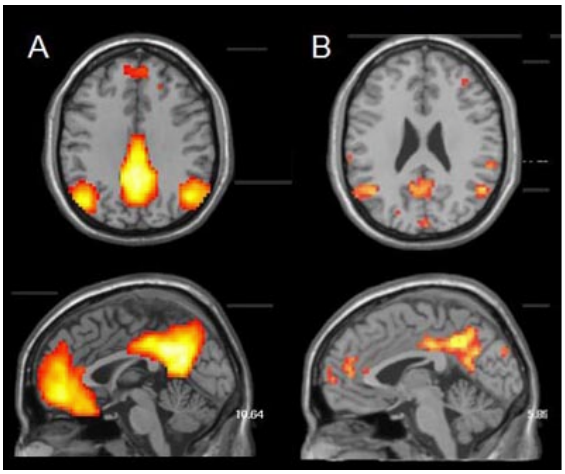
The DMN is a large-scale brain network, principally comprised of the PC, the PCC, the angular gyrus (AG), and the medial prefrontal cortex (MPC), that exhibits remarkably high metabolic activity in resting state. It is hypothesized that when an individual is awake and alert but not consciously engaged in a particular task the PC and its interconnected areas (i.e., the DMN) are engaged in conscious information gathering and representation of the self and the external world (Trimble & Cavanna, 2008). Overall, the DMN is best known for its role in various cognitive processes including episodic memory (Buckner et al., 2008; Raichle et al., 2001). The observed functional connectivity impairment in the DMN in AD can be explained by the amyloid pathology, which is evident in these nodes, years before the onset of the disease. The changes in the DMN, induced by the amyloid pathology, comprised of a set of functionally interconnected areas (e.g., PCC/PC, interior parietal lobule, dorsomedial prefrontal cortex; Buckner et al., 2005; Sperling et al., 2009) that project heavily to MTL structures signifying hippocampus' cell death by years (Weintraub et al., 2012).

Figure 1.8 Impaired functional connectivity patterns in AD patients compared to cognitive normal subjects



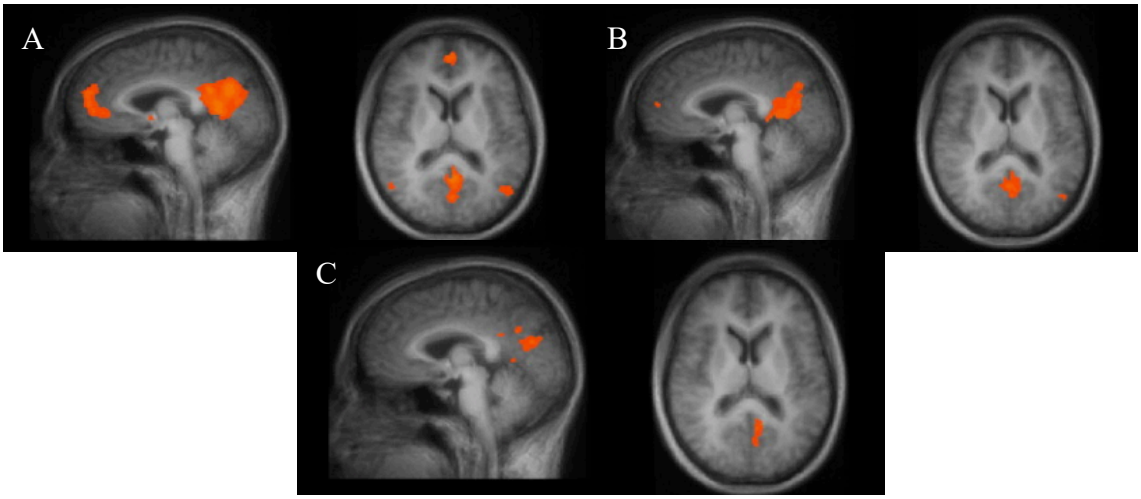
Note: A) Connectivity and the most significantly affected nodes of the DMN in three-dimensional representation; B) Distribution of the altered functional connectivity indicating the most affected type of connectivity disruption. The blue colored lines represent the interlobe functional connectivity while the black ones represent the intralobe connectivity. It is evident that the interlobe connections, such as the temporal lobe to the frontal and parietal lobes are the most affected whereas the temporal lobe is the most affected lobe. SFGmed = Medial superior frontal gyrus; PCC=Posterior cingulate gyrus; PCL=Paracentral lobule; PCUN=Precuneus; PHIL=Parahippocampal gyrus; MCC=Median cingulate gyrus; SOG=Superior occipital gyrus. From "Aberrant Functional Connectivity Architecture in Alzheimer's Disease and Mild Cognitive Impairment: A Whole-Brain, Data-Driven Analysis," by B. Zhou et al., 2015, *BioMed Research International, 2015*, Results section, Figure 3 (https://doi.org/10.1155).

Figure 1.9 The default mode network



Note: A) In healthy ageing and in B) familial AD. Retrieved from Alzheimer's Association International Conference 2012 (Part 11 of 18): Jasmeer Chhatwal, Massachusetts General Hospital.

Figure 1.10 Functional connectivity of default mode network as shown by resting state functional MRI



Note: A) Healthy elderly controls; B) MCI; C) Sporadic AD. The regions in orange indicate those areas that show temporal correlation of their BOLD signal at test. From "Diagnostic power of default mode network resting state fMRI in the detection of Alzheimer's Disease," by W. Koch et al., 2012, *Neurobiology of Aging, 33*(3), Results section, Figure 1 (https://doi.org/10.1016)

It is well documented that even from the early stages of AD, functional connectivity in the DMN is impaired. This abnormal functional connectivity hinders the communication between the hippocampus and the rest of the brain causing cognitive impairment (Zhou et al., 2015; Chen et al., 2011). Thus, a key question is whether an improvement of functional connectivity within the DMN, will alleviate cognitive impairment in MCI and AD patients.

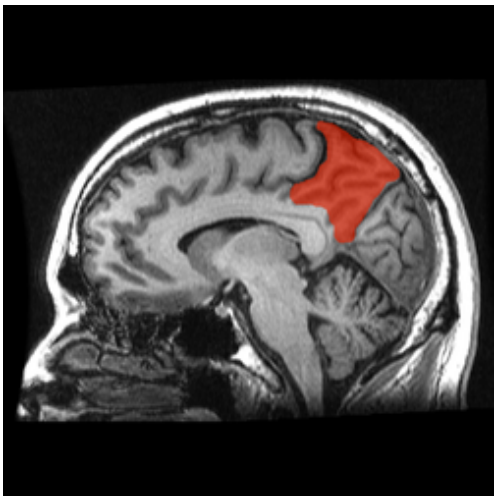
1.6 Role of the Precuneus in the DMN and Episodic Memory

The PC is located on the posterior medial parietal cortex (Brodmann's Area 7), hidden in the depths of the longitudinal fissure (Figure 1.11). Because of its hidden position it

is only recently, due to the advance of neuroimaging techniques, that this area was investigated and its crucial role in cognition confirmed (Trimble & Cavanna, 2008). Converging lines of evidence indicate the PC as the functional core of the DMN, supporting complex cognition and behavior (Cavanna & Trimble, 2006; Utevsky et al., 2014). Its role has been of particular interest as it shows the highest metabolic activity in resting state within the DMN, that is 35% more glucose than any other brain area (Gusnard & Raichle, 2001). The PC has extensive reciprocal and bilateral cortical and subcortical connections, including the association cortices, the medial and lateral parietal cortices, the MTL, the thalamus, the striatum, and the brainstem. It has also been demonstrated that the PC is strongly interconnected with the frontal lobes. In addition, the PC is more highly developed in terms of comprising a greater portion of the brain volume, while at the same time demonstrating the most complex columnar cortical organization and it is among the last areas to be myelinated.

Overall, anatomical, and functional connectivity data suggest that the PC is a major association area that is implemented in a variety of higher-order cognitive functions (Cavanna & Trimble, 2006). Finally, the PC/PCC node is considered to play a pivotal role in the DMN as it is the only node that directly interacts with all the network's cortical structures (Fransson & Marrelec, 2008).

Figure 1.11 Sagittal MRI slice of precuneus, portrayed in red



Note: Picture retrieved from: wikimedia.org/Precuneus.

The PC exhibits decreased activation during external tasks. However, it shows significantly increased activation in response to rest and specific cognitive tasks, such as in episodic and autobiographical memory (Addis et al., 2004; Eustache et al., 2004; Lundstrom et al., 2005). Functional imaging data on brain activation patterns during episodic memory tasks suggest strong involvement of the PC in most episodic memory tasks (Krause et al., 1999; Rugg et al., 2002; Schmidt et al., 2002; Shallice et al., 1994). PC activation is evident during the classic laboratory episodic memory tasks (e.g., word lists or paired association tasks), but importantly it is also observed in naturally acquired autobiographical memories (Gilboa et al., 2004; Lundstrom et al., 2005).

Concerning the AD, it has already been mentioned that aberrant functional connectivity on the DMN is evident in preclinical stages and the extent of the aberrance is significantly correlated with the disease's severity and patients' cognition (Zhou et al, 2015). Moreover, further research has demonstrated that functional connectivity between the hippocampus and the rest of the brain is substantially decreased in MCI and AD patients, in relation to healthy controls, with the hippocampus-precuneus network to be the most affected (Greicius et al., 2004; Kim et al., 2013; Sorg et al., 2007). Furthermore, non-demented APOE ε4 (i.e., the most prominent susceptibility AD-related gene) carriers, exhibit PC cortical thickness, decreased functional connectivity with key DMN nodes and abnormal PC activation during memory-encoding tasks, in contrast with non-carriers. Brain degeneration patterns in APOE carriers at the preclinical stage follow the same degeneration pattern evidenced in AD. In fact, AD patients who carry the APOE ε4 exhibit PC progressive atrophy relative to non-carriers (Hashimoto et al., 2009). These findings suggest that the APOE-related damage pattern is PC-based (Chen et al., 2016). In a further point, MCI patients exhibit structural atrophies limited to the PC and PCC relative to AD patients, indicating the starting point of degeneration (Gili et al., 2011). Overall, it is suggested that the PC is particularly vulnerable to the amyloid deposition (Sperling et al., 2009), and its structural deficit starts before the disease's onset (Chen et al., 2016).

Based on the research discussed in this chapter, it is evident that the PC is a pivotal cortical region, affected by AD neuropathology before the onset of the disease. The PC shows cortical atrophy and abnormal activation during memory tasks while presenting aberrant functional connectivity with the medial temporal lobe structures (i.e., hippocampus) and other important nodes of the DMN leading to episodic memory

dysfunctions (Buckner et al., 2005; Seeley et al., 2009). Taking all of this into account, PC might be an ideal brain region to target in future interventions aiming to improve AD related cognitive impairment.

1.7 The Long Road to a Cure for AD

As already discussed, AD is a neurodegenerative disorder that eventually leads to severe brain shrinkage and death. Despite the extensive research over the last decades and billions of dollars invested in this research, the exact etiology of the disease is still unknown and there are no available treatments to effectively stop or reverse the neurodegeneration. Aside from a few medications that only temporarily alleviate symptoms, the controversial monoclonal antibody aducanumab (Khanna et al., 2022) is the closest thing to an effective treatment. However, even though the aducanumab was approved by the US Food and Drug Administration (FDA)—based on evidence indicating its effectiveness in reducing the accumulated amyloid plaques— its efficacy in improving cognitive function remained ambiguous (Moutinho, 2022). In addition, due to severe side effects such as brain swelling and bleeding, together with the fact that at least four patients who were talking the medication died (although a clear link between their deaths and the medication has not been proven yet) the aducanumab was rejected by the European Medicines Agency and later the pharmaceutical company (i.e., Biogen Netherlands) withdrew the application before the scheduled re-evaluation (Moutinho, 2022; European Medicine Agency, 2022).

The road to the development of an effective treatment has been long and until today is paved mostly with failures. Over 140 medications are being investigated in more than 170 clinical trials. The majority of these drugs are disease modifying medications which try to prevent or delay the onset or progression of AD. Nevertheless, Cummings et al. (2014) reported that 99% of AD drug clinical trials have failed to find a positive effect—among the greatest failure rate for any disease (Moutinho, 2022).

The poor performance of drugs can be explained by many factors, one of which states that maybe the field has been extensively focused on the amyloid plaques at the expense of other possible targets. The amyloid hypothesis is the most well-funded and investigated hypothesis of AD. It suggests that the disease is caused by the amyloid plaques aggregation which leads to cell death and cognitive impairment. The

observation of the amyloid accumulation dates back to Lois Alzheimer who first observed them in the brain of his famous patient Augusta. Since then, accumulative evidence (e.g., Hampel et al., 2021; Morgan, 2006; Murphy & Levine, 2010) has supported the concept that this pathology was the most possible cause of AD. Therefore, hundreds of drugs have been developed to clean up or prevent amyloid-β deposits from accumulating. Yet, even when the reduction of amyloid-β succeeded the patients did not show cognitive improvement (Salloway et al., 2014).

Following constant failures, scientists have increasingly shifted towards the belief that amyloid-β is one of the AD symptoms, but not necessarily a cause or the primary cause of the disease. The disadvantage of the observed hyperfocus on the amyloid pathology is that it has hindered investments in research on other possible targets. While the amyloid is still the focus of many clinical trials, alternative hypotheses are being developed and AD pathology is currently under the microscope for the identification of other possible targets. For instance, drugs are now targeting the observed chronic neuroinflammation (Cummings et al., 2022; Kumar et al., 2016) while different perspectives approach AD as a type 3 diabetes (Kyrtata et al., 2021; Xue et al., 2019) or as a viral infection (Jansen et al., 2019; Tzeng et al., 2018). These are among the few innovative drug approaches which clearly indicate a new era in AD research while showing that scientists are now open to new unbiased observations for the causes of AD and the possible mechanisms that might eventually lead to an effective treatment (Moutinho, 2022).

1.7.1 Current Treatment of Alzheimer's Disease

To date, AD treatment is being approached pharmacologically only to counterbalance the known neurotransmitter disturbance and improve patients' behavioral symptoms (Yiannopoulou & Papageorgiou, 2020).

It is well known that loss of cholinergic neurotransmission is a main characteristic of AD (Beach et al., 2000; Giacobini, 1990; Perry et al., 1977), therefore, routinely AD is treated with cholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine (Onor et al., 2007; Rogers & Friedhoff, 1996; Sharma, 2019). Their development was based on the cholinergic hypothesis which indicates that the gradual loss of cholinergic neurotransmission from neocortical and limbic brain areas is critical for higher

cognitive functions, like learning and memory. In addition, the neurofibrillary pathology in the basal forebrain, which is probably the primary cause of dysfunction and death of cholinergic neurons in this region, generates a widespread presynaptic cholinergic denervation. The cholinesterase inhibitors increase the availability of acetylcholine at synapses leading to increasing communication between the nerve cells, which in turn, may temporarily improve cognitive function in AD patients (Hampel et al., 2018).

Even though the above-mentioned medications are approved treatments for AD, their effectiveness has been questioned. For instance, a long-term study, using donepezil treatment, demonstrated no significant benefit of the drug compared to placebo for institutionalization and progress to disability (Courtney et al., 2004). Burns et al. (2008) found that the response to donepezil in AD patients varied from 26% to 63%, while that of placebo reached 47%. In a meta-analysis of randomized, placebo-controlled clinical trials of cholinesterase inhibitors, a substantial and marked benefit was found for only 2.3% of the patients (Lanctôt et al., 2003). Lastly, it is known that medications have only limited and transient effects while their adverse side effects (e.g., cardiovascular events, nausea, dizziness, fatigue, insomnia, diarrhea) cannot be tolerated by some patients (Howes, 2014; Kröger et al., 2015; Valladales-Restrepo et al., 2019).

Overall, AD pharmacological treatment involves typically (but not only, i.e., glutamatergic drugs) cholinesterase inhibitor medications, which have played a pivotal role in stabilizing symptoms (Haake et al., 2020). However, considering the limited and transient effects of medications, the development of novel non-pharmacological interventions to slow the progressions or to improve patients' symptoms, has gained increased interest over the last decade. The entrainment of gamma brain activity has recently gained scientific attention while non-invasive brain stimulation approaches have been tested in AD patients, providing promising results as an alternative potential treatment (Rajji, 2019).

1.8 Gamma Oscillations in Alzheimer's Disease and Their Potential Therapeutic Role[1]

It is more than 110 years since AD was discovered. Even though scientific knowledge has increased enormously since then, and our understanding of the pathological mechanisms involved in AD have been well-identified, clinical trials that have targeted these mechanisms have not succeeded in identifying effective methods to treat or reverse the disease (Fan et al., 2020). Considering the alarming rise and the tremendous personal, social, and financial burden of AD, scientists have tried to move away from the well-recognized hypotheses. AD pathogenesis has recently been explored from different perspectives, such as infection, cerebral vasoconstriction, and prion transmission (Jeong et al., 2018; Seminara et al., 2018; Tian et al., 2019), offering new insights into the potential treatments of AD.

A recent pioneering approach targets brain waves to treat AD pathology (for a review please see Traikapi & Konstantinou, 2021). Brain oscillations, particular gamma oscillations, are altered in AD patients and animal models of the disease (e.g., Jelles et al., 2008; Klein et al., 2016). On that basis, a novel approach investigates the effectiveness of a therapy based on modulation of neuronal gamma oscillations using sensory inputs, signifying a new and promising era in AD research.

[1] An adapted version of this section has been published in the journal Frontiers in Systems Neuroscience as: Traikapi, A., & Konstantinou, N. (2021). Gamma oscillations in Alzheimer's disease and their potential therapeutic role. *Frontiers in Systems Neuroscience*. https://doi.org/2021.782399

1.8.1 Aberrant Gamma Neural Activity in AD: Evidence from Animal Studies

Gamma waves are the fastest brainwaves in the human brain, produced by synchronized electrical pulses from masses of neurons communicating with each other, resonating between approximately 25 and 100 Hz (Hughes, 2008). Several human studies have investigated their role in object representation and visual feature binding (Tallon-Baudry & Bertrand, 1999) as well as in higher cognitive functions (Griffiths et al., 2019; Miller et al., 2018; van Vugt et al., 2010). Gamma rhythms have been recorded ubiquitously across the human brain. They are being widely encountered in the visual system (Murty et al., 2018; Zhigalov et al., 2021) in addition to different cortical and subcortical brain structures (Cohen et al., 2009; Manabe & Mori, 2013; van der Werf et al., 2010). What is more, it has been suggested that gamma-band synchronization supports fundamental functions critical for various cognitive processes (Bosman et al., 2014). All this evidence reveals gamma oscillations' multifunctionality, which supports a wide range of both sensory and higher cognitive functions (for further information on gamma oscillations, please see Bosman et al., 2014; Cannon et al., 2014; Cole & Voytek, 2017; Fries, 2015).

Mounting evidence suggests that gamma rhythms are also prominent in the hippocampus, playing a crucial role in memory functions (e.g., Buzsáki, 2015; Carr et al., 2012; Colgin & Moser, 2010). It is, therefore, not surprising, that disorders characterized by memory impairment, such as AD, are associated with aberrant activity of gamma oscillations (Mably & Colgin, 2018). The presence of gamma oscillations has been identified in vivo in the hippocampus and the entorhinal cortex of healthy rodents (Penttonen et al., 1998), while changes in this brain activity have been evident in several rodent models of AD. In fact, Klein et al. (2016) reported changes in rodents' gamma oscillations in the entorhinal cortex at an early stage of the disease. Another study found impaired theta-gamma cross-frequency coupling in the hippocampus before plaque formation, in 1-month old transgenic mice (Goutagny et al., 2013). Verret et al. (2012) identified that both AD patients and transgenic mice presented dysfunctions on the parvalbumin cells and inhibitory synaptic activity which resulted in aberrant gamma oscillatory activity and cognitive disfunction. Restoring the levels of the interneuron-specific and parvalbumin cells sodium channel proteins had

profound and beneficial effects on gamma brain activity and cognitive function. Goutagny et al. (2013) indicated that the reduction of slow gamma activity (25–50 Hz) in the hippocampal area CA1 can result in impaired memory function. Similar findings were reported by Mably et al. (2017) who demonstrated that decreased gamma activity in mice models of AD can result in memory dysfunction. Cumulatively, current evidence suggests that gamma brain activity is decreased in mice models of the disease, causing cognitive dysfunction. The exact mechanisms responsible for this alteration are not known, however, it has been suggested that synaptic and neuronal functions are affected by either soluble Aβ or its fibrillary forms (Walsh & Selkoe, 2004), contributing to network alterations (Palop & Mucke, 2016). In rodents, these changes are reported to appear before plaques formation (Etter et al., 2019; Iaccarino et al., 2016).

Evidence that aberrant gamma activity and cognitive dysfunction arise in mice models of AD before the accumulation of amyloid plaques provides convincing evidence that abnormalities in gamma brain oscillations may represent an early biomarker for AD (Goutagny et al., 2013; Mably & Colgin, 2018). Nevertheless, the question of whether the aberrant gamma oscillations activity is responsible for the observed cognitive impairment in AD patients or if it is just another by-product of the disease pathology, which produces the cognitive symptoms, remains to be answered. Additionally, it is unclear whether inducing gamma oscillations in transgenic mice can affect AD pathophysiology and cognition. It has been shown, however, that steady-state brain gamma oscillations can be stimulated or driven by sensory stimulation (e.g., Ross et al., 2013) and that neuronal activity has the potential to modulate the Aβ load (Bero et al., 2011; Cirrito et al., 2005).

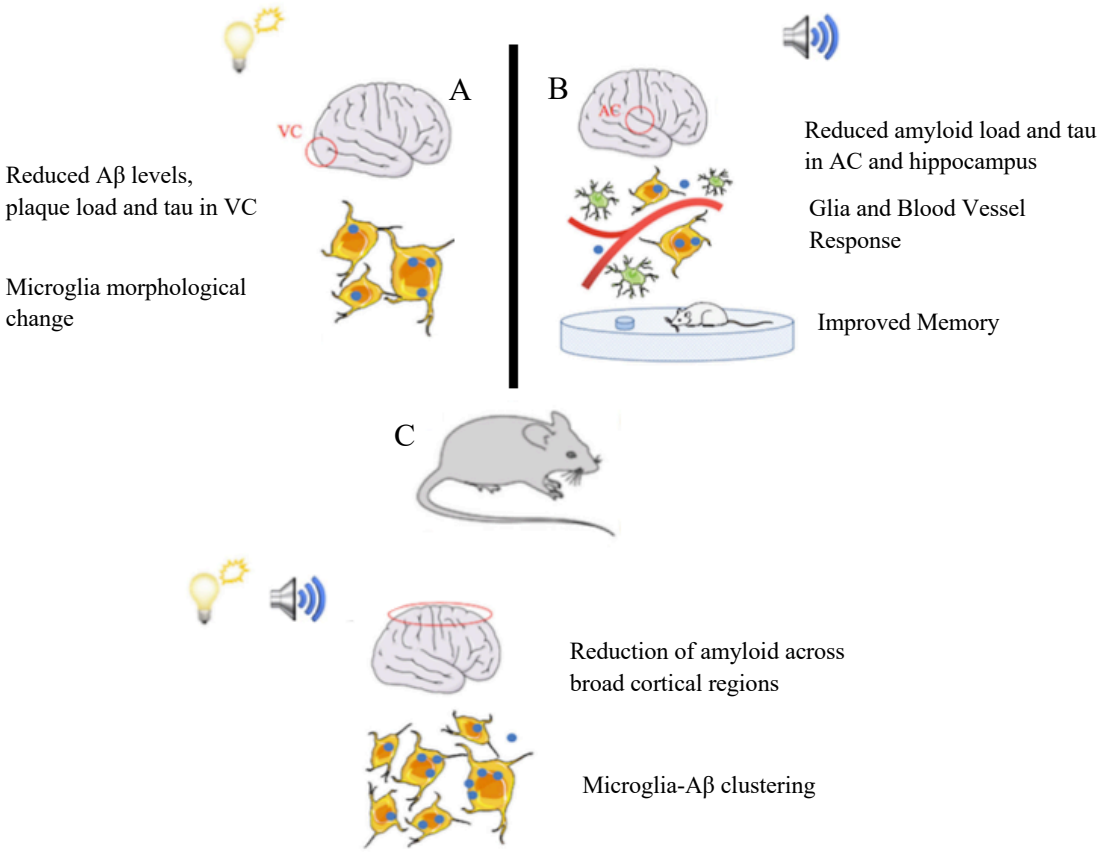
1.8.2 The Effects of Sensory Gamma Stimulation in Mice

In light of the accumulative evidence, an important set of studies demonstrated that restoration of gamma oscillations has the potential to alleviate AD pathology and cognitive function in mice. First, Iaccarino and colleagues (2016) used a non-invasive brain stimulation technique to manipulate gamma brainwaves. Specifically, the authors used light flicker stimulation at three different frequencies (20, 40, 80 Hz), constant light or dark, and random flicker to treat the pathology of 5XFAD mice. After only one hour of stimulation the authors observed reduction of Aβ levels in visual cortex by

almost 60%, compared with dark controls. Another critical finding was the transformation of microglial morphology consistent with increased phagocytic activity and the elevation of microglia/Aβ interactions. These effects were specific to 40 Hz light exposure as neither constant light nor 20 Hz, 80 Hz or random flicker, led to significant changes in mice pathology. After treating 5XFAD mice for one hour daily over seven days, the investigators found that 40 Hz visual stimulation significantly decreased both soluble and insoluble $A\beta_{1-40}$ and $A\beta_{1-42}$ levels and reduced the accumulated amyloid pathology in visual cortex by almost 67%, compared with dark controls. Finally, they observed reduction of the tau tangles in a mouse model of tauopathy, indicating the generalization of 40 Hz stimulation effect to other pathogenic proteins. Interestingly, these findings were replicated in several mice models, including WT, 5XFAD, and APP/PSI, suggesting that the effects are not specific to one animal model.

In a more recent study Martorell et al. (2019) presented mice models of AD with noise stimuli at 8 Hz, 40 Hz, 80 Hz and random stimulation tones for one hour, daily, for seven days. The authors reported that only 40 Hz stimulation produced similar with Iaccarino et al. (2016) results, that extended from the primary auditory cortex to the hippocampus and were accompanied by memory improvements. When the authors combined the auditory with the visual (A+V) 40 Hz stimulation they observed reduction of amyloid dispositions not only to the primary sensory cortices and the hippocampus, but also to the medial prefrontal cortex and within the whole neocortex. Amyloid reduction was frequency-specific, as it was observed only at 40 Hz but not at 8 Hz, 80 Hz or at random A+V frequency stimulation. In addition, the authors observed profound glial responses after the concurrent A+V 40 Hz stimulation to the aforementioned areas, versus visual or auditory stimulation alone and no stimulation controls.

Figure 1.12 Series of gamma sensory stimulation experiments indicating AD pathology amelioration



Note: A) Gamma activity produced by light flicker decreased pathology in the VC; B) 40 Hz auditory stimulation led to AD pathology reduction in the AC and hippocampus; C) Combination of auditory and visual gamma stimulation had a unique effect of reducing the amyloid load in broad brain areas and induced a cluster phenotype response by microglia. From "New Insights. Into the Pathogenesis of Alzheimer's Disease," by L. Fan et al., 2020, *Frontiers in Neurology, 10*(1312), Gamma Oscillations Ameliorate Pathology and Cognitive Impairment in AD section, Figure 2 (https://doi.org/10.3389)

Finally, from a study of the same research group (Adaikkan et al., 2019), it became evident that 40 Hz visual stimulation entrains gamma oscillatory activity not only to the visual cortex but also to the hippocampus, the prefrontal, and the somatosensory cortices. In addition, gamma activity was not enhanced only at local networks but also between these areas, indicating that 40 Hz light stimulation improves inter-area communication, whereas stimulation at 80 Hz did not produce similar results. Finally, the authors delivered 40 Hz visual stimulation or no stimulation to tau P301S mice for 22 days. It was found that prolonged daily 40 Hz visual stimulation had a

neuroprotective effect, in terms of reduction of neuronal and synaptic loss in broad brain areas, which was accompanied by cognitive improvements.

Overall, these studies provided evidence that inducing gamma oscillations through sensory 40 Hz stimulation has the potential to ameliorate several of AD's key neuropathologies such as amyloid plaques, neurofibrillary tangles, and neuronal and synaptic loss, in several mice models of AD. While the exact mechanisms under which the observed changes occurred remain to be determined, these findings raised the interesting question of whether an increase in gamma frequency neural activity in humans can be a promising strategy to alleviate AD's pathological changes and hence, to restore patients' cognitive deficits. In any case, generalization of these 40 Hz protocols has gained interest and it is currently one of the most promising areas of research (McDermott et al., 2018).

1.8.3 Sensory Gamma Frequency Stimulation in Alzheimer's Disease Patients

The accumulating evidence on gamma entrainment through visual and auditory stimulation in mice was a major stride towards establishing the importance of gamma brain waves, particularly at 40 Hz, in the amelioration of AD neuropathology. The research on the therapeutic efficacy of gamma sensory stimulation in AD patients, although still in its infancy, provides encouraging data. Clements-Cortes et al. (2016) evaluated the effects of 40 Hz sound stimulation versus non-rhythmic visual stimulation in AD patients. The study indicated that somatosensory stimulation, via a device (i.e., NextWave chair) which produced 40 Hz sound waves through six speakers, had a significant effect on the cognitive function of patients with mild to moderate AD, in contrast with the visual stimulation which involved nature pictures displayed on a television screen. While patients' gamma brain activity or possible changes on AD pathology were not assessed, this study provided solid evidence regarding the efficacy of gamma-based treatment in AD. More recently, (Suk et al., 2020) developed a light and noise delivery device and stimulated at 40 Hz cognitively healthy, AD, and epileptic patients while their electrophysiological responses were recorded. The concurrent auditory and visual stimulation was proved safe in all subject groups, including the epileptic patients, while induced highly coordinated 40 Hz oscillations.

Even though patients' cognitive abilities were not examined, this study provided preliminary evidence regarding the safety and feasibility of 40 Hz sensory stimulation in AD patients.

To investigate the efficacy of sensory stimulation as a novel disease modifying therapy in AD patients, Chan et al. (2021) conducted a longitudinal, placebo-controlled trial. Specifically, 15 patients with mild AD were recruited and divided into experimental and control groups. Both groups were given the same sensory stimulation device to use at home for one hour daily. The devise was programmed to deliver constant white light and noise to the control group and synchronized audiovisual stimulation at 40 Hz to the active group. AD patients who received real auditory and visual stimulation treatment daily, over a period of three months, presented reduced loss of functional connectivity, improved memory performance and ameliorated sleep markers in relation to controls. Additionally, the active group showed less brain atrophy and more importantly did not show further hippocampal atrophy or ventricular expansion in relation to the control group, indicating a possible delay in the disease progression. In the same manner, He et al. (2021) recruited 10 patients with prodromal AD who received daily 40 Hz audiovisual sensory stimulation for 1 hour over the course of 4 or 8 weeks. Even though, control group or sham stimuli were not included for comparison reasons, the study indicated that the treatment was safe and resulted in improved functional connectivity in the default mode network and altered cytokines and immune factors in the cerebrospinal fluid. Overall, both studies provided compelling evidence that gamma-based therapy, through visual and auditory stimulation, may have a disease modifying effect and may be used to alleviate AD pathology.

1.8.4 Gamma Frequency Non-Invasive Brain Stimulation in AD Patients

Sensory brain stimulation is currently the most commonly used technique to change brain waves activity in AD research. However, there are other approaches available which allow interference with brain activity and stimulate in desirable frequencies. Among these, transcranial alternating current stimulation (tACS), a non-invasive brain stimulation technique, has been proposed as an alternative technique to sensory stimulation and has the potential to result in stronger effects (Strüber & Herrmann,

2020). TACS delivers sinusoidal alternating electric currents over cortical areas of interest, at specific frequencies, entraining cortical oscillations at these frequencies. Hence, it has the potential to modulate cognitive functions that are related with the applied frequencies (for reviews please see Herrmann et al., 2013; Paulus, 2011). A few studies have employed 40 Hz tACS in AD patients providing indications of cognitive improvements (e.g., Benussi et al., 2021). For instance, Kehler et al. (2020) examined whether 40 Hz stimulation over the left dorsolateral prefrontal cortex, through tACS, could improve cognitive function in AD patients. Eleven patients with mild to moderate AD received two 30-min stimulation sessions per day, accompanied by cognitive exercises, for four consecutive weeks (active group) while six patients received cognitive exercises alone, for 4 weeks (control group). Memory improvements were observed in both groups, however, these improvements were maintained only to the active group at the follow up, at the 1-month post-treatment assessment.

The most notable results for the use of non-invasive gamma stimulation in AD, come from Liu et al. (2021). The authors employed repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique that induces a pulsing electric current to the brain (a comprehensive description of TMS is provided below) and demonstrated the clinical efficacy of 40 Hz in improving cognitive impairments in AD. The authors recruited 37 AD patients divided into active and sham TMS groups who received 12 sessions of 40 Hz TMS bilaterally at the angular gyrus, over the course of 4 weeks, and found significant cognitive improvement which lasted for up to 8 weeks in relation to sham stimulation. The authors also reported that 40 Hz TMS stimulation led to prevention of gray matter volume loss, and modulated gamma activity in the temporoparietal cortex as measured with power spectral density analysis of the resting-state electroencephalography (EEG) recordings, while at the same time increased local, long-range, and dynamic connectivity within the brain, enhancing information flow and integration. Importantly, the intervention was proven safe with no side effects. Accordingly, TMS might also have the potential to promote gamma rhythm synchronization, providing a novel non-pharmacological intervention for AD.

The non-invasive brain stimulation techniques provide the benefit of selecting specific brain areas for stimulation. Even though up to date no specific area has been identified as ideal to provide the most beneficial effects, it is suggested that several areas or pathways that are known to be negatively affected in AD, could provide potential

targets. On that basis, by targeting these areas, crucial for normal cognitive function brain connections and pathways could be strengthened or rescued (e.g., stimulating the precuneus to alleviate abnormal functional connectivity in the default mode network) leading to cognitive improvements (Heath et al., 2018).

1.8.5 Gamma-Band Stimulation: A Pioneering Approach to Treat Alzheimer's Disease?

Gamma oscillations reflect a fundamental brain process, critical for healthy intra-brain communication and cognitive functions, especially memory, and, if disturbed, results in cognitive disfunction (Başar, 2013). Decreased gamma brain activity has been observed in both mice models of AD and human patients. Evidence, indicating aberrant gamma brain rhythms in mice, before the accumulation of amyloid plaques (Goutagny et al.,2013; Iaccarino et al., 2016) has drawn scientific interest toward the investigation of their role in AD pathology and their potential role in its treatment. Etter et al. (2019) showed that restoration of gamma oscillations in the hippocampus by optogenetic gamma stimulation of parvalbumin neurons is sufficient to rescue memory loss in mice without decrease of plaque load. In that respect, it is evident that gamma brain waves play a crucial role in memory function that appears to be independent from plaque accumulation.

Whether the observed disruption in gamma brain activity is responsible for the cognitive impairment in AD, or if it is just another outcome of the disease's pathology remains to be answered. However, the entrainment of this brain activity and the consequent impact on the disease's pathology has gained interest and has signified a new and promising era in AD research. Even though the investigations are still at their infancy, evidence suggests that restoration of gamma oscillations, through auditory and visual gamma stimulation, may have the potential to ameliorate AD pathology and improve cognition. The first evidence regarding the effectiveness of 40 Hz gamma entrainment through sensory stimulation in human patients (Chan et al., 2021; He et al., 2021), supports the notion regarding the essential role that gamma brain activity plays in AD pathology. In addition to sensory stimulation, scientists have investigated the effects of 40 Hz stimulation using other techniques that allow interference with brain activity and stimulate at desirable frequencies. For instance, non-invasive methods,

such as transcranial magnetic stimulation, have been used generating positive results. On that basis, the new and promising research area of investigating the potential of gamma stimulation as a disease modifying therapeutic for AD, has emerged.

1.9 Non-Invasive Brain Stimulation

Non-invasive brain stimulation (NIBS) in rehabilitation is an emerging field experiencing rapid growth over the last few years. Many clinical trials test the effectiveness of such strategies to reduce pathology and improve patients' cognitive function. In AD clinical trials NIBS techniques such as focused ultrasound (e.g., Ning et al., 2022; Jeong et al., 2021; Mehta et al., 2021) and transcranial direct current stimulation (e.g., Cammisuli et al., 2022; Chen et al., 2022; Majdi et at., 2022) appears to enhance cognitive function. For example, Beisteiner et al (2020) found that two weeks of transcranial pulse stimulation with ultrasound led to significant cognitive improvements in AD patients that remained for three months post stimulation. Similarly, two weeks of transcranial direct current stimulation improved AD patients cognitive function and prevented the amyloid beta accumulation (Khedr et al., 2019).

In addition to NIBS approaches, several studies have verified the potential significant effects of cognitive training and cognitive stimulation in AD. These approaches involve various activities and tasks, designed to stimulate, and train patients' cognitive abilities such as memory and executive functions. The aim is to slow down the effects of neuropathological changes observed in AD (Glovagnoli et al., 2017; Kallio et al., 2017). Cognitive training together with NIBS represent the current innovative strategies to improve cognitive impairment in AD. The combination of these approaches has recently gained interest in an effort to maximize the effect on patients' behavior (Vecchio et al., 2022; Brem et al., 2020; Thams et al., 20220.

Transcranial magnetic stimulation represents a promising and well investigated strategy among NIBS approaches to modify brain activity and reduce pathology in neurology and psychiatry (for review see Somaa et al., 2022; Turi et al., 2021).

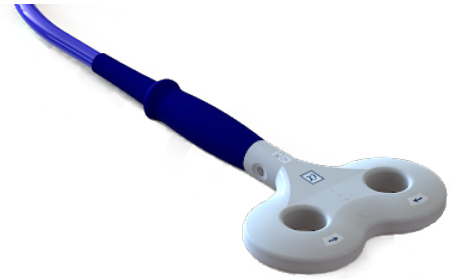
1.9.1 Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is an effective and safe non-invasive brain stimulation method, which is based on electro-physical principles, discovered by Michael Faraday. Fundamentally, TMS uses electromagnetic induction to induce electric currents in the brain. Pulses of current in an external specialized coil (Figure 1.13 A) generate a rapidly changing magnetic field that can penetrate the scalp and skull with little impedance. The induced electrical field can cause an eddy current to flow into the brain area underneath the coil. Depending on the stimulation parameters, the induced current can modulate cortical excitability, increasing it or decreasing it, activating, or deactivating cortical and subcortical networks with multiple effects (Iglesias, 2020). Sufficient evidence suggests that TMS produces aftereffects on the brain that outlast the stimulation period leading to subsequent behavioral changes (Chervyakov et al., 2015).

TMS can be applied one pulse at a time, single-pulse TMS, or in trains, repetitive TMS (rTMS). Single pulses are used basically to explore brain functioning in healthy subjects (Figure 1.13 B), whereas rTMS is used to induce changes in cortical areas of interest. It is estimated that the coil, which is positioned superficially above the brain area of interest, produces a magnetic pulse to a depth of 1.5 to 3 cm beneath the scalp (Rossi et al., 2009). Low-frequency rTMS, which is defined as <1 Hz, produces inhibitory aftereffects, reducing cortical excitability, increasing cortical silent period, and decreasing the motor-evoked potential amplitudes in the brain area of application. In contrast, high frequency rTMS, defined as >1Hz, leads to facilitatory aftereffects enhancing the cortical excitability (Iglesias, 2020).

Figure 1.13 Transcranial Magnetic Stimulation

A



B

Note: A) A Figure of Eight TMS Coil used in TMS. During TMS application, the coil is connected to a magnetic stimulator unit. Then, the coil is placed superficially above the brain site of interest, producing a magnetic pulse in a depth of 1.5 to 3 cm underneath the scalp, leading to cortical excitability modulation. Picture retrieved from magstim-rapid2; B) The picture illustrates an area (depicted in red) of coil-induced stimulation on the left posterior-occipital region. Changes were induced on the contra-lateral visual field, demonstrating inhibition of vision, scotomas and phosphenes. These phenomena produced by the TMS application have been documented in several experiments crucial for understanding the utility and underlying mechanisms of TMS (e.g., Amassian et al., 1989; Kammer et al., 2005). From "Transcranial Magnetic Stimulation as Treatment in Multiple Neurologic Conditions," by A. H. Iglesias, 2020, *Current Neurology and Neuroscience Reports, 20*(1), Introduction section, Figure 2 (https://doi.org/10.1007/s11910-020-1021-0).

Even though the exact pathophysiological mechanisms underlying the long-lasting effects of TMS remain unclear, it has been proposed that the effects on synaptic plasticity, through long-term potentiation (LTP) and long-term depression (LTD), are the key mechanism that supports the changes following the TMS exposure. LTP increases synaptic strength which can be evident for days, weeks, months or years and is induced by high-frequency stimulation, whereas LTD results in long-term reduction of synaptic strength and is caused by low-frequency stimulation (Duffau, 2006). Furthermore, rodent studies have demonstrated that TMS enhances neurogenesis and has a positive effect on differentiation and growth of neural stem cells (Arias-Carrión et al., 2004; Meng et al., 2009; Ueyama et al., 2011). In addition, Vlachos et al. (2012) studied the effects of TMS in the hippocampal CA1 cells of mice and found that

magnetic stimulation caused a remodeling of the dendritic spines. Additionally, a large body of literature suggests that TMS has an impact on the brain's neuroprotective mechanisms, including neuronal protection against death, alteration of blood flow and metabolism, while at the same time enhancing the recovery of neuronal function after brain injury (Fujiki et al., 2003; Funamizu et al., 2005; Ogiue-Ikeda et al., 2005; Sun et al., 2012).

The overall therapeutic effect of TMS can be determined by its impact in several brain processes (for a review see Chervyakov et al., 2015). Most importantly, TMS has the capability to facilitate the function of certain areas after brain damage or dysfunction, giving it a unique therapeutic potential. In fact, the last decade has witnessed a rapid increase in TMS application to study cognition, pathophysiology, and brain-behavior relations in various psychiatric and neurological disorders (George et al., 2007; Iglesias, 2020a). Today, TMS is an approved method for treating depression and obsessive-compulsive disorder, and accumulated evidence suggests its effectiveness in a variety of neurological diseases such as Parkinson's disease, stroke, multiple sclerosis, aphasia, tinnitus, epilepsy, and pain syndromes (Lefaucheur et al., 2014). rTMS has been used as an alternative therapeutic strategy in MCI and AD, demonstrating its ability to enhance cognitive function (Lee et al., 2016).

1.9.2 Repetitive TMS Safety Issues

Safety precautions and ethical recommendations on the application of TMS, guided by consensus conferences, exist and are being modified according to new evidence to guide researchers and clinicians (Lefaucheur et al., 2014, 2020). Guidelines include recommendations on four key parameters (i.e., intensity, train duration, inter-train interval and frequency). Even though the safety of TMS has been supported by several meta-analyses of the published literature (see Janicak et al., 2008; Loo et al., 2008), there are side effects linked to TMS use. The most hazardous side effect is seizure induction during the TMS session, however it is extremely rare (1.4% possibility in epileptic patients & less than 1% in normal individuals). More common but less serious side effects include headaches, local pain, neck pain and toothache (Rossi et al., 2009).

1.10 Transcranial Magnetic Stimulation in Alzheimer's Disease

The use of brain stimulation in MCI and AD has gained considerable clinical interest. A large and growing body of literature has demonstrated the beneficial effect of rTMS in various cognitive domains (for a review see Dong et al., 2018). Cotelli et al. (2006) enrolled 15 patients with probable AD to investigate the effect of high frequency rTMS at 20 Hz, applied bilaterally to the dorsolateral prefrontal cortices (DLPFCs), on picture naming. They reported significant improvement in action naming. Based on this promising result, they conducted another trial with 24 AD patients suffering from mild to severe dementia. Similar to previous findings, the authors pointed out that rTMS to bilateral DLPFCs improved action naming at all stages of AD. In addition, they observed significantly improved object naming in patients with moderate to severe AD (Cotelli et al., 2008). Considering that in these studies the authors had adopted only single rTMS sessions to investigate the immediate effect of rTMS in naming, in 2011 the same research team conducted a multiple baseline design study adopting a 4-week rTMS treatment for one group and a 2-week placebo rTMS followed by two weeks of active rTMS on a second group. Patients underwent 20 Hz rTMS on bilateral DLPFCs. The authors noted significant differences between the real rTMS and the placebo rTMS groups in sentence comprehension, with respect to the 2 first weeks, while both groups exhibited a lasting effect on the enhanced performance up to 8 weeks after the end of the experiment (Cotelli et al., 2011).

In a randomized control trial (RCT) Ahmed et al. (2012), randomized 45 patients with probable AD into three intervention groups: 20 Hz rTMS, 1 Hz rTMS or sham rTMS. Patients underwent rTMS, bilaterally to the DLPFC, for five sessions in a week. The authors discovered trends of improvement in overall cognition [measured by the Mini Mental State Examination, (MMSE)] in the 20 Hz group of patients, but only for those in the mild to moderate stages of AD. In particular, the effect of MMSE changes was medium to large (Cohen's $d = 0.7$) within the 20 Hz group, but very small within the sham group (Cohen's $d = 0.05$). (Wu et al., 2015), recruited 54 patients with mild to moderate AD and allocated them into an active 20 Hz rTMS group or a sham rTMS group. They delivered 20 rTMS sessions to the left DLPFC and reported that 20 Hz rTMS resulted in enhancement of overall cognition, as measured by the Alzheimer's

Disease Assessment Scale-cognitive subscale (ADAS-cog), and, in behavioral symptoms, measured by the Behavioral Pathology in AD (BEHAVE-AD). The difference in ADAS-cog, between the active and the sham group, was medium to large (Cohen's $d = 0.7$).

One RCT assessed the rTMS efficacy in MCI patients. In this study, 10 Hz or sham rTMS was delivered for 10 sessions to the left DLPFC of 34 patients. The authors reported only a modest improvement in everyday memory in the active rTMS group (Drumond Marra et al., 2015). In a recent RCT, Padala et al. (2018) investigated the rTMS as a potential treatment for apathy in MCI patients. It was indicated that 10 sessions of 10 Hz rTMS to the left DLPFC was efficacious in improving apathy in MCI patients.

A multisite rTMS approach has recently been introduced as a possible intervention in AD. Known as NeuroAD, this approach involves the stimulation of DLPFC, the parietal somatosensory association cortex, Broca, and Wernicke's areas, combined with cognitive training (Bentwich et al., 2011). This technique has demonstrated positive effects in cognition for months after the end of the stimulation (Nguyen et al., 2017). However, the effect of the stimulation has not been investigated in isolation with cognitive training, therefore, the contribution of rTMS alone in the observed improvements is not yet clear (Buschert et al., 2010). Finally, some research has been undertaken adopting a multisite TMS approach without cognitive training, indicating improvements in overall cognition, but only in mild AD patients (Zhao et al., 2017) and only in attention (Anderkova et al., 2015).

1.10.1 Identifying New Brain Regions as Possible Targets to Treat Cognitive Decline in AD

The DLPFC is the most commonly targeted area in AD research and its therapeutic value has been well documented. However, TMS over the DLPFC is an FDA approved treatment for medication-resistant depression. Therefore, bearing in mind that the prevalence of depression in AD is almost 50% (Rutherford et al., 2013) and that even mild depression is associated with significant cognitive dysfunction (Starkstein et al., 2005), it is impossible to control for the possibility that AD patients are benefitting from rTMS secondary to stimulation effects on comorbid depression. In addition, while

the DLPFC has been well investigated for the improvement of language and neuropsychiatric symptoms there is a chance that research regarding other possible targets could be effective in treating the profoundly affected cognitive functions manifested in AD, such as memory. Therefore, research should be focused on identifying new key target areas aiming to maximize the benefits from an rTMS treatment.

One possible strategy to identify new brain regions as possible targets for rTMS in AD is to assess brain areas and connections that have been negatively affected by AD pathophysiology. For instance, it is well documented that the DMN is the most severely affected brain network, therefore, the amelioration of the impaired functional connectivity between key nodes of the DMN could be a possible alternative strategy. In addition, it is evident that the hippocampus is severely affected by the neurofibrillary tangles early in the disease, resulting in profound episodic memory impairment. As it cannot be stimulated directly, targeting cortical areas associated with the hippocampus could improve memory function. As has been discussed already, the main mechanism that underlies TMS effectiveness is the induced plasticity and strengthening of brain connections. It is evident that rTMS can alter cortico-hippocampal connectivity in healthy subjects (Wang et al., 2014), therefore, identifying the areas that present loss of functional connectivity with the hippocampus in AD could also provide possible targets. Focusing on addressing fundamental questions like which areas present early changes from the AD pathophysiology and how these changes lead to cognitive impairment or which neuronal circuitries need strengthening in AD will give rise to a new era of brain stimulation research in AD.

1.11 Rationale for the Study, Aim and Objectives

The aim of this thesis was to combine the most recent scientific evidence to create a novel non-invasive brain stimulation protocol for patients with aMCI and mild-to-moderate AD. We aimed to investigate the effect of gamma-band rTMS, targeting bilaterally the PC, as a potential treatment of cognitive dysfunction. The PC represented a perfect new target brain area as: it exhibits cortical atrophy, has a strong involvement in episodic memory processes, it is a key node of the DMN, it holds connections with the hippocampus which demonstrates impaired functional connectivity early in the

disease and finally, has extensive reciprocal and bilateral cortical and subcortical connections (Chen et al., 2017; Kim et al., 2013; Schmidt et al., 2002). In fact, recent evidence suggests that application of rTMS on key DMN nodes, such as the PC, improves episodic memory performance in healthy controls (Bonnì et al., 2015; Rose et al., 2016). Therefore, stimulation of the PC through TMS may improve the disrupted connectivity between the PC and the hippocampus, as well as the abnormal functional connectivity between the PC and other important nodes of the DMN and hence may have the potential to reverse the AD related cognitive decline. In addition, targeting the brain's gamma oscillation activity using gamma-band stimulation, especially at 40 Hz, has provided encouraging results and is considered a new and promising research area for the treatment of AD. In this research, the promising potential of the gamma-band brain stimulation was tested by delivering 40 Hz magnetic stimulation on the PC and provided the first scientific evidence about the effectiveness of the above methodology in the treatment of cognitive disfunction in AD.

To our knowledge, up until now only one study has investigated the effect of high frequency stimulation over the PC in AD (Koch et al., 2018). In this study, TMS at 20 Hz was applied bilaterally to the PC demonstrating a significant effect in episodic memory recall. In addition, TMS induced neural activity modulation in PC and medial frontal cortex, suggesting relevant modulation over the medial parieto-frontal circuit. Finally, TMS at 20 Hz (i.e., a frequency that falls within the range of betta oscillations) prompted an enhancement of beta activity over the PC. These findings provide the first piece of evidence that the PC may be a novel stimulation target to enhance the affected networks and improve AD patients' memory performance. The effect that a gamma frequency stimulation will have on the disrupted gamma oscillations documented in AD, and hence on patients' cognitive performance, remains to be seen.

The aim of this thesis was to address the following research question:

Is a 40 Hz transcranial magnetic stimulation delivered bilaterally to the PC, effective in mitigating cognitive dysfunction in patients with aMCI and mild-to-moderate Alzheimer's Disease?

To answer the above major research question, the below steps were followed:

1. A 40 Hz rTMS protocol was developed according to the latest recommendations for the therapeutic application of TMS (Lefaucheur et al., 2020). This step is discussed in Chapter 2.

2. The safety, tolerability, and the subsequent aftereffects on cortical excitability of the developed gamma frequency rTMS protocol were investigated. This study is presented in Chapter 2.

3. Normative studies were conducted to develop alternative and equally difficult forms of neuropsychological tests. These studies were conducted to develop the necessary for step 4 material and are presented and discussed in Chapter 3.

4. A randomized, single case experimental design methodology was employed to investigate the effect of 40 Hz rTMS in aMCI and AD patients. Chapter 4 presents the study's methodology and reports the treatment effects in aMCI patients. The effects of 40 Hz rTMS in AD patients are presented in Chapter 5.

1.12 Chapter Summary

AD is a devastating neurodegenerative disorder and the most prevalent form of dementia. Despite hundreds of clinical trials and investments of billions of dollars in medication research, AD remains a progressive and lethal disease. Recent breakthrough evidence has pointed towards the investigation of gamma-based interventions for the reduction of AD related neuropathology and patients' symptoms alleviation. At the same time, non-invasive brain stimulation through TMS has generated promising results as a potential treatment of cognitive dysfunction in AD. This technique produces lasting aftereffects modulating cortical excitability and strengthening neuronal networks. The aim of this thesis was to investigate the effectiveness of a novel gamma frequency brain stimulation protocol in enhancing cognitive function in patients with aMCI and mild-to-moderate AD. The following chapters present the steps that were followed to answer this thesis research question. Chapter 2 describes the development of a novel gamma rTMS protocol and its aftereffects on cortical excitability of healthy participants. Chapter 3 presents and discusses the studies that were conducted for the development of the necessary alternative forms of neuropsychological measures.

Chapter 4 presents a single case experimental design study, conducted to investigate the effects of 40 Hz rTMS in aMCI patients. In Chapter 5 the effects of 40 Hz rTMS in AD patients are presented. Finally, in Chapter 6 a summary of the results and a discussion for the conducted research of this thesis, is provided.

Chapter 2 Neurophysiological Effects of 40 Hz Transcranial Magnetic Stimulation on the Human Motor Cortex[2]

Chapter 1 provided an overview of the recent evidence demonstrating that gamma entrainment might have a disease-modifying effect in AD. Furthermore, the use of rTMS as a non-invasive technique to modulate cortical excitability in AD patients was discussed. While the TMS has been widely used in neurological and psychiatric patients, and healthy participants, there are no gold standards regarding the protocols used. Additionally, stimulation in high frequencies, such as in the gamma-band, has not been investigated in terms of safety and the aftereffects on cortical excitability. In this chapter a study aiming to investigate the effects of a 40 Hz rTMS protocol on the primary human motor cortex of healthy subjects is presented.

2.1 Introduction

Recently, TMS has emerged as a promising therapeutic intervention in a variety of neurological and psychiatric conditions, from AD to pain and schizophrenia (for a review see Lefaucheur et al., 2020). The first evidence indicating that trains of stimuli delivered through TMS could produce minutes of suppression (e.g., Chen et al., 1997) or excitation (e.g., Pascual-leone et al., 1994; Peinemann et al., 2004) of human motor networks provided the impetus for studies aimed at exploring this drug-free technique as a possible therapeutic approach. Since then, it has been widely accepted that TMS can trigger effects

[2] An adapted version of this chapter has been published in the journal Neurophysiologie Clinique-Clinical Neurophysiology as: Traikapi A., Phylactou P., Konstantinou N. (2022). Repetitive transcranial magnetic stimulation of the human motor cortex in the gamma band reduces cortical excitability. *Neurophysiologie Clinique, 52*(5):407-409. https://doi.org/10.1016/j.neucli.2022.09.005

on cortical excitability, via inducing long-term potentiation or depression of synaptic activity (Esser et al., 2006). TMS has been investigated as a means to treat cognitive dysfunction (e.g., in AD), psychiatric symptoms and motor deficits (Lefaucheur et al., 2020).

In the field of psychiatry, the application of TMS is widely recognized and represents an applied treatment option for major depressive disorder (Garnaat et al., 2018; Voigt et al., 2019) and obsessive-compulsive disorder (Cocchi et al., 2018; Rehn et al., 2018). In the motor cortex TMS has been investigated as a potential therapeutic intervention for selected movement disorders. For instance, rTMS over the primary motor cortex (M1) in Parkinson's disease has shown beneficial effects on patients' motor behavior (Filipović et al., 2010; Pascual-Leone et al., 1994; Siebner et al., 1999; Siebner, Mentschel, et al., 2000; Siebner, Rossmeier, et al., 2000). Similar results have been reported, among others, in patients with Huntington's disease (Brusa et al., 2005; Shukla et al., 2013), amyotrophic lateral sclerosis (di Lazzaro et al., 22006; Dileone et al., 2010; Zanette et al., 2008) and multiple sclerosis (Agüera et al., 2020; Centonze et al., 2007; Nielsen et al., 1996). While the application of TMS as a non-invasive technique in neurorehabilitation has not been approved yet as a first stage of intervention, extensive research has been conducted in a wide variety of neurological diseases, providing evidence for its therapeutic efficacy. For instance, the efficacy of the application of rTMS in rehabilitation of neuropathic pain and in hand motor recovery after stroke has been ranked as Level 1 of evidence (e.g., definite efficacy) (Lefaucheur et al., 2020). This rank is the same with the TMS approved intervention for the treatment of depression. Evidence exists for the therapeutic utility of TMS across conditions, which as a matter of fact is very promising, there is however, a need for further support and evidence-based clinical data (Somaa et al., 2022). As the potential clinical significance of TMS is enormous and affects a large number of patients with devastating conditions (Rossi et al., 2009), new protocols are being developed (Balderston et al., 2021; Chen et al., 2021; Tang et al., 2019).

An important factor regarding the application of TMS is that depending on the stimulation parameters, can suppress or enhance cortical excitability (Huang et al., 2005). For instance, amyotrophic lateral sclerosis and Huntington's disease are characterized by cortical hyperexcitability (Vucic et al., 2009; Vucic & Kiernan, 2006; Wainger et al., 2014), and therefore, suppressive TMS protocols are used to inhibit the extensive excitability (Brown et al., 2014; Brusa et al., 2005). In contrast, in Parkinson's disease,

which is characterized by cortical activation abnormalities, TMS protocols which are known to trigger excitatory effects are used (Wagle Shukla et al., 2016).Therefore, it is important to investigate the exact effects of a given protocol prior to its clinical application. This is possible by applying TMS to healthy adult human participants. Participants receive short magnetic pulses to their scalp to induce an electric current on the surface of their brain. This leads to a temporary disruption or facilitation of function in the underlying brain region. By observing the effects of such disruption in carefully controlled experiments in healthy adult participants, the effect of specific patterns of stimulation can be identified and hence new therapeutic protocols can be developed (Tang et al., 2019).

2.1.1 Gamma Frequency TMS

Recently, entrainment of gamma brain activity has gained scientific interest, and gamma brain stimulation is being investigated as a potential therapeutic approach in several diseases (Benninger et al., 2012; Strüber & Herrmann, 2020). For instance, as mentioned in Chapter 1, a pioneering approach, which targets gamma brain waves in AD, has been introduced as a potential treatment of the disease (for a review please see Traikapi & Konstantinou, 2021). Preliminary evidence suggests that induction of gamma oscillations through 40 Hz sensory stimulation or via 40 Hz non-invasive brain stimulation may have a potential therapeutic effect in AD pathology alleviation (e.g., He et al., 2021; Liu et al., 2021). Additionally, aberrant gamma brain activity has been observed in other diseases, such as in chronic pain. For instance, increased electroencephalographic activation in the gamma-band has been observed in several studies with chronic pain patients and has been indicated as a potential biomarker of pain perception (May et al., 2019; Mussigmann et al., 2021). On the other hand, disrupted low-gamma brain activity (25-40 Hz) has been observed in mild traumatic brain injury (Wang et al., 2017). The authors indicated that the alterations in EEG on these patients' intrinsic gamma synchronization might be a characteristic of functional pathology and could be useful for developing new treatment interventions. In conclusion, disruption of gamma brain activity has been observed in several diseases and the link between this interruption and cognitive impairment is currently under investigation (e.g., Cho et al., 2020; Mably & Colgin, 2018).

While evidence suggests that the induction of gamma oscillations using TMS has therapeutic potential, and that impaired gamma band activity can represent a potential

biomarker for specific diseases, there are currently no studies investigating the physiological effects of such a high frequency stimulation protocol.

Due to the potential clinical implications of gamma stimulation, the aim of this study was:

- to develop a gamma frequency TMS protocol, according to the latest safety recommendation for the application of TMS;
- to test the developed protocol in terms of its potential to modulate cortical excitability that outlasts the stimulation period (for a period of up to 45 minutes after stimulation);
- to identify the nature of effect on motor neural networks and the duration of these aftereffects; and
- to assess the feasibility, tolerability, and safety of the gamma TMS protocol.

2.2 Methodology

2.2.1 Participants & Study Design

This was a TMS-EMG study to investigate the effects of a single session of 40 Hz rTMS in healthy participants. The study was conducted in the Brain and Cognitive Science Lab (BaCS) at the Rehabilitation Clinic of the Cyprus University of Technology, in Limassol, Cyprus. The experiment was approved by the Cyprus National Bioethics Committee (AP. Φακ.: ΕΕΒΚ/ΕΠ/2021/22; Appendix 1). A non-random sampling method was used by the chain-referral or snowball sampling technique. Accordingly, the existing participants provided referrals to recruit friends or family members that were meeting the inclusion criteria and might be interested in participating. Additionally, an advertisement outlining the aim of the study with a request for assistance with participant recruitment was shared on the investigators' social media. To participate in this study participants had to meet the following criteria: age between 18 and 35, have no history of epilepsy, have no diagnosis of mental illness or any neurological disease, have no metal or implanted medical devises, have no history of migraines, have not consumed alcohol 24 hours prior to the experiment. Contraindicators for participating in the study were: history of

epilepsy, family history of epilepsy or an epileptic event in the past, diagnosis of a mental illness, alcohol consumption 24 hours prior to the study, history of brain injury, surgery to the heart or stroke, chronic severe headaches, pregnancy, implanted stimulators (e.g., pacemaker), electrodes for monitoring brain activity, any magnetic implants and generally any other metal device or object implanted in participants' body.

Prior to the experiment a questionnaire evaluating participants' ability to participate was used (Appendix 2). Participants were informed about the possible TMS adverse side effects and that they could withdraw at any time without any consequence. All participants provided a written consent form (the consent form can be found here: Motor Study-Consent Form).

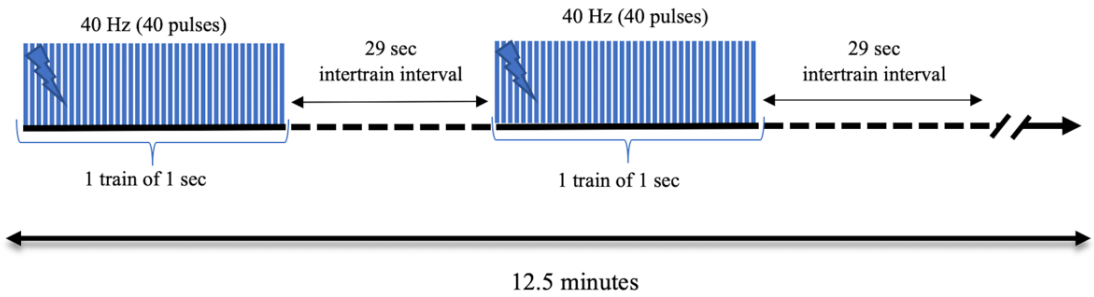
2.2.2 rTMS Protocol Development

There are several important divergent parameters that must be considered when developing a new TMS protocol that can affect its safety as well as its effect on cortical excitability. These are: (1) frequency of stimulation (Hz); (2) intensity (%threshold/output); (3) duration: each train and total; (4) intertrain interval: period of no stimulation among trains; and (5) number of pulses: each train and total (Rossi et al., 2009). Currently, safety precautions and practice recommendations for the therapeutic application of TMS, are guided by the latest consensus paper published by a group of European experts (Lefaucheur et al., 2020). In this paper, the guidelines and recommendations are based on published evidence regarding TMS efficacy and TMS parameters safety. These recommendations were followed to minimize as much as possible the likelihood of side effects. Hence the parameters of the developed TMS protocol were established as follows:

- frequency of stimulation: 40 Hz;
- intensity: 80% of participants resting motor threshold (RMT);
- duration: 1 second per train, 12.5 minutes in total;
- intertrain interval: 29 seconds; and
- number of pulses: 40 per train (i.e., 40 Hz), 1000 in total.

The developed gamma-band rTMS protocol is illustrated in Figure 2.1.

Figure 2.1 40 Hz Transcranial Magnetic Stimulation Protocol



Note: Graphical illustration of the TMS protocol. The stimulation protocol consisted of 25 trains, each train consisting of 40 pulses in 1 second (i.e., 40 Hz) followed by 29 seconds of no stimulation. In total, 1000 pulses were included (40 pulses per train for 25 trains) for a total duration of 12.5 minutes. The protocol was set to be delivered on 80% of each participant's RMT. From 'Repetitive transcranial magnetic stimulation of the human motor cortex in the gamma band reduces cortical excitability,' by Traikapi A., Phylactou P., Konstantinou N. (2022), *Neurophysiologie Clinique - Clinical Neurophysiology, 52*(5), Figure 1 (https://doi.org/10.1016/j.neucli.2022.09.005).

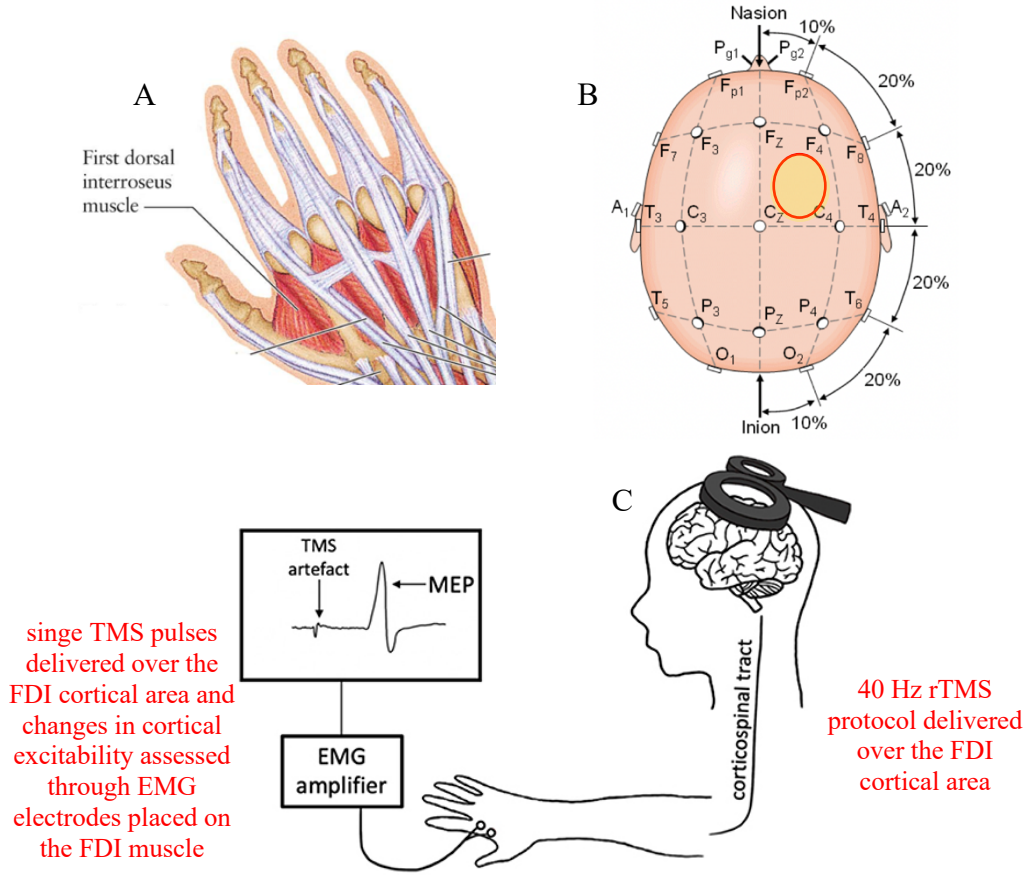
2.2.3 Methods

As mentioned above, the stimulation protocol consisted of 25 trains, each train consisting of 40 pulses in 1 second (i.e., 40 Hz) followed by 29 seconds of no stimulation. Stimulation was delivered using the Magstim Super Rapid2 Plus1 System with a vacuum-cooled D70 figure-of-eight alpha coil. In total, 1000 pulses were delivered to each participant in 12.5 minutes. A neuronavigation system (Visor2, ANT Neuro, Enschede, Netherlands) was used to localize the primary motor cortex hotspot, guide the sessions, and ensure stable coil positioning. The coil was held at an angle of approximately 45^{o} to the midline with the hand pointing laterally and posteriorly such that the current flowed from posterior to anterior. The stimulation was applied contralateral to each participant's dominant hand (i.e., left hemisphere on right-handed participants). After localizing the hot spot, the coordinates of each participant were saved in the neuronavigation system and were used to guide the rTMS session and all the RMT assessments. Thereby, the

same stimulation parameters were ensured throughout the experiment for all participants (i.e., coil orientation, distance, and tilt).

Each participant received 40 Hz TMS at 80% of individual RMT over the primary motor cortex (M1). The influence on cortical excitability was assessed by comparing RMT before stimulation with RMT immediately after (0′ time point) and up to 45 minutes after stimulation at 15-minute intervals (i.e., at 0, 15, 30 and 45 minutes post-stimulation). RMT was defined as the minimum TMS intensity needed to elicit MEPs of > 50μV in five out of 10 trials in the relaxed first dorsal interosseous muscle (FDI) and was established using single-pulse TMS. MEPs were obtained by surface electromyography (EMG) leads placed over the left or the right FDI muscle and MEPs were recorded from each participant's dominant hand (i.e., contralateral to the stimulation site). RMT was measured before delivering the gamma stimulation protocol and an additional four times post-stimulation (immediately after stimulation, and every 15 minutes up to 45 minutes post-stimulation). The TMS intensity in the first post-stimulation measurement of RMT was set at the pre-stimulation RMT intensity and during the RMT measurement phase was being reduced or increased in steps of 1% or 2% until 5 MEPs of > 50μV out of 10 trials were recorded. Each of the following post-stimulation measurements (i.e., 15′, 30′ and 45′) followed the same procedure and TMS intensity started at the previously identified RMT. Figure 2.2 illustrates the experimental procedures that were followed in this study.

Figure 2.2 Experimental procedures and set up



Note: A) The FDI hand muscle was chosen as an output target; B) The 10-20 electrode system of the International Federation system (Jasper, 1958) was used to find each participant's hot spot in their primary motor cortex (i.e., the FDI). Accordingly, initially the vertex was located (i.e., Cz) and then single TMS pulses were delivered approximately 5 cm lateral, until MEPs were evident. The intensity was set at 30% of machine output and increased in steps of 5%. Several spots were tested until the hot spot was identified. Then, the TMS intensity was lowered progressively, until the minimum intensity needed to elicit MEPs of > 50mV in five out of 10 trials was found; C) RMT was assessed as a baseline measure before the gamma rTMS stimulation. Then, the 40 Hz rTMS was delivered over the same area. After the stimulation, single pulses of TMS were applied on the same area. When a single pulse is applied, the magnetic field penetrates the scalp inducing a perpendicular secondary electric field within the cortex. This electric current depolarizes the cortical neurons, in our case in the FDI cortical area, evoking a descending volley along the corticospinal tract and subsequently a motor response. This response was measured with EMG electrodes that were placed on the FDI muscles. RMT was assessed four times post-stimulation (i.e., immediately after, after 15, 30 and 45 minutes) and differences between the different time measures in relation to the pre-stimulation were evaluated. Picture retrieved from "Transcranial magnetic stimulation to assess exercise-induced neuroplasticity," by

Turco & Nelson, 2021, Frontiers in Neuroergonomics, Introduction section, Figure 1 (https://doi.org/10.3389/fnrgo.2021.679033).

2.2.4 Statistical Analysis

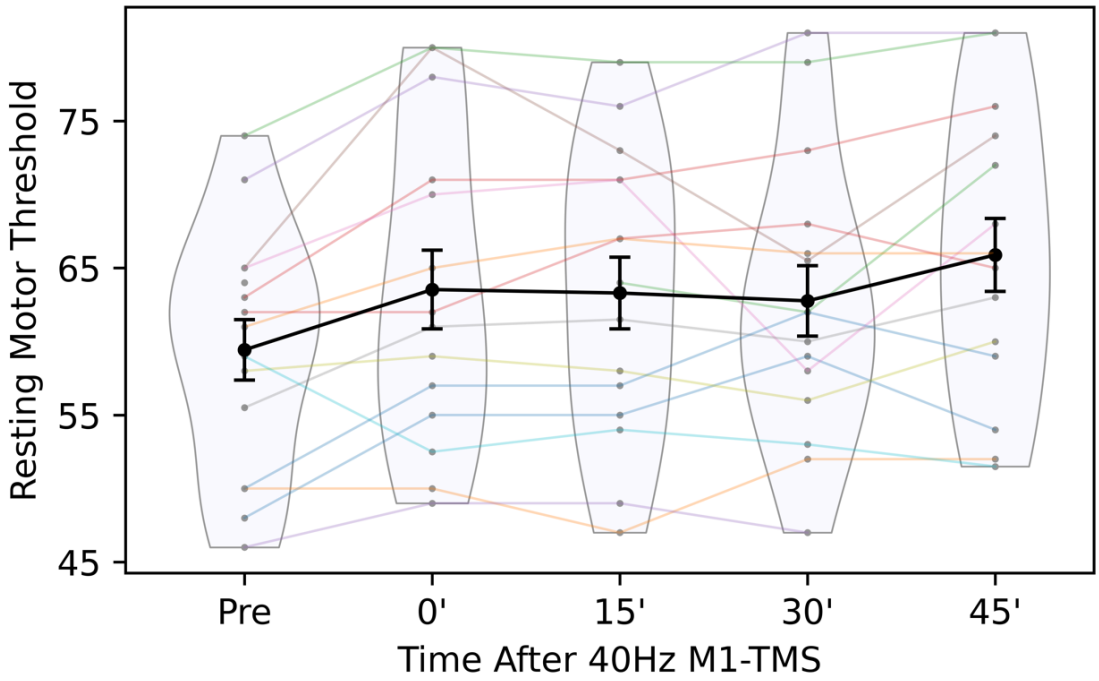
To test the effect of the 40 Hz TMS protocol on participants' cortical excitability the RMT measurements before the rTMS stimulation were compared with the four post-stimulation measurements of RMT: (1) immediately after the stimulation (time point 0)′; (2) 15 minutes after the stimulation (time point 15); (3) 30 minutes after the stimulation (time point 30); and (4) 45 minutes after the stimulation (time point 45). The Bayesian repeated measures analysis of variance (ANOVA) was used. The statistical analyses were conducted with the Jamovi statistical software.

2.3 Results

Fifteen participants participated in the study. The mean age of the total sample was 24.9 years (SD=4, range=20 to 36), of which 73.3% were females. The results provided strong evidence in favor of a TMS timing effect (BF10=22.24), indicating that RMTs differed across the stimulation periods (Figure 2.3). Specifically, compared to the pre-stimulation measures (Mean=59.43 SD = 7.99), RMTs were increased in the 0′ time point (Mean=63.54 SD=10.39, BF10=9.48), the 15′ time point (Mean=63.3 SD=9.47, BF10=18.9), the 30′ time point (Mean=62.76, SD=9.3, BF10=1.56), and the 45′ time point (Mean=65.89, SD=9.63, BF10=34.87). The inhibitory effect was observed immediately after the stimulation (i.e., time point 0′) and reached the highest point at 45 minutes after the stimulation.

The TMS protocol was well tolerated, and participants did not complain about any side effects.

Figure 2.3 Changes on resting motor threshold following 40 Hz rTMS



Note: Mean participant resting motor threshold before receiving the TMS protocol, and at 0, 15, 30, and 45 minutes after receiving the TMS protocol. The increase of the RMT indicates suppression of corticospinal excitability. Error bars depict ± 1 standard error. TMS; Transcranial magnetic stimulation, RMT; Resting motor threshold.

2.4 Summary of the Results and Conclusion

The aim of this study was to develop a low gamma frequency rTMS protocol and investigate its feasibility, safety, and the aftereffects on healthy participants' cortical excitability. The stimulation was well tolerated by all participants and no side-effects were reported while it generated long-lasting effects that outlasted the stimulation. Specifically, the developed 40 Hz rTMS protocol was found to significantly influence cortical excitability by inducing suppression over the stimulated cortical networks. Participants' MEPs were found to be suppressed for at least 45′ post-stimulation, increasing RMT measures. A strong immediate effect after the stimulation was indicated which reached the highest level of suppression 45′ post-stimulation.

High-frequency TMS at 40 Hz over the human motor cortex can have inhibitory physiological aftereffects that outlast the stimulation period by at least 45 minutes. Considering that the suppressive effect was at its strongest at 45 minutes after stimulation, a longer lasting effect can be assumed. Overall, these findings revealed that the specific high-frequency gamma TMS protocol is well tolerated and, importantly, it can induce long-lasting effects on neural plasticity. Future work needs to investigate the connection of the effects we report here to known neuronal mechanisms, such as long-term depression.

2.5 Chapter Summary

This chapter has presented the neurophysiological effects of a newly developed gamma-band rTMS protocol. Aftereffects were produced on participants' motor cortex and changes that outlasted the application of the stimulation in motor neuronal networks were investigated. The study indicated that stimulation in such a high frequency is feasible, the protocol is well-tolerated, safe, and can affect cortical excitability for up to 45 minutes. The effects of gamma-band stimulation, through TMS, in diseases characterized by gamma-rhythm dysfunctions, such as AD, remains to be seen.

Chapter 3 Development of Neuropsychological Measures for the Greek-Cypriot Population

In clinical trials and studies in which the effectiveness of new treatments is investigated, serial cognitive evaluations are required to assess the impact of an intervention on patients' behavior. Repeated neuropsychological evaluations lead to increased familiarity and subsequently changes in test performance due to prior exposure. As a consequence, it is not clear whether the noticed changes in test scores are attributable to the study's intervention or to practice effects (Wesnes & Pincock, 2002). As it is described in detail in Chapter 4, in the primary study of this thesis, several cognitive evaluations separated by only a few days were conducted for the assessment of primary and secondary outcomes. Thus, to avoid misleading results that might stem from increased familiarity and not from the intervention itself, and thus to minimize the possibility of committing Type I error, several cognitive measures were created before the beginning of the single-case design study. This chapter presents the development of the first Cypriot dialect-based corpora and the Cypriot word pool (CWP), a list of approximately 2,850 words used in the Cypriot dialect and their respective normative data. In addition, it presents the two alternative forms of the Cypriot version of the Alzheimer's Disease Assessment Scale-cognitive subscale-12 (ADAS-cog) and the developed alternative and equally difficult neuropsychological assessment tests that were used for the primary and secondary outcome measures in this thesis.

3.1 Practice Effects in Serial Cognitive Assessments

Longitudinal and repeated cognitive assessments are often necessary; these are pivotal in the interpretation of the efficacy of a given intervention in studies and clinical trials. For instance, in single-case design studies, which have recently been classified as Level 1 evidence for treatment decision purposes, the methodology should include at least 20 assessments (in an ABAB design; five per phase with at least four phases) of each outcome variable to meet evidence standards (Tate et al., 2014). Clinical trials in MCI and AD typically use designs that include cognitive evaluations on several occasions within relatively short periods (Rutherford et al., 2015). The endpoint or final assessment is considered a study's final outcome; however, the results gained after previous testing

can be strongly influenced by practice effects. A study's validity can hence be severity compromised, which may lead to erroneous conclusions (Benedict & Zgaljardic, 1998; Calamia et al., 2012; Eagger et al., 1992; Elman et al., 2018; Goldberg et al., 2015; Wesnes & Pincock, 2002).

Practice effects are characteristic phenomena in serial cognitive assessments defined as changes in one's performance attributed to prior exposure to a test, as opposed to truthful cognitive improvement (Calamia et al., 2012; Heilbronner et al., 2010). It has been hypothesized that practice effects in AD patients stem from procedural learning, a relatively uncompromised aspect of cognition early in the disease (Budson & Price, 2005). Therefore, cognitive improvements in AD patients, when practice effects have not been considered, can be seen after serial testing. These are due to procedural memory enhancement, which will not produce significant benefit to patients' every day cognitive function (Wesnes & Pincock, 2002). Practice effects in AD have not been widely discussed, probably because AD is predominantly characterized by an amnestic syndrome, and, hence, patients present difficulties in learning and consolidating information. However, other cognitive domains may not have suffered the same extent of degeneration as the memory's neuronal system, so the likelihood of practice effects (e.g., some learning may engage the relatively unaffected striatal procedural learning systems; Goldberg et al., 2015) exists. In fact, practice effects have been observed and discussed in several studies and clinical trials (Birks & Harvey, 2018; Eagger et al., 1992; Rogers et al., 1998). Regarding MCI, failure to account for practice effects in repeated testing, leads to delay of diagnosis and detection of conversion to AD. Subsequently, there are serious implications not only for clinical practice but also for clinical trials. Therefore, accounting for practice effects is critical for the early detection of MCI and investigation of interventions' efficacy (Elman et al., 2018; Goldberg et al., 2015; Mathews et al., 2014).

One method proposed, which seems to be a straightforward approach, to minimize practice effects is the use of alternative tests forms (Beglinger et al., 2005). Alternative forms use different stimuli than the original ones and hence eliminate gains from the memorization of test items (e.g., words). Even though practice effects cannot be completely eliminated, alternative forms have been associated with decreased levels in several studies and are considered a reliable strategy when multiple cognitive evaluations are necessary (Benedict & Zgaljardic, 1998; Watson et al., 1994; Zgaljardic & Benedict,

2001). The major limitation when using alternative forms is that they may differ significantly in their psychometric properties (e.g., item difficulty). For example, easier forms could result in increased scores, while difficult ones will lead to significantly lower scores. When a difficult form precedes an easy one at retest, a patient may mistakenly appear to present cognitive improvement, and vice versa. Nevertheless, a considerable need exists to minimize the practice effects in clinical trials and studies that require serial neuropsychological evaluations. As such, the development of equivalent alternative forms is paramount to maximize a study's validity and thus to deduce reliable conclusions (Calamia et al., 2012).

3.2 Development of the First Cypriot-Based Corpora and the Cypriot Word Pool

In laboratories, where experiments require the use of multiple random lists (alternative forms) for the serial evaluation of verbal learning, memory, and several other cognitive domains, it is common practice to use word pools that include standardized common words derived from culturally appropriate sources such as books, newspapers, and subtitles (van Heuven et al., 2014). The most well-known pools are that created by Paivio et al. (1968), which contains 925 nouns; the Toronto word pool, developed by Friendly et al. (1982); and Battig and Montague's (1969) categorized word pool, comprising 5,231 words divided into 56 categories. These classical pools are widely used in psychological studies of learning and memory and have been continuously revised and expanded over the years and across languages (Clark & Paivio, 2004; Coltheart, 1981; Gilhooly & Logie, 1980; Newcombe et al., 2012; Stadthagen-Gonzalez & Davis, 2006). More recently, Brysbaert et al. (2014) created a novel database with 37,000 English words and approximately 3,000 two-word expressions to be used as reference in experimental research.

Psycholinguistic word databases that include words used in a specific language have been created and made available in a variety of languages (e.g., Hellenic National Corpus, 2009; The British National Corpus; Balota et al., 2007). These corpora are constructed primarily from the analysis of the written language from books, newspapers, subtitles, and even the internet (e.g., Brysbaert & New, 2009; Lund & Burgess, 1996; Thorndike, 1921). For the development of standardized word pools, scientists tend to select words

from these corpora according to criteria that best fit their research and/or clinical needs. For instance, Stadthagen-Gonzalez and Davis (2006) selected to normilize a set of 1,526 words that were fairly representative of the types of words typically used in their psycholinguistic experiments. Nelson et al. (2004) reported that they chose to normalize words they thought would be appropriate for their experiments on priming and also added verbs for a student's study needs. The well-established Toronto word pool (Friendly et al., 1982) was developed by selecting 1,080 words from Thorndike's (1921) database, originating from the analysis of 41 different resources, including English literature, cookbooks, and farming books.

Despite the widespread use of word pools in research in general and in psychological research in particular, their availability for Cypriots is scarce. Terzopoulos et al. (2017) developed a word frequency database for Greek and Cypriot primary school children from the analysis of 116 textbooks used in primary education. However, even though the educational systems in Greece and Cyprus share the same books and Greek-Cypriots are taught the standard Greek language, the Cypriot dialect presents clear functional differentiation and linguistic varieties (Arvaniti, 2006). Over the years, the use of the Greek language in Cyprus has increasingly diverged from the language as spoken in Greece, to the point that today, the two are recognizably different (for a review see Arvaniti, 2006). Therefore, it is understood that word corpora or cognitive measures developed for Greek populations might not be appropriate or sensitive to be used to target the Cypriot-Greek population. The lack of word lists created for the Cypriot dialect is thus a major obstacle for conducting neuroscientific research in which serial cognitive evaluations through alternative test forms are required. As such, the aim of the research presented below is to overcome this gap by developing the first Cypriot-based corpora and the Cypriot word pool, a powerful tool for conducting cognitive research with Greek-Cypriot participants.

3.3 Development of the First Cypriot-Based Corpora

It has been emphasized in the literature that when constructing a corpus, several aspects affect its quality. For instance, Brysbaert et al. (2011) stressed that the extent to which materials included in a corpus represent the language that participants typically have been exposed to is of paramount importance for creating a qualitative and language-

representative corpus. On that basis, Brysbaert and New (2009) recommended three sources that should be used to extract reliable language materials to be included in a corpus. The first and, according to the authors, most important and reliable source is subtitles of television series and films. The second source refers to books used in primary and secondary school; finally, materials from widely read newspapers and/or magazines and discussion groups on the internet. The authors explained that these three sources capture the "body" of a language, with the subtitles representing the best source and the newspapers and magazines the least relevant.

According to the aforementioned recommendations, several limitations in the creation of a corpus based on the Cypriot dialect exist. For example, as mentioned above, the books used in the educational system in Cyprus are the same used in Greece and are based on the Greek language as it is spoken in Greece. Moreover, the subtitles of movies and series are again created based upon the Greek language. Therefore, none of these sources can reliably capture the exact form of the Greek language as it is used by Greek-Cypriots. For the creation of a qualitatively Cypriot dialect corpus, only materials from newspapers, magazines and discussion groups on the internet should consequently be used. Bearing in mind the aforementioned limitations, and the fact that Greek-Cypriots likely use the dialect mostly in verbal communication, it was thought essential to create three different corpora generated from the following:

- newspapers and magazines, as they are considered reliable sources and can capture the formal expressions of the language that Greek-Cypriots are exposed to;

- discussion groups on the internet, as they can capture the informal expressions of the Cypriot dialect; and

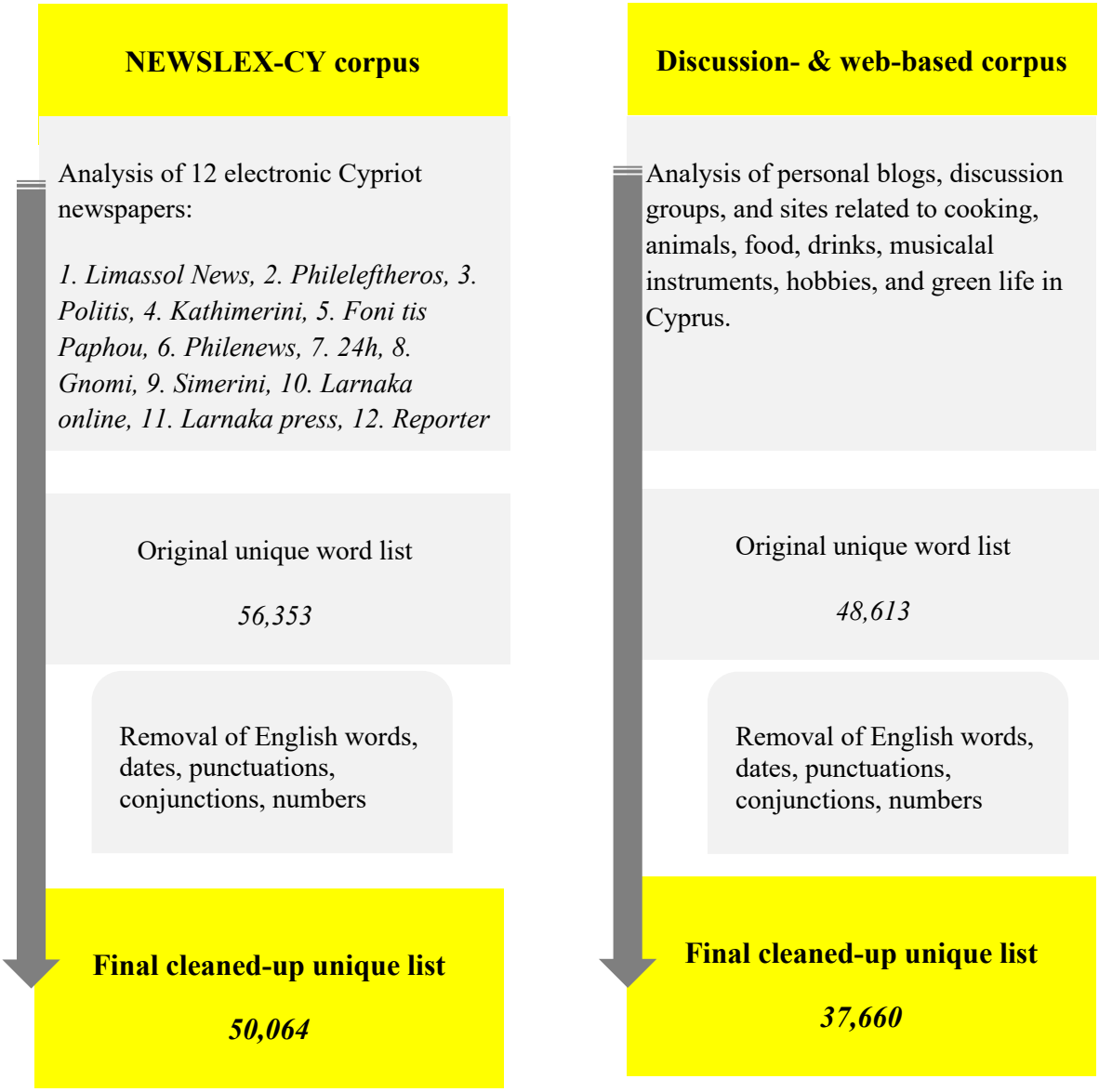
- material obtained through a survey, in which participants were asked to recall as many words as possible from specific categories, a method that allowed us to capture the verbal usage of the Cypriot dialect. This corpus was created to capture the words used to describe specific topics/things, with the intention to be later added to the corpus, created by informal electronic materials and thus to develop a large corpus representative of the informal use of the dialect.

3.3.1 Electronic-Based Material

Method. Two corpora were created: one from the most read Cypriot newspapers and one from websites and discussion groups. The reason for creating two different corpora was twofold. On the one hand, Cypriot journalists write mostly in standard Greek, and even though the audience is Greek-Cypriots, such language might not be representative of the Cypriot dialect. On the other hand, was the intention to create a corpus that would be as representative of the Cypriot dialect as possible. This method allowed us to capture the language as it appears in informal settings and is thus expressed more casually than in the news or the formal form of the language to which Greek-Cypriots are exposed through newspapers. For the creation and the analysis of the corpora, Sketch Engine, a widely used corpus tool software, was used (Kilgarriff et al., 2014). Sketch Engine builds corpora either by uploading materials or via web searches. To build the news-based corpus, 12 websites of the electronic version of Cypriot newspapers were selected and analyzed (see Figure 3.1). For the second corpus, personal blogs, discussion groups, and sites related to cooking, animals, musical instruments, hobbies, and green life in Cyprus were selected and analyzed. These topics were selected to be in accordance with the categories given in the survey for the development of the third corpus. Figure 3.1. illustrates the steps followed for the corpora development.

Results. The news-related corpus included 10,648,408 tokens, and the analysis revealed a unique list of 56,353 items. This corpus was named the NEWSLEX-CY corpus. The second corpus included 1,064,531 tokens, which led to the creation of 48,613 unique items. It should be noted that when language materials are analyzed, every word appearing in the analyzed context is included in the list. For instance, if a word is written in different ways (e.g., play/plays/played), each word will appear as a distinct item. In addition, punctuation, articles, conjunctions, and prepositions are all included as separated lemmas. Therefore, the actual size of a list, when all the aforementioned lemmas have been deleted, is remarkable smaller. Accordingly, English words, dates, punctuations, conjunctions, and numbers were removed from both lists. This step left the NEWSLEX-CY with 50,064 words and the second corpus with 37,660 words.

Figure 3.1 Steps followed for development of electronic corpora



Note: A. Steps followed for the development of the news-based corpus; B. Steps followed for the development of the corpus based on informal websites and discussion groups. The original unique lists, together with the final lists, can be found here: Unique Wordlists.

3.3.2 Survey-Based Material

Method

Experimental Design. This study comprised an online and face-to-face survey. Participants 60 and above underwent personal interviews, while participants under 60 participated by completing an online questionnaire. A consent form was obtained from

all the participants (see Table 3.1 for participants' characteristics stratified by age group and educational level).

Participants. A total of 141 individuals voluntarily participated in the study. This sample excludes non-Cypriot participants (n=4); those who did not write or verbally recall the minimum number of required words, indicating non-engagement in the study (n=31); those who presented cognitive impairment as evaluated by cognitive testing during the face-to-face interview (n=4; see materials); and those who stated that were experiencing thinking and concentration difficulties during the online completion (n=2). Thus, from the initial sample of 182 participants, 41 were excluded from the study. The remaining 141 participants were all Cypriots, coming from all Cyprus districts, with the majority from Limassol (52%) and Nicosia (32%). Data were collected from January to April of 2020.

Materials. A questionnaire with seven categories from which participants were asked to recall as many words as they could was developed by the research team. Categories were selected based on the following criteria: (1) they lead primarily to the production of nouns; (2) they include words typically used in lists for the assessment of learning and memory (e.g., the words "nose" and "desk" are found in the Rey Auditory Verbal Learning Test; therefore, the categories "parts of the human body" and "things one finds in an office" were included); (3) they make it easy for participants to produce various words; (4) they are relatively easy to recall from; and (5) the lead to the recall of words that participants are exposed to in their everyday lives.

Each category included sub-categories to further enhance the recall (e.g., category: animals; subcategory: birds). The questionnaire comprised 11 pages, including information about the study and instructions for completion.

Table 3.1 Participants' demographic characteristics

	Age group	
	<60	**60≧**
N	117	24
Mean Age (SD)	36 (11)	70.5 (8)
Gender (%Female)	73	36
Education(%)		
Primary school	1	25
High school	9	30
Bachelor	35	30
Master/PhD	55	15

The selected categories included the following:

- Animals (carnivores; animals one sees in a jungle, zoo, farm, or sea; fish; seafood; pets; birds; insects);
- Things one eats (foods; legumes; traditional Cypriot foods; sweets; traditional Cypriot sweets; spices; cheeses; vegetables; fruits);
- Things one buys at the supermarket (free recall; things for the bathroom);
- Clothes (women's; men's; summer; winter);
- Objects (objects one finds in a kitchen or office; furniture; tools);
- Beverages (free recall; spirits; traditional; beverages one drinks in the winter/summer); and
- General (musical instruments; vehicles; buildings; flowers; trees; parts of the human body; words related to school).

The online questionnaire can be found here: Cypriot Word Pool Questionnaire.

A demographic questionnaire was used in both the online and face-to-face conditions to obtain participants' demographic characteristics. The Addenbrooke's Cognitive Examination-Revised (ACE-R; Konstantinopoulou et al., 2011), which include the Mini

Mental State Examination (MMSE), was used to evaluate participants' cognitive states during the face-to-face interviews (i.e., participants over 60 years).

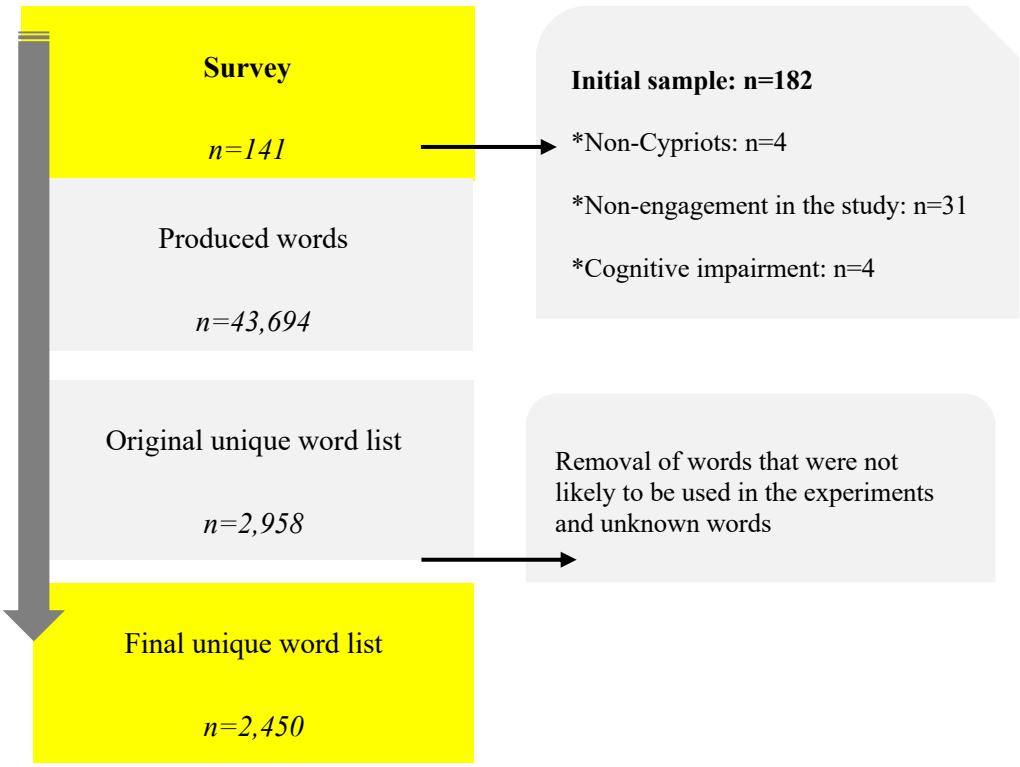
Procedure. *Online survey.* The questionnaire link was shared on investigators' social media accounts inviting people to participate in the study. An invitation email with the questionnaire link attached was sent to friends and colleagues, motivating them to participate and to forward the link to others. In addition, the questionnaire was promoted in several newspapers and on various Cypriot social media pages (e.g., Paphos News; All About Limassol; SciNews; Kypriaki Topolialia; Dialektos tis Kyprou). Participants could complete the questionnaire at their own convenience. Two questions asking participants to state whether they experience any thinking and/or concentration difficulties or if they live with a chronic neurological disease were included in the demographic questionnaire to ensure that only cognitively typical participants comprised the sample. Participants were asked to write as many words as they could in each category but to write each word only once, even it might fit in more than one subcategory. They were also instructed to write the words as they use them verbally in their everyday lives. Each category and/or subcategory had instructions, and participants were asked to write a minimum number of words. Completion time was approximately 1 hour.

Face-to-face survey. Considering the difficulty that older adults might face with the online questionnaire, face-to-face interviews were conducted to obtain reliable data from individuals over 60 years. Participants were recruited from local institutes (e.g., Patticheio Center) and via word of mouth. Interviews were conducted in participants' chosen locations and lasted for approximately 1 hour. Participants were instructed to recall as many words as they could from each category/subcategory. It was specifically emphasized to recall the words as they use them in everyday life. The interviewer moved on to next category or subcategory when participants could not recall more words without effort. The ACE-R was used to ensure participants' normal cognition. Participants with MMSE scores under 26 and/or total ACE-R scores under 92 were excluded from the analysis and referred to a neurologist or neuropsychologist for further cognitive evaluation.

Results. The data from both studies' conditions were integrated to develop a unique word list. Specific rules were predefined to avoid the same word being written differently and thus being present in the unique word list more than once. Each word was rewritten

following the predefined rules. For instance, all words were written in lowercase, in singular, and keeping the same spelling, despite how participants may have written them. In total, 43,694 words were produced. A unique list was created indicating 2,958 words. A correction of spelling and intonation mistakes within the unique word list left it with 2,856 words. Keeping in mind that the word pool would be used in the context of this thesis research, words that were not likely to be used in the experiments, such as two-word phrases (e.g., *φέρι μποτ* or *πάστα φλώρα*), were deleted from the list (n=324). From the remaining 2,532 words, a list with 232 words that had only been recalled from the vast minority of the participants (from 1 to 5 participants) were given to five native Cypriots (M_{age}=36.3, SD=10.2) to indicate whether they knew each word. This allowed us to retain only well-known words and exclude extremely rare ones (e.g., *τσιαττάλη*, another word that is used in Cyprus for *παντελόνι*/trousers). The words that were indicated as unknown by all five (n=100) were deleted from the list. Finally, the list included 2,450 unique words. The unique list from the survey alone was created to be used in future research (Figure 3.2).

Figure 3.2 Flow diagram for development of survey-based corpus



Note: The original unique word list and the final unique lists can be found here: Unique Wordlists.

3.3.3 Incorporation of Electronic and Survey Materials

According to Brysbaert and New (2009), to extract reliable language materials for inclusion in a corpus, several sources can be used, including subtitles. Materials originated from the oral expression of the language, as well as from web sources—the written expression of the language. In addition, the extraction of reliable statistics for words' characteristics depends heavily on corpus size (Brysbaert et al., 2011). As the topics that selected to be included in the development of the second electronic corpus were in accordance with the categories given in the survey, and thus the obtained data were similar from both sources, these two corpora were incorporated. This method allowed the creation of an even larger corpus, which was crucial for the development of reliable statistics. This corpus is considered the most representative of the Cypriot dialect.

The 43,694 words obtained through the survey were incorporated with the second electronically developed corpus, which led to a larger list of 1,108,225 words. The analysis of the incorporated corpus led to a list of 39,563 unique words. Whether the

incorporation of these two corpora led to the extraction of reliable statistics was investigated and is discussed below.

3.3.4 Conclusion

The aim of this research was to develop qualitative Cypriot dialect-based corpora. We built one news-based corpus, NEWSLEX-CY, with approximately 10,650,000 tokens, which led to a list of 50,064 unique words. Furthermore, from materials that were obtained via both survey and internet materials, a second corpus, DIALEX-CY, comprised of 1,108,225 total words and 39,563 unique words was developed. These two corpora are thought to represent both the formal and informal expression of the Cypriot dialect and thus can be used for a word pool development.

3.4 Development of the Cypriot Word Pool

The selection of words to be included in the CWP occurred according to criteria that best suited the research needs of the Brain and Cognitive Science (BaCS) laboratory of the Cyprus University of Technology. As such, one-word nouns and a small number of verbs, adverbs, and adjectives have been included. For reasons explained above, the DIALEX-CY is considered the most representative of the Cypriot dialect, and thus the CWP was comprised mostly of this corpus. However, the NEWSLEX-CY includes more than 10,500,000 words, which is important for extracting highly accurate statistics for each word (Brysbaert et al., 2011). Including words from both corpora was deemed necessary to create a reliable list capturing both formal and non-formal words used by Cypriots.

NEWSLEX-CY was examined, and 750 words considered suitable for research use were retained. Similarly, 2,500 words were selected from DIALEX-CY. Altogether, 3,250 words considered proper for research and clinical use were included in the CWP.

3.5 Normative Data for the Cypriot Word Pool

The development of the CWP was the first step toward establishing a valuable tool for research use in Cyprus. However, words are extremely complex stimuli, and a strict control of their properties is required for reliable use in cognitive research (Soares et al.,

2017). Much literature has indicated a variety of variables that affect the accuracy and speed with which each word can be recognized and recalled (Balota et al., 2004; Hulme et al., 2003; Roodenrys et al., 1994; Whaley, 1978). These variables do not only include word characteristics that depend on the objective analysis of their properties at the lexical levels (objective properties), such as word length, including number of syllables and letters (e.g., Ferrand et al., 2011; New et al., 2006); word frequency (e.g., Balota et al., 2004; Brysbaert et al., 2011), and their orthographic similarity with other words (e.g., Yarkoni et al., 2008), but also include word properties that depend on the personal experiences individuals have had with the use of these words in their native language (i.e., subjective properties; Soares et al., 2017). For instance, it is well established that high-frequency words (i.e., words that occur often in language) lead to better performance in free recall tests than the low-frequency ones (Balota & Chumbley, 1984; Johnston & Barry, 2006), while in contrast, low-frequency words are better recognized in recognition tasks (Glanzer & Adams, 1985, 1990; Shepard, 1967). Therefore, when using multiple lists in memory assessments, if the word frequency parameter has not been controlled, conclusions cannot be safe (Soares et al., 2017).

Considering the complexity of words together with their paramount usefulness in cognitive experiments, where the need for serial word lists with similar psychometric properties is required, collection of ratings (i.e., norms) for words' objective and subjective variables is a necessary process. The limited availability of norms for each word, poses particular problems for researchers and leads to questionable conclusions (Stadthagen-Gonzalez & Davis, 2006). Therefore, when designing experimental stimuli, researchers who wish to match one stimulus with another similar one must typically undergo their own normative study, lest they forgo the possibility of matching the words based on their properties, and as Stadthagen-Gonzalez and Davis (2006) state, "Hope for the best."

To overcome this situation, normative data were collected for the words included in the CWP. Obtaining data for the objective properties of words (e.g., number of syllables or letters) is, in general, not problematic and can be easily done using various software tools (Davis, 2005). In contrast, the collection of measurements for subjective variables, which is done by asking people to subjectively rate words in relation to their specific characteristics, is a relatively time-consuming process, and thus published normative studies have concentrated on only one or two variables. In this study, normative data were

collected for the three most important subjective word characteristics, namely (1) imageability or imagery, (2) concreteness, and (3) word frequency (Brysbaert et al., 2011; Fliessbach et al., 2006; Ljubešić et al., 2018; Richardson, 1975).

3.5.1 Cypriot Norms for Imageability and Concreteness

In this work we aimed to provide subjective norms of imageability (i.e., the ease and speed with which a word evokes a mental image) (e.g., Paivio et al., 1968) and concreteness (i.e., the degree to which words refer to objects, persons, places, or things that can be experienced by the senses (e.g., Paivio et al., 1968). These two variables have also been indicated to affect the accuracy and speed of word recognition and recall (Stadthagen-Gonzalez & Davis, 2006). It is known that imageability and concreteness are not totally independent from each other (e.g., Altarriba et al., 1999; Connell & Lynott, 2012), however, an increasing body of evidence suggests that they theoretically and empirically constitute distinct constructs and therefore, capture distinct word properties (Dellantonio et al., 2014; Kousta et al., 2011). For that reason, normative data were collected separately for each variable (Soares et al., 2017; Friendly et al., 1982; Yao et al., 2017; Yee, 2017).

Method

The study was approved by the Cyprus National Bioethics Committee (ΑΡ. Φακ.: ΕΕΒΚ/ΕΠ/2021/22; Appendix 1).

Materials. The 3,250 words from the CWP were randomly assigned to 13 lists (each comprising 250 words). Five words were randomly chosen from each list and were repeated within the list to obtain a measure of internal reliability. In addition, to investigate whether the mean ratings were similar across participants, 12 words were repeated in different booklets. These approximately 255 words were used to create 13 unique booklets of 15 pages each. Each word was written in capitals and positioned to the left of the page. A box was placed on the right of each word to be checked if the word was unknown. Two sets of these booklets were produced—one for the assessment of imagery (i.e., imageability) and one for concreteness. Each word was followed by a 7-point scale running from low imagery (1) to high imagery (7) for the imagery condition and from abstract (1) to concrete (7) for the concreteness condition. In view of the fact

that emergency measures due to the COVID-19 pandemic were imposed during the conduction of the study, the booklets were also designed as online questionnaires, following the exact structure of the booklets.

An example of an imagery online questionnaire can be seen here: Imagery Questionnaire: Form 1. An example of a concreteness online questionnaire can be seen here: Concreteness Questionnaire: Form 2. The first booklet of the imagery condition can be found in Appendix 5. The first booklet of the concreteness condition can be found in Appendix 6.

Participants. Participants were recruited through social media postings, several public and private universities in Cyprus, and word of mouth. Only Cypriots over 18 years old who agreed to sign a consent form participated in the study. Participants who did not answer more than 33% of the items, those who demonstrated random or inattentive ratings (e.g., rating the majority of words with the same response), those who did not meet the predefined correlation on the repeated words within their questionnaire, and non-Cypriots were dropped from the analysis. All participants provided a written consent form (the consent forms can be found here: Imagery-Consent Form / Concreteness-Consent Form).

Procedure. Each participant was given one booklet (imagery or concreteness) accompanied with written instructions to complete at their own convenience. Written instructions on both conditions were based on those used by Paivio et al. (1968) and Friendly et al. (1982). These included precise definitions of imagery and concreteness, together with rating directions. Specifically, in the imagery condition, they were asked to rate the words that aroused mental images easily and quickly with (7), words that aroused mental images with the greatest difficulty or not at all with (1), and words with intermediate ease and speed of imagery to be rated between the two extremes. Identical directions were given for the concreteness condition, apart from the rating scale, in which (1) represented the abstract words and (7) the concrete words. Participants were shown two completed examples for each condition (e.g., *ΜΟΛΥΒΙ*/PENCIL, as an example of a high imagery word and *ΔΕΔΟΜΕΝΟ*/FACT as a low imagery word; *ΚΑΡΕΚΛΑ*/CHAIR as an example of a concrete word and *ΔΗΜΟΚΡΑΤΙΑ*/DEMOCRACY as an example of an abstract word). They were asked to take as much time as needed to rate each word accurately and to not be concerned about how often they used a particular number, as long as it represented their true judgment.

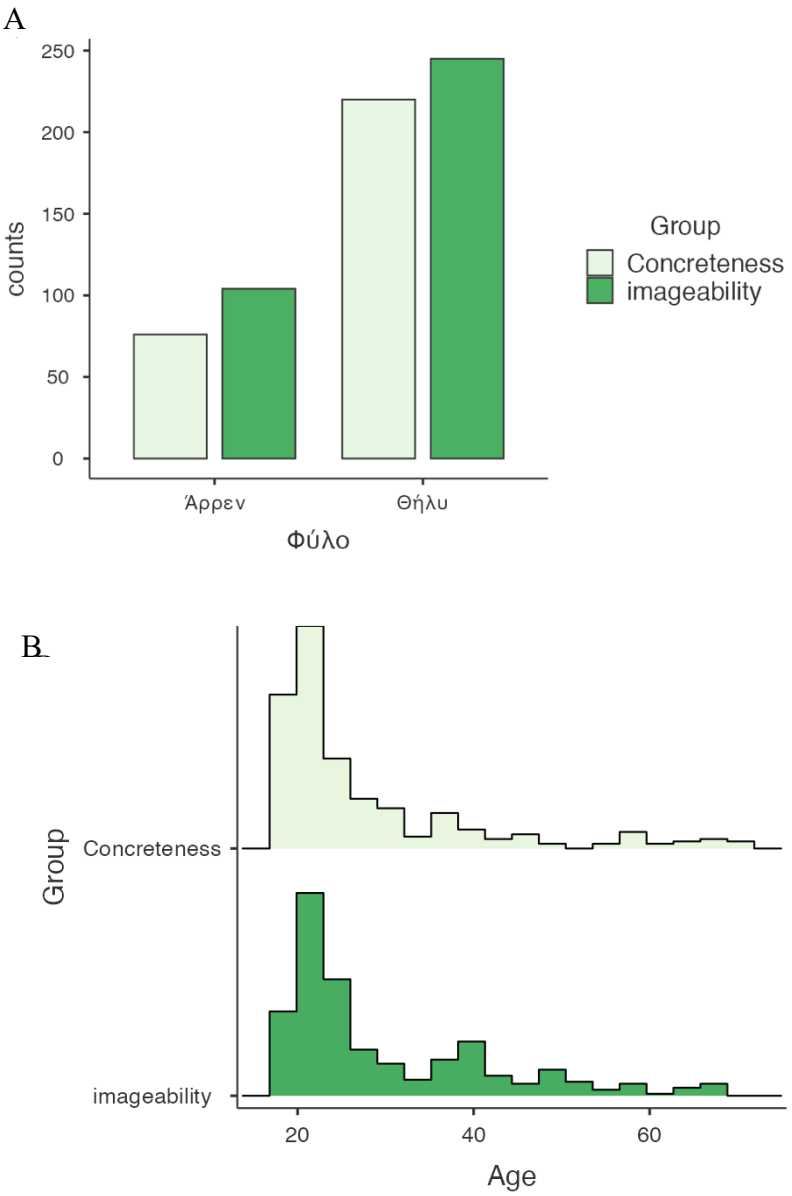
To ensure the creation of reliable norms, a minimum number of 20 responses on each item was predefined. Therefore, words that had 19 or less ratings were deleted from the CWP and the analyses.

Results

Participants. A total of 749 participants voluntarily participated in both study conditions. From this initial sample, those who did not answer more than 33% of the items (n=27), those who demonstrated random or inattentive ratings (n=29; these participants rated the majority of words with the same response, indicating non-engagement in the study), those who did not meet the predefined correlation on the repeated words within their questionnaire (n=40; this is discussed further below), and finally, non-Cypriots (n=8) were excluded from the analysis. Hence, from the initial sample, 160 participants were dropped from the analysis, leaving 645 participants.

From this sample, 349 participated in the concreteness condition (divided among the 13 different booklets), while the remaining 296 participated in the imageability condition (similarly, divided among the 13 different booklets). The demographic characteristics for the participants who participated with each booklet are illustrated in Table 4.5 for imageability and Table 3.6 for concreteness. In both conditions, the vast majority were female (Figure 3.3 A) from the Limassol district. Age distribution was the same in both conditions (Figure 3.3 B), with a mean age of 27 (SD=12) in concreteness and 30 (SD=12) in imageability. Regarding participants' educational levels, in the concreteness condition, 41.5% of the sample had a high school diploma, 38% had a bachelor's degree, and 20.5% had a master's and/or doctoral degree. In the imagery condition, 25% of the sample had a high school diploma, 37.5% had a bachelor's degree, and 37.5% had a master's and/or a doctoral degree.

Figure 3.3 Gender and age distribution in both study conditions



Note: The plots illustrate total sample distribution in the concreteness and imageability conditions. A. Gender distribution in the sample. The vast majority of the sample were female in both conditions. In the concreteness condition, 74% of the sample were female (n=220). Similarly, 70% were female in the imageability condition; B. Age distribution in both conditions. Both distributions are right skewed, with a mean age of 27 (SD=12) in the concreteness condition and 30 in imageability.

Table 3.2 Participants' demographic characteristics for each imageability booklet

				Origin (%)				Education		
Booklet	Sample	Gender (% female)	Age mean (SD)	Lim	Nic	Pap	Lar	12	16	>16
B1	23	65	28.5(10)	52	26	22	-	52	30	18
B2	25	84	23(8)	40	16	32	12	20	72	8
B3	22	60	32(14)	45	37	4.5	13.5	50	18	32
B4	24	83	23(5)	54	16.5	17	12.5	37.5	50	12.5
B5	23	61	28(9)	60	13.5	17.5	9	26	26	48
B6	21	67	32(14)	62	19	14	5	19	28.5	52.5
B7	21	71.5	32(13)	57	14	19.5	9.5	19	48	33
B8	21	67	29(14)	38	28.5	24	9.5	33	33	34
B9	67	61	40(11)	45	37	12	6	4.5	10.5	85
B10	20	50	29(12)	55	25	10	10	25	35	40
B11	22	77	25(8)	45.5	9	27	18.5	36.5	45.5	18
B12	30	90	24(9)	30	30	20	20	53	40	7
B13	30	76	24(8)	60	16.5	17	6.5	20	60	20

Note: B1=Booklet 1, etc.; SD=standard deviation; Lim=Limassol; Nic=Nicosia; Pap=Paphos; Lar=Larnaka; 12=12 years of education, etc. The educational levels in the study were high school, bachelor's degree, master's degree, and doctoral degree. In the table, master's and doctoral degrees are both depicted under >16.

Table 3.3 Participants' demographic characteristics for each concreteness booklet

				Origin (%)				Education		
Booklet	**Sample**	**Gender (% Female)**	**Age Mean (SD)**	**Lim**	**Nic**	**Pap**	**Lar**	**12≤**	**16**	**>16**
B1	20	55	29(10)	55	10	30	5	30	40	30
B2	22	82	26(10)	32	32	27	9	27	50	23
B3	23	70	30(14.5)	39	35	17	9	30.5	56.5	13
B4	28	79	26(13.5)	61	15	18	6	65	14	21
B5	21	57	30(11)	48	33	9.5	9.5	24	47	29
B6	25	80	32(17)	52	24	20	4	52	28	20
B7	20	70	35(18)	45	25	15	15	25	50	25
B8	23	82	23.5(7)	22	43.5	26	8.5	39	43.5	17.5
B9	20	80	25(10)	45	30	20	5	70	5	25
B10	24	75	23(9)	29	41.5	17	12.5	71	17	12
B11	20	80	28(11)	45	15	5	35	45	40	15
B12	20	70	26(10)	50	40	10	-	45	35	20
B13	30	76	24(7)	47	32.5	17	3.5	20	63	17

Note: B1=Booklet 1, etc.; SD=standard deviation; Lim=Limassol; Nic=Nicosia; Pap=Paphos; Lar=Larnaka; 12=12 years of education, etc. The educational levels in the study were high school, bachelor's degree, master's degree, and doctoral degree. In the table, master's and doctoral degrees are both depicted under >16.

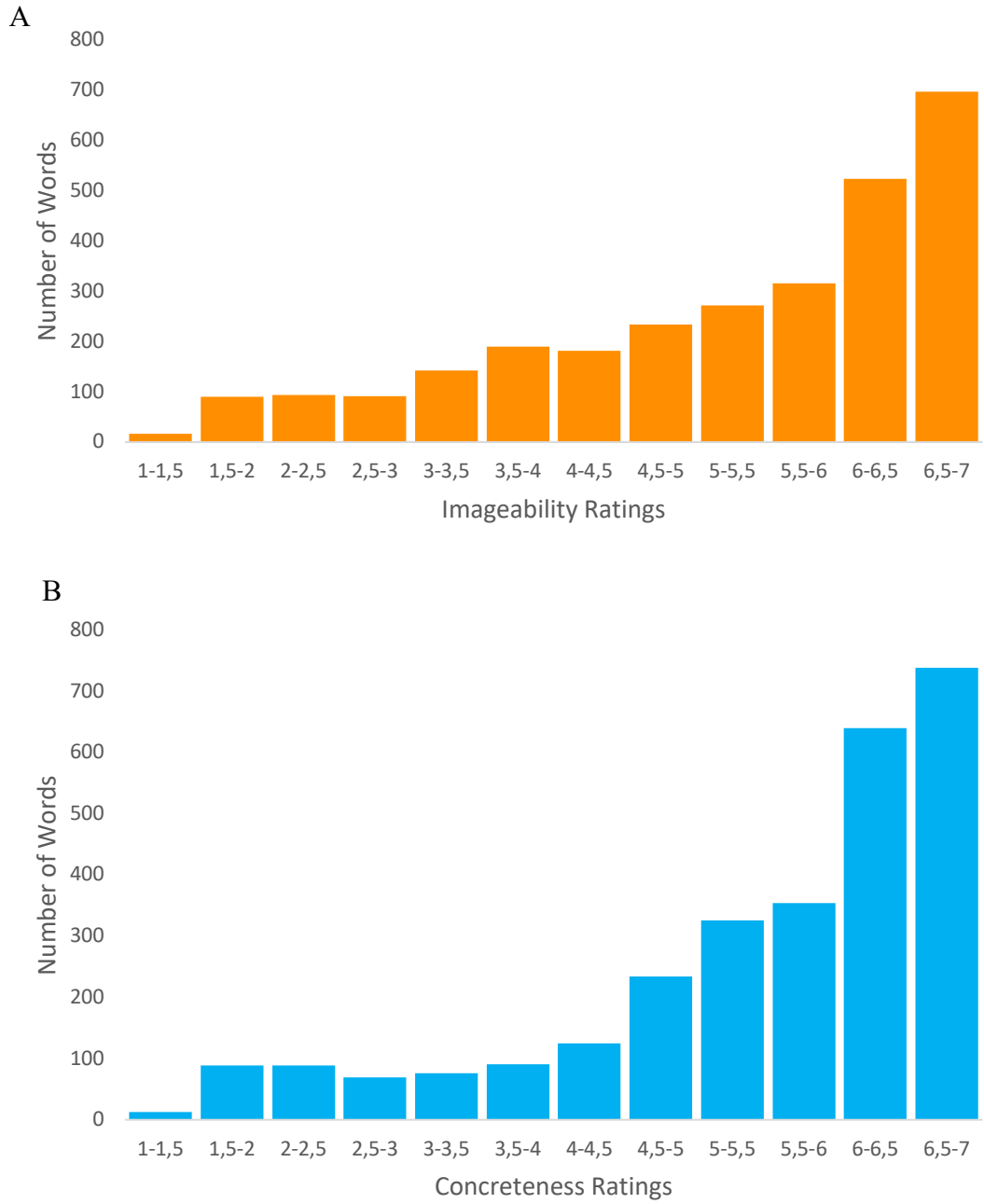
Total number of words in the CWP. In total, 398 words that did not meet the predefined minimum number of responses (i.e., 20) were deleted from the CWP and thus from the analysis. Accordingly, 2,852 words remained on the list and in the analyses.

Imageability and concreteness ratings. The mean rating for concreteness was 5.4 with a standard deviation of 1.4, while the mean for imageability was 5.2 with a standard deviation of 1.5. The ratings frequency distributions, demonstrated in Figure 3.4, and show that both ratings are negatively skewed, with only 4% of the words rated between 1 and 2 in the imagery and approximately 3.5% in the concreteness condition. The majority of words have been rated as high imagery or concrete words. Specifically, 1,459 words (47.5%) have been rated within 6 and 7 in the concreteness condition and 1,271 words (41%) in the imagery condition. In addition, 43.5% of the items were rated between

the two scales' extremes (i.e., between 3 and 5) for concreteness and 48% in the imageability condition.

The imagery ratings compare closely with Paivio et al. (1968). In contrast, in the concreteness condition, the authors noted a bipolar distribution. Friendly et al. (1982) observed a high proportion of ratings in the middle range, an observation also evident in the CWP. Furthermore, the mean ratings for imagery and concreteness in Friendly et al. (1982) were 4.19 (SD=1.4) and 4.34 (SD=1.4), respectively. Both variables were rated similarly, an observation evident also in Paivio et al. (1968). Comparably, in this study, both variables indicated approximately identical mean ratings and standard deviations. In general, the majority of the CWP words are concrete, high imagery words.

Figure 3.4 Frequency distribution of imagery and concreteness ratings



Note: A. Frequency distribution of ratings in the imagery condition. Data were obtained for 2,852 words. Among them, 1,222 (43%) were rated between 6–7 (high imagery words), 588 (21%) between 5–6, 416 (14.6%) between 4–5, 333 (11.7%) between 3–4, 186 (6%) between 2–3, and 107 (3.7%) between 1–2 (very low imagery words); B. Frequency distribution of ratings in the concreteness condition. Data were obtained for 2–844 words. Among them, 1–378 (48.5%) words were rated between 6–7 (highly concrete words), 680 (24%) were rated between 5–6, 359 (12.6%) between 4–5, 167 (5.8%) between 3–4, 158 (5.5%) between 2–3, and finally, 102 (3.6%) were rated between 1–2 (abstract words).

Reliability. Correlations within participant responses to the five repeated words were used to judge internal reliability. Prior to the analysis, the criterion of .20 was adopted (Friendly et al., 1982); therefore, participants who showed correlations less than .20 were considered unreliable and excluded from the analysis. Accordingly, 13 participants (five female and eight male) were dropped from the imagery condition, and 27 (11 female and 16 male) from the concreteness condition. The overall correlations for concreteness and imagery for the remaining participants are presented in Table 3.4. The analyses revealed moderate to strong correlations among the responses on the five repeated words in all booklets in both conditions. The mean correlations for the 13 booklets in both the imagery and concreteness conditions were strong (imagery: r=.825; concreteness: r=.780). Pearson's r among the booklets ranged from .540 to .915, indicating satisfactory internal reliability.

Table 3.4 Correlations of ratings on repeated words

	Imageability		Concreteness	
Booklet	***r***	***p*-value**	***r***	***p*-value**
1	.826	<.001	.900	<.001
2	.766	<.001	.810	<.001
3	.855	<.001	.774	<.001
4	.839	<.001	.733	<.001
5	.813	<.001	.495	<.001
6	.907	<.001	.889	<.001
7	.912	<.001	.916	<.001
8	.894	<.001	.859	<.001
9	.843	<.001	.672	<.001
10	.718	<.001	.866	<.001
11	.915	<.001	.904	<.001
12	.690	<.001	.789	<.001
13	.750	<.001	.540	<.001
Mean	.825		.780	

Note: The correlations have been calculated from all participants' responses on each booklet's repeated words. From the analysis, the responses of those who did not complete the whole questionnaire were removed; therefore, the repeated words were not rated.

To further investigate reliability, a Mann-Whitney U test was conducted to examine whether the mean ratings of the 12 repeated words that were randomly distributed among the different booklets significantly differed across participants (Table 3.5). The analysis revealed nonsignificant differences among the first ratings in the imagery condition

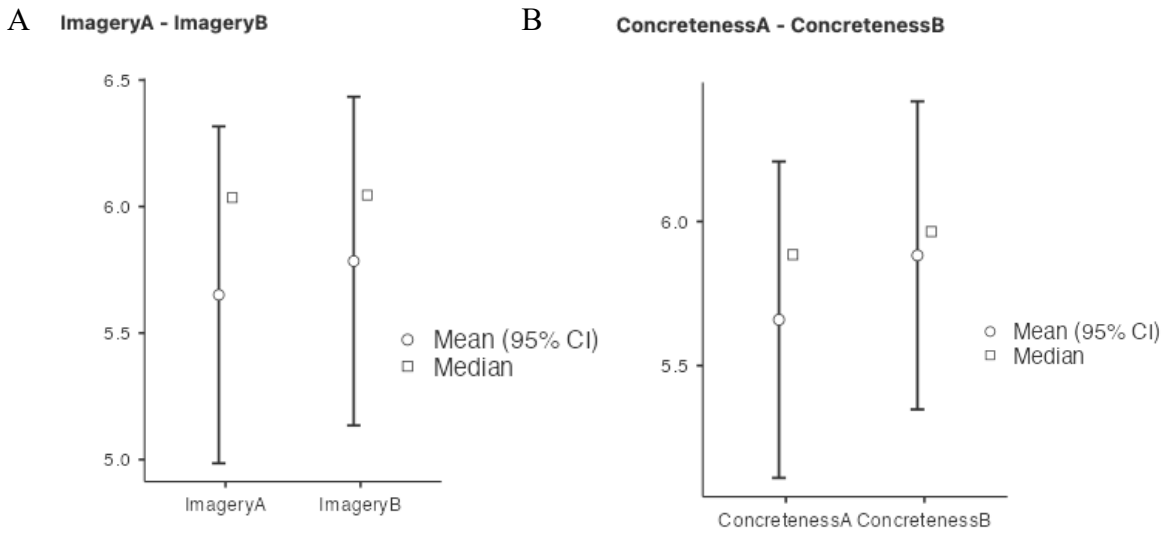
(M=5.65, SD=1.2, median=6.05) from the ratings on the same words from the different booklets and participants (M=5.8, SD=1.15, median=6.05); *U*=64.5, *p*=.686. Similarly, nonsignificant differences were found among the first ratings on the concreteness condition (M=5.5, SD=1.3, median=6) with the same words from the different booklets and participants (M=5.7, SD=1.35, median=6); *U*=60, *p*=.506. A nonparametric correlation analysis revealed a strong correlation among the different ratings of the 12 repeated words (Table 3.5). Figure 3.5 visually demonstrates the mean scores of the repeated words among the booklets and participants.

Table 3.5 Mean ratings of the 12 repeated words

	Imagery		Concreteness	
Word	Mean rating A	Mean rating B	Mean rating A	Mean rating B
αγελάδα	6.68	6.78	6.75	6.75
ανάγνωση	3.27	4.05	2.4	2.22
ανοιχτήρι	6.54	7	6.46	6.95
δίχτυ	6.32	6.82	6.1	6.75
έδρα	6.1	6.38	6.35	6.45
εκτυπωτής	6.9	6.9	6.55	6.83
εργαστήριο	4.4	5.52	4.04	4.7
	4	3.64	5.67	5.14
ηλεκτρολόγος	5.97	4.9	5.42	5.48
θαλασσινά	5.7	5.71	4.38	5.36
θώρακας	5.29	5.19	5.17	5.35
κάδρο	6.64	6.52	6.62	6.61
Man-Whitney *U*	*U*=64.5, p=.686		*U*=60, p=.506	
Spearman's *rho*	*rho*=867, *p* <001		*rho*=837, *p* <.001	

Note: The repeated words were rated by different participants. A nonparametric independent sample t-test (i.e., Mann-Whitney *U* test) indicated nonsignificant differences among the two mean ratings of the 12 repeated words. Similarly, Spearman's rank correlation coefficient showed the mean scores to be strongly correlated, indicating that the items have been rated similarly across the participants.

Figure 3.5 Visual representation of mean scores of repeated words among different booklets



Note: The 12 repeated words in the different booklets were rated similarly by the participants both in the imagery (A) and concreteness (B) conditions.

Validity. Following the suggestion of Stadthagen-Gonzalez and Davis (2006), the present word norms were compared with two other international normative scaling studies, those by Scott et al. (2019) and Soares et al. (2017). Unfortunately, to date, there are no available normative studies providing norms for these variables in Cyprus or Greece; therefore, comparison was not possible with national databases. The comparison allowed us to cross-validate the CWP with its international counterparts by comparing its ratings with the ones obtained in other studies in the same subjective dimensions. A total of 210 items that appeared both in the CWP and the Minho word pool (Soares et al., 2017) and 100 words that were in both the CWP and the Glasgow word pool (Scott et al., 2019) were selected. Correlations were computed among the mean ratings on concreteness and imagery (i.e., the mean rating of each word in the pool) for the selected words among the three datasets. The correlations are shown in Table 3.6.

Table 3.6 Correlations among mean ratings in three-word pools

	Imageability			Concreteness		
			CWP			
	r	***p***	**95% CI**	***r***	***p***	**95% CI**
Glasgow	.85	<.001	.78-.9	.64	<.001	.51-.74
Minho	.606	<.001	.35-.64	.65	<.001	.52-.75
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
Glasgow	6.5	0.6	2.5-6.9	6.4	0.5	3.6-6.9
CWP*	6.5	0.8	1.8-7	6.3	0.87	2.3-7
Minho	5.8	1.5	3.1-6.75	6.5	0.87	3-6.8
CWP**	6.4	0.8	2.9-7	5.85	1.2	1.7-7

Note: *Descriptive statistics of the selected words from the CWP that also appear in the Glasgow pool; **Descriptive statistics of the selected words form the CWP that appear also in the Minho pool.

The correlations among the CWP and the other two pools in both conditions are all above .60. The highest correlation is between the CWP and the Glasgow pool in the imagery condition (.85), while the rest lie between .60 and .65. The Minho word pool is a normative study of Portuguese words (English words were provided in this study), while the Glasgow provides norms for English words; as such, a very strong correlation was not expected, due to cultural differences. In contrast, a strong correlation would have been expected among national databases. Thus, the overall validity of the present norms seems quite satisfactory. Concreteness and imagery among the three international word pools are statistically correlated, providing evidence that these variables form fairly stable attributes of word meaning, since evident agreement exists in mean ratings over time and geographical samples.

Significant differences exist among the mean item ratings in the overlapping sets, as shown in Table 3.7. The mean imagery rating in the Minho word pool is lower than the mean ratings on the same items found on the CWP (means are presented in Table 3.6). In addition, the mean concreteness rating in the Minho word pool is higher than in the CWP. Similar findings were observed in Friendly et al. (1982). These differences can be attributed to cultural differences and in the different sets of items that happened to overlap among the two variables. The mean ratings of the selected common words from the

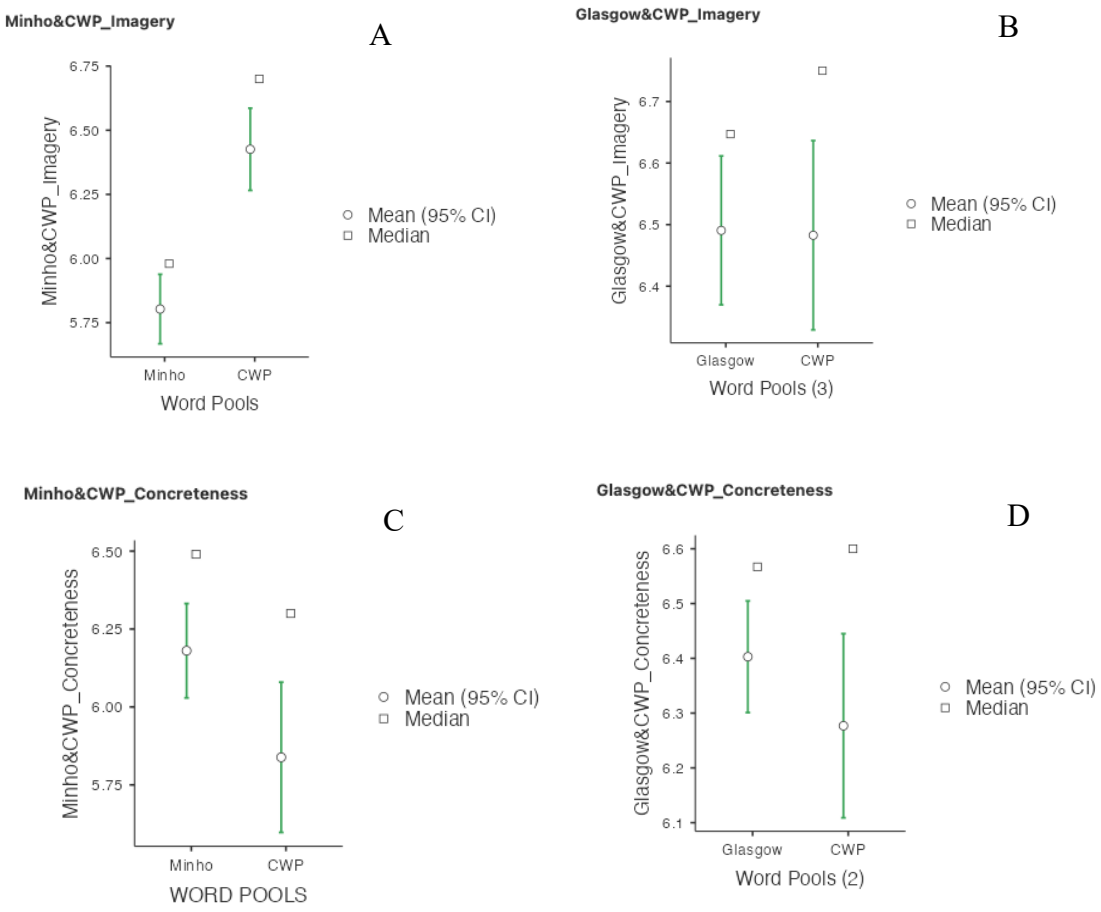
Glasgow and Minho pools are illustrated in comparison with the CWP ratings in Figure 3.7.

Table 3.7 Mean differences among three word pools

	Imageability	Concreteness
	CWP	
Glasgow	$t(206)=0.08$, $p=0.9$*[1]	$t(206)=1.26$, $p=0.210$*[2]
Minho	$t(200)=-5.82$, $p<.001$*[3]	$t(200)=2.35$, $p=0.019$*[4]

Note: *[1]Hypothesis: Glasgow imageability ≠ CWP imageability; *[2] Hypothesis: Glasgow concreteness ≠ CWP concreteness; *[3]Hypothesis: Minho imageability ≠ CWP imageability; *[4]Hypothesis: Minho concreteness ≠ CWP concreteness.

Figure 3.6 Graphical illustration of mean CWP ratings with Glasgow and the Minho pools



Note: A. Mean rating of imagery on the words that appeared in both the CWP and Minho pool; B. Mean rating of concreteness on the words that appeared in both the CWP and Minho pool; C. Mean rating of imagery on the words that appeared in both the CWP and Glasgow pool; D. Mean rating of concreteness on the words that appeared in both the CWP and Glasgow pool.

Conclusion

The aim of this study was the development of subjective norms for imageability and concreteness for the words included in the CWP. The analysis indicated high internal reliability and validity. Imagery norms were created for 2,852 words and concreteness norms for 2,844 words. The rigorous adopted methodology allowed us to deeply investigate participants' commitment in the study and only the responses of participants

who truly engaged in the study were used in the analyses. These norms were considered reliable for use in the alternative forms' development.

3.5.2 Normative Data for Word Frequency

Word frequency is among the most important variables in experimental psychology in general, and in memory research, in particular (Brysbaert et al., 2011). When participants are asked to memorize a list of words and later required to recall them and discriminate them from lures (i.e., new items), the pattern of results depends heavily on word frequency in the list (Cortese et al., 2010; Gregg et al., 2006; Higham et al., 2010). Given the weight of word frequency, no study in memory research can afford not to control this variable. For this reason, numerous frequency lists have been generated and several variables influencing the quality of word frequency estimates have been identified. For instance, the size of the corpus used for the generation of word frequency measurements seems to determine the list quality, primarily because this produces more reliable estimates for very low-frequency words (Brysbaert et al., 2011).

To create frequency estimates for the words included in the CWP, the two previously created corpora were used. NEWSLEX-CY comprises more than 10,500,000 words, and thus highly reliable statistics could be extracted. Although DIALEX-CY contains only approximately 1,100,000 words, which is the minimum length required to extract frequency estimates, the criteria under which the sources were selected were extremely strict to ensure only words from specific categories (e.g., food, animals) were included. Therefore, since every available electronic source related to the desired categories has been included in the corpus, together with the survey material, the corpus was thought to be representative of the words that are used when discussing about these topics.

Method. As words' frequency depends on the size of a corpus, investigators typically employ a standardized measure so that the various counts can be compared (Brysbaert et al., 2018). To date, the primary standardized measure has been the frequency per million words (***fpmw***). To extract statistics about a word's fpmw, its raw frequency is divided by the total number of words in the corpus and multiplied by one million. Accordingly, high-frequency words are defined as those having a value of above 100 fpmw, and low-frequency words are those with a value of below five fpmw (Brysbaert et al., 2018). In addition, frequency estimates are also calculated depending on a word's raw occurrence

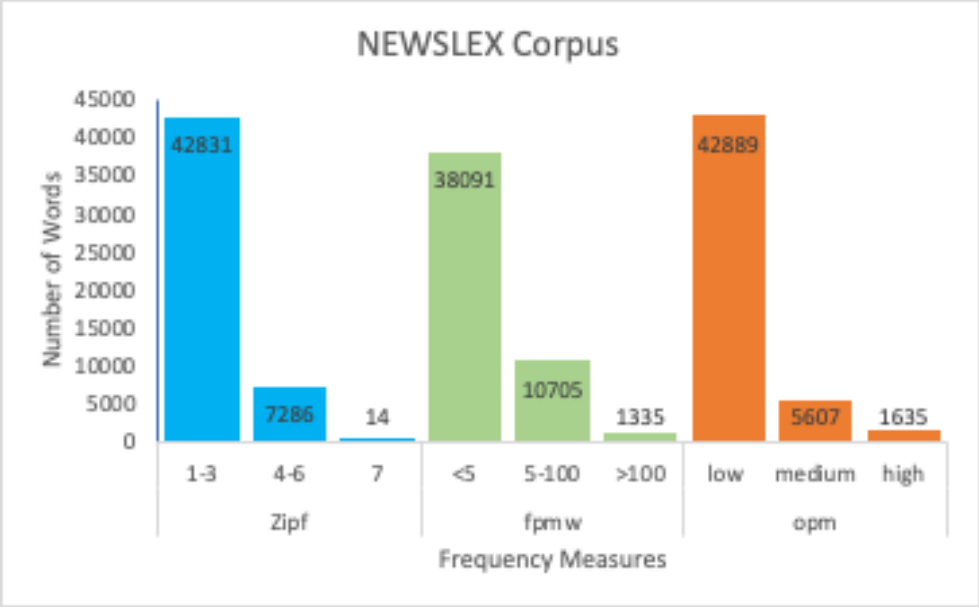
per million words (***opm***). As such, a word is considered a high-frequency word when it occurs 75 or more times per million words, medium-frequency words are those that appear between 11 and 74 times per million, and low-frequency words are those that occur 10 or fewer times per million (Soares et al., 2017b). Finally, van Heuven et al. (2014) introduced a new measure of word frequency, the ***Zipf*** scale. This measure aims to resolve the major disadvantages of the fpmw scale, the most critical of which is that the estimates are strongly dependent on the size of the corpus. The Zipf scale is a logarithmic scale running from 1 (very low frequency) to 6 (very high frequency) or 7, within which only a few words fall. Zipf values are easily calculated and are equal to log10 (fpmw)+3 or log10 (frequency per billion words; van Heuven et al., 2014).

In this study, frequency measures were calculated (following the calculations as described above for each method) and are presented in all the aforementioned scales (i.e., fpmw, opm, and Zipf scales) for all the words included in both corpora. The reasons for (1) calculating the frequency estimates for the complete unique lists, not only for those included in the CWP, and (2) calculating the three aforementioned well-defined and known estimators were to develop reliable frequency lists for future use and provide researchers the opportunity to decide among the three estimators which one best fits their needs.

Sketch Engine software (Kilgarriff et al., 2014) was used to extract the number of times that each word appeared in each corpus. According to the fpmw scale, in both corpora, most words have a value of less than five. Specifically, approximately 76% of the words in the NEWSLEX corpus have a value below five (i.e., low-frequency words), 21.5% have a fpmw value between 5 and 100 (i.e., medium-frequency words), and only 2.5% are high-frequency words with a value above 100. Comparably, in the DIALEX corpus, 74% of the words have a value below five, 23% are between five and 100, and 3% have a fpmw value above 100. According to the opm scale, the three levels of frequency (i.e., high, medium, low) follow similar distributions in both corpora. Most words are characterized as low-frequency words (85.5% in the NEWSLEX and 83% in the DIALEX corpus), followed by the medium-frequency words (approximately 11% in the NEWSLEX and 13% in the DIALEX corpus). Only 1,635 (3%) and 1,586 (4%) high-frequency words are evident in the NEWSLEX and DIALEX corpora, respectively. Finally, using the Zipf scale as the standardized measure, approximately 85% of the words fall between 1 and 3, and 15% between 4 and 7 in both corpora. Figure 3.7

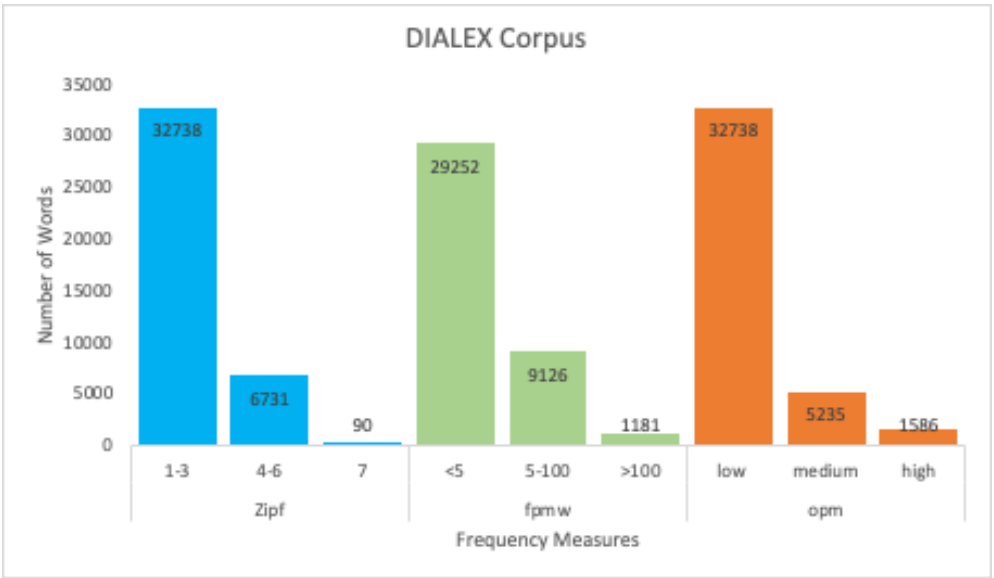
illustrates the frequency distribution of the words included in the NEWSLEX-CY corpus. Figure 3.8 illustrates the frequency distribution of the words included in the DIALEX-CY corpus.

Figure 3.7 Comparison of frequency measures of NEWSLEX-CY corpus



Note: Following the opm method, 4,798 more words are characterized as low frequency in comparison with the fpmw scale. These words fall into the medium-frequency range in the fpmw. The Zipf scale follows a very similar distribution as the opm method, even though the medium-frequency range is not clearly defined for the Zipf scale.

Figure 3.8 Comparison of the frequency measures of DIALEX-CY corpus



Note: As with the NEWSLEX corpus, following the OPM method, most words are defined as low frequency in comparison to the FPMW. The FPMW criteria allow a wider distribution between the low- and medium-frequency ranges. Even though the medium-frequency range is not defined in the Zipf scale, it is evident that the lower and upper halves of the Zipf and opm scales are identical.

For the needs of this thesis and considering the advantages and disadvantages of each method, each word's *opm* was considered the most suitable method for the development of the tests' alternative forms. The *opm,* allows the generation of reliable frequency statistics with a relatively small corpus of 1,000,000 words. The followed methodology is described in detail below. Henceforth, the described methodology involves only the words included in the CWP.

OPM Estimations. Three levels of taxonomy regarding words' frequency are evident in the literature (i.e., high-, medium-, and low-frequency words). Estimates are calculated depending on a word's raw occurrence per million words. Accordingly, as described above, a word is considered high-frequency when it occurs 75 or more times per million words, medium-frequency words are those that appear between 11 and 74 times per million, and low-frequency words are those that occur 10 or fewer times per million (Soares et al., 2017). Sketch Engine software (Kilgarriff et al., 2014) was used to extract the number of times that each word appeared in each corpus.

According to the abovementioned criteria, each word was characterized as high, medium, or low frequency, depending on its occurrence in the corpus. Specifically, the estimation of the frequency criteria for the NEWSLEX-CY was made following the below calculations (Table 3.8):

- high-frequency words: (74,1 x 10,648,408)/1,000,000=789)
- medium-frequency words: (10,1 x 10,648,408)/1,000,000=107) & (74 x 10,648,408)/1,000,000=788)
- low-frequency words: (10 x 10,648,408)/1,000,000=106).

Estimation of the frequency criteria for DIALEX-CY was made following the below calculations (Table 3.9):

- high-frequency words: (74,1 x 1,108,225)/1,000,000=789)

- medium-frequency words: (10,1 x 1,108,225)/1,000,000=107) & (74 x 1,108,225)/1,000,000=788)

- low-frequency words: (10 x 1,108,225)/1,000,000=106).

Considering that each word from the alternative neuropsychological tests that were developed in this thesis had to be matched with another word with exactly the same psychometric properties, the frequency criteria were further expanded from three to six levels of taxonomy. This allowed us to create multiple neuropsychological tests with the same difficulty level to the greatest degree possible. Therefore, each level (i.e., low, medium, high) was further divided into two levels. Specifically, the length of each frequency level was divided to two equal parts. The smaller part was characterized as "low" and the larger as "high." For instance, the medium-frequency words in the news-based corpus were the words that occurred between 107 and 788 times. This length, which is 681 words, was divided approximately in half (i.e., 340 and 341), and the words that occurred between 107 and 447 times in the corpus were characterized as "low–medium-frequency" words, and those that occurred between 448 and 788 were characterized as "high–medium-frequency" words (Tables 3.8 and 3.9). With this level of taxonomy, each word in multiple learning tests can be replaced with higher accuracy regarding their frequency level.

To investigate the reliability of the produced frequency estimates, the words included in the CWP that appeared in both corpora were searched and their estimates compared. As shown in Table 3.10, the words were characterized in the same manner in both corpora, not only on the usual three levels of taxonomy but also in the six levels, providing evidence that both corpora represented each word reliably. This might be explained by the fact that the newspapers include, in addition to news-related articles, regular columns related to general topics, such as cooking.

Table 3.8 Frequency estimates per million for DIALEX-CY

DIALEX-CY			
	Established frequency criteria (per million)	Criteria according to corpus length	Further taxonomy & final corpus criteria
Corpus length in words		10,648,408	
Unique words		56,353	
High-frequency	≧75	≧789	low–high: 789–1,500 high–high: >1,501
Medium-frequency	11–74	107–788	low–medium: 107–447 high–medium: 448–788
Low-frequency	≦10	≦106	low–low: 1–53 high–low: 54–106

Table 3.9 Frequency estimates per million for DIALEX-CY

DIALEX-CY			
	Established frequency criteria (per million)	Criteria according to corpus length	Further taxonomy & final corpus criteria
Corpus length in words		1,108,225	
Unique words		49,348	
High-frequency	≧75	≧83	low–high: 83–150 high–high: >151
Medium-frequency	11–74	12–82	low–medium: 12–46 high–medium: 47–82
Low-frequency	≦10	≦11	low–low: 1–5 high–low: 6–11

Table 3.10 Selection of words appearing in both corpora and their frequency statistics

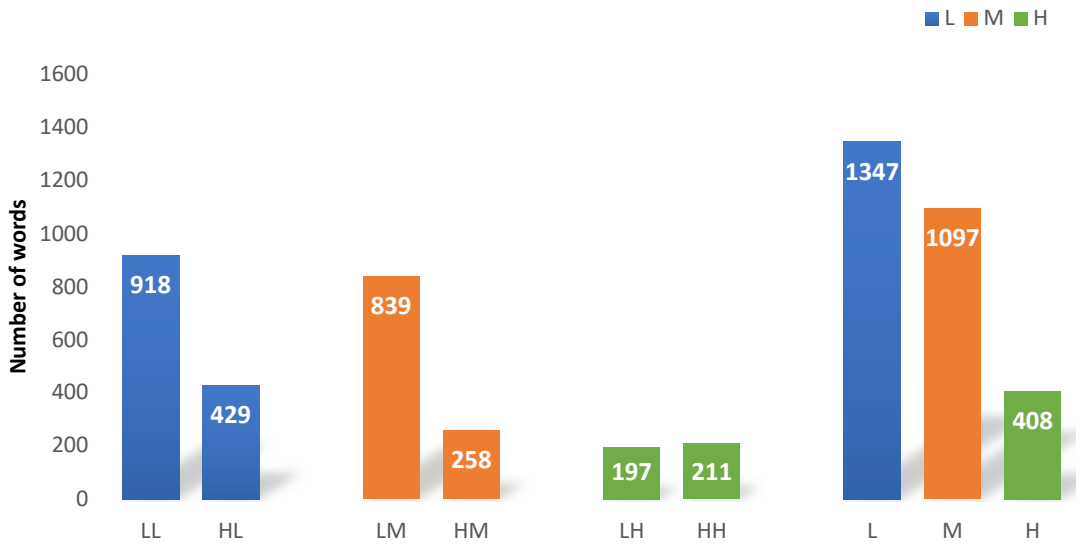
	Frequencies in the corpora		**Words frequency in both corpora**	
Word	NEWSLEX-CY	DIALEX-CY	Frequency in 3 categories	Frequency in 6 categories
αγελάδα	1,923	336	H	HH
ακτή	185	35	M	LM
αλκοόλ	124	24	M	LM
αναρή	2,111	1,156	H	HH
άνοιξη	157	13	M	LM
αρμονία	17	3	L	LL
αστυνομικός	152	36	M	LM
αυγά	2,314	1,182	H	HH
βραδινό	1,963	250	H	HH
βράδυ	1,771	239	H	HH
διατροφή	2,063	906	H	HH
ένδυμα	1,920	244	H	HH
εκπομπή	337	13	M	LM
ένδυμα	1,920	244	H	HH
εποχή	3,841	424	H	HH
ευτυχία	111	15	M	LM
ζάχαρη	3,199	1,591	H	HH
ζώνη	499	55	M	HM
ηθοποιός	154	16	M	LM
ήλιος	116	31	M	LM
ιερό	126	22	M	LM
ιστορία	1,574	333	H	HH
καθηγητής	688	71	M	HM
καταστροφή	424	24	M	LM
κλινική	299	24	M	LM
κοινότητα	1,272	83	H	LH
κορυφή	151	35	M	LM
κρασί	2,914	1,502	H	HH
κρεμμύδι	2,627	1,388	H	HH
κριτική	284	23	M	LM
λάδι	2,375	1,340	H	HH
λίμνη	149	15	M	LM
λωρίδα	98	6	L	HL
μανιτάρια	1,649	844	H	HH
μπαρ	298	23	M	LM
ομάδα	2,172	161	H	HH

Note: The words have been defined according to the frequency criteria seen in Tables 4.8 & 4.9.

Results. As depicted in Figure 3.9, the majority of words in the CWP are low-frequency words (43%), followed by medium-frequency words (47%). In contrast, the high-frequency words constitute only 14% of the data. In the six-level taxonomy, the high-

frequency words are almost equally divided among its two parts, while in contrast, the low–low words and low–medium words represent 68% and the 76% of the words, respectively.

Figure 3.9 Distribution of CWP's 2,852 words according to per-million written word frequency intervals



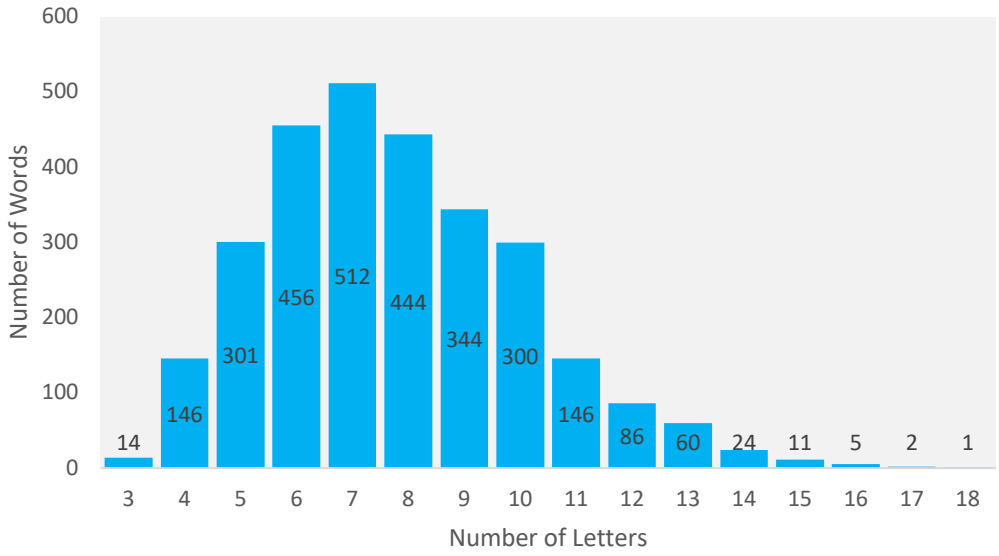
Note: The distribution is presented in six levels of frequency taxonomy; LL: low-low; HL: high-low; LM: low-medium; HM: high-medium; LH: low-high; HH: high-high; on the left; and in three levels of frequency taxonomy (low, medium, high) on the right.

3.5.3 Objective Variables of the CWP Items

Besides the abovementioned normative data, the CWP provides values for the objective variables of number of letters, number of syllables, and part of speech for the 2,852 words.

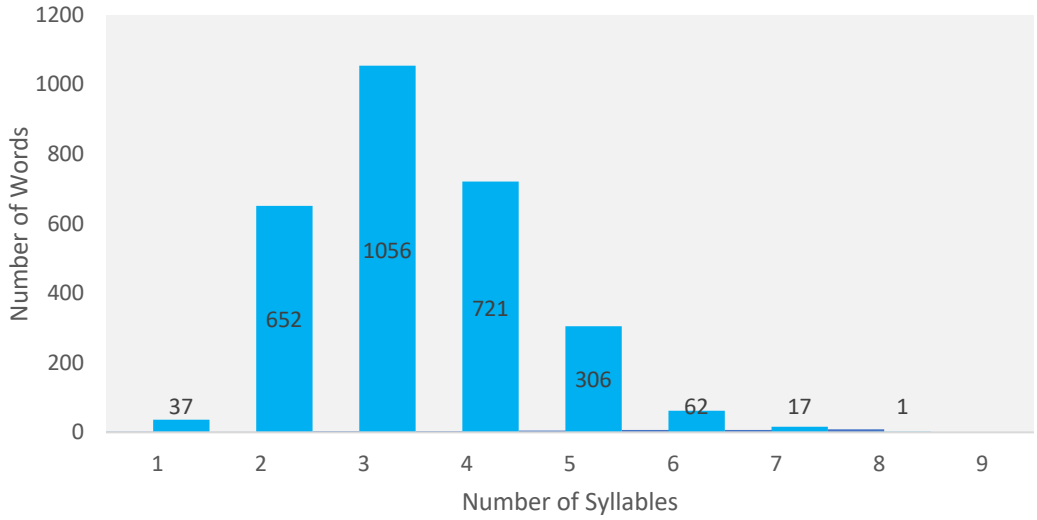
Number of letters: As illustrated in Figure 3.10, the number of the CWP words' letters ranges between 3 (n=14, 0.5% of the data) and 18 (n=1), with an average of 7.7 per word. The lengths of 72% of the words range between six and 10 letters, while 16% range between three and five letters. Only 12% range between 11 and 18 letters.

Figure 3.10 Letter number distribution of 2,852 CWP words



Number of syllables: The number of syllables ranges between 1 (n=37, 1.3% of the data) and 8 (n=1, 0.1% of the data), with an average of 3.3 syllables per word. The majority of the words are three- (1.056, 37% of the data) and four-syllable (721, 25% of the data) words. The number of syllables distribution is depicted in Figure 3.11.

Figure 3.11 Syllable number distribution of 2,852 CWP words



Part of speech (PoS): The words in the CWP cover four grammatical classes (i.e., nouns, adverbs, adjectives, and verbs), although the vast majority are nouns (2,815 words, 98.5%

of the data). Only 0.6% (17 words) are adjectives, and 0.6% (18 words) are verbs, while only two words are adverbs.

The CWP can be found here: The Cypriot Word Pool

3.6 Cypriot Alzheimer's Disease Assessment Scale-Cognitive Subscale[3]

The ADAS-cog is considered the gold standard for the evaluation of antidementia treatment efficacy (Skinner et al., 2012), and it is the most widely used neuropsychological measure in clinical trials (e.g., Connor & Sabbagh, 2008; Ihl et al., 2012; Rabey & Dobronevsky, 2016; Rozzini et al., 2007). It was developed with the purpose of being used as an index of global cognition in response to therapeutic interventions in AD patients. The original ADAS-cog, created by Rosen et al. (1984), was later modified to include additional items. The discussion henceforth uses ADAS-cog to refer to Mohs et al.'s (1997) revised form.

The ADAS-cog includes 11 items, including participant-completed tasks and examinee-based observations. As a whole, the test evaluates the cognitive domains of memory, orientation, praxis, and language. The included participant-completed tasks, in the order presented, are word recall, naming object and fingers, commands, constructional praxis, ideation praxis, orientation, and word recognition. The examinee-based observations include the comprehension of spoken language, word-finding difficulty, and remembering test instructions. These items are scored based on an open-ended conversation about neutral topics at the beginning of the session and on the participant's

[3] The two alternative forms of the ADAS-cog-12, created for the needs of this thesis, are described here. Two improved versions of the ADAS-cog (the ADAS-cog-14) have been created, and a standardization study is currently running for the cognitive and the non-cognitive scales. This research project is not presented in this thesis.

spontaneous language and behavior during testing. The total score in the classic 11-item test is 70; this score represents the most severe impairment. Optional items, such as delayed word recall and the maze test, are available and are used according to researcher needs. A score of 0 represents the least impairment. A reduction in score at retest signifies cognitive improvement (Mohs et al., 1997), and a reduction of 3 or more points at retest signifies an effective treatment effect (Schrag & Schott, 2012).

For the needs of this thesis, the ADAS-cog-12 (including the original aforementioned 11 items and the optional delayed word recall) has been translated and adapted for the Cypriot population (Figure 3.12). Considering Dr. Mohs' recommendation of not repeating the same word lists in a study more frequently than every six months (Schafer et al., 2012), two alternative forms of equal difficulty were created for the word recall, word recognition, and object naming subscales. All words used for the development of the Cypriot ADAS-cog-12 were chosen from the CWP.

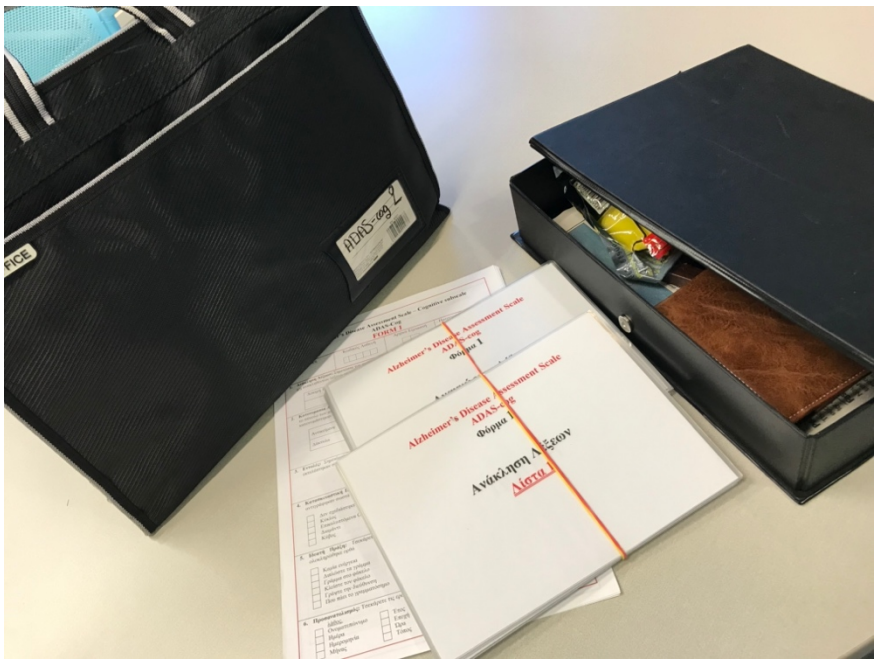
3.6.1 Method

Word recall item. This task originally comprised 10 high-frequency and -imagery nouns that are presented to the participant printed in block letters on white cards. The task contains three learning trials. Following the authors' criteria, one list of high-frequency and -imagery words was created for Form A of ADAS-cog-12. Then, each word from Form A was matched with another word with identical psychometric properties to create Form B list. The selected words had similar numbers of syllabi, frequency level (high frequency according to the six levels of taxonomy), and concreteness and imagery ratings (between 6 and 7). In the three recall trials, the words' presentation sequence followed the same as in the original ADAS-cog.

Naming item. In the naming task, the participant is asked to name 12 real objects that differ in their frequency values. For this task, 12 words differing in frequency level (four high, four medium, and four low, as in the original form) were selected. Each of the selected words from Form A was matched with another one with similar properties to create Form B. As with the recall lists, the words were identical in their concreteness and imagery levels. Since in the naming subtest, the items must be real objects that are presented in the participant, all words represented real objects that could be easily found (e.g., καρύδα/coconut, πυξίδα/compass).

Word recognition item. In this task, the participant is given one trial to learn 12 new words that are printed in block letters on white cards and one trial to recognize these words among 12 lures. For Form A, 12 words were selected for the learning trial and another 12 as distractors. The distractors were six semantically related and six non-relevant words. The words for Form B were matched in frequency, concreteness, and imagery values with those from Form A. Figure 4.12 demonstrates the Cypriot ADAS-cog-12 testing materials.

Figure 3.12 The Cypriot ADAS-cog-12



Note: For the needs of this thesis, five identical ADAS-cog-12 testing materials were created for each form. This allowed each member of the research team involved in patient assessment to hold exactly the same stimuli material, thus ensuring reliable data collection.

3.6.2 Investigation of ADAS-cog-12 Alternative Forms' Difficulty Levels

To investigate whether the two alternative forms had similar difficulty levels and could thus be used to evaluate the treatment's effectiveness, both forms were administered in participants with and without symptoms of dementia. The healthy participants were recruited to investigate whether the developed ADAS-cog-12 could differentiate patients

with dementia from the healthy population and thus if it could be used for future clinical reasons as well.

Participants and Methods

In total, 19 participants were recruited for this study. The healthy participants (MMSE ≥ 26) were matched in age and gender with the patients. Two sessions were scheduled with each participant, with a 2-week interval between them. In the first session, a demographic questionnaire, the MMSE, and the ADAS-cog A′ were administrated. At the following session, the participants were evaluated with the ADAS-cog B′.

Results

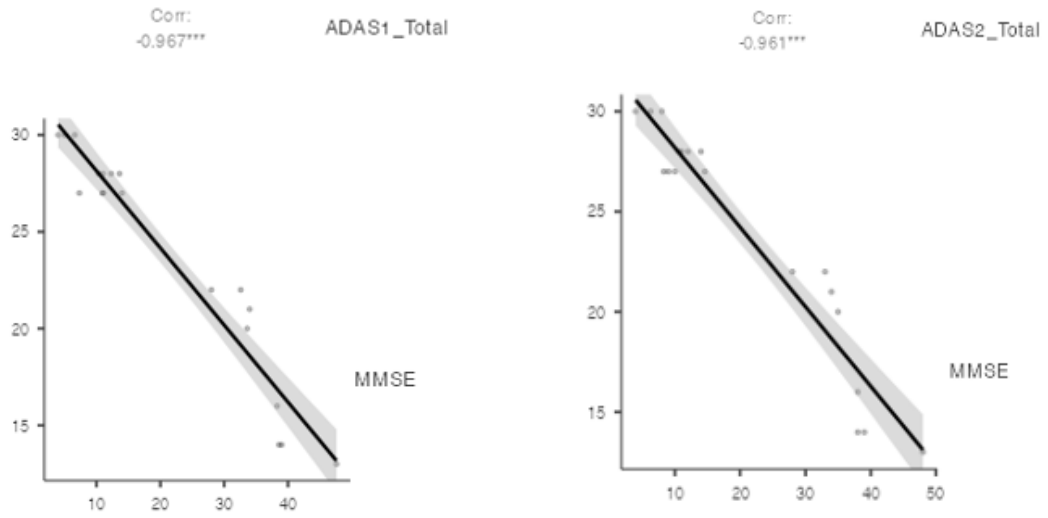
Table 3.11 outlines participant demographic characteristics. The Mann-Whitney *U* test was conducted to determine whether differences in age and education existed between participants with and without dementia. The results indicated a nonsignificant difference between the two groups in both age (U=31, p=.236) and education (U=39, p=.58).

As expected, both forms presented almost perfect negative correlation with the MMSE (Form A: r=-.967, p<.001; Form 2: r=-.96, p<.001). Figure 3.13 illustrates the correlation matrices between the ADAS-cog forms and the MMSE.

Table 3.11 Participants demographic characteristics

	Participants		
	No dementia	**Dementia**	
N	10	9	
Age			
Mean (SD)	72.9 (2.56)	75.7 (6.75)	p>.05
Minimum	68	62	
Maximum	75	85	
Gender			
Male	5	5	
Female	5	4	
Education			
Mean (SD)	7.10 (2.6)	7.11 (4.7)	p>.05
Origin			
Ammochostos	0	4	
Nicosia	8	0	
Limassol	2	4	
Paphos	0	1	
MMSE			
Mean (SD)	28.2 (1.3)	19 (5)	

Figure 3.13 Graphical illustration of correlation between ADAS-cog and MMSE



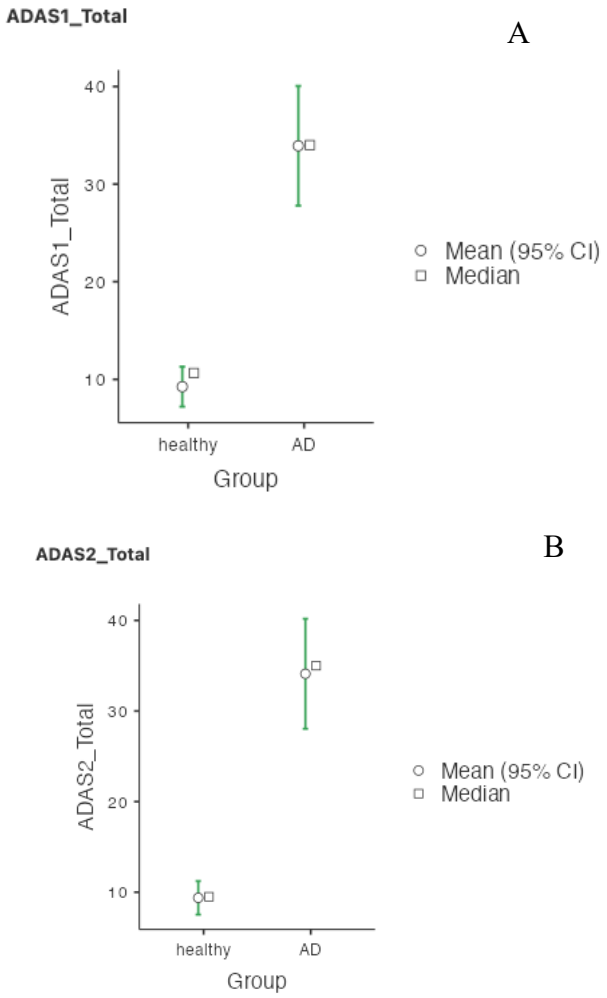
Note: A. Correlation matrix of ADAS-cog A′ with MMSE; B. Correlation matrix of ADAS-cog B′ with MMSE.

The Mann-Whitney *U* test was used to investigate whether the two ADAS-cog forms could differentiate between participants with and without dementia. Significant differences were found between the two groups in Forms A (U=1, p<.0001) and B (U=1, p<.0001). Descriptive statistics for both groups are outlined in Table 3.12. A comparison of the two groups' mean scores is illustrated graphically in Figure 3.14.

Table 3.12 Descriptive statistics of both groups

	Group	**N**	**Mean (SD)**	**Median**
ADAS-cog A	No dementia	10	9.25 (3.3)	10.65
	Dementia	9	34 (9.4)	34
ADAS-cog B	No dementia	10	9.4 (3)	9.5
	Dementia	9	34 (9)	35

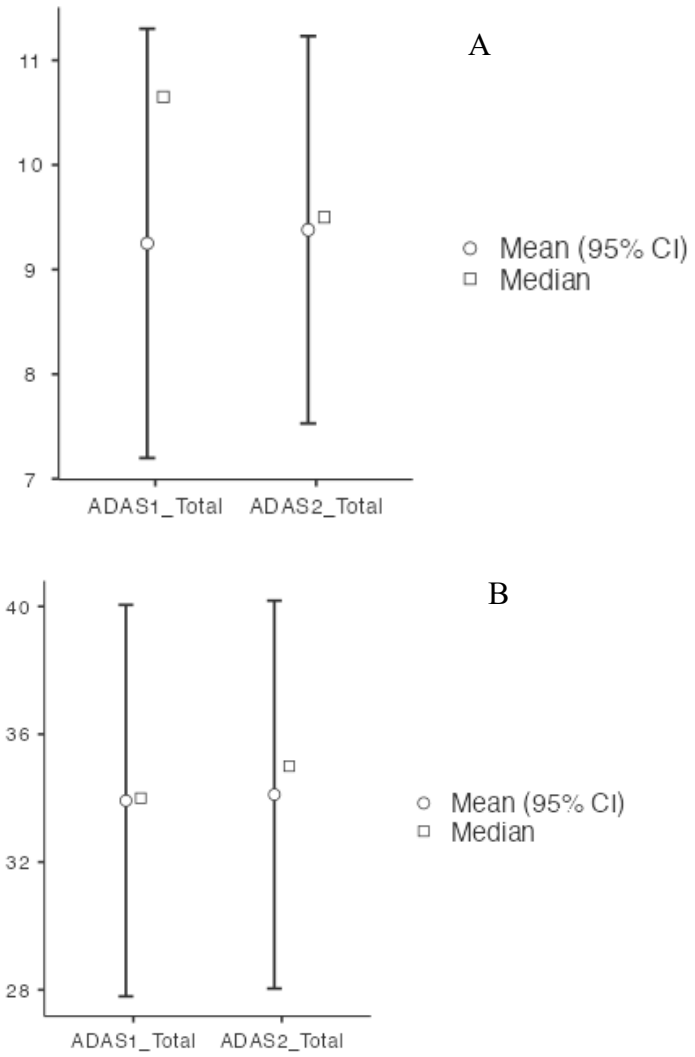
Figure 3.14 Comparison of two groups' mean scores in Forms A and B



Note: A. Plotted mean scores of both groups in ADAS-cog A′. The healthy participants averaged 9.25, while the patients averaged 34. B. Plotted mean scores of both groups in ADAS-cog B′. The healthy participants averaged 9.4, while the patients averaged 34.

A Wilcoxon signed-rank test resulted in nonsignificant differences between the scores on the ADAS-cog A′ (Md=34) and B′ (Md=34) for patients with dementia; W=6, p=.4. Similarly, nonsignificant differences were observed between the scores of the healthy participants on the ADAS-cog A′ (Md=10.65) and B′ (Md=9.5); W=19, p=.7. In Figure 3.15 the mean scores for each form of the two groups are graphically illustrated.

Figure 3.15 Comparison of mean scores between two alternative forms



Note: A. Comparison of the healthy participants' mean scores on ADAS-cog A′ and B′. B. Comparison of the patients' mean scores on ADAS-cog A′ and B′.

Paired samples *t*-tests were used to determine whether the participants scored differently in Form B in any specific item of the ADAS-cog. The results indicated nonsignificant differences in all items (all $p>0.05$). In addition, nonsignificant differences were found between the scores of the developed alternative items. Specifically, nonsignificant differences were found among the scores on the following:

- Word recall of Forms A (mean recalled words=5.25) and B (mean recalled words=5.3), $t(18)=-.36$, $p=.7$

- Naming of Forms A (mean score=0.68) and B (mean score=0.78), $t(18)=-1.15$, $p=.16$
- Word recognition of Forms A (mean score=5.7) and B (mean score=5.9), $t(18)=-1.3$, $p=.21$

ADAS-cog Forms A′ and B′, which were used in this research, can be found here: Cypriot ADAS-cog-12. For clinical reasons, a new version of these tools is currently under standardization and will be available in the near future.

3.7 Development of Alternative Neuropsychological Tests for the Assessment of Primary and Secondary Outcomes

For the development of equally difficult alternative neuropsychological tests, the standardized words from the CWP were used. Form NO1 of the 17 alternative test batteries used for the assessment of the primary and secondary outcomes can be found in Appendix 4 (the need for 17 alternative test batteries it is discussed in detail in Chapter 4).

3.7.1 Word Learning Lists

Word learning list tasks are among the most widely used tools for the assessment of episodic memory in AD patients and are recognized as critical tools for early AD detection. Performance patterns obtained by list learning tasks provide valuable information about underlying brain–behavior relationships. In these tasks, a word list is verbally presented across several trials. Participants are asked to recall the words immediately after every presentation and after a relatively short delay (e.g., 25 or 30 minutes). A recognition task, wherein participants are asked to recognize the previously learned words among lures, follows.

For the needs of this thesis, 17 alternative word learning lists were created to evaluate patients' verbal learning abilities during the study's two phases (i.e., baseline and intervention) and at follow-up. Each assessment included three learning trials, one immediate recall, and a recognition trial. The word learning task Form 1 (WLT-1), which included five low-, five medium-, and four high-frequency words (14 total words in the

learning condition), was initially developed. For each WLT-1 word, 16 alternative words that were equal in frequency, imageability, concreteness, length, and part of speech were then selected from the CWP to create the remaining 16-word lists. In addition, all selected items were matched in living (e.g., dog) and non-living (e.g., pencil) items. The recognition condition included the 14 original, and 14 new words equal in all properties to the original ones. The 17 word learning tasks were consequently considered identical regarding item properties.

3.7.2 Naming Task

Seventeen alternative and equally difficult forms were created for the naming task. Each form comprised of 15 items of living (e.g., cat) and non-living (e.g., pencil) items that were presented to the patients printed in color on A4 paper (Figure 3.16). As with the word learning tasks, 15 words were first selected to create Form 1, and then each word was matched with 16 others in terms of frequency, imageability, and concreteness to develop the remaining 16 forms. Each form comprised five high-, five medium-, and five low-frequency words. The six levels of frequency taxonomy were used during word selection. For instance, in all 17 alternative forms, the five medium-frequency words comprised three low–medium and two high–medium words. In addition, the lists included four living and 11 non-living items. Finally, for each word, a color picture was selected as a stimulus, and participants were asked to name it aloud. Following this methodology, the difficulty of the alternative forms was considered reliably equal. Each word was used only once as a stimulus among the 17 alternative forms. The words that were used as stimuli in the word learning lists were excluded from the selection.

Figure 3.16 Examples of naming task stimulus

Note: Example of a living (A) and non-living (B) stimulus from the naming task Form 1.

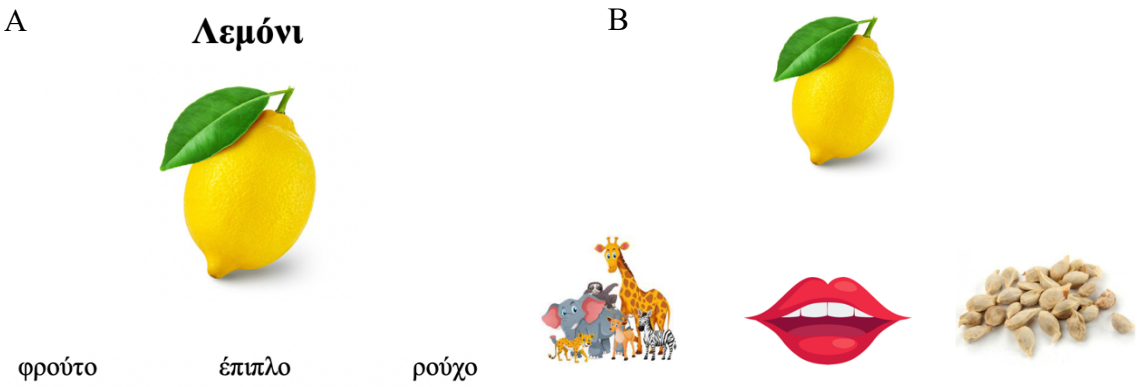
3.7.3 Semantic Association Tasks

Seventeen alternative and equally difficult forms comprising living and non-living items were developed. The tasks included verbal and visuo-perceptual forms. This test is designed to evaluate ability in four semantic associations: (1) part–whole, (2) function, (3) superordinate relationship, and (4) contiguity (Di Giacomo et al., 2012). In the verbal condition, participants are asked to pair a target figure with one of three noun word choices. The correct choice is distributed among the four semantic associations. Accordingly, each target figure is presented four times (i.e., one for each semantic association). For instance, the following words are presented, one at a time, together with the lure words for the target stimulus "pencil": "stationery" (superordinate), "tip" (part–whole), "write" (function), and "eraser" (contiguity). In the verbal form, the targets are presented in both lexical and visuo-perceptual modalities to allow for double access to semantic information (Figure 3.7 A; Caputi et al., 2016). The lure words were semantically unrelated and were matched to the target words in terms of length and frequency. The visuo-perceptual task included color drawings. As with the verbal task, the items were balanced between living and non-living items and were distributed among the four associative relations. However, in this condition, participants were asked to pair the target drawing, presented at the top of the form, with one of the three given drawings that corresponds to the target (Figure 3.7 B).

In the verbal condition, each of the 17 forms included four living and four non-living items. The visuo-perceptual task included three non-living (out of the four stimuli from the verbal condition) and two living items (out of the four living items of the verbal condition). Only three associated words were included (superordinate, contiguity, and part–whole) for the living items. The function category was not included, as there are no appropriate and unanimously recognized functions for living things(Di Giacomo et al., 2012). In both tasks, there is no self-generation of the name of the objects. Participants could say or point to the correct word in the verbal condition or to the drawing in the visuo-perceptual condition.

All target items were gathered from the naming task of the same form (e.g., eight of the items included in the naming task Form 1 were added in the semantic association task Form 1, etc.), as proposed in the literature (Di Giacomo et al., 2012; Caputi et al., 2016). During the assessments, the naming task was administered first, and the semantic associations followed.

Figure 3.17 Semantic associations task



Note: A. Example of the item “lemon” in the verbal form. The target is given as both word and photo. In this example, participants should pair the target “lemon” with its class membership (the word fruit/φρούτο). B. Example of the target item “lemon” in the visuo-perceptual form. The target is given in color drawing and should pair it with its part–whole (seeds/κουκούτσια).

The reason for including in each form only 13 items in total (i.e., eight in the verbal and five in the visuo-perceptual form) was that otherwise, the task would have become too long, and participants would become tired and answer randomly. As mentioned above, each non-living item was presented four times (i.e., seven non-living items x four

times=28 presentations) and each living item three times (i.e., six living items x three times=18 presentations). Accordingly, each of the semantic association tasks (both verbal and visuo-perceptual conditions) comprised 46 stimulus cards.

3.7.1 Trail Making Tests

The trail-making test (TMT) was used to assess patients' attention and executive function. Seventeen alternative forms of TMT A′ and B′ were developed. In each alternative form, the original cycle positions (Reitan, 1955) were maintained, with the numbers and letters randomly allocated in the cycles, which, however, were maintained on the same half of the page for each alternate form (e.g., the number 1 was in the bottom part of the page on every form).

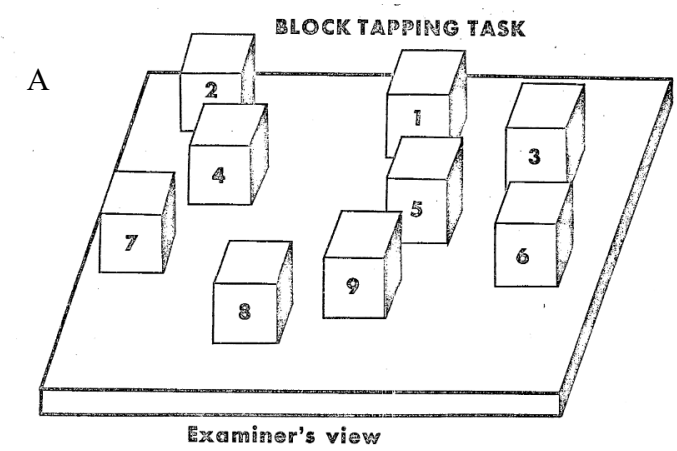
3.7.2 Corsi Block-Tapping Task

The Corsi block-tapping task is a widely used test for the assessment of visuo-spatial memory with minimal verbal mediation. It was developed in the early 1970s by Dr. Philip M. Corsi and described in his doctoral thesis in 1972 (Corsi, 1972). The task material comprises nine (numbered) identical cubes, which are arranged on a 9″ x 11″ wooden board (Figure 3.18 A). The assessment involves an examiner who taps the cubes with specific sequences; participants are then required to point or tap the cubes in the same order presented by the examiner. The task was based on the digit span task, but instead of a verbal form, it requires the use of visuo-spatial memory. Nowadays, the task is widely used for the assessment of memory loss, spatial memory, and non-verbal spatial memory (Kessels et al., 2000).

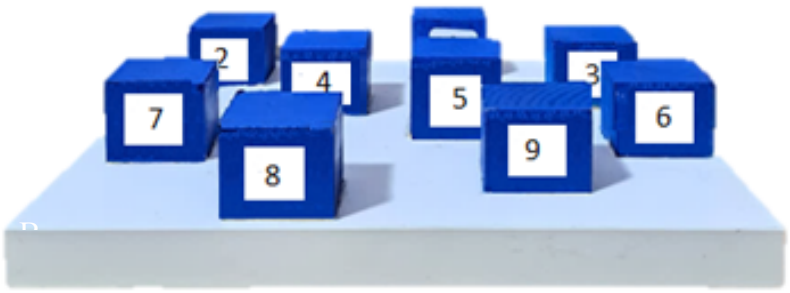
For this thesis, five boards were created of approximately the same size as the one described by Corsi (1970; Figure 3.18 B). This allowed every member of the research team involved in patient assessments to hold the same task material, which is crucial for reliable data collection. The number sequences (lists of the order that the examiners should tap the blocks) were generated using an algorithm that randomly assigned numbers to each form. The task was created to start with a small number of two blocks (e.g., one, eight; the examiner should first tap Block 1 and then Block 8) and was gradually increased in length up to nine blocks. Each block was tapped only once in any particular sequence, with one second intervals between each tapping.

Figure 3.18 Corsi block-tapping task board

A



B



Note: A. The Corsi Block-Tapping board as described by Dr. Corsi in his thesis in 1972. Nine wooden blocks are spatially arranged on a board . From "Memory and the medial temporal region of the brain," by P. M. Corsi, 1972, *Dissertation Abstracts International, 34*(2-B), 891, Corsi-Tapping Task section, Figure 9 (DR Corsi Doctoral Thesis). B. The board was created for the needs of this thesis. Five identical boards were created by the research team following the technical instructions described by Dr. Corsi.

3.8 Chapter Summary

This chapter has presented the development of NEWSLEX-CY and DIALEX-CY, two Cypriot dialect-based corpora used as a basis to develop the first standardized Cypriot word pool. The CWP is a powerful tool for conducting cognitive research with Greek-Cypriot participants and provides subjective and objective normative data for 2,852 words. Specifically, the CWP provides frequency estimates in three and six levels of taxonomy and objective measures, such as number of syllables, number of letters, and

part of speech, for all included words. Moreover, it includes normative data for imageability and concreteness. It is important to note that the databases were created from the analysis of written material which might lead to potential bias in favor of those with higher educational level. In addition, the normative data for the words frequency have not been stratified by educational level which might compromise the calculated statistics. This database can be reliably used in the development of equally difficult alternative cognitive tests. The CWP was used in the development of two alternative and equally difficult Cypriot versions of the ADAS-cog and the neuropsychological tests that were used to assess the efficacy of TMS treatment intervention in AD patients. Despite a rigorous methodology being followed for the development of the 17 alternative neuropsychological forms used for the assessment of primary and secondary outcomes in this thesis experimental work, the forms were not administered to a healthy population for the confirmation of equal difficulty levels. This limitation was encountered by the use of standardized neuropsychological tools before and after the rTMS treatment in addition to the development of the two alternative ADAS-cog forms, of which their psychometric properties were investigated, and their identical difficulty level established.

Chapter 4 Effects of 40 Hz Precuneus rTMS in aMCI

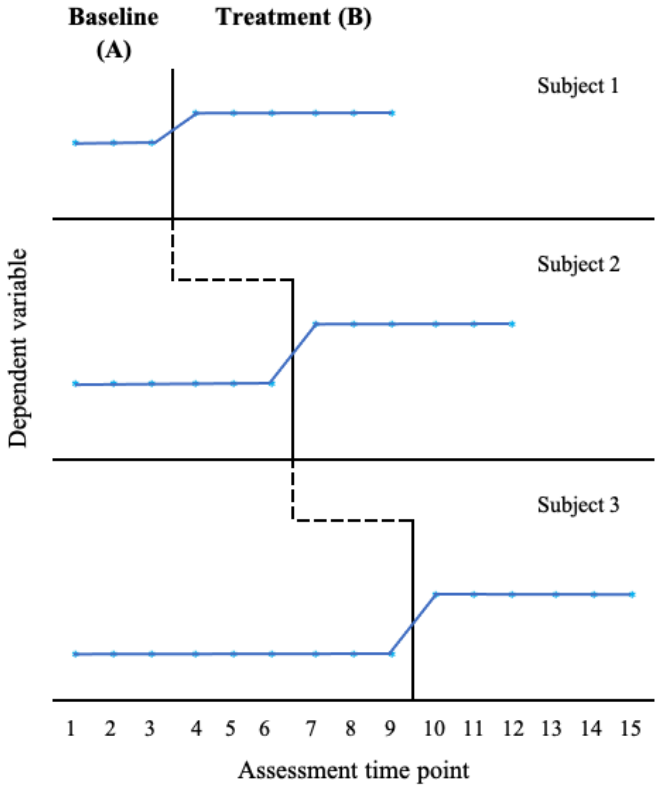
Previous chapters presented the theoretical background of a newly introduced and pioneering approach which targets brain waves to treat AD pathology as well as the effects of gamma frequency stimulation in healthy participants. It is evident that gamma frequency stimulation has the potential to modulate gamma brain oscillations (Liu et al., 2022) and to change the neurophysiological activity both in healthy participants (Traikapi et al., 2022) and AD patients (Suk et al., 2020) while effectively mitigating the accumulative pathology and improve cognitive function in AD (Liu et al., 2022; Chan et al., 2021). Due to the potential clinical implications of the aforementioned evidence, this study aimed to investigate the efficacy of 40 Hz rTMS in patients with aMCI. This chapter presents in detail the study's methodology and design along with a justification for that choice. In addition, it reports the results of the 40 Hz rTMS intervention, in the patients with aMCI. The patients' clinical characteristics, along with their performance throughout the study and statistical analyses, are presented for each patient individually and collectively. As the study's design was developed following well-defined guidelines for behavioral intervention in single-case experimental studies (Heyvaert & Onghena, 2014; Tate et al., 2014, 2016), the results are reported accordingly. Hence, a graphical illustration of patients' scores on each test is provided to assist the visual analysis, which is accompanied with randomization tests and effect size indices to quantify the treatment effect. Finally, patient performance on the ADAS-cog-12 and neuropsychological evaluations are presented, individually and collectively, and the average percentage of change after treatment introduction is presented for each variable.

4.1 Experimental Design

The study was conducted in the rehabilitation clinic of the Cyprus University of Technology (CUT), in Limassol, Cyprus, and was approved by the Cyprus National Bioethics Committee (Protocol number: EEBK/EP/2021/22; Appendix 1). A single-case, randomized, concurrent multiple baseline design, across two patients with aMCI was employed (Krasny-Pacini & Evans, 2018). This design involves multiple AB series (i.e., A=baseline, B=intervention), in which the baseline phase begins at the same time for each

participant while the intervention is introduced staggered across time and participants. The staggered introduction of the intervention allows to demonstrate that the targeted behaviors do not change over time, but only after the introduction of the treatment (Lobo et al., 2017). A schematic representation of a typical multiple baseline design is illustrated in Figure 4.1.

Figure 4.1 Multiple baseline design study



Note: The principle of a multiple baseline design is that each patient acts as their own control. The baseline phases (i.e., A) begin at the same time for all participants while the intervention is introduced to each participant at different points in time. Therefore, if the intervention is the sole determinant of improvement changes in the dependent variables are expected only in those who have received the interventions but not to those who remain at the baseline phases.

4.1.1 Why a Single-Case Design

The concept of a single-case design implementation for the investigation of this thesis' primary research question, was decided due to concerns on whether the recruitment of a larger pool of patients was a feasible option. Due to the Covid-19 pandemic, that was still a primary health issue, families were skeptical about their loved ones' safety while the

percentage of patients that were visiting the day care centers (from where we would recruit patients) had dropped dramatically due to the imposed measures and/or families' safety concerns. Nevertheless, despite the small sample size, single subject methodology can provide a rigorous experimental evaluation of intervention effects (Kratochwill et al., 2010). Although single subject methodology has many variations, these designs involve repeated, systematic measurement of a dependent variable before, during, and after the active manipulation of an independent variable. These studies, when designed and conducted according to the well-established *standards*, can provide a strong basis for establishing causal inference and are widely used in neurorehabilitation (Evans et al., 2014; Heyvaert et al., 2017; Krasny-Pacini & Evans, 2018; Kratochwill & Levin, 2010; Levin et al., 2014). The randomized n-of-1 trial (i.e., single-case design) has been ranked, by the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net) as Level 1 evidence for treatment decision purposes in individual patients, together with systematic reviews and randomized control trials (Howick et al., 2011; Tate et al., 2013). A single-case methodology, therefore, was considered an evidence-based approach to rigorously investigating this thesis's primary question with a relatively small sample size.

4.1.2 Study's Design

The study was designed, conducted, and reported according to the What Works Clearinghouse criteria for single case studies (Kratochwill et al., 2010). According to these criteria, to meet evidence standards multiple AB series repetitions with at least three measurements of the outcome variables on each phase is recommended. In addition, to minimize major threats of internal and external validity, randomization should be implemented to yield control over confounding variables; the targeted behaviors must be assessed by more than one assessor collecting the necessary inter-assessor agreement, and finally procedures that will ensure that the interventions and the assessments will be delivered as planed (treatment fidelity), are highly recommended (Kratochwill & Levin, 2014). All the above criteria are discussed below.

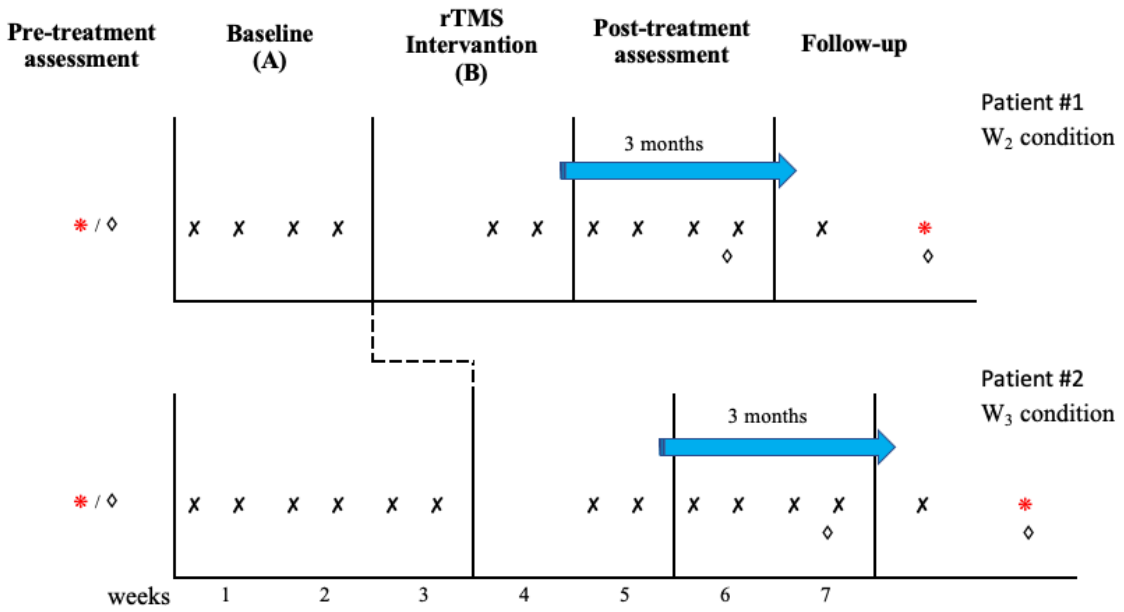
The study comprised two AB series repetitions (two aMCI patients). Randomization was ensured by designing five experimental conditions, characterized by the length of their periods: one (W_1), two (W_2), three (W_3), four (W_4) and five-week (W_5) baseline periods. Each patient was randomly allocated to one of the five conditions (without overlapping). The first patient was allocated to the two-week baseline and the second patient to the

three-week baseline condition. After the end of each experimental condition patients received a two-week gamma frequency TMS treatment. With this design the treatment was introduced at different time periods to each participant (i.e., after two weeks to the first patient, after three weeks to the second patient). The sequential introduction of the intervention makes the participant that stay at the baseline phase the control group. Therefore, when the intervention was introduced to the first patient, the remaining patient at the baseline phase served as the control group and hence, no improvements were expected. Accordingly, if the TMS intervention was the sole determinant of improvement, no changes to the targeted behaviors would be expected for the participant reimaging in the baseline phase.

The targeted behaviors were systematically evaluated throughout the study. Specifically, they were evaluated at: (1) pretreatment, (2) treatment, (3) post-treatment and, (4) three months post-treatment.

Baseline phases. Five baseline phases of different length were designed (i.e., one to five weeks; W_1-W_5) and the aMCI patients were randomly allocated to one of the five. The first patient was randomly allocated to the two-week baseline and the second patient to the three-week baseline condition. The targeted behaviors were evaluated two times per week. Therefore, the first patient was evaluated four times and the second patient was evaluated six times. Each assessment session lasted between 30 and 40 minutes. A schematic representation of the study's design and timeline is illustrated in Figure 4.2.

Figure 4.2 Schematic representation of the study's design and timeline



Note: The patients underwent neuropsychological evaluation before the beginning of the study and three months after the end of the rTMS intervention (i.e., follow-up). The targeted behaviors were repeatedly and systematically measured throughout the AB phases (i.e., single-case data). During the AB and the follow-up phases, the targeted behaviors were assessed 11 times in the W_2 baseline condition and 13 times in the W_3 baseline condition. Each ❋ on the figure represents a neuropsychological evaluation. Each ✗ represents one targeted behavior assessment. Each ◊ represents the time point of the primary measures assessment using the ADAS-cog and the MMSE.

Intervention phases. Patients underwent a two-week TMS intervention immediately after the end of their experimental baseline condition. The TMS sessions were being delivered daily (Monday to Friday) for a total of 10 TMS sessions. The targeted behaviors were assessed six times in total. As a delayed effect was expected from the TMS treatment (e.g., Cotelli et al., 2011), the data collection started one week after the beginning of the intervention. Therefore, two assessments were conducted during the treatment phase and four post-treatment (two assessments/week; see Figure 4.2).

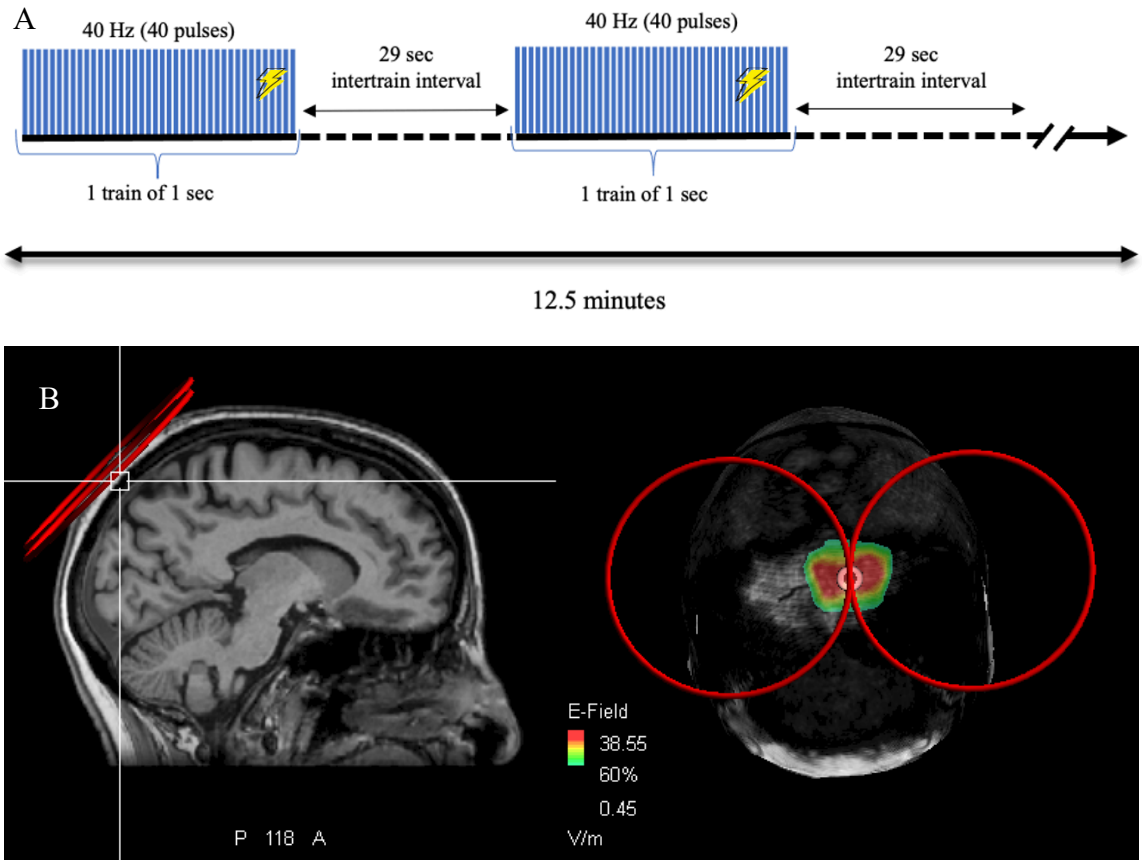
Follow-up phase: The targeted behaviors were assessed again three months after the end of the intervention phases.

4.2 TMS: Sites Protocol, and Procedure

In each B phase (i.e., intervention phase) patients received daily treatment sessions for 2 weeks (one session per day; five sessions per week; total of 10 sessions). Each session included 25 trains consisting of 1 sec of 40 Hz each (40 pulses/train; 1000 total pulses), with 29 sec inter-train intervals and delivered at 90% of participant's resting motor threshold, or with the intensity of 65% of the maximum machine output (for safety reasons; Figure 4.3 A) using the Magstim Super Rapid2 Plus1 Therapy System with a figure-of-eight coil. The coil was oriented parallel to the midline with the handle pointing down-ward. Motor threshold (MT) was evaluated at the begging of each treatment week (two times total) and TMS intensity was adjusted accordingly. MT was defined as the minimum TMS intensity needed to elicit MEPs of >50μV in five out of 10 trials in the first dorsal intereosseous muscle.

Stimulation was delivered over the left and right PC on separate days (i.e., one day left PC and the contralateral PC the following day). The exact stimulation sites were identified by targeting at the peak voxels that have been previously reported to be activated during episodic memory tasks. Therefore, the left PC located at the MNI coordinates x= -14, y=-66, z=56 (Hebscher et al., 2020) and the right PC at x=6, y=-70, z=44 (Kwok et al., 2012; Ye et al., 2019). The patients underwent an anatomical MRI scan prior to the study and the exact position of the stimulation coil was guided by the Visor2 TMS neuronavigation system (Visor2, ANT Neuro, Enschede, Netherlands; Figure 4.3 B). Prior to the beginning of the TMS sessions, MNI coordinates were inserted into the neuronavigation system and the most superficial regions closest to the coordinates, that could be accessible with TMS, were selected. Due to participants' anatomical differences, the stimulation sites varied slightly from the initial coordinates.

Figure 4.3 Stimulation protocol and site



Note: A. Graphical illustration of the TMS protocol. The stimulation was delivered at 90% of patients' resting motor threshold. B. Stimulation site and coil orientation. Stimulation was applied over the right and left PC using a neuronavigation system to ensure that the same sites were stimulated across sessions with stable coil orientations.

Assessment of resting motor threshold. Resting motor threshold was established using single-pulse TMS with a 70 mm figure-eight coil. Surface electromyography (EMG) leads were placed over the first dorsal interosseous (FDI) muscle of the left hand to monitor muscle evoked potentials (MEPs). Patients were asked to sit comfortably, with both arms fully supported on a pillow. Full muscle relaxation was ensured through visual and online EMG monitoring. The TMS coil was then placed over the primary motor cortex at the optimal site for obtaining an MEP in the FDI. Single-pulse stimulation at supra-threshold intensities were applied over the primary motor cortex position for eliciting an FDI contraction. The stimulation intensity was progressively reduced in 2% steps until a level was reached below which reliable EMG responses disappear. A reliable response was defined as a MEP of 50-100 μV occurring in 5 out of 10 consecutive trials.

4.3 Participants and Research Documentation

In total, two patients with a diagnosis of aMCI, as described by Petersen (2016), were recruited for the study. An open call was made to the media outlining the aim of the study and asking for assistance with patient recruitment. Additionally, a flyer advertising the study was uploaded to the investigators' social media and the CUT official website and social media pages (Appendix 3). The flyer was distributed to neurologists and psychiatrists' private offices across the city of Limassol as well as in day care centers for people with dementia. Finally, a collaboration was made between the research team and certified neurologists who referred their patients who met the inclusion criteria. Recruitment was on rolling base for 5 months and interested patients and/or carers were invited for the initial evaluation of the inclusion/exclusion criteria. Participants were asked to provide a detailed clinical history in the presence of the carer and/or family member that included demographics, medical history, current health status, current medication use, education, and employment background. Permission to access this information was granted through the signed informed consent form (the consent form can be found here: AD Study - Consent Form).

All the gathered data and personal information were stored at the principal investigator's office in a secure cabinet at the rehabilitation clinic. The access was limited to the primary investigator and the supervisor of the study. The computers used in the study were password protected. All rooms with computers used in the study were protected by alarm systems. In addition, the building that houses the offices of the researchers at the CUT were equipped with anti-theft systems and firefighting equipment. The building was also protected by a security company during non-working hours.

4.3.1 Inclusion Criteria

To participate in the study patients had to meet all the below inclusion criteria:

- 55 years of age and above.
- Speaking Cypriot-Greek as a first language.
- Diagnosis of aMCI (confirmed by a neurologist and neuropsychological evaluation).

- Absence of other medical or psychiatric condition that may induce cognitive deterioration.
- Score between 30 and 26 on the Mini Mental State Examination.
- Score of 3 on the Global Deterioration Scale (GDS).
- Score bellow 10 (i.e., 0-9) on the Greek version of the Instrumental Activities of Daily Living (IADL).
- Score no less than 6 on the Basic Activities of Daily Living (BADL).
- Score below 15 on the Geriatric Depression Scale-30 (GDS-30).
- Stable medical and pharmacological condition for at least 2 months prior to the study.
- Patients under cholinesterase inhibitors medication were included in the study only if they were taking the medication for more than 2 months prior to the study.
- Visual and hearing abilities within normal range.
- Absence of any clinically significant medical history that may induce cognitive impairment (psychiatric, neurological, cerebrovascular).
- Willingness to undergo an MRI scan.
- Having a caregiver who will agree to be responsible for their participation throughout the study.
- Being fully vaccinated for the Covid-19 (first shot and booster dose).

4.3.2 Exclusion Criteria

Patients were excluded from the study if one or more of the below mentioned exclusion criteria were evident:

- History of excessive alcohol consumption.
- Diagnosis of epilepsy or family history of epilepsy.

- Moderate or severe depression as was assessed by the Geriatric Depression Scale – 30 (score no more than 15).
- Severe loss of hearing or visual ability.
- Medical implants in the head or a pacemaker.
- History of brain injury.
- Previous heart surgery or stroke.
- Under drugs with anticholinergic properties.
- No caregiver who could take the responsibility for their commuting throughout the study.
- Diagnosis of another neurodegenerative disorder, psychiatric or cerebrovascular condition.

4.4 Outcome Measures

The primary outcome measures were the changes on episodic memory tasks and measures of global cognitive function. Episodic memory was evaluated using word learning lists which are the gold standard neuropsychological tests for evaluating the ability to learn and recall new information in AD (Albert, 2011). Global cognitive function was evaluated by the ADAS-cog-12 and the Mini Mental State Examination (MMSE). A detailed description is discussed below. We hypothesized that the proposed rTMS protocol delivered bilaterally to the PC would have an effect not only at local, but at network level as well (Mancini et al., 2017). Therefore, the secondary outcomes were related to measures of semantic and spatial memory, as well as attention and executive functions. Bearing in mind the study's design, which required repeated and constant evaluations of the targeted behaviors (see Figure 4.2), alternative forms with equal levels of difficulty were developed for the tests used during the A, B, and follow-up phases. A detailed description regarding the development of these measures and the measures per-se is provided in Chapter 3.

4.4.1 Neuropsychological Evaluation

Patients underwent a neuropsychological evaluation with standardized and well recognized measures pretreatment (before the baseline phase) and in the follow up phase (Table 4.1). The purpose was to evaluate the effect of our proposed treatment beyond the targeted behaviors (Krasny-Pacini & Evans, 2018). Moreover, the participants' episodic memory abilities were evaluated with more than one cognitive assessment test (word learning test & logical memory). The length of each assessment was approximately 120 minutes.

Table 4.1 Neuropsychological assessment battery

Cognitive Domain	Neuropsychological Test
General cognition	Mini Mental State Examination (Mougias et al., 2020)
Memory	Logical Memory (Wechsler, 2008) Rey Osterrieth Complex Figure (immediate & delayed recall) (Osterrieth, 1944)
Attention	Trail Making Test A' (Reitan, 1955) Digit Span Forward (Wechsler, 2008)
Working memory	Digit Span Backwards (Wechsler, 2008)
Visuospatial abilities	Rey Osterrieth Complex Figure Test (copy)
Executive functions	Verbal Fluency Test (Kosmidis et al., 2004) Frontal Assessment Battery (Nucci et al., 2012) Trail Making B' (Reitan, 1955)
Cognitive reserve	Cognitive Reserve Questionnaire (Nucci et al., 2012)
Neuropsychiatric symptoms / mood	Neuropsychiatric Inventory (Cummings et al., 1994) Geriatric Depression Scale – 30 (Fountoulakis et al., 1999) Beck Anxiety Inventory (Beck et al., 1988)
Quality of life	Quality of Life in Alzheimer's Disease (Logsdon et al., 1999)

4.4.2 Primary Outcome Measures

Episodic Memory

Word Learning List. Episodic memory during the A, B and follow-up phases was assessed using a word learning list, which is one of the most well-established tests for

assessing episodic memory function in patients with early dementia (Beck et al., 2012). Seventeen alternative and equally difficult word learning lists were developed. Each list was comprised of 5 low, 5 medium and 4 high frequency words. The assessments included 3 learning trials, one immediate recall, one delayed recall and a recognition trial. The recognition task of each form contained the 14 original words and 14 new words with equal difficulty as the original ones.

Global Cognition

Patients' global cognitive function was assessed by the standard 11-items ADAS-cog (Mohs et al., 1997), including the optional delayed recall item, and the MMSE, at pretreatment, immediately after the end of the treatment and at the follow-up phase.

Alzheimer's Disease Assessment Scale. The ADAS-cog is considered the gold standard for the evaluation of antidementia treatments efficacy (Skinner et al., 2012) and it is the most widely used neuropsychological measure in clinical trials (e.g., Ihl et al., 2012; Rabey & Dobronevsky, 2016; Rozzini et al., 2007). The ADAS-cog contains 11 items, including participant-completed tasks and examinee-based observations. As a whole the test evaluates the cognitive domains of memory, orientation, praxis, and language. The ADAS-cog was adjusted for the Cypriot population and two alternative and equally difficult forms were developed for the word recall, the object naming, and the word recognition subscales.

Mini Mental State Examination. The MMSE is a 30-point simple pen-and-paper questionnaire that briefly assesses patients' cognitive status. It was developed by (Folstein et al., 1975) and since then has been extensively used in clinical and research settings and has been adjusted and standardized is several countries, including Greece (Fountoulakis et al., 2016; Mougias et al., 2020). It includes evaluation of orientation to time and place, verbal memory, concentration/attention, language, visuospatial abilities, and the ability to understand and follow instructions. It is worth mentioning that while a high score in the MMSE does not necessarily translate to absence of cognitive impairment (Arevalo-Rodriguez et al., 2015), it is a useful tool to observe possible changes in research (Bernard & Goldman, 2010).

4.4.3 Secondary Outcome Measures

The secondary outcomes during the A, B and the follow-up phases were evaluated using the bellow mentioned neuropsychological tests. Each test is described in detail in Chapter 3.

Semantic Association Task (SAT). The SAT is a neuropsychological test that evaluates the multiple levels of semantic knowledge organization (Caputi et al., 2016). Seventeen alternative and equal in difficulty forms, comprising 15 living and nonliving items, were developed, and included a verbal and a visuospatial form.

Naming Task. The naming test is a widely used assessment tool that evaluates one's ability to visually identify and name objects that are presented printed on white paper. Seventeen alternative and equal in difficulty forms were used, comprising of 15 living and nonliving items, to assess patient's ability to access semantic knowledge

Corsi Block Task (CBT). The CBT is used for the assessment of spatial memory. Using an algorithm, 17 different task forms, with randomly assigned numbers were created. The task was started with a small number of two blocks and gradually was increased in length up to nine blocks.

Trail Making Test A΄ and B΄ (TMT). The TMS was used for attention and executive function assessment. In each of the 17 forms that were created, the original position of the cycles (Reitan, 1955) was maintained, however the numbers and letters in the cycles were randomly assigned.

Collectively, the assessment battery for the targeted behaviors' evaluation during the multiple baseline study (i.e., during the A, B, and the follow-up phase; Appendix 4) was comprised of:

- Word learning task
- Trail making test A΄ and B΄
- Naming test
- Corsi block forward
- Semantic association task

The tests were administered in the same order within all participants. First, the word learning list was given followed by the TMT A′ & B′, the naming test, the SAT and finally the CBT. The delayed recall and the recognition task from the word learning task were administered 25′ after the immediate recall tasks.

4.4.4 Qualitative Assessment

To qualitatively evaluate possible changes to patients' cognitive and emotional function as well as their ability to function in everyday situations, the 'Post Study Interview' (PSI) questionnaire was developed. The PSI comprised of a patient and a caregiver version and included questions that aimed to record the thoughts of both the patients and their caregivers regarding their observations about possible behavioral changes after the study. Among others, the PSI included the questions *'Did you observe any change in your ability to remember new information after the end of the study?', 'How is your ability to participate in a conversation in relation with six months ago (before your participation in the study?'*, *'Did you observe any change in the way you think after the end of the study?'* and '*Did you observe any change in your father's behavior after the end of the study?'*. The questionnaire was given in the follow up phase.

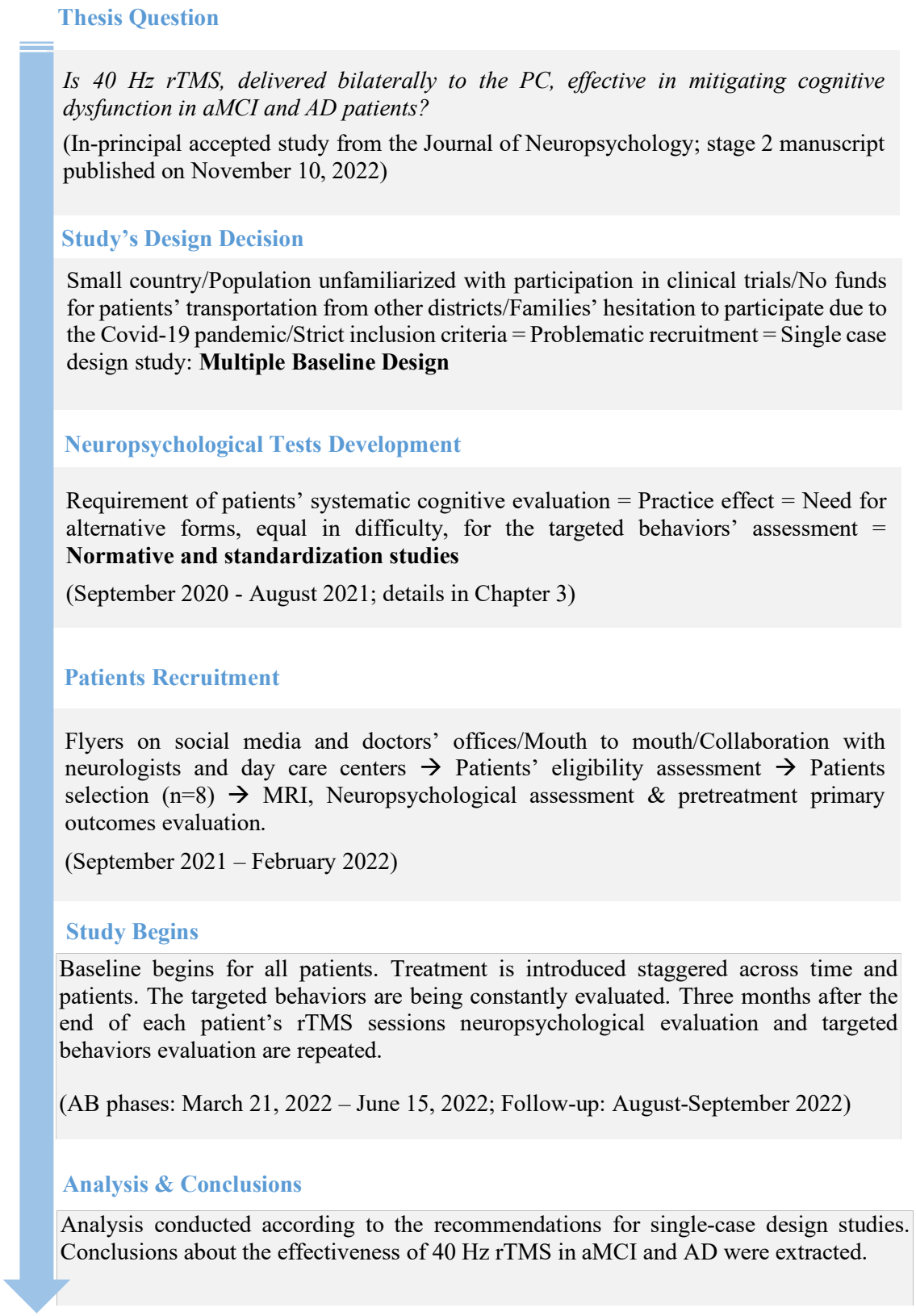
4.4.5 TMS Therapy: Tolerance Assessment

To evaluate patients' experience after the 40 Hz rTMS, to monitor for possible discomfort and therefore to adjust the protocol to every patient but also to investigate whether a more intense protocol can be developed in the future, the Wong-Baker Faces® Pain Rating Scale (https://wongbakerfaces.org/) was used. Donna Wong and Connie Baker originally developed this tool to help children communicate about their pain. The scale uses a series of faces ranging from a happy face with score 0, which represents the complete absence of any pain, to a crying face with a score of 10 which represents the worst pain (Figure 4.4). The patients were given the scale after every TMS session and were instructed to choose the face that best depicted their pain and discomfort during the rTMS application.

A schematic representation of the study's methodological steps is presented in Table 4.5.

Figure 4.4 An emoji representation of Wong-Baker scale

Figure 4.5 Thesis methodology steps



Note: This flow chart diagrams the steps of this thesis methodology from the conceptualization to data acquisition and conclusion.

4.5 Analysis Plan

Inter-assessor agreement was calculated by the percentage agreement (PA) for each phase on each outcome variable. Minimum acceptable inter-assessor agreement was considered a range between 0.80 and 0.90 (Hartmann et al., 2004) on at least 20% of all sessions (Lobo et al., 2017). Two raters, members of the research team, independently marked the scores of 12 assessment forms (i.e., six from the baseline phases and six from the treatment phases) previously obtained by a different assessor. The forms included all the obtained assessment tests.

4.5.1 Visual Analysis

At the first stage of the analysis in order to determine whether there was a functional relation between the rTMS protocol and the outcome measures, visual analysis was conducted by examining six features of the single case design graphed data: level, trend, stability, immediacy of the effect, overlap, and consistency. Each feature was assessed individually and collectively across phases. Visual analysis was supplemented by randomization tests and effect size indices methods, to evaluate the magnitude of the intervention effect and interpret the results in terms of statistical significance. The collected data were displayed graphically and a within and between phase examination was performed.

Within-phase examination: Consistency of level, trend and stability within each phase was examined. The mean score of each variable was used to assess the within phase level, and trend was evaluated by determining whether the data points were decreasing or increasing monotonically. In addition to the visual analysis, quantification indices were used in an attempt to increase internal and external validity. To quantify the within phase differences in level and thus to identify whether there was substantial increase in the targeted behaviors, the ***Percentage Change Index (PCI)*** was used. The PCI converts the raw measures into percentages and thus makes the results comparable. Possible changes in the trend of the within phase were estimated by the least squares regression. Within-phase stability (or consistency) was assessed by calculating the percentage of data points, within 15% of the phase mean. Stability criterion was satisfied if 80-90% of data points fall within a 15% range of the mean.

Between-phase examination. Subsequently, overlap and immediacy of the effect between the baseline phases and the intervention phases as well as the consistency between similar phases were evaluated. The ***Percentage of Nonoverlapping Data*** index (PND) was used to quantify the proportion of data points in the intervention phase that did not overlap with the baseline phase. A PND above 70 was considered as an indication of effective intervention, a PND between 50-70 was an indicator of a questionable effect, whereas a PND below 50 was considered as no observed effect (Scruggs & Mastropieri, 1998). Immediacy of the effect is usually examined by comparing changes in level between the last three data points of one phase and the three first data points of the next phase. However, TMS protocol was expected to have a delayed effect and therefore the immediacy of effect for the intervention phases was examined using the last three data points instead of the first.

4.5.2 Effect Size Estimation

A number of non-parametric methods are available for analyzing single-case design data. As each of this method has its advantages and disadvantages sensitivity analyses was conducted, as it is strongly recommended (Kratochwill et al., 2010). Sensitivity analyses involves the use of more than one index as indicator of the effect size and then results can be compared over estimators to investigate whether they yield similar effect. Accordingly, to estimate the effect size the below indices were calculated and reported:

- Percentage of Data Exceeding the Median (PEM). This is a non-parametric statistical method for effect size evaluation. The null hypothesis of this index is that if the treatment has no effect, then the data in the treatment phase will concentrate around the middle line. The PEM identifies the percentage of data exceeding the median of the baseline phase. The score ranges from 0 to 1. A PEM of .7 to .9 reflects moderate effectiveness while score of .90 to 1 reflects a highly effective treatment. A PEM of less that .7 reflects treatment that is no effective (Alresheed et al., 2013). To calculate the PEM the total number of data points (i.e., assessments) that exceeded the baselines' median were counted and then were divided by the total number of data points in the treatment phase. For the PEM calculation only the data points that collected during the treatment phases were used.

- Non-overlap of All Pairs (NAP). The NAP was developed to improve upon existing single-case overlap-based methods, and it is interpreted as the percentage of data which improve across phases or simply, the present of non-overlapping data between phases (i.e., baseline and treatment phases) (Parker & Vannest, 2009). The NAP was calculated by the 'Single-Case research' (http://singlecaseresearch.org) a web based calculator for single-case design analysis, developed by Vannest et al. (2016). The corresponding ranges of the NAP are: 0-.31 weak effect, .32-.84 medium effect and .85-1 large or strong effect.

- The PND and PCI (as described above) indices were also used to evaluate the treatment's effect.

4.6 Statistical Analysis

The visual analysis and the effect size indices were followed by non-parametric statistical analysis in which the patients scores on the MMSE, ADAS-cog and neuropsychological evaluations were analyzed. The non-parametric equivalent of the paired samples *t*-test, the Wilcoxon *W*, was used to explore whether the patients average scores changed significantly immediately after the end of the treatment and three months post-treatment.

4.7 Treatment Fidelity

Treatment fidelity was monitored during the study to ensure that the TMS protocol and the outcome variables assessments were implemented as intended. This allowed us to truly test the effectiveness of our proposed protocol and therefore the danger to commit a Type 1 or Type 2 error was eliminated (Krasny-Pacini & Evans, 2018). A checklist was developed to ensure that all the key elements of the study were implemented as planned. The assessors and the treatment providers underwent training to ensure their skill acquisition. During the intervention sessions, a supervisor continuously observed the procedure to confirm the consistent and accurate administration of the treatment. During the different phases the patients were closely monitored to identify possible variables that could influence the effectiveness of the treatment (e.g., changes in the pharmacological treatment).

4.8 Protective Measures for Covid-19

All the members of the research team, who were interacting with the patients and/or their family members were fully vaccinated. Additionally, they took a rapid antigen test twice per week throughout the study. The equipment used, both for the cognitive assessments and the rTMS sessions, was carefully sanitized after every use. The patients and their companions were asked to take a rapid test twice per week, when visiting the clinic for the rTMS treatment, either by themselves or by a member of the team in the clinic. Patients were given a box with 10 KN95 type masks to use throughout the rTMS sessions (1 mask per day). Finally, entrance to the rehabilitation clinic, for the employees, students and visitors was allowed only with a vaccination certificate and a negative PCR or rapid antigen test.

4.9 Patients

Two aMCI patients were recruited and completed the study.

Patient #1. The first patient, henceforth referred to as Mrs. A.B., was a 65-year-old female with 16 years of education and an overall medium level of cognitive reserve (CRIq=109). Mrs. A.B. has had a diagnosis of aMCI since 2020 (nearly 2 years prior to her participation in the study). During the time of the study, she was working as a secondary school teacher. While she was still working and there was an absence of significant impairment of instrumental activities of her daily living, over the last few years, she had observed changes in her ability to remember the lectures (that she had taught in recent years), and she had to prepare extensive notes for each class, something that was not necessary before. Two episodes where she was confused about how to return to her house were reported. In addition, 1 year prior to her participation in the study, she reported an incident in which she could not remember what she had done with her students' final exam sheets. Mrs. A.B. was diagnosed with MCI and was treated with cholinesterase inhibitors and antidepressants to manage depressive symptomatology. Mrs. A.B. was completely independent; she was driving, she completed her house's daily chores the same as before, and she was visiting her mother and sister twice per week. She had two children and was living with her husband. She reported, and her son confirmed, no significant difficulties or changes with her sleep patterns (although in the last year, she

had begun taking a 2-hour nap after school), no alcohol extensive consumption, and no other significant medical condition. She had been smoking 10–12 cigarettes per day for the last 20 years. Her history and recent medical testing did not indicate any cardiovascular risk factors. Her father was diagnosed with AD in his 70s. Mrs. A.B. reported memory difficulties, which in turn caused her anxiety and depressive symptomatology. She indicated a lack of energy and consistent fatigue, along with her memory difficulties, as the most disturbing symptoms. From clinical observation, it became evident that Mrs. A.B. was an emotional and independent woman; she was becoming easily overwhelmed and suffering from mental exhaustion (i.e., cognitive fatigue; Li et al., 2020). The pre-study examination for inclusion criteria evaluation revealed an unaffected level of independence (through the instrumental activities of daily living and basic activities of daily living evaluations), a normal score in the MMSE, and a high, but acceptable, level of depressive symptomatology. The stage of her cognitive function was estimated at Level 3 in the global deterioration scale (GDS), which represents a mild cognitive decline, or mild cognitive impairment. Mrs. A.B.'s clinical characteristics are illustrated in Table 4.2. Mrs. A.B. was randomly allocated to a 2-week baseline condition.

Patient #2. The second patient, henceforth referred to as Mr. E.C., was a 69-year-old male, with 16 years of education and an overall medium–high cognitive reserve (CRIq=127). Mr. E.C. has had the diagnosis of aMCI since 2019 (nearly 3 years prior to the study). He was a highly motivated, sociable, and energetic person who was still working as an agent in a well-known and developed insurance company. Mr. E.C. was working not for subsistence reasons but due to his inner need for being socially energetic and productive. He did not present any significant impairment in the instrumental activities of his daily living, but he was experiencing cognitive difficulties that were observed by himself and his wife. Mr. E.C. had a great level of self-awareness, and he could indicate his difficulties very accurately. Several incidents of confusion while driving on well-known streets were reported, along with failing to remember phone conversations with some of his clients. Recognizing his difficulties, he had adopted compensatory strategies, such as calendars.

Mr. E.C. was independent and responsible for paying the bills; he was picking up his grandchildren from school every day, driving across Cyprus for his appointments, meeting his friends on a weekly basis, and would often invite over his children and friends

for dinner. Recognizing the changes in his cognitive function and considering how his diagnosis would affect his independence in the future, he suffered depressive symptomatology. He was treated with cholinesterase inhibitors, antidepressants, and a variety of vitamin supplements. The pre-study examination for inclusion criteria evaluation revealed an unaffected level of independence (through the instrumental activities of daily living and basic activities of daily living evaluations) and a borderline score in the MMSE. Mr. E.C. reported some depressive symptoms, but no evidence of clinical depression was present. His cognitive function stage was estimated at Level 3 in the GDS, representing a mild cognitive decline, or mild cognitive impairment. His clinical characteristics are illustrated in Table 4.2. Mr. E.C. was randomly allocated to a 3-week baseline condition.

Table 4.2 Patient demographic and clinical characteristics

Characteristics	**A.B.**	**E.C.**
Age (years)	65	69
Sex	Female	Male
Education (years)	16	16
MMSE	28	26
BADL	9	8
IADL	6	6
GDS	3	3
Diagnosis	aMCI	aMCI
GDS-30	14	7
CRIq	109	127
Baseline week	2	3
rTMS intensity	90%	90%

Note: The table shows patients' clinical characteristics as evaluated during inclusion criteria evaluation, the baseline week, and the intensity in which the rTMS protocol was administered to each patient. MMSE: Mini mental state examination; BADL: Basic activities of daily living; IADL: Instrumental activities of daily living; GDS: Global deterioration scale; GDS-30: Geriatric depression scale-30.

4.10 Adherence to the Study

Both patients completed the study with 100% adherence. The provided schedule that was given to each one prior to the beginning of the study was followed without any deviation, both in assessment appointments and treatment sessions.

4.11 TMS Therapy Tolerance and Side Effects

The mean rating on the Wong-Baker FACES pain rating scale was 1.1 for Mrs. A.B. and 1 for Mr. E.C. Both patients indicated no pain or any kind or disturbance during or after each of their rTMS sessions. Figure 4.6 illustrates the patients' ratings on the scale. The patients did not report any side effects during and/or after the rTMS sessions.

Figure 4.6 Illustration of the mean score of both patients on the Wong-Baker FACES scale

Note: The red line indicates the mean score of patient ratings. Both patients rated their rTMS sessions experience as painless and well tolerated.

4.12 Results: Single-Case Data[4]-Primary Outcomes

4.12.1 Episodic Memory: Immediate Word Recall

Phase characteristics (i.e., mean score and standard deviation of each patient in each phase) are illustrated in Table 4.3. A schematic representation of the patients' scores in immediate word recall during the A, B, and follow-up phases is illustrated in Figure 4.7.

Table 4.3 Phase characteristics for immediate recall

			Baseline		Treatment		
Patient	Baseline condition (weeks) and total assessments	Number of assessments on the treatment phase	Mean (SD)	Median	Mean (SD)	Median	PCI
A.B.	2 (4)	6	16 (1.7)	16	17.5 (2.8)	17.5	▲9%
E.C.	3 (6)	6	14.5 (2.8)	14.5	16.5 (2)	15.5	▲14%

Note: SD: Standard deviation. ▲: Change indicates behavioral imrovement.

Patient #1 (i.e., Mrs. A.B.): ***Within-phase examination.*** The stability criterion was satisfied in Mrs. A.B.'s scores in both the A and B phases, with all her scores falling within a 15% range from each phase's mean. A visual inspection of the phase trend lines (Figure 4.7) indicates an uptrend after treatment introduction. An increase in her average level was observed for the total number of recalled words in the three learning trials (on

[4] The single-case data refer to the data that were obtained through the alternative test forms during the baseline, treatment, and follow-up phases (see Figure 4.2 for a visual representation of these data).

average, 1.5 more words were recalled in the treatment phase). The PCI signified an increase of 10% in the total recalled words in Phase B, indicating improved performance.

Between-phase examination. The immediacy of the effect was observed in Mrs. A.B.'s performance. The average of her last three assessments during the baseline phase increased from 16.3 words to 18.6 words in her last three assessments during the treatment phase (Figure 4.8). The PND index did not indicate a significant effect of the intervention (PND=.50, p>.05; 50% of the data points in the treatment phase did not exceed those from the baseline phase). However, the PEM index showed that 66.5% of the treatment data exceeded the baseline's median (PEM=.65).

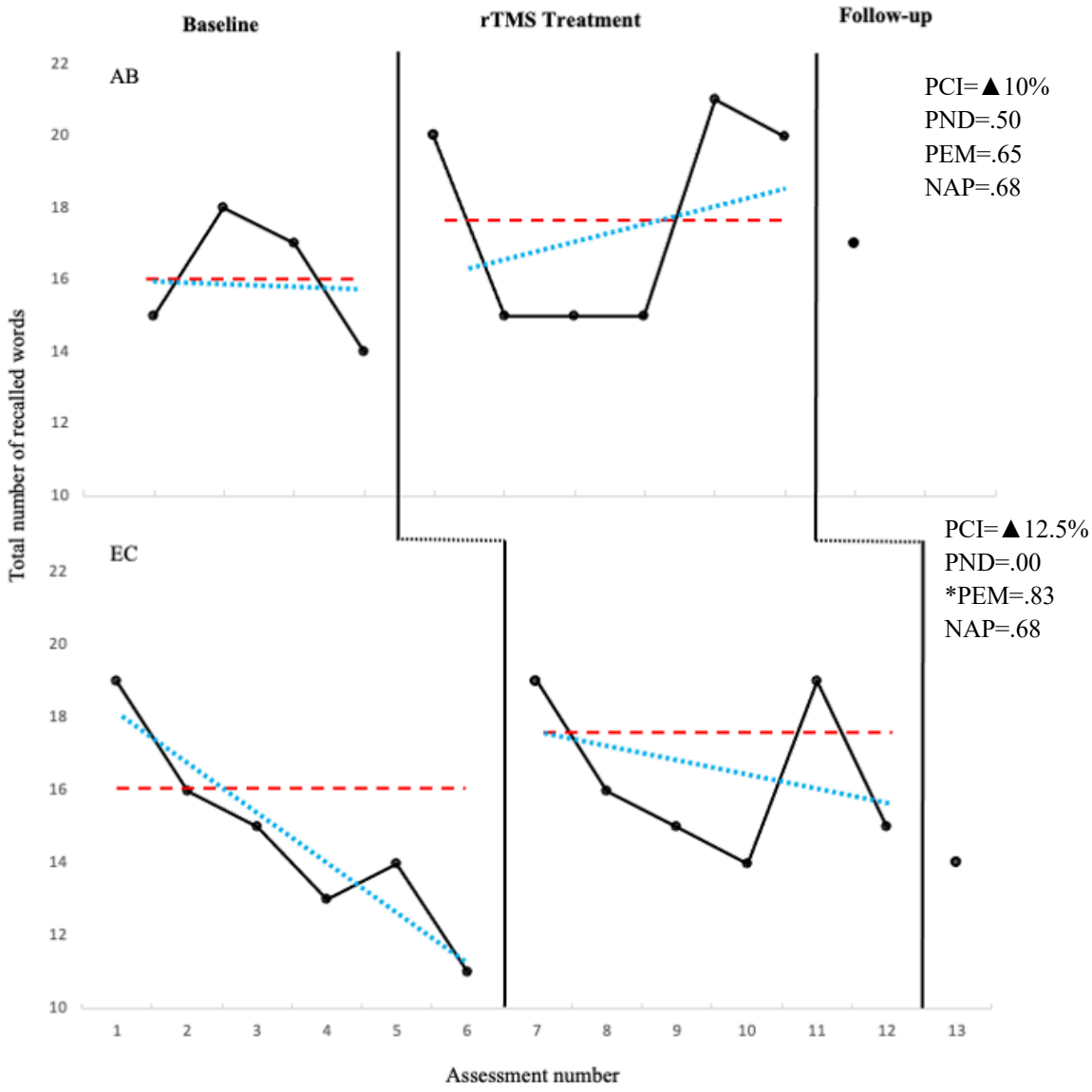
The calculated p-value for the NAP estimator did not provide evidence of a significant treatment effect (NAP=.68, p>.05).

Patient #2 (i.e., Mr. E.C.): ***Within-phase examination.*** Mr. E.C. had unstable performance in the baseline condition, with only the 66% of his data falling within a 15% range from the mean. His performance was stable in the treatment phase (100% of his data fell within a 15% range from the phase's mean). His unstable performance was also evident via a visual inspection of the phase trend lines (Figure 4.7). A negative slope was evident in both phases. However, an increase in his average level was observed for the total number of recalled words in the three learning trials (on average, two more words were recalled in the treatment phase). The PCI signified an increase of 12.5% in the total recall words after treatment introduction, indicating improved performance.

Between-phase examination. A great immediacy of the effect was observed on Mr. E.C.'s performance. The average of his last three assessments during the baseline phase increased from 12.5 words to 16 words in his last three assessments during the treatment phase (Figure 4.8). The PND index did not indicate a significant effect of the intervention (PND=0, p<.05; none of the data points in the treatment phase exceeded those from the baseline phase). However, the PEM index showed that 83.5% of the treatment data exceeded the baseline's median (PEM=.83), indicating a moderate treatment effect (Alresheed et al., 2013).

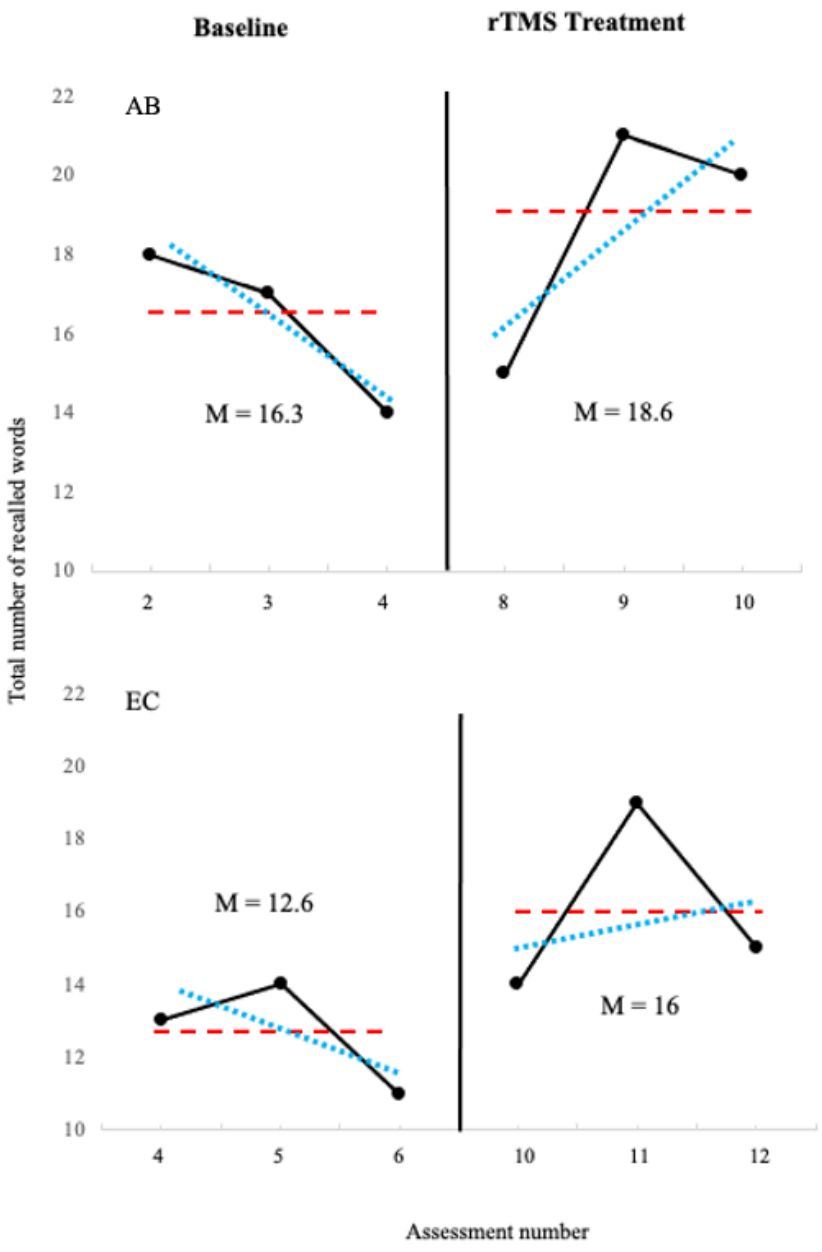
The calculated p-value for the NAP estimator did not provide evidence of a significant treatment effect (NAP=.69, p>.05).

Figure 4.7 Schematic representation of observations on immediate word recall from baseline to follow-up between participants



Note: The vertical black lines indicate the start of the subsequent phase. The baseline conditions began at the same time for both patients, but treatment introduction was staggered across time and patients. The dotted red horizontal lines represent the average score in each phase. The dotted blue lines illustrate the trend lines for each baseline and treatment phase. The PCI, PND, PEM, and NAP indices have been calculated without the follow-up phase. PCI: Percentage change index; PND: Percentage on nonoverlapping data; PEM: Percentage of data exceeding the median; NAP: Nonoverlap of all pairs; ▲: Increase.

Figure 4.8 Visual illustration of immediacy of effect in immediate word recall



Note: Immediacy of the effect is calculated by comparing changes in the mean level of the last 3 data points (i.e., assessments) of the baseline conditions with the mean level of the last 3 data points of the treatment conditions. M: mean.

4.12.2 Episodic Memory: Delayed Word Recall

Phase characteristics are illustrated in Table 4.4. A schematic representation of the patients' scores in the delayed word recall during the A′, B′, and follow-up phases is illustrated in Figure 4.9.

Table 4.4 Phase characteristics for the delayed word recall

			Baseline		Treatment		
Patient	Baseline condition (weeks) and total assessments	Number of assessments on the treatment phase	Mean (SD)	Median	Mean (SD)	Median	PCI
A.B.	2 (4)	6	2.75 (0.9)	2.5	3.5 (1)	3.5	▲27%
E.C.	3 (6)	6	1.6 (1)	2	3.5 (0.8)	3	▲118%

Note: SD: Standard deviation. ▲: Change indicates behavioral improvement.

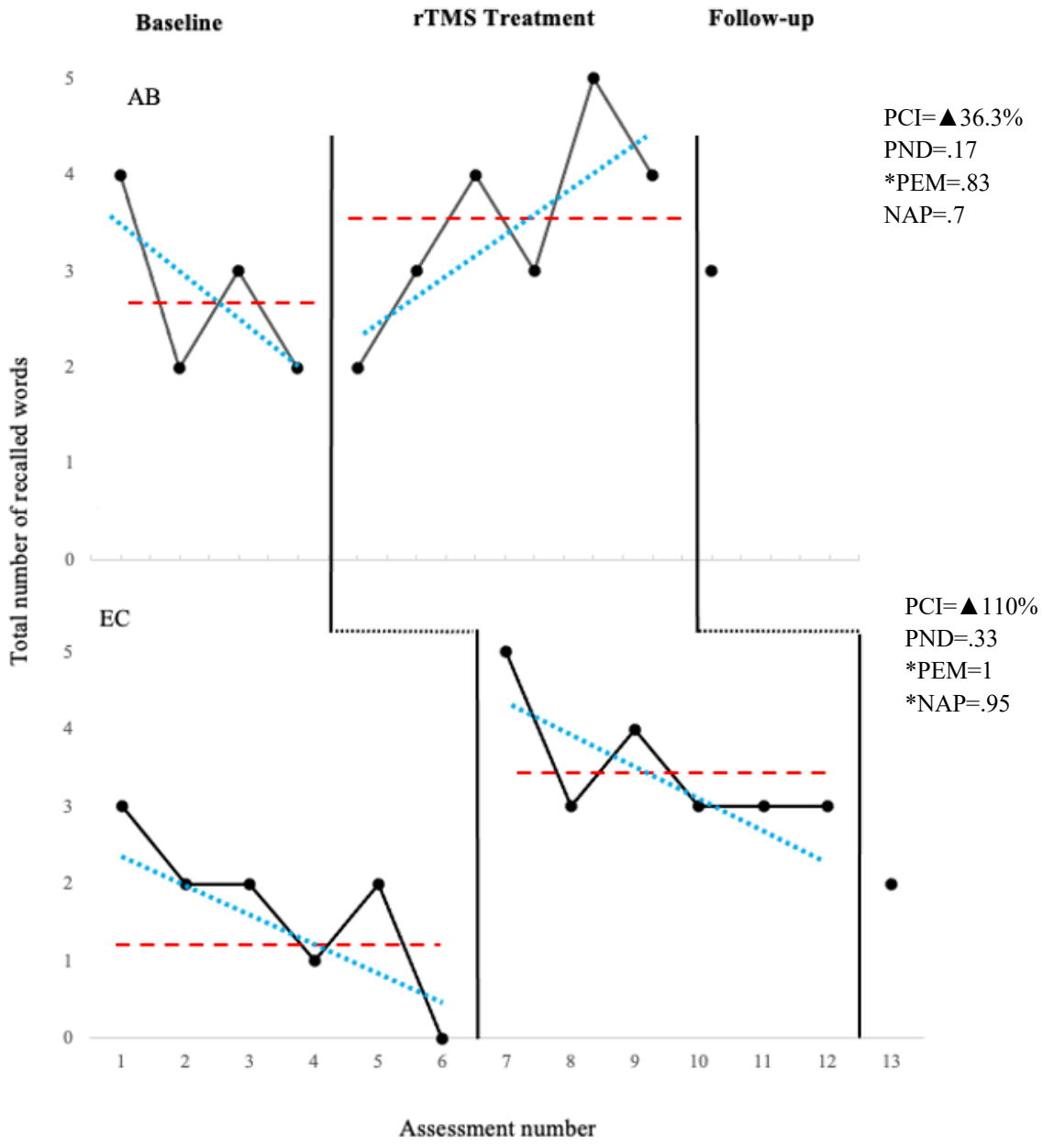
Patient #1 (i.e., Mrs. A.B.): ***Within-phase examination.*** The stability criterion was satisfied in Mrs. A.B.'s scores in both the A and B phases, with all of her scores falling within a 15% range in the A phase and 83.3% in the B phase. While the stability criterion was satisfied, a visual inspection of the phase trend lines (Figure 4.9) indicated a negative slope in Phase A, indicating unstable performance. In Phase B, an upward trend is evident, indicating performance improvement during the treatment phase. An increase in the average level was observed for the total number of delayed-recall words (on average, 0.75 more words were recalled in the delayed recall in the treatment phase). The PCI signified an increase of 27% in the total number of delayed-recall words in Phase B, indicating improved performance.

Between-phase examination. The immediacy of the effect was observed on Mrs. A.B.'s performance. The average of her last three assessments during the baseline phase increased from 2.3 to four words in her last three assessments during the treatment phase (Figure 4.10; 74% improvement). The PND index did not indicate a significant effect of the intervention (PND=.17, p>.05; 17% of the data points in the treatment phase exceeded those from the baseline phase). However, the PEM index showed that 83% of treatment

data exceeded the baseline's median (PEM=.83), indicating a moderate treatment effect (Alresheed et al., 2013).

The calculated *p*-value for the NAP estimator did not provide evidence of a significant treatment effect (NAP=.7, *p*>.05).

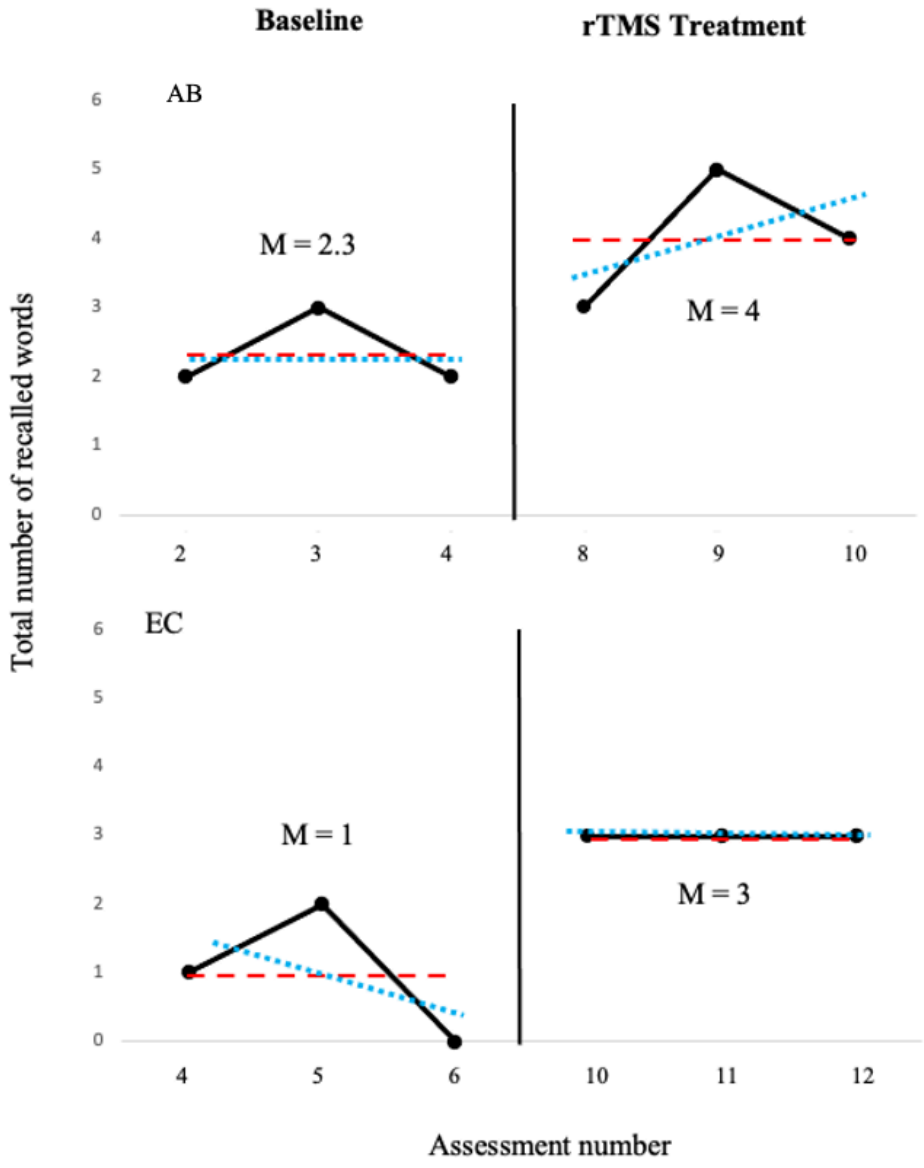
Figure 4.9 Schematic representation of observations of delayed word recall from baseline to follow-up between participants



Note: The vertical lines indicate the start of the subsequent phase. The baseline conditions began at the same time for both patients, but treatment introduction was staggered across time and

patients. The dotted red horizontal lines represent the average score in each phase. The dotted blue lines illustrate the trend lines for each baseline and treatment phase. The PCI, PND, PEM, and NAP indices have been calculated without the follow-up phase. PCI: Percentage change index; PND: Percentage on nonoverlapping data; PEM: Percentage of data exceeding the median; NAP: Nonoverlap of all pairs; ▲: Increase; *: Significant treatment effect.

Figure 4.10 Visual illustration of immediacy of effect in delayed word recall



Note: Immediacy of the effect by comparing changes in mean levels of the last 3 data points of the baseline conditions, with the last 3 of the treatment conditions.

Patient #2 (i.e., Mr. E.C.): ***Within-phase examination.*** The stability criterion was not satisfied in Mr. E.C.'s scores in the A phase, with only 66% of his score falling within a 15% range of the phase's mean. After treatment introduction (i.e., phase B), his performance was stabilized, with all of his data falling within the appropriate range from the phase's mean. A visual inspection of the phase trend lines (Figure 4.9) indicated a negative slope in both phases. However, a significant increase in average level was observed for the total number of delayed-recall words (on average, two more words were recalled in the delayed recall in the treatment phase). The PCI signified an increase of 110% in the total number of delayed-recalled words in Phase B.

Between-phase examination. The immediacy of the effect was observed on Mr. E.C.'s performance. The average of his last three assessments during the baseline phase increased from one delayed-recall word to three words in his last three assessments during the treatment phase (Figure 4.10; 200% improvement). The PND index did not indicate a significant effect of the intervention (PND=.33, p>.05; 33% of the data points in the treatment phase exceeded those from the baseline phase). However, the PEM index showed that 100% of treatment data exceeded the baseline's median (PEM=1), indicating a highly effective treatment (Alresheed et al., 2013).

The calculated p-value for the NAP estimator provided evidence of a significant treatment effect (NAP=.95, p=.01). It also provided evidence of a significant treatment effect when both cases' data were combined (NAP=.84, p=.001), indicating an effective treatment effect across cases.

4.12.3 Episodic Memory: Recognition

Visual analysis and effect size indices did not provide evidence of differences between the patients' performance before compared to after treatment in the recognition task.

4.13 Results: Single-Case Data - Secondary Outcomes

4.13.1 Trail Making Test A´

Phase characteristics are illustrated in Table 4.5. A schematic representation of the patients' scores in the trail-making test A′ (TMT A′) during the A′, B′, and follow-up phases is illustrated in Figure 4.11.

Patient #1 (i.e., Mrs. A.B.): ***Within-phase examination.*** The stability criterion was not satisfied in Mrs. A.B.'s scores in either phase, indicating unstable performance. A visual inspection of the A phase's trend line (Figure 4.11) indicated a negative slope, which also demonstrates her unstable performance. As shown in Figure 4.11, in the third assessment, Mrs. A.B. needed a significant amount of time to complete the task, in relation with the other assessments. In the B phase, a decrease in the average level was observed (i.e., total time to complete the task), indicating behavioral improvement. The PCI signified a decrease of 39% in the time needed to complete the task, indicating improved performance.

Table 4.5 Phase characteristics for trail making test A'

			Baseline		Treatment		
Patient	Baseline condition (weeks) and total assessments	Number of assessments in the treatment phase	Mean (SD)	Median	Mean (SD)	Median	PCI
A.B.	2 (4)	6	85 (47)	63	52 (13)	58.5	▲39%
E.C.	3 (6)	6	110 (29)	100	54 (14)	58	▲51%

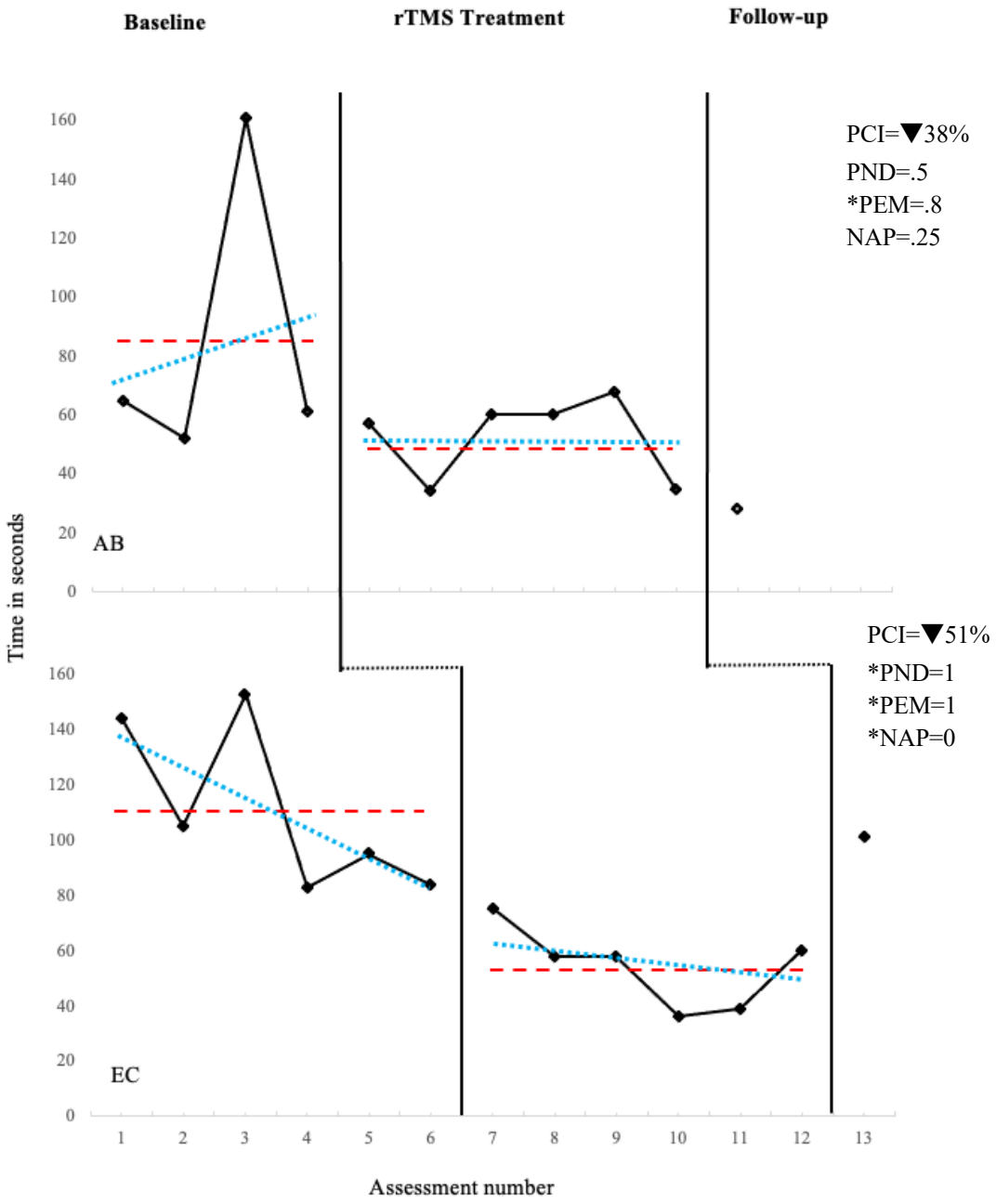
Note: SD: Standard deviation. ▲: Change indicates behavioral improvement.

Between-phase examination. The immediacy of the effect was observed on Mrs. A.B.'s performance. The time needed to complete TMT A′ was decreased from 91.3 seconds in the baseline condition to 54 seconds in her last three assessments during the treatment phase (Figure 4.12; 41% improvement). The PND index did not indicate a significant effect of the intervention (PND=.5, p>.05; 50% of the data points in the treatment phase

exceeded those from the baseline phase). However, the PEM index showed that 83% of treatment data exceeded the baseline's median (PEM=.83), indicating a moderate treatment effect (Alresheed et al., 2013).

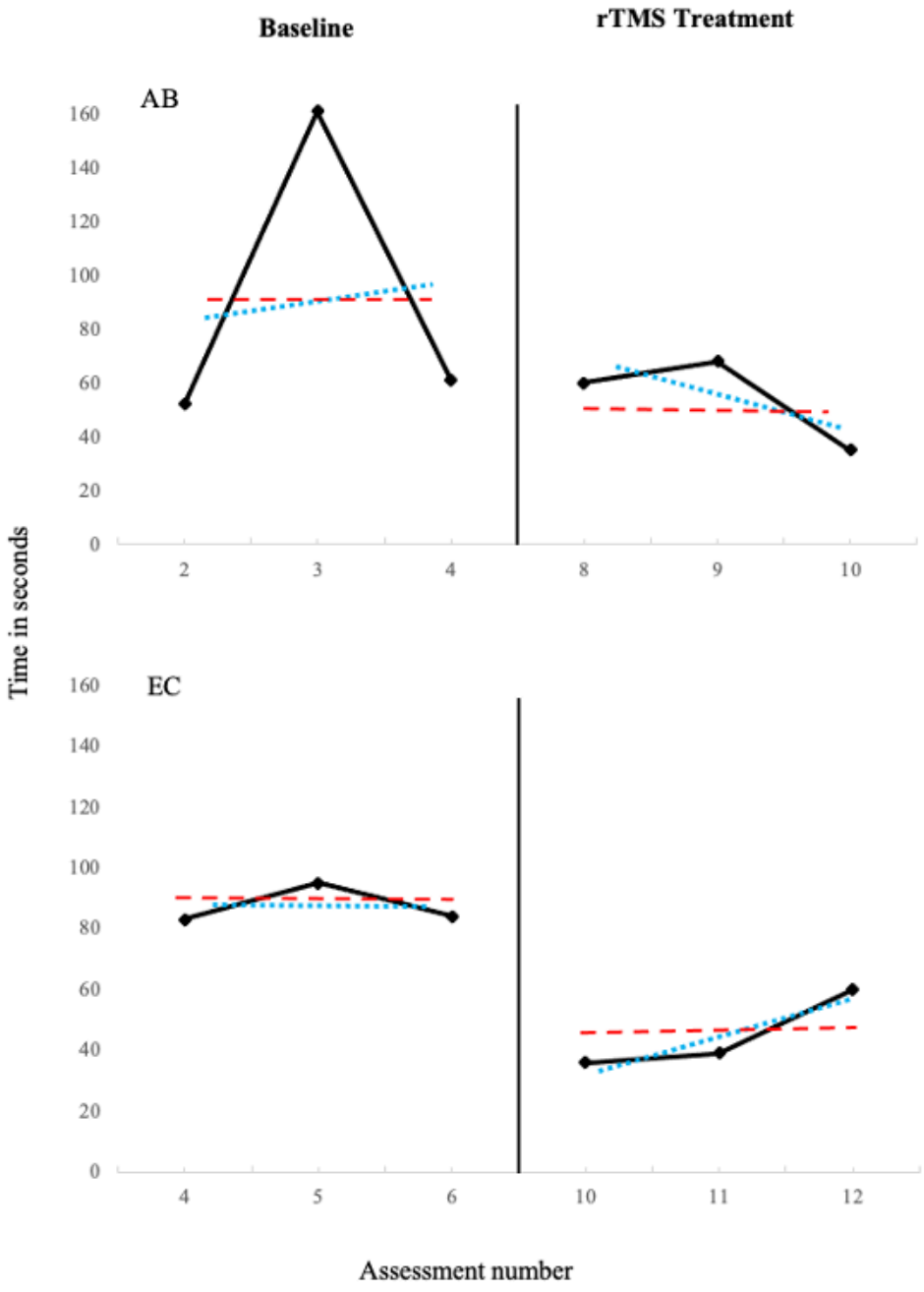
The calculated *p*-value for the NAP estimator did not provide evidence of a significant treatment effect (NAP=.25, $p>.05$).

Figure 4.11 Schematic representation of observations in trail making test A' from baseline to follow-up between participants



Note: The vertical lines indicate the start of the subsequent phase. The baseline conditions began at the same time for both patients, but treatment introduction was staggered across time and patients. The dotted red horizontal lines represent the average score in each phase. The dotted blue lines illustrate the trend lines for each baseline and treatment phase. The PCI, PND, PEM, and NAP indices have been calculated without the follow-up phase. PCI: Percentage change index; PND: Percentage on nonoverlapping data; PEM: Percentage of data exceeding the median; NAP: Nonoverlap of all pairs; ▲: Increase; *: Significant treatment effect.

Figure 4.12 Visual illustration of immediacy of effect in trail making test A'



Note: Immediacy of the effect was calculated by comparing changes in mean levels of the last 3 data points of the baseline conditions, with the last 3 of the treatment conditions.

Patient #2 (i.e., Mr. E.C.): ***Within-phase examination.*** As with Mrs. A.B.'s performance, the stability criterion was not satisfied for Mr. E.C.'s scores in either phase. A visual inspection of the phase trend lines (Figure 4.11) indicated a negative slope in both phases. However, a significant decrease in average level was observed for the total time needed to complete TMT A′ (on average, Mr. E.C. improved his performance by 56

seconds). The PCI signified a decrease of 51% in the total time needed to complete the task after the treatment's introduction, indicating improved performance.

Between-phase examination. The immediacy of the effect was observed on Mr. E.C.'s performance. The average time of his last three assessments during the baseline phase decreased by 43 seconds in his last three assessments during the treatment phase (Figure 4.12; 48.5% improvement). The PND index provided evidence of a significant treatment effect (PND=1, p<.0001; all of the data points in the treatment phase exceeded those from the baseline phase). Similarly, the PEM index showed that 100% of treatment data exceeded the baseline's median (PEM=1), indicating a highly effective treatment (Alresheed et al., 2013).

The calculated *p*-value for the NAP estimator provided evidence of a significant treatment effect (NAP=0, *p*=.003).

4.13.2 Trail Making Test B´

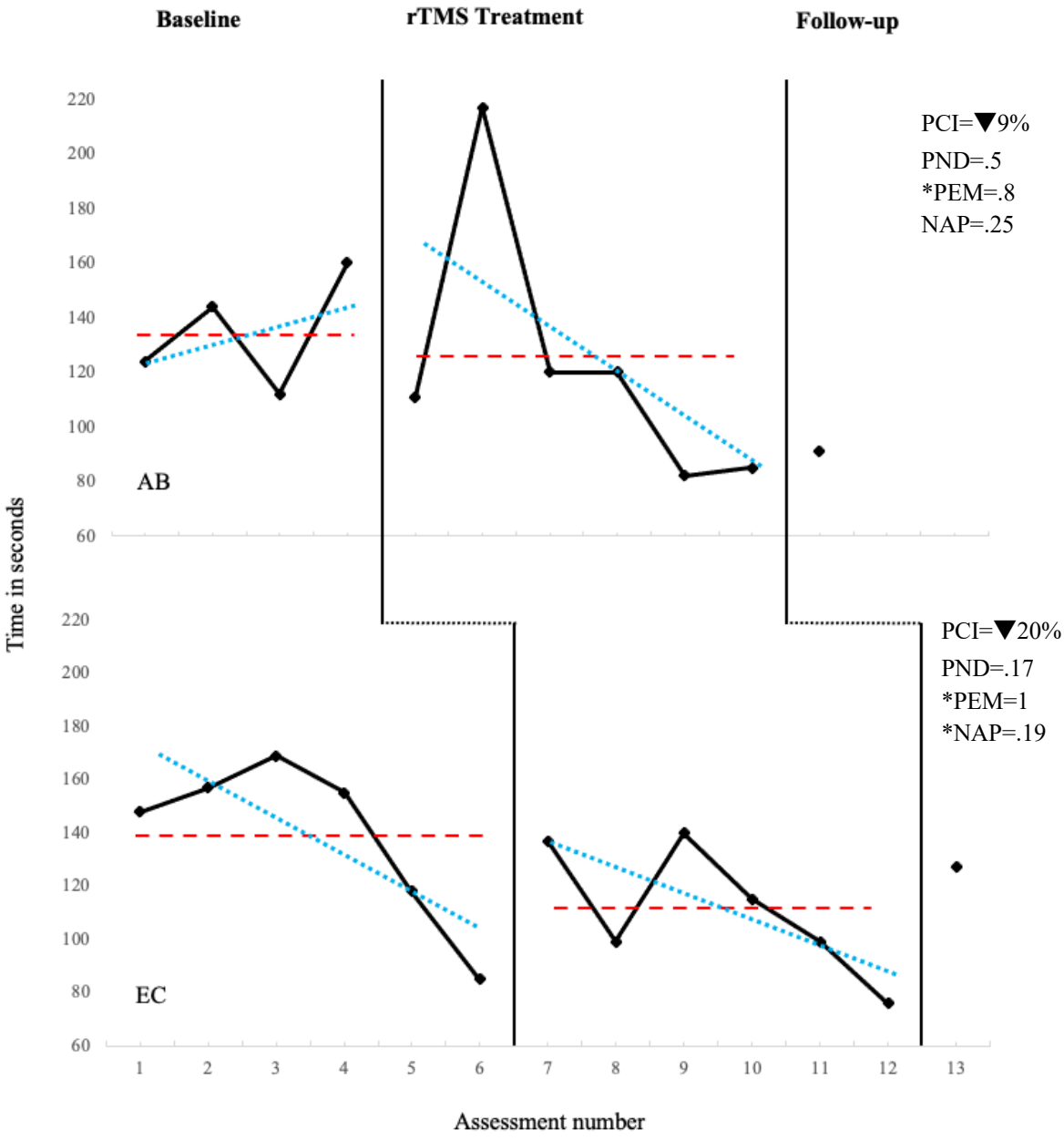
Phase characteristics are illustrated in Table 4.6. A schematic representation of the patients' scores on the trail-making test B′ (TMT B′) during the A, B, and follow-up phases is illustrated in Figure 4.13.

Table 4.6 Phase characteristics for trail-making test B′

			Baseline		Treatment		
Patient	Baseline condition (weeks) and total assessments	Number of assessments in the treatment phase	Mean (SD)	Median	Mean (SD)	Median	PCI
A.B.	2 (4)	6	135 (19.5)	134	122.5 (47)	115.5	▲9%
E.C.	3 (6)	6	139 (30)	151.5	111 (23)	107	▲20%

Note: SD: Standard deviation. ▲: Change indicates behavioral improvement

Figure 4.13 Schematic representation of the observations on the trail-making test B′ from baseline to follow-up across participants



Note: The vertical lines indicate the start of the subsequent phase. The baseline conditions began at the same time for both patients, but treatment introduction was staggered across time and patients. The dotted red horizontal lines represent the average score in each phase. The dotted blue lines illustrate the trend lines for each baseline and treatment phase. The PCI, PND, PEM, and NAP indices have been calculated without the follow-up phase. PCI: Percentage change index; PND: Percentage of nonoverlapping data; PEM: Percentage of data exceeding the median; NAP: Nonoverlap of all pairs; ▲: Increase; *: Significant treatment effect.

Patient #1 (i.e., Mrs. A.B.): ***Within-phase examination.*** The stability criterion was not satisfied in Mrs. A.B.'s scores in either phase, indicating lack of stable performance. A visual inspection of the A phase's trend line (Figure 4.13) indicated an upward slope, which shows a deterioration in her performance through time (e.g., more time is needed to complete the task). After the treatment's introduction, a negative slope is observed, indicating behavioral improvement. As Figure 4.13 demonstrates, in the second assessment during the treatment phase, Mrs. A.B. needed a significant amount of time to complete the task (the highest in the study), which increased the phase's average level. Even in the presence of such a high score, the slope indicates improvement from the baseline condition. The PCI signified a decrease of 9% in the time needed to complete the task, indicating improved performance.

Between-phase examination. A great immediacy of the effect was observed on Mrs. A.B.'s performance. The time needed to complete TMT B′ was decreased from 138.5 seconds in her last three assessments during the baseline condition to 95.5 seconds in her last three assessments during the treatment phase (Figure 4.14; 31% improvement). The PND index did not indicate a significant effect of the intervention (PND=.5, p>.05; 50% of the data points in the treatment phase exceeded those from the baseline phase). However, the PEM index showed that 83% of treatment data exceeded the baseline's median (PEM=.83), indicating a moderate treatment effect (Alresheed et al., 2013).

The calculated p-value for the NAP estimator did not provide evidence of a significant treatment effect (NAP=.25, p>.05).

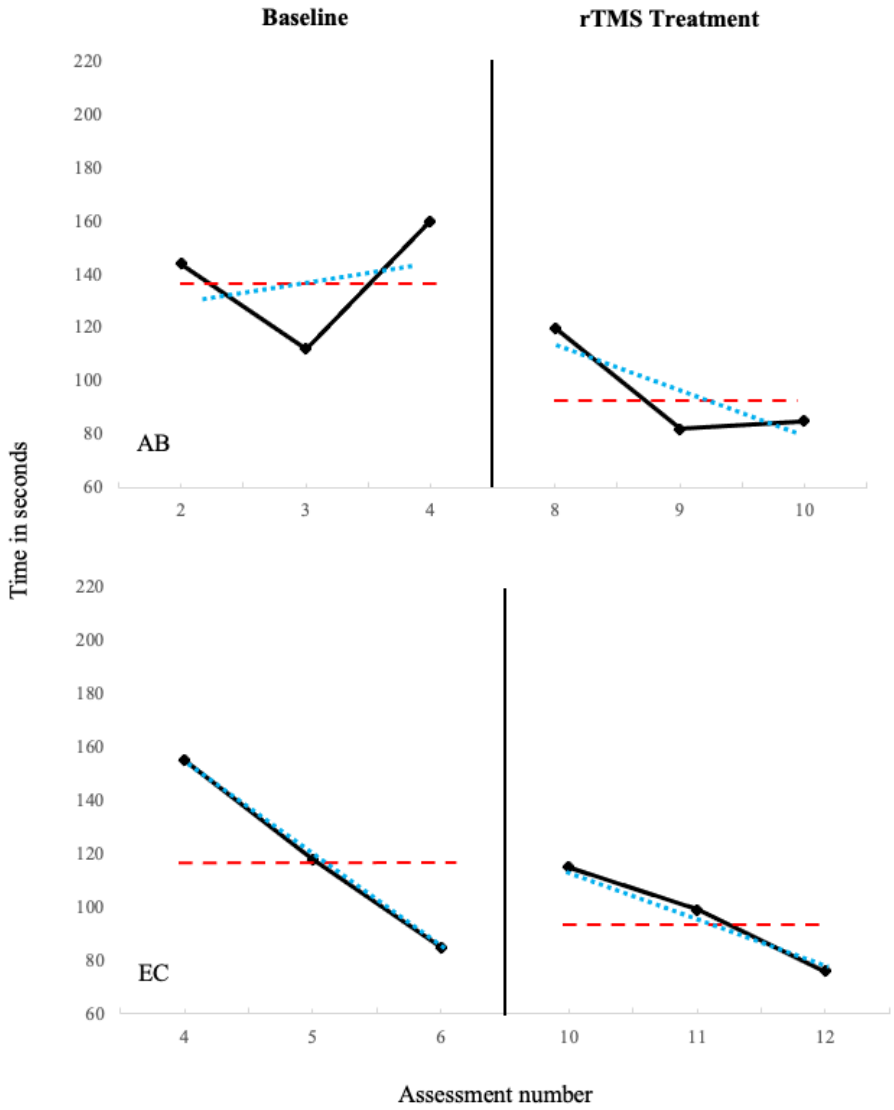
Patient #2 (i.e., Mr. E.C.): ***Within-phase examination.*** The stability criterion was not satisfied in either phase in Mr. E.C.'s performance. A visual inspection of the phase trend lines (Figure 4.13) indicated a negative slope in both phases. However, a significant decrease in average level was observed for the total time needed to complete TMT B′ (on average, Mr. E.C. improved his performance by 27.5 seconds). The PCI signified a decrease of 20% in the total time needed to complete the task after the treatment's introduction, indicating improved performance.

Between-phase examination. An immediacy of the effect was observed in Mr. E.C.'s performance. The average time of his last three assessments during the baseline phase decreased by 23 seconds in his last three assessments during the treatment phase (Figure

4.14; 19% improvement). The PND index did not provide evidence of a significant treatment effect (PND=.17, p>.05; 17% of the data points in the treatment phase exceeded those from the baseline phase). However, the PEM index showed that 100% of treatment data exceeded the baseline's median (PEM=1), indicating a highly effective treatment (Alresheed et al., 2013).

The calculated p-value for the NAP estimator did not provide evidence of a significant treatment effect (NAP=.19, p=.07).

Figure 4.14 Visual illustration of immediacy of effect in trail-making test B′



Note: Immediacy of the effect by comparing changes in the mean levels of the last 3 data points of the baseline conditions, with the last 3 of the treatment conditions. M: mean.

4.13.3 Naming Test

Phase characteristics are illustrated in Table 4.7. A schematic representation of the patients' scores on the naming test during the A, B, and follow-up phases is illustrated in Figure 4.15.

Table 4.7 Phase characteristics for naming test

			Baseline		Treatment		
Patient	Baseline condition (weeks) and total assessments	Number of assessments in the treatment phase	Mean (SD)	Median	Mean (SD)	Median	PCI
A.B.	2 (4)	6	12.25 (1.5)	12.5	13.6 (1.3)	14	▲11%
E.C.	3 (6)	6	12 (1.2)	11.5	14 (.7)	14	▲16.5%

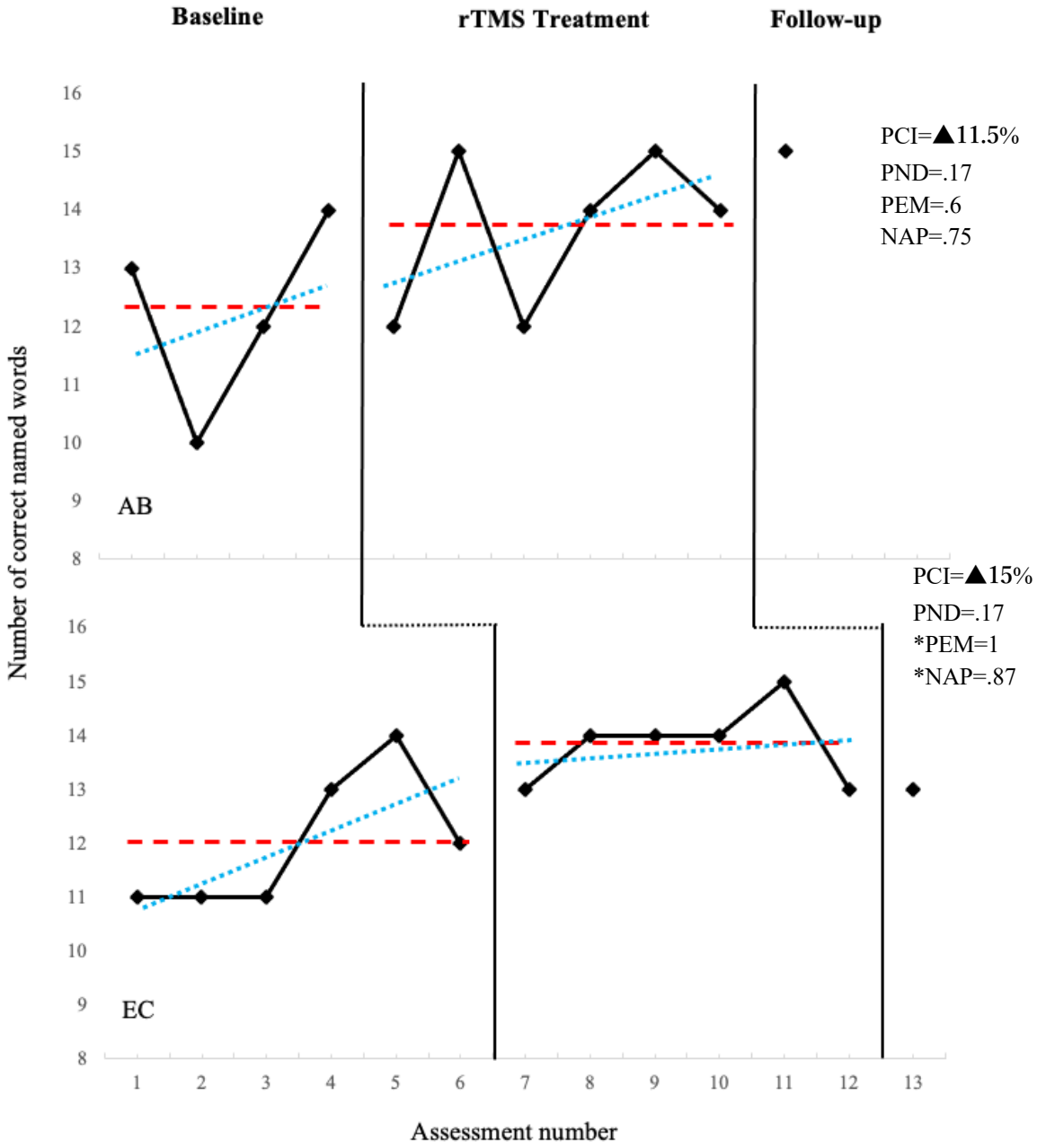
Note: SD: Standard deviation. ▲: Change indicates behavioral improvement.

Patient #1 (i.e., Mrs. A.B.): ***Within-phase examination.*** Mrs. A.B.'s performance was stable throughout the study in the naming task, reaching the stability criterion in both phases. A visual inspection of both phases' trend lines (Figure 4.15) indicated an upward slope. However, an increase in the treatment's phase level is evident (the correct named stimulus increased by 1.4 after intervention). The PCI signified an increase of 11% in the correct named stimulus.

Between-phase examination. An immediacy of the effect was observed in Mrs. A.B.'s performance. When comparing her last three assessments from the baseline phase with her last three assessments from the treatment phase, an increase of 2.3 correct named stimulus is observed (Figure 4.16; 19.5% improvement). The PND index did not indicate a significant effect of the intervention (PND=.17, p>.05; 17% of the data points in the treatment phase exceeded those from the baseline phase). The PEM index showed that 66% of treatment data exceeded the baseline's median (PEM=.66).

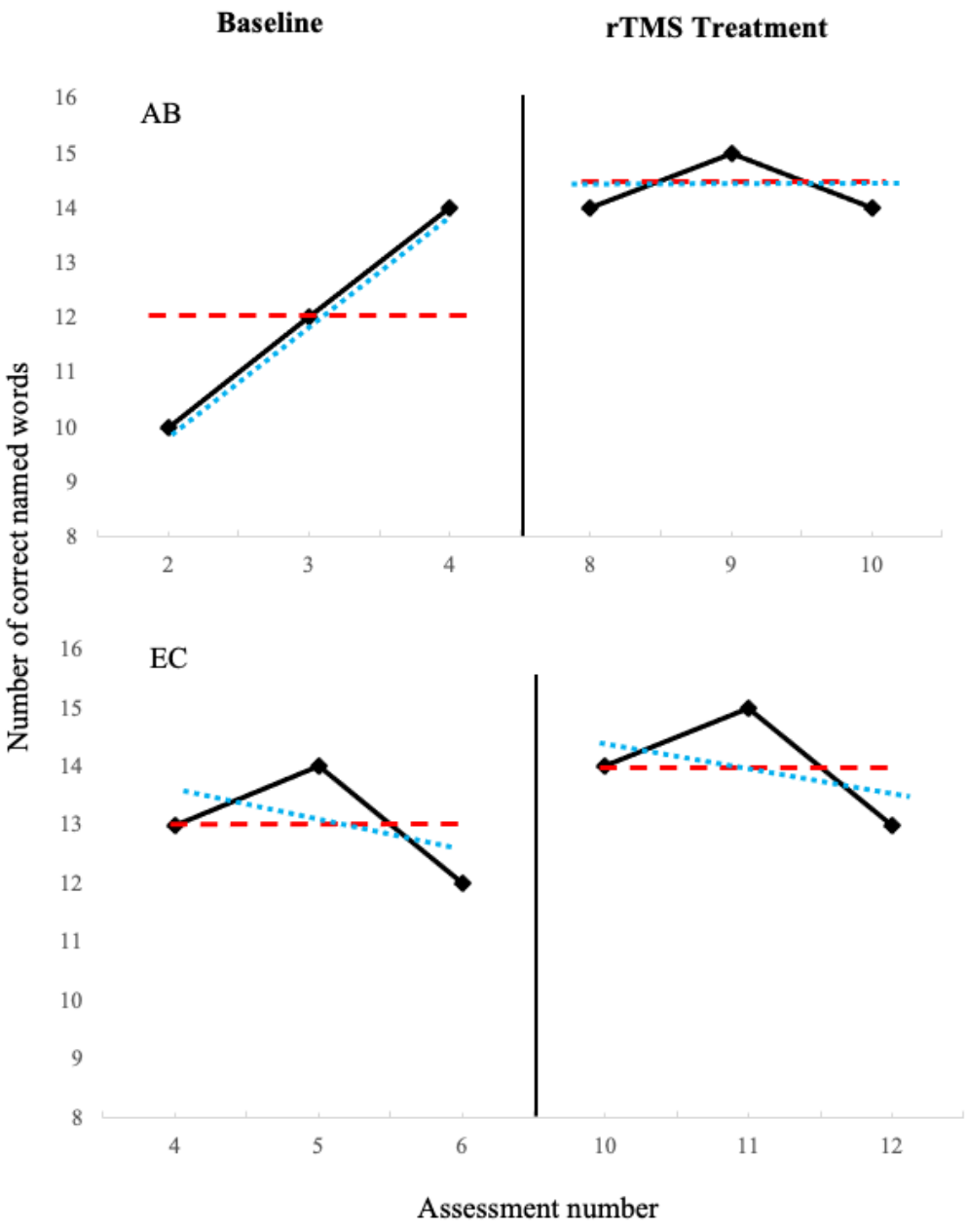
The calculated p-value for the NAP estimator did not provide evidence of a significant treatment effect (NAP=.75, p>.05).

Figure 4.15 Schematic representation of observations in naming test from baseline to follow-up between participants



Note: The vertical lines indicate the start of the subsequent phase. The baseline conditions began at the same time for both patients, but treatment introduction was staggered across time and patients. The dotted red horizontal lines represent the average score in each phase. The dotted blue lines illustrate the trend lines for each baseline and treatment phase. The PCI, PND, PEM, and NAP indices have been calculated without the follow-up phase. PCI: Percentage change index; PND: Percentage of nonoverlapping data; PEM: Percentage of data exceeding the median; NAP: Nonoverlap of all pairs; ▲: Increase; *: Significant treatment effect.

Figure 4.16 Visual illustration of immediacy of effect in naming test



Note:

Immediacy of the effect was calculated by comparing changes in mean levels of the last 3 data points of the baseline conditions, with the last 3 of the treatment conditions.

Patient #2 (i.e., Mr. E.C.): ***Within-phase examination.*** The stability criterion was satisfied in both phases in Mr. E.C.'s performance. A visual inspection of both phases' trend lines (Figure 4.15) indicated an upward slope. An increase in the treatment's phase level was evident (the correct named stimulus increased by 1.8 after intervention). The PCI signified an increase of 16.5% in the correct named stimulus.

Between-phase examination. A slight immediacy of the effect was observed on Mr. E.C.'s performance. A comparison of his last three assessments from the baseline phase with his last three assessments from the treatment phase indicated an increase of one correct named stimulus (Figure 4.16; 7.5% improvement). The PND index did not indicate a significant effect of the intervention (PND=.17, p>.05; 17% of the data points in the treatment phase exceeded those from the baseline phase). However, the PEM index showed that all treatment data exceeded the baseline's median (PEM=1), indicating a highly effective treatment (Alresheed et al., 2013).

The calculated p-value for the NAP estimator provided evidence of a significant treatment effect (NAP=.87, p=.03).

4.13.4 Semantic Associations, Corsi Block Tapping Task

Visual analysis and effect size indices did not provide evidence of differences between the patients' performance before compared to after treatment in the semantic associations (verbal and visuo-perceptual forms).

4.14 Global Cognition

Patients' scores on measures of global cognition are illustrated on Table 4.8. An immediate treatment effect was evident in both patients in both measures of global cognition (i.e., MMSE and ADAS-cog). Their performance was found to have further improved 3 months after the end of treatment.

Table 4.8 Patients performance on measures of general cognition

	A.B.			E.C.		
Tests	***pre***	***immed***	***post***	***pre***	***immed***	***post***
MMSE	28	29	30	26	28	28
ADAS-cog-12 A′	21.6		13	16		12
ADAS-cog-12 B′		16.3			10.33	

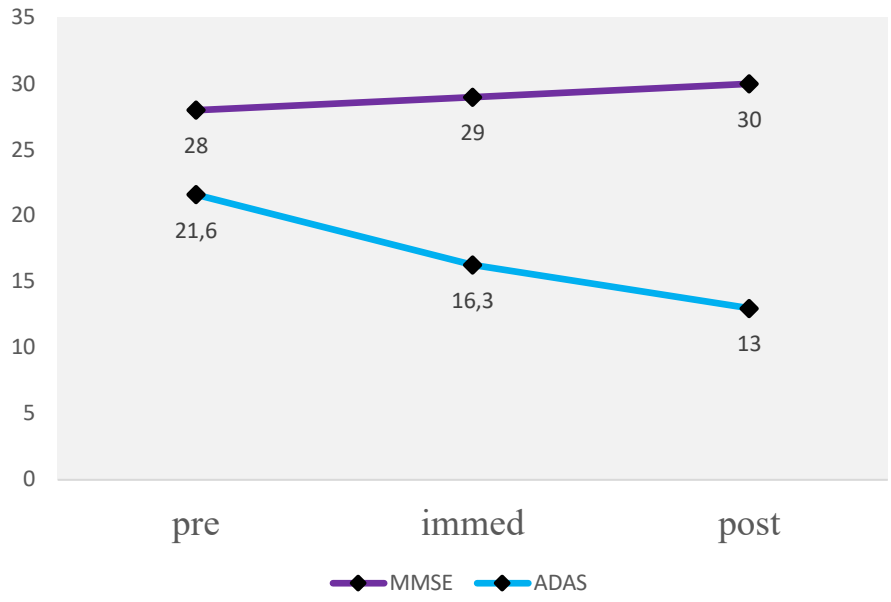
Note: pre: Pretreatment evaluation; immed: Immediately after the end of treatment evaluation; post: Post-treatment evaluation (i.e., 3 months after the end of treatment).

Mrs. A.B.: During the initial assessment (i.e., pretreatment), Mrs. A.B. received a scored of 28 on the MMSE, failing to recall one word and to follow one command. Immediately

after the treatment, she improved her performance by following all commands, but she was not able to recall all words (score: 29). Three months after the end of treatment (i.e., post-treatment), Mrs. A.B. further improved, her performance recalling all words (score: 30).

At pretreatment, she scored 21.6 on the ADAS-cog. She presented difficulties in word recall (she failed to recall 4.6 of the 10 presented words on average) and delayed word recall (she failed to recall seven of the 10 words), and in the recognition trial, she incorrectly recognized eight words. Immediately after the end of treatment, she improved her performance in the recognition trial (she mistakenly recognized four words); she failed to recall 4.3 words in the immediate word recall on average and performed correctly all steps in the ideation praxis (total score 16.3). At the follow-up condition, she was found to have further improved; she scored 13 total points. Her recognition was improved (only one mistake was made), she recalled on average four out of the 10 presented words in the immediate recall on average, and she constructed the cube correctly. However, she was able to remember only two words on the delayed word recall. Figure 4.17 demonstrates Mrs. A.B.'s scores throughout the study.

Figure 4.17 Schematic representation of Mrs. A.B.'s performance on measures of global cognition

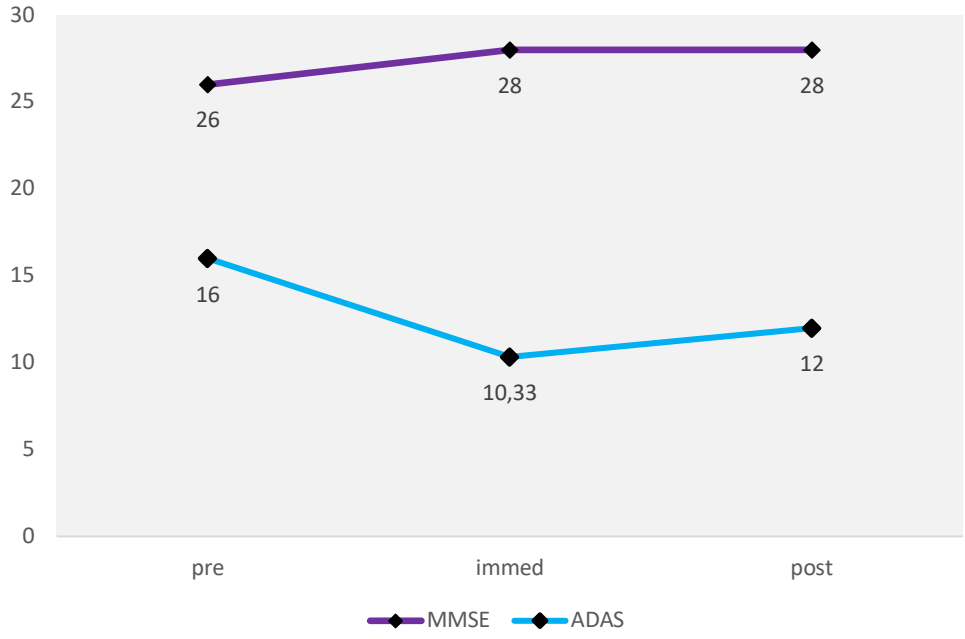


Mr. E.C.: During the initial assessment (i.e., pretreatment), Mr. E.C. scored 26 points on the MMSE. He failed to recall two out of the three presented words, and he failed to

indicate the season and to follow all commands correctly. Immediately after the end of treatment, he improved his performance, scoring 28 total points. The missing points were from the word recall. The same performance, with two mistakes in the words recall task, was observed at follow-up.

At the initial ADAS-cog examination, Mr. E.C. scored 16 total points. He failed to recall five words in the immediate word recall on average, he did not remember six out the 10 words in the delayed recall, he mistakenly recognized three words in the recognition trial, he failed to indicate the season of the year, and he failed to correctly name two items and two fingers. Immediately after treatment, he significantly improved his performance, scoring 10.33 total points. Here, he failed to immediately recall 5.33 words, he forgot four words in the delayed word recall, and he mistakenly recognized one word. At follow-up, he was found to have improved (score=12) in relation to pretreatment. He immediately recalled five words, and in the delayed recall, he forgot six words and mistakenly recognized one. Figure 4.18 demonstrates Mr. E.C.'s scores throughout the study.

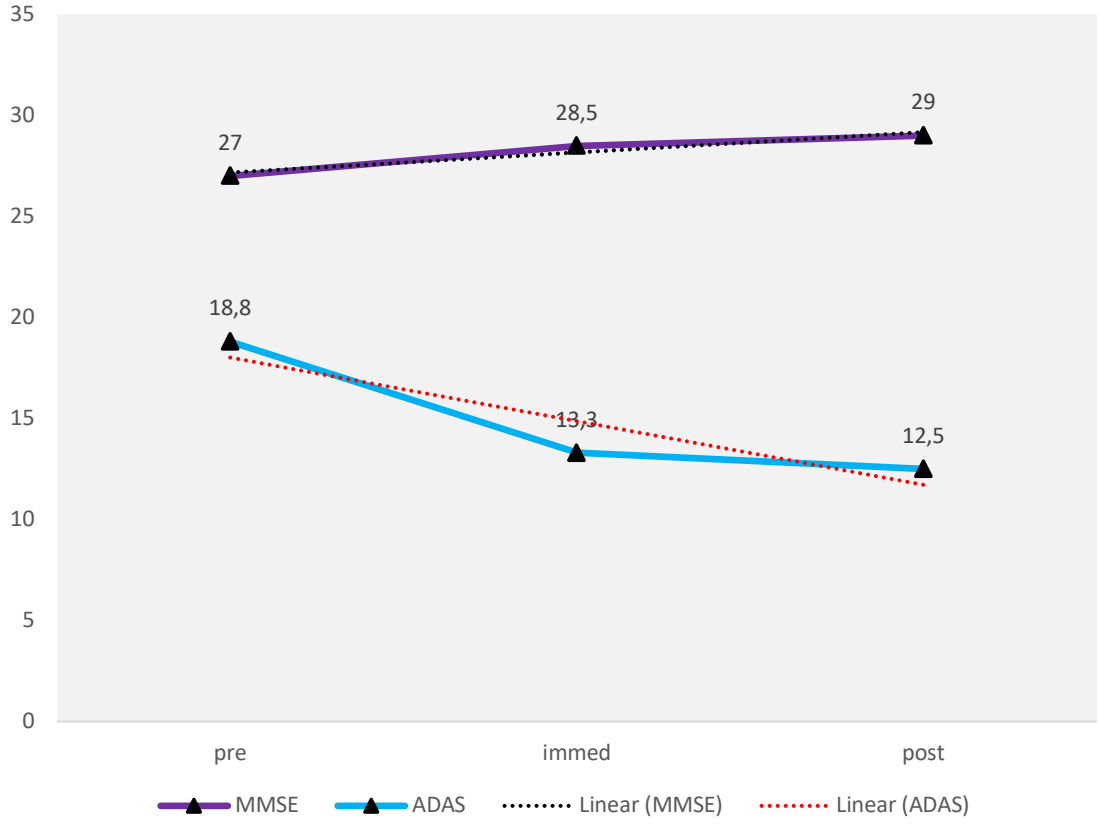
Figure 4.18 Schematic representation of Mr. E.C.'s performance on measures of global cognition



4.14.1 Average Global Cognition Scores

Average scores on measures of global cognition indicate an overall improvement after rTMS intervention (Figure 4.19). The patients' performance on the ADAS-cog improved between pretreatment (M=18.8) and immediately after the end of treatment (M=13.3) by 30%, and it further improved 3 months after the end of treatment (M=12.5). Similarly, the patients' performance on the MMSE improved between pretreatment (M=27) and immediately after the end of treatment (M=28.5) by 1.5 points, which was maintained at follow-up (M=29).

Figure 4.19 Schematic representation of ADAS-cog and MMSE mean scores at pretreatment, post-treatment, and follow-up



Note: The ADAS-cog score is based on errors made in each subtest. The highest score (i.e., 80) indicates severe impairment, while the least impairment is indicated by the minimum score (i.e., 0). Therefore, a drop in score indicates cognitive improvement. Pre: Pretreatment; immed: Immediately after the end of treatment; Post: Follow-up phase. In the MMSE, an increase of the score indicates behavioral improvement.

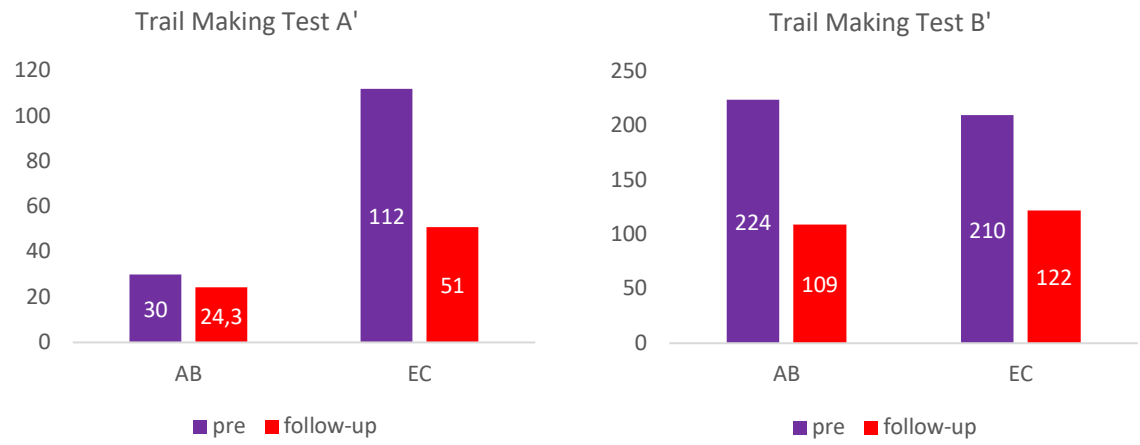
4.15 Neuropsychological Assessments

Patients' raw scores on the two neuropsychological evaluations are presented in Table 4.9. The PCI index was used to quantify the change between the two assessments.

Mrs. A.B.

Cognitive profile: In relation to her pretreatment performance, Mrs. A.B. recalled one more item in the immediate recall of the logical memory task (7.5% improvement), while her ability to recognize the previously learned items improved by 40% (she correctly recognized four more items from the story). This finding aligns with her performance in the ADAS-cog, where her recognition ability was improved by 87.5% at follow-up. In contrast, her ability to recall what had happened in the stories after a 30-minute interval was reduced by 22% (one less item was recalled). As indicated in the single-case data, her performance improved in TMT A´, where she needed 5.7 seconds less to complete the task (19% improvement). The effect was more significant in TMT B´, where she improved her performance by 51% (nearly 2 minutes faster; Figure 4.20). Her processing speed improved at follow-up, where she presented a 16% improvement.

Figure 4.20 Patients' scores in TMT A' and B'



Note: The scores in TMT A´ and B´ signify the total time needed to complete the tasks, and thus a reduction in the time indicates behavioral improvement. Pre: Pretreatment evaluation.

Table 4.9 Patients' raw scores on neuropsychological assessment at pre-treatment and follow-up

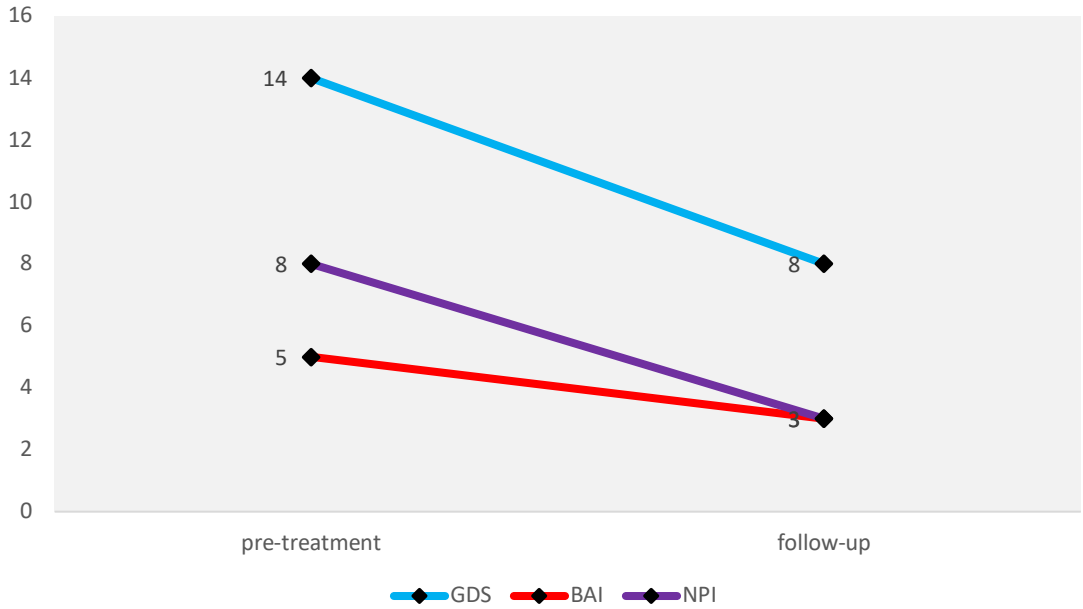
		A.B.			E.C.		
Cognitive Domain	Neuropsychological test	Pre	Follow-up	PCI %	Pre	Follow-up	PCI %
Memory	Logical memory						
	Immediate recall	13.5	14.5	▲7.5	10.5	20.5	▲95
	Delayed recall	4.5	3.5	▼22	1	5	▲400
	Recognition	10	14	▲40	6	8	▲33
	Rey Osterrieth complex figure						
	Immediate recall	4	5	▲25	4	4	-
	Delayed recall	4	4	-	3	3	-
Attention	Trail making test A'	30''	24.3''	▲19	112''	51''	▲54
	Digit span forward	7	7	-	8	7	▼12
Processing speed	Symbol digit Modalities test	32	37	▲16	14	24	▲100
Working memory	Digit span backwards	6	6	-	8	7	12
Visuospatial abilities/praxis	Rey Osterrieth complex figure test - copy	31	32	▲3	32	32	-
Executive functions	Phonological verbal fluency	40	42	▲5	29	24	▼17
	Frontal assessment battery	17	18	▲6	17	17	-
	Trail making test B'	224''	109''	▲51	210''	122''	▲42
Mood/psychiatric symptoms	Geriatric depression Scale-30	14	8	▲43	7	4	▲43
	Beck anxiety inventory	5	3	▲40	11	4	▲64
	Neuropsychiatric inventory	8	3	▲62	4	1	▲75
Quality of life (QoL)	QoL in AD, patients' form	34	38	▲12	45	46	▲2
	QoL in AD, caregivers' form	34	37	▲9	37	40	▲8

Note: The table shows the raw scores of patients' performance, obtained by neuropsychological testing before the study and 3 months after the 2-week TMS intervention. The interval between the two neuropsychological assessments was 24 weeks for Mr. E.C. and 23 for Mrs. A.B. PCI: Percentage of change index; ▼ Shows that the observed change led to a reduction of the behavior; ▲ Shows that the observed change improved the behavior.

Mood/psychiatric symptoms: Mrs. A.B.'s profile at retest was characterized by a significant reduction of her depressive and neuropsychiatric symptoms (Figure 4.21). Specifically, in relation with her pretreatment scores in the GDS-30, a reduction of 8

points was observed. In addition, at retest, Mrs. A.B. reported to experience fewer anxiety symptoms (a reduction of 2 points in the Beck anxiety inventory). These changes were also reported by Mrs. A.B.'s caregiver, who indicated an alleviation in depression and anxiety symptomatology in the neuropsychiatric inventory questionnaire (a reduction in both the severity and frequency of both domains).

Figure 4.21 Schematic representation of Mrs. A.B.'s scores in mood and psychiatric evaluation at pretreatment and follow-up



Note: A drop in the total score in all three tests signifies symptom alleviation. GDS: Geriatric depression scale; BAI: Beck anxiety inventory; NPI: Neuropsychiatric inventory.

Quality of life: The evaluation of Mrs. A.B.'s quality of life indicated improvements, as reported by both Mrs. A.B. and her caregiver. In her initial evaluation, Mrs. A.B. had not rated any item as excellent. At retest, she reported her living situation, her relationship with her family members and her friends, and her financial situation as excellent. At retest, her caregiver reported improvements in her energy levels, her mood, her memory, and her ability to do things for fun.

Post-study interview: From the clinical observation, a significant improvement in her mood was evident. In contrast with her initial evaluation, at retest, Mrs. A.B. was cheerful, she had energy to discuss irrelevant things, and her commitment in the evaluation was improved. Her mental fatigue, which had been characteristic in the first

evaluation, was still evident but noticeably alleviated. In the interview, she reported that her family had noticed a significant change in her behavior, something that was evident to her. Specifically, she reported ,“I feel more clarity; it is like I had a cloud in my mind and know it’s gone.” Her son reported that her mood was significantly improved, that she was able to remember small things, such as what she had eaten or where she had put her keys, and that in general, she was “faster” in her daily living.

Treatment fidelity: Two weeks before the second neuropsychological evaluation, Mrs. A.B. had finished with her job responsibilities, as the schools had closed for summer break. This change could influence her mental status and explain the observed improvements in her cognition and mood. Her son, however, stated that the observed changes were not evident during Christmas or Easter breaks.

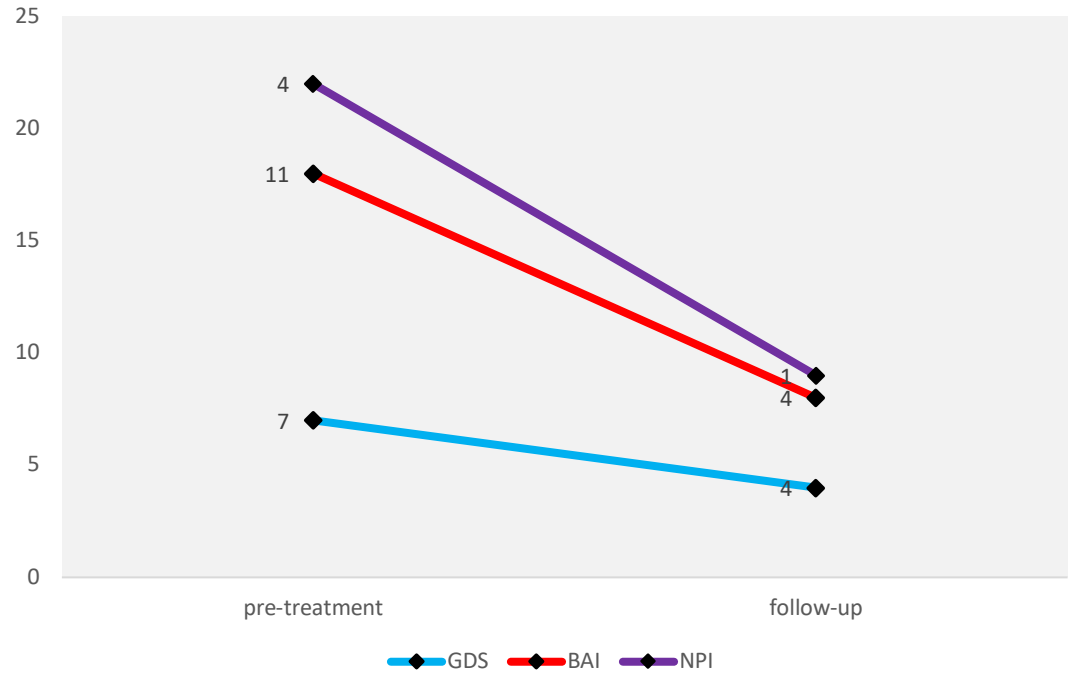
Mr. E.C.

Cognitive profile: In relation to his pretreatment performance, Mr. E.C. recalled 10 more items in the immediate recall of the logical memory task (100% improvement), while his ability to recognize the previously learned items was improved by 33% (he correctly recognized 2 more items from the story). As with Mrs. A.B., this finding aligns with his performance in the ADAS-cog, where his recognition ability was improved by 66% at follow-up. Notably, his ability to recall what had happened in the stories, after an interval of 30 minutes, was improved significantly (four more items were recalled). As indicated in the single-case data, his performance was improved on TMT A′, where he needed approximately half the time to complete the task, in comparison with his pretreatment performance (54% improvement). The effect was the same on TMT B′, where he improved his performance by 42% (Figure 4.20). His processing speed ability was notably improved; he substituted 10 more digits in contrast with his first evaluation.

Mood/psychiatric symptoms: Mr. E.C.’s profile at retest presented identical improvements with Mrs. A.B.’s and was characterized by a significant reduction of his depressive and neuropsychiatric symptoms (Figure 4.22). Specifically, in relation with his pretreatment scores in the GDS-30, a reduction of 3 points was observed. In addition, at retest, Mr. E.C. reported the experience of fewer anxiety symptoms (a reduction of 6 points in the Beck anxiety inventory). These changes were also reported by Mr. E.C.’s caregiver, who indicated an alleviation in the frequency of his depressive

symptomatology and improvement on the anxiety and irritability items in the neuropsychiatric inventory questionnaire.

Figure 4.22 Schematic representation of Mr. E.C.'s scores in mood and psychiatric evaluation at pretreatment and follow-up



Note: A drop in the total score in all three tests signifies symptom alleviation. GDS: Geriatric depression scale; BAI: Beck anxiety inventory; NPI: Neuropsychiatric inventory.

Quality of life: The evaluation of Mr. E.C.'s quality of life indicated improvement, as reported by both Mr. E.C. and his caregiver. In his initial evaluation, Mr. E.C. had rated most of the questioner's items as excellent, with only the memory item rated as poor. At retest, Mr. E.C. rated his memory abilities as fair, indicating an improvement. At retest, his caregiver reported improvements in his ability to do things for fun, and in his relationship with his wife and friends.

Post-study interview: From the clinical observation, a significant improvement in his mood was evident. While in his first evaluation, he was emotional and sensitive when he described his difficulties, at retest, he was found to be relaxed and calm. In the interview, he reported improvements in his memory, mood, and balance. His wife stated that his memory difficulties were stable and that she had not observed any improvements in his

daily living. She noticed, however, improvements in his concentration, ability to read books and watch television, and irritability and anxiety symptoms.

Treatment fidelity: No variable that could affect Mr. E.C.'s performance throughout the study was observed.

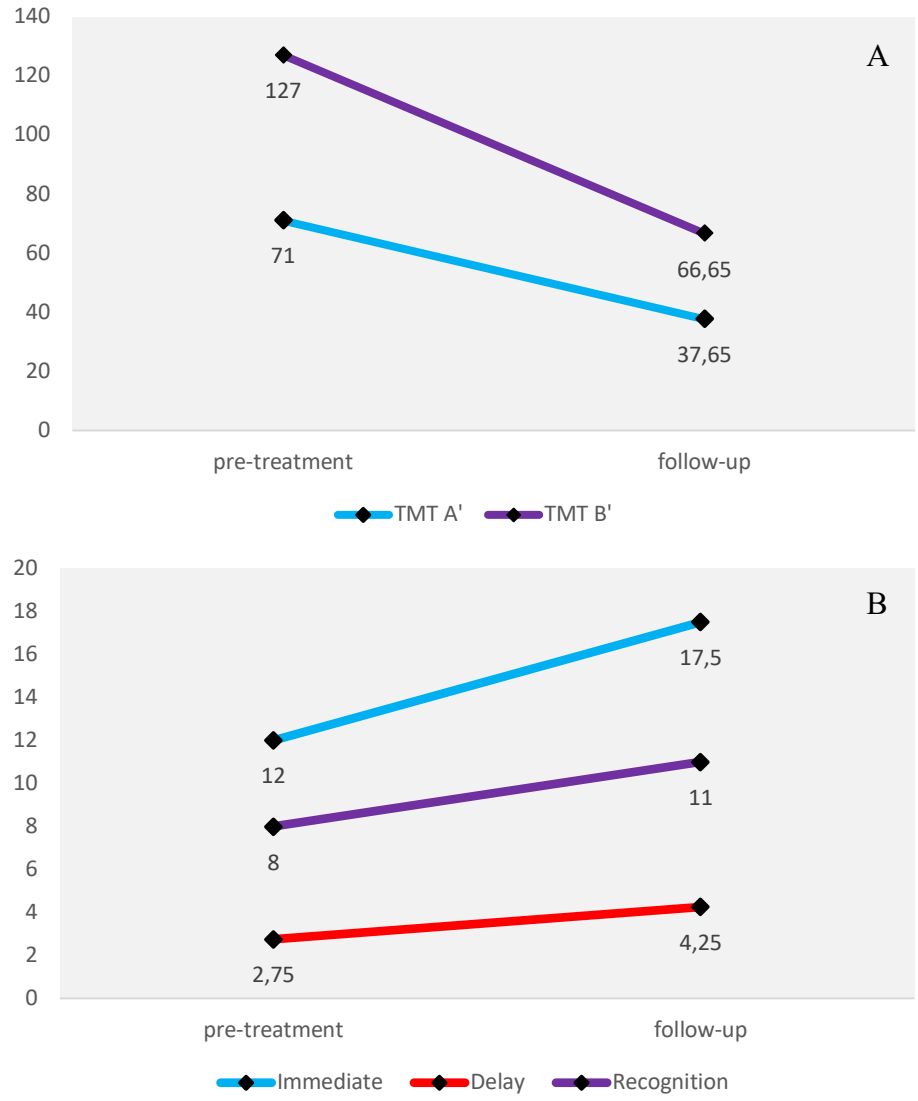
4.15.1 Total Effect of Treatment in aMCI Patients

The neuropsychological evaluations indicated cognitive improvements in aMCI patients 3 months after the end of rTMS intervention. The average scores of the patients' performance on TMT A′ improved between pretreatment (M=71 seconds) and follow-up (M=37.65 seconds) by 47%. Similarly, the patients' performance on TMT B′ improved between pretreatment (M=127 seconds) and follow-up (M=66.65) by 47.5% (Figure 4.23A).

The average scores of the patients' performance on the immediate recall of the logical memory test improved between pretreatment (M=12 items) and follow-up (M=17.5 items) by 46%. The patients' performance in delayed recall improved between pretreatment (M=8 items) and follow-up (M=11 items) by 37.5%. Patients' performance on the recognition task improved between pretreatment (M=2.75 items) and follow-up (M=4.75) by 72.7% (Figure 4.23 B).

The neuropsychological evaluations indicated improvements in the mood and psychiatric symptoms in the aMCI patients 3 months after the end of rTMS intervention. The average scores of patients on the GDS decreased between pretreatment (M=10.5) and follow-up (M=6) by 43%. Patient performance on the BAI decreased between pretreatment (M=8) and follow-up (M=3.5) by 56%. Patients' neuropsychiatric symptomatology decreased between pretreatment (M=6) and follow-up (M=2) by 66% (Figure 4.24 A).

Figure 4.23 Schematic representation of TMT A′, B′, and logical memory average scores at pretreatment and follow-up



Note: A. Patients' average scores on TMT A′and B′. B. Patients' average scores on the logical memory task. The score on the recognition task signifies the total correct recognized items. TMT A: Trail-making test A; TMT B: Trail-making test B. Immediate: Immediate word recall; Delay: Delayed word recall.

Finally, the mean scores for the self-rated quality of life improved from the pretreatment (M=39.5) to follow-up (M=42) by 6%. Approximately the equal amount of improvement indicated by the caregivers' ratings (an improvement of 8.5%; Figure 4.25 B).

Figure 4.25 demonstrates the overall percentage of change, from the pretreatment neuropsychological evaluation to the follow-up evaluation, on each task.

Figure 4.24 Schematic representation of patients' average scores in mood, neuropsychiatric symptoms, and quality-of-life measures at pretreatment and follow-up

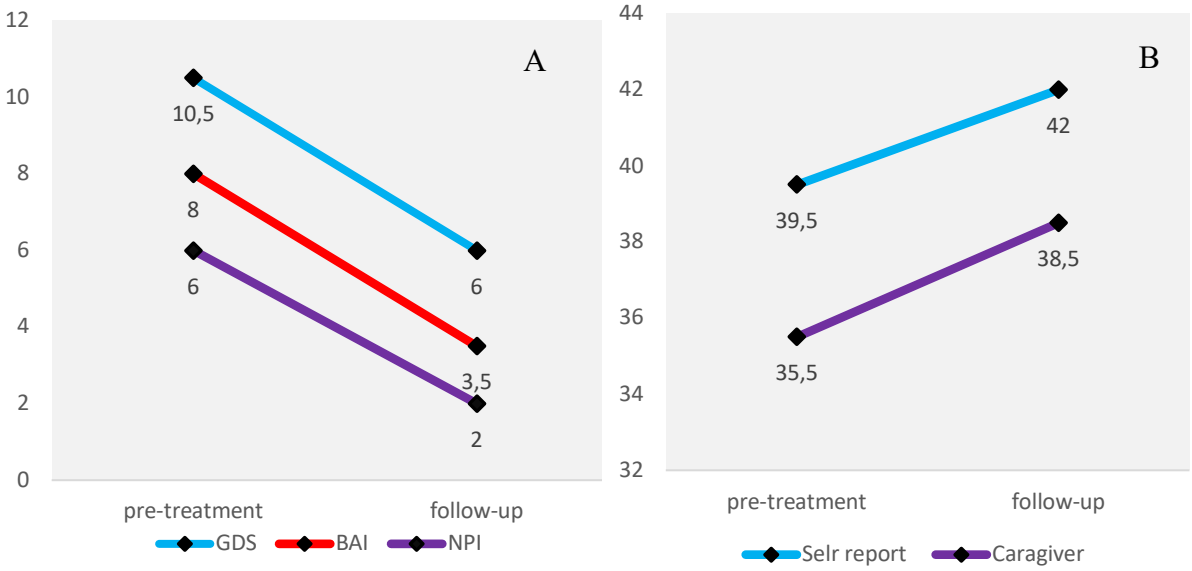
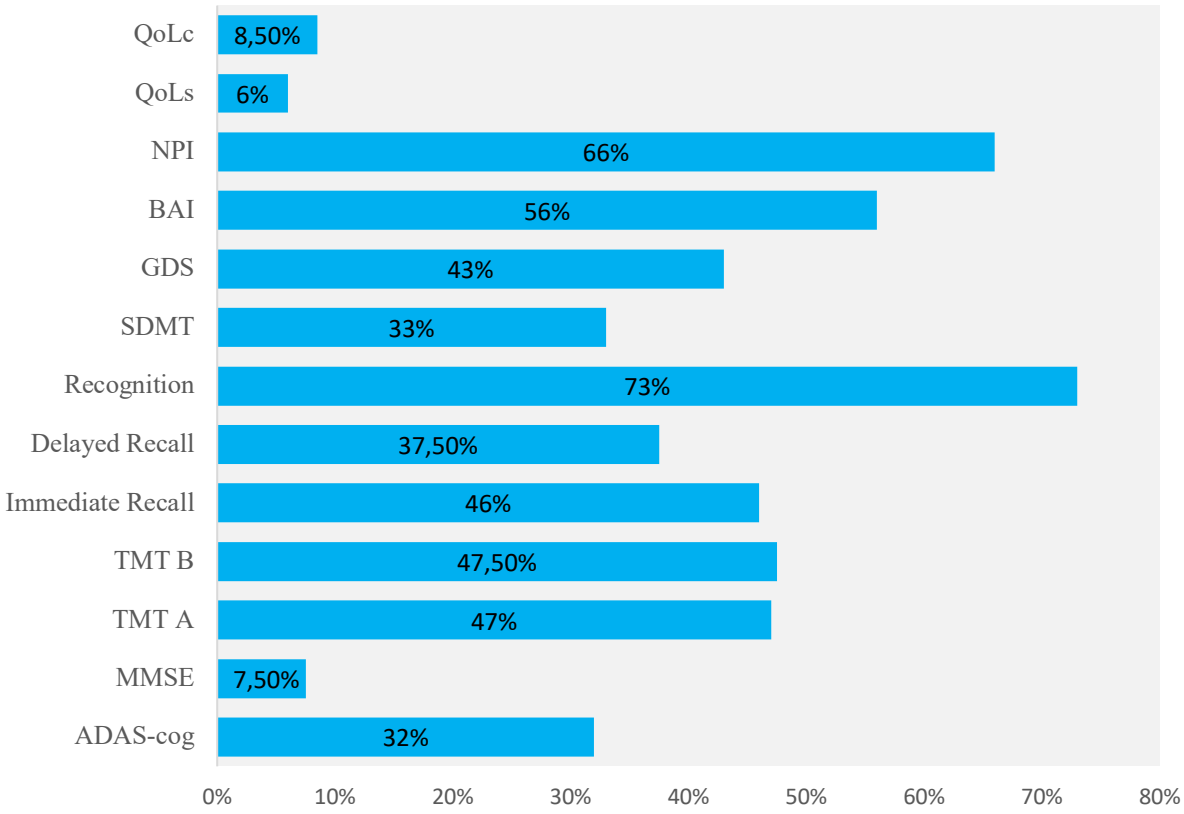


Figure 4.25 Overall percentage of change in aMCI patients from pretreatment to follow-up



Note: QoLc: Quality of life, caregivers' form; QoLs: Quality of life, self-rated form; NPI: Neuropsychiatric inventory; BAI: Beck anxiety inventory; GDS: Geriatric depression scale; SDMT: Symbol digit modalities test; TMT A: Trail-making test A; TMT B: Trail-making test B; MMSE: Mini mental state examination; ADAS-cog: Alzheimer's disease assessment scale.

4.16 Chapter Summary

The aim of this study was to investigate the efficacy of 40 Hz rTMS, delivered bilaterally to the precuneus, in mitigating cognitive dysfunction in patients with aMCI. The results supported the hypothesis that gamma frequency precuneus stimulation would have a wide effect on patients' cognitive function. The obtained single-case data indicated improvement in both patients' episodic memory (immediate and delayed recall), attention, and executive functions. No effects were observed in patients' recognition abilities, visual memory, and semantic associations. An immediate treatment effect was observed in both patients' ADAS-cog scores, which was maintained and further improved 3 months post-treatment. The data from the neuropsychological evaluations revealed a wide and positive effect in both patients' cognitive and emotional function. Both patients presented improvement in episodic memory, attention, executive functions and a remarkable alleviation of their depressive, anxiety, and neuropsychiatric symptoms. Importantly, the TMS treatment was safe—no side effects were reported—and highly tolerable. The results of this study provided preliminary evidence for the efficacy and safety of a novel non-pharmacological treatment, using gamma-band TMS, in addressing cognitive dysfunction and psychiatric symptoms in aMCI. A key question that needs to be addressed is whether gamma-band stimulation would also be effective in improving cognitive function in patients who have entered the AD continuum. Addressing this question is important to identify whether such an intervention could be useful in demented patients, or its effect is limited in the pre-dementia stage (i.e., MCI).

Chapter 5 Effects of 40 Hz Precuneus rTMS in Mild- to-Moderate AD[5]

The study presented in the previous chapter provided evidence that 40 Hz rTMS is a safe and effective intervention for improving aMCI patients' cognitive and mental status. This chapter presents a single-case study aiming to identify whether a similar effect would be observed in patients with mild-to-moderate AD. A randomized, concurrent, multiple baseline design study was employed, and the same methodology as described in Chapter 4 was applied. The only deviations related to the inclusion criteria, which were amended to include the diagnosis of probable AD, and the number of the AB phases repetitions, which increased due to a larger sample. The effects of 40 Hz rTMS in AD patients, as well as the overall effect of the gamma-band treatment in all patients who participated in both studies (i.e., aMCI and AD), are also presented in this chapter.

5.1 Methods

5.1.1 Experimental Design

A single-case, randomized, concurrent, multiple baseline design, across six patients with probable AD was employed (Krasny-Pacini & Evans, 2018). The baseline phases

[5] To ensure the highest possible standards and to be transparent about our research processes, the study was submitted in the Journal of Neuropsychology as a pre-registered report. Our proposed methods and analyses were peer-reviewed prior to the data collection and analyses. The study was in-principle accepted and all the proposed methods and analyses were conducted based on the initial accepted plan without deviations. The stage-two manuscript was published in the Journal of Neuropsychology as: Traikapi, A., Kalli, I., Kyriakou, A., Stylianou, E., Symeou, R. T., Kardama, A., Christou, Y. P., Phylactou, P., & Konstantinou, N. (2022). Episodic memory effects of gamma frequency precuneus transcranial magnetic stimulation in Alzheimer's disease: A randomized multiple baseline design. *Journal of Neuropsychology.* https://doi.org/10.1111/jnp.12299

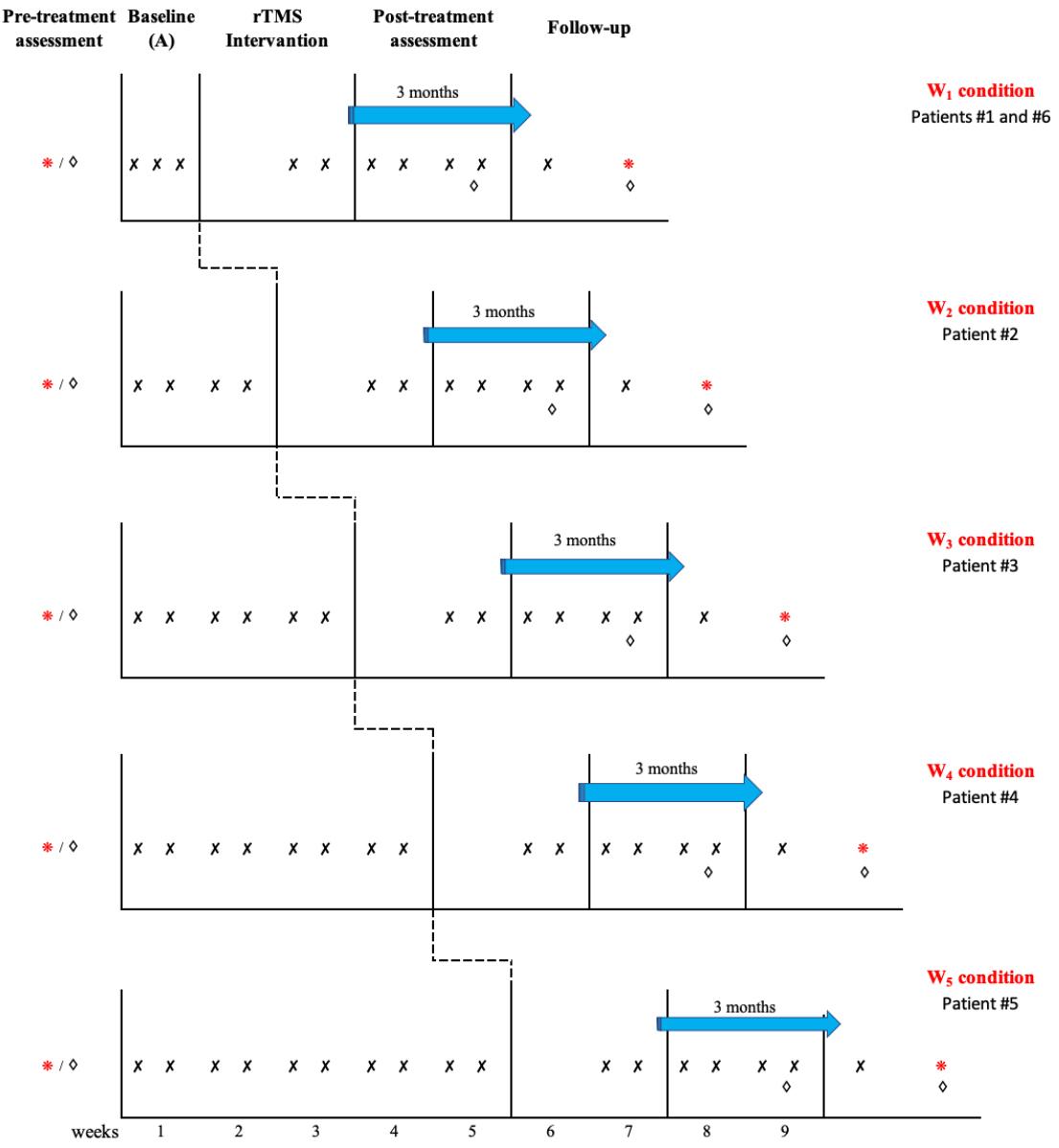
comprised five experimental conditions characterized by the length of their periods: one (W_1), two (W_2), three (W_3), four (W_4) and five-week (W_5) baseline periods. The six patients were randomly allocated to the experimental conditions. Two patients were allocated to the one-week baseline and each of the other patients to one of the remaining four. After the end of each experimental condition patients received a two-week gamma frequency TMS treatment. The targeted behaviors were systematically evaluated throughout the study. Specifically, they were evaluated at: (1) pretreatment, (2) treatment, (3) post-treatment and, (4) three months post-treatment. A schematic representation of the study's design and timeline is illustrated in Figure 5.1.

Baseline phases. Five baseline phases of different length were implemented (i.e., one to five weeks; W_1-W_5). The targeted behaviors were evaluated two times per week except for the participants in the one-week condition who were evaluated three times in order to meet evidence standards, which require at least three assessments on each phase. Therefore, the patients in the one-week baseline were evaluated three times, the patient in the two-week baseline condition was evaluated four times, the patient in the three-week condition six times etc. Each assessment session lasted between 30 and 40 minutes.

Intervention phases. Patients underwent a two-week TMS intervention immediately after the end of their experimental baseline condition. The TMS sessions were being delivered daily (Monday to Friday) for a total of 10 TMS sessions. The targeted behaviors were assessed six times in total. As a delayed effect was expected from the TMS treatment (e.g., Cotelli et al., 2011), the data collection started one week after the beginning of the intervention. Therefore, two assessments were conducted during the treatment phase and four post-treatment (two assessments/week; see Figure 5.1).

Follow-up phase: The targeted behaviors were assessed again three months after the end of the intervention phases.

Figure 5.1 Schematic representation of the study's design and timeline



Note: The patients underwent neuropsychological evaluation before the beginning of the study and three months after the end of the rTMS intervention (i.e., follow-up). The targeted behaviors were repeatedly and systematically measured throughout the AB phases (i.e., single-case data). During the AB and the follow-up phases, the targeted behaviors were assessed: in the W_1 condition 10 times, in the W_2 11 times, in the W_3 13 times, in the W_4 15 times and in the W_5 17 times. Each ❋ on the figure represents a neuropsychological evaluation. Each ✗ represents one targeted behavior assessment.

Each ◊ represents the time point of the primary measures assessment using the ADAS-cog and the MMSE.

5.1.2 TMS: Sites Protocol, and Procedures

The stimulation protocol, the targeted cortical areas, as well as the procedures that were followed throughout the TMS intervention were the same as those described in Chapter 4. Therefore, the patients received daily treatment sessions for 2 weeks (one session per day; five sessions per week; a total of 10 sessions). Each session included 25 trains consisting of 1 sec of 40 Hz each (40 pulses/train; 1000 total pulses), with 29 sec inter-train intervals and delivered at 90% of participant's resting motor threshold, or with the intensity of 65% of the maximum machine output (for safety reasons) using the Magstim Super Rapid2 Plus1 Therapy System with a figure-of-eight coil.

5.1.3 Sample and Inclusion Criteria

Six patients with a diagnosis of probable AD, according to the NIA-AA criteria (McKhann et al., 20211), were recruited for the study. A diagnostic protocol was implemented in order to verify the presence of AD and eliminate other possible conditions that may induce dementia. The diagnosis was provided by certified neurologists and supported by neuropsychological assessments. The patients and families were provided with all the study's information and asked to provide written informed consent. Patients were asked to provide a detailed clinical history in the presence of the carer and/or family member that included demographics, medical history, current health status, current medication use, education, and employment background. Permission to access this information was granted through the signed Informed Consent form.
To participate in this study patients had to meet all the below inclusion criteria:

- 55 years of age and above.
- Speaking Cypriot-Greek as a first language.
- Diagnosis of Probable AD.
- Absence of other medical or psychiatric condition that may induce cognitive deterioration.
- Score between 25 and 15 on the Mini Mental State Examination.

- Score between 4 and 6 on the Global Deterioration Scale (GDS).
- Score between 10 and 24 on the Greek version of the Instrumental Activities of Daily Living (IADL).
- Score no less than 5 on the Basic Activities of Daily Living (BADL).
- Score below 15 on the Geriatric Depression Scale-30 (GDS-30).
- Stable medical and pharmacological condition for at least 2 months prior to the study.
- Patients under cholinesterase inhibitors medication were included in the study only if they were taking the medication for more than 2 months prior to the study.
- Visual and hearing abilities within normal range.
- Absence of any clinically significant medical history that may induce cognitive impairment (psychiatric, neurological, cerebrovascular).
- Willingness to undergo an MRI scan.
- Having a caregiver who will agree to be responsible for their participation throughout the study.
- Being fully vaccinated for the Covid-19 (first shot and booster dose).

5.1.4 Exclusion Criteria

Patients were excluded from the study if one or more of the below mentioned exclusion criteria were evident:

- History of excessive alcohol consumption.
- Under psychoactive medication within the past two months.
- Diagnosis of epilepsy or family history of epilepsy.
- Moderate or severe depression as was assessed by the Geriatric Depression Scale – 30 (score no more than 15).
- Severe loss of hearing or visual ability.
- Medical implants in the head or a pacemaker.
- History of brain injury.

- Previous heart surgery or stroke.
- Under drugs with anticholinergic properties.
- No caregiver who could take the responsibility for their commuting throughout the study.
- Diagnosis of another neurodegenerative disorder, psychiatric or cerebrovascular condition.

5.1.5 Outcome Measures

The primary and secondary outcomes in this study were the same as those described in detail in Chapter 4. Therefore, the primary outcomes were the changes on episodic memory tasks and in measures of global cognitive function. The secondary outcomes were related to measures of semantic and spatial memory, as well as attention and executive functions.

In addition, the patients underwent a neuropsychological evaluation with standardized and well recognized measures pretreatment (before the baseline phase) and in the follow up phase (Figure 5.1; the same neuropsychological test battery, as in the MCI study, was used). The *Post Study Interview* was used to qualitatively evaluate possible changes to patients' cognitive and emotional function as well as their ability to function in everyday situations. Finally, the Wong-Baker Faces® Pain Rating was used to evaluate patients' experience after the 40 Hz rTMS, to monitor for possible discomfort and therefore to adjust the protocol to every patient.

5.1.6 Analyses Plan

The same analyses plan, as in the MCI study (Chapter 4), was implemented. Therefore, visual analysis was used to determine whether there was a functional relation between the rTMS protocol and the outcome measures. The effect size indices (1) Percentage of Data Exceeding the Median (PEM), and (2) Non-overlap of All Pairs (NAP) were used to evaluate the treatment's effect.

5.2 Patients

All patients passed the inclusion criteria checklist (Appendix 7). Table 5.1 presents the patients' clinical characteristics, their baseline allocation, and the intensity with which the treatment was administered to each of them.

Patient #1 (Mrs. M.X.) was a 75-year-old female with 6 years of education and an overall cognitive reserve at the medium level (CRIq=87). Specifically, her education fell on the medium level, while her working activity and leisure time total scores fell on the medium–low level. She was a retired dressmaker who was diagnosed with AD nearly 3 years prior to her participation in the study. Mrs. M.X. lived with her husband and had two children. Her history and recent medical testing did not indicate any cardiovascular risk factors or other significant medical conditions. Her daughter reported that her mother suffered from memory difficulties (i.e., she forgot conversations she had had with her children, plans she had, or to take her medications), and she had lost her desire to participate in any kind of social events or go outside the house. Her husband stated that her memory difficulties were observable in her everyday living and that she was afraid of what others might think about her, so she refused to participate in family dinners or gatherings. Mrs. M.X. was treated with cholinesterase inhibitors and antidepressants to manage depressive symptomatology. The IADL, which was reported by her husband, indicated mild dysfunction (score=17), with the most affected instrumental activities being her ability to shop without assistance, to manage her finances, to be responsible for her own medication, and to travel alone. Her independence in the ADLs was unaffected. While the patient did not report any depressive symptomatology (GDS-30=3), it was evident from clinical observation and interviews that her responses did not represent her actual mood state. The stage of her cognitive function was estimated at Level 4 in the GDS, which represents a moderate cognitive decline, or mild dementia. Mrs. M.X. clinical characteristics are illustrated in Table 5.1. She was randomly allocated to the 1-week baseline condition.

Patient #2 (Mrs. P.K.) was a 74-year-old female with 15 years of education and an overall medium level of cognitive reserve (CRIq=98). Mrs. P.K. was a retired secretary with a diagnosis of AD for almost 7 years. She had a son and three grandchildren and lived with a housekeeper who was responsible for her safety and daily living. Her son

reported severe cognitive impairment, which resulted in her inability to live alone a few years prior. Two decades ago, she had lost her daughter from cancer, and more recently, her husband. Her medical history revealed hypothyroidism, which however was well managed through medication. No evidence of any cardiovascular risk factors, excessive alcohol consumption, or the presence of other significant medical conditions was indicated. Mrs. P.K. had suffered from depression after the loss of her daughter and been treated with antidepressants to manage depressive symptomatology. Currently, she was treated with cholinesterase inhibiting antipsychotic, and antidepressant drugs. When entering the study, she was not able to survive without assistance, and she could not recall major relevant aspects of her current life (her address or telephone number), but she was able to recall her family members' names and provide nearly accurate instructions of how to navigate around her living area. The IADL, which was reported by her son, indicated moderate dysfunction (score=23; borderline with severe dysfunction), with most instrumental activities being affected. Her independence in the basic activities of daily living was unaffected (ADL=6). Mrs. P.K. reported mild depressive symptomatology (GDS-30=9). The stage of her cognitive function was estimated at Level 5 in the GDS, which represents a moderately severe cognitive decline, or moderate dementia. Mrs. P.K. clinical characteristics are illustrated in Table 5.1. She was randomly allocated to the 2-week baseline condition.

Patient #3 (Mr. A.P.) was a 68-year-old male with 6 years of school education and a medium overall cognitive reserve level (CRIq=104). While his education was classified under the medium–low level, he was a hardworking man, with numerus hobbies (working activity=medium and leisure time=medium–high level). He was a retired worker and lived with his wife. He was diagnosed with AD 2 years prior to his participation in the study. His history and recent medical testing did not indicate any cardiovascular risk factors or other significant medical conditions. His wife reported changes in his ability to remember small things, such as which road to take, what he had done the day before, or to take his medicine, which in turn affected his independence and mood. Mr. A.P. was aware of the changes to his mental status and was concerned about his future. He was treated with cholinesterase inhibitors and antidepressants to manage depressive symptomatology. The IADL, which was reported by his wife, indicated very mild dysfunction (score=10), with the most affected instrumental activities being his ability to perform light daily tasks and to use the telephone. He was able to manage activities such

as finances and transportation; however, his family reported changes from his previous level of autonomy. His independence in basic ADLs was unaffected. Mr. A.P. reported depressive symptomatology (GDS-30=11). The stage of his cognitive function was estimated at Level 4 in the GDS, which represents a moderate cognitive decline, or mild dementia. His clinical characteristics are illustrated in Table 5.1. Mr. M.P. was randomly allocated to the 3-week baseline condition.

Table 5.1 Patient characteristics

Note: F: Female; M: Male; MMSE: Mini mental state examination; BADL: Basic activities of daily living; IADL: Instrumental activities of daily living; GDS: Global deterioration scale; GDS-30: Geriatric depression scale-30; AD: Alzheimer's disease; Mi.D.: Mild dementia; Mo.D.: Moderate dementia; MS.D.: Moderate–severe dementia. CRIq: Cognitive reserve index questionnaire

	Patients					
Characteristic	1	2	3	4	5	*6*
Age (years)	75	74	68	58	75	*71*
Sex	F	F	M	F	M	*M*
Education (years)	6	15	6	16	16	*18*
MMSE	22	13	18	21	19	*15*
BADL	6	6	6	6	5.5	*6*
IADL	17	23	10	20	23	*24*
GDS	4	5	4	4	5	*6*
AD stage	Mi.D.	Mo.D.	Mi.D.	Mi.D.	Mo.D.	*MS.D.*
GDS-30	3	9	11	2	7	*0*
CRIq	87	98	104	112	109	*119*
Baseline week	1	2	3	4	5	*1*
rTMS intensity	90%	90%	90%	80%	90%	*90%*

Patient #4 (Mrs. T.P.) was a 58-year-old female who had been experiencing memory difficulties 2 years prior to her participation in the study. At the time of her participation, she had received the diagnosis of familial AD. Mrs. T.P. had 16 years of education and a medium overall level of cognitive reserve (CRIq=112). She was an active physical education teacher; however, due to her cognitive difficulties, she was under a medical leave. She did not report changes in her sleep patterns or excessive alcohol consumption,

and she had smoked for 2 years in the past. Her medical history and recent testing did not indicate the presence of other significant medical conditions. In her family history, her father had experienced cognitive dysfunction in his 70s without taking a dementia diagnosis. Her husband reported difficulties in her memory, which reduced her independence. She was conscious and anxious about her difficulties and treated with cholinesterase inhibitors. The IADL, which was reported by her husband, indicated moderate dysfunction (score=20), with the most affected instrumental activities being her ability to perform light daily tasks, prepare meals, shop on her own, travel without company and manage financial matters. Her independence in basic ADLs was unaffected. She did not report depressive symptomatology (GDS-30=2). The stage of her cognitive function was estimated at Level 4, which represents a moderate cognitive decline, or mild dementia. Mrs. T.P. clinical characteristics are illustrated in Table 5.1. She was randomly allocated to the 4-week baseline condition.

Patient #5 (Mr. A.I.) was a 75-year-old male with 16 years of education and an overall medium level of cognitive reserve (CRIq=109). He was a retired tax officer living with his wife. At the time of the study, he had been living with an AD diagnosis for nearly 5 years. His wife reported the absence of any significant medical history and the presence of substantial cognitive dysfunction, which reduced his independence. Mr. A.I. was unable to recall major aspects of his current life (e.g., his telephone number or address), but he was able to name his family members and discuss major current events when asked. He was partially disoriented in terms of time. He was treated with cholinesterase inhibitors. The IADL, which was reported by his wife, indicated moderate dysfunction (score=22; borderline with severe dysfunction), with most instrumental activities affected. In the basic activities of daily living, his wife reported mild dysfunction of self-control over urination (ADL=5.5). He reported mild depressive symptomatology (GDS-30=7). The stage of his cognitive function was estimated at Level 5, which represents a moderately severe cognitive decline, or moderate dementia. His clinical characteristics are illustrated in Table 5.1. Mr. A.I. was randomly allocated to the 5-week baseline condition.

Patient #6 (Mr. S.V.) was a 71-year-old male with 18 years of education and an overall medium–high cognitive reserve level (CRIq=119) and all questionnaire subscales (e.g., education, working activity, and leisure time) being scored at the medium–high level. He was a retired businessman who had studied and lived abroad for several years in his past.

He had had the diagnosis of AD for more than 7 years prior to his participation in the study. His history did not indicate any cardiovascular risk factors or other significant medical conditions. The IADL, which was reported by his son, indicated severe dysfunction (score=24), with all instrumental activities being affected. While his independence in the activities of daily living were reported unaffected (ADL=6), he was entirely dependent for survival. At the beginning of the study, he was unaware of all recent events and most of his life experiences. It was evident that he suffered from anosognosia. The stage of his cognitive function was estimated at Level 6, which represents severe cognitive decline, or moderately severe dementia. His clinical characteristics are illustrated in Table 5.1. Mr. S.V. was randomly allocated to the 1-week baseline condition.

5.3 Adherence to the Study

Patients 1–5 completed the study with 100% adherence. The provided schedule given to each one prior to the beginning of the study was followed without any deviation in either assessment appointments or treatment sessions. Patient 6 was not able to finish his treatment schedule due to behavioral difficulties (i.e., he was not eager to leave the house). In total, he received four rTMS session in 2 weeks. His data were removed from the analyses.

5.4 TMS Therapy Tolerance and Side Effects

The mean ratings on the Wong-Baker FACES pain rating scale ranged between 1 and 1.4, with an overall mean rate of 1.15. The patients indicated no pain or any kind of disturbance during or after each rTMS session. Figure 5.1 illustrates patients' ratings on the scale. No side effects were reported during and/or after rTMS sessions.

Figure 5.2 Illustration of patients' average ratings on Wong-Baker FACES scale

Note: The red line indicates the mean score of the patients' ratings. The patients rate their rTMS sessions experience as painless and well tolerated

5.5 Inter-Rated Reliability

The analysis indicated a high level of agreement in all administered neuropsychological tests (PA=1) during the baseline and treatment phases. A lower, but still acceptable, level of agreement was observed for the naming task (i.e., 0.92).

5.6 Results: Single-Case Data[6]- Primary Outcomes

5.6.1 Episodic Memory: Immediate Word Recall

Phase characteristics (i.e., mean score and standard deviation of each patient on each phase) are illustrated in Table 5.2. A schematic representation of patients' scores in the immediate word recall during the A, B, and follow-up phases is illustrated in Figure 5.3.

Table 5.2 Phase characteristics for word immediate recall

			Baseline		Treatment		
Patient	Baseline condition in weeks and (total assessments)	Number of assessments in the treatment phase	Mean (SD)	Median	Mean (SD)	Median	PCI
#1	1 (3)	6	10.7 (3.5)	11	15.8(4.4)	17.5	▲48%
#2	2 (4)	6	2.5(.5)	2.5	4.2(1)	4	▲68%
#3	3 (6)	6	6.3 (1.75)	5.5	8.8 (2.3)	8	▲40%
#4	4 (8)	6	11.1 (2.4)	12	10 (1.1)	10	▼10%
#5	5 (10)	6	8.4 (1.7)	8.5	9.5 (1.5)	9.5	▲13%

Note: SD: Standard deviation; ▲: Change indicates behavioral improvement

Within-phase examination. The stability criterion was not satisfied within phases. Only Patient 2 demonstrated stable performance during both phases. The percentage of the data points falling within the predefined range for the remaining patients was between 12.5% to 66.5%, indicating unstable performance during data collection in both the A and B phases. The patients' unstable performance during baseline was also evident by a visual inspection of phase trend lines (Figure 5.3). However, an increase in average level was

[6] The single-case data refer to the data that were obtained through the alternative test forms during the baseline, treatment, and follow-up phases (see Figure 3.2 for a visual representation of these data).

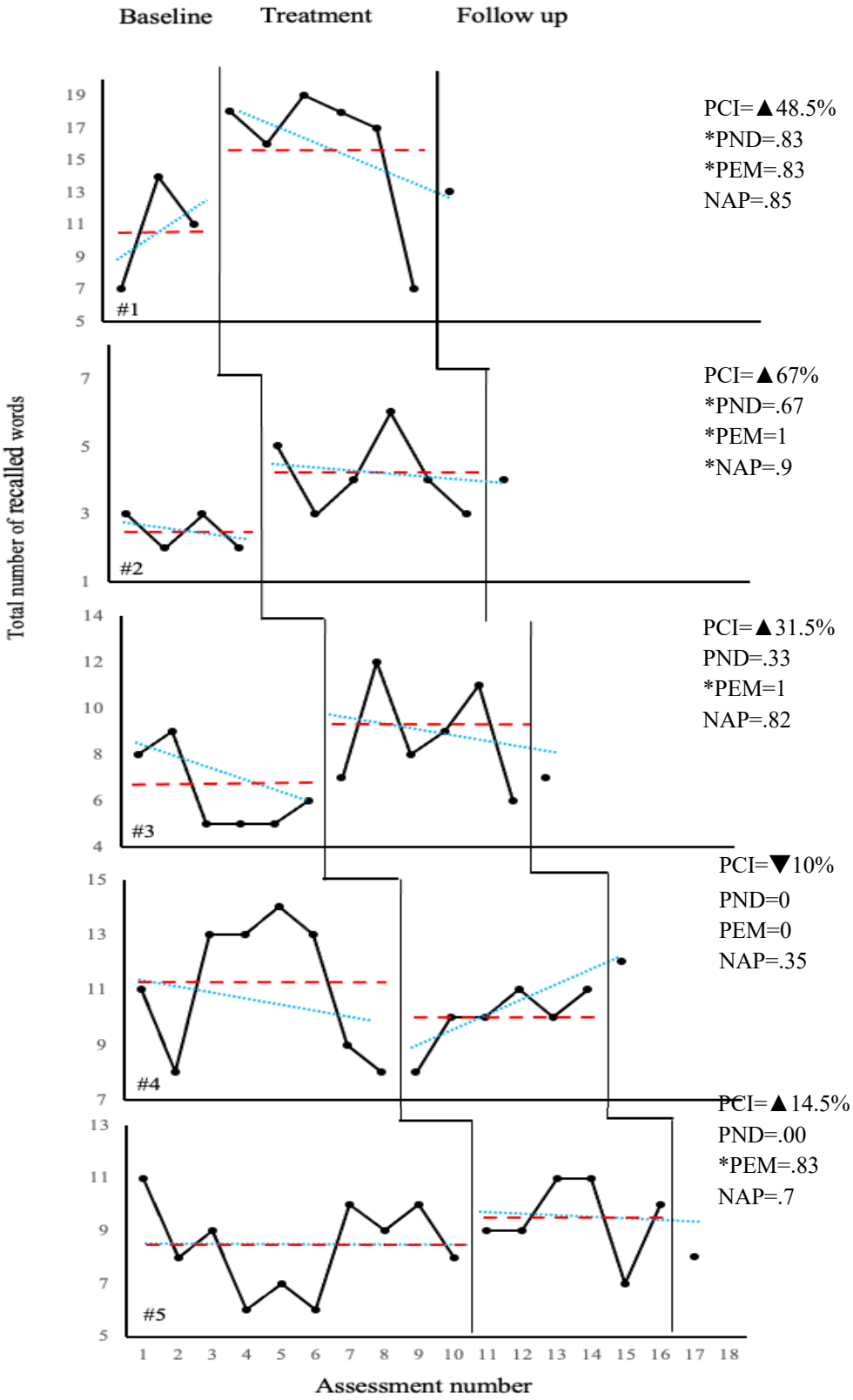
observed for the total number of recalled words in the three learning trials for Patients 1, 2, 3, and 5 (Figure 5.3). The PCI signified an increase of 48.4% in the total recalled words after the intervention for Patient 1, 68% for Patient 2, 40% for Patient 3, and 13% for Patient 5. Patient 4 showed a 10% reduction in total recalled words after the intervention.

Between-phase examination. An immediacy of the effect was observed in Patients 1 (32% improvement), 2 (87% improvement), and 3 (62% improvement). An immediate effect was not observed in Patients 4 or 5 (Figure 5.4). The PND index indicated a significant effect of the intervention in Patients 1 (PND=.83, $p<.05$; 83% of the data points in the treatment phase did not overlap with those from the baseline phase) and 2 (PND=.67, $p<.05$). No observed effect of the treatment was indicated for Patients 3, 4, or 5 ($p>.05$). However, the PEM index showed the following:

- In Patient 1, 83.5% of treatment data exceeded the baseline's median (PEM=.83), indicating a moderate treatment effect.
- In Patient 2, 100% of treatment data exceeded the baseline's median (PEM=1), indicating a highly effective treatment.
- In Patient 3, 100% of treatment data exceeded the baseline's median (PEM=1), indicating a highly effective treatment.
- In Patient 5, 83.5% of treatment data exceeded the baseline's median (PEM=.83), indicating a moderate treatment effect.

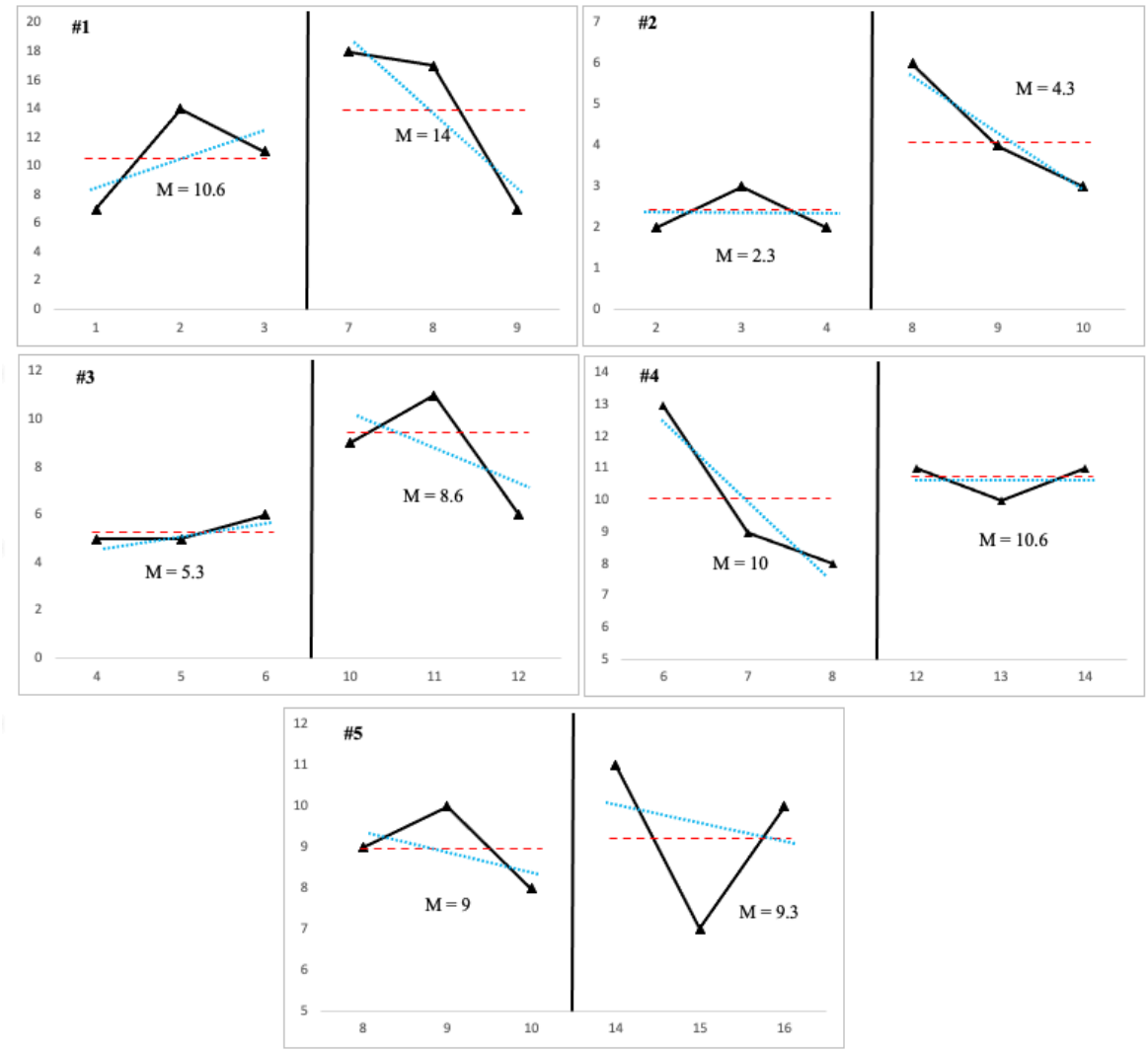
In Patient 4, none of the treatment data exceeded the baseline's median (PEM=0). The calculated *p*-value for the NAP estimator provided evidence of a significant treatment effect on Patient 2 (NAP=.9, $p<.05$). Nonsignificant effects were observed in Patients 1 ($p=0.09$), 3 ($p=0.06$), and 4 and 5 ($p>.05$).

Figure 5.3 Schematic representation of observations on immediate word recall from baseline to follow-up between participant



Note: The vertical black lines indicate the start of the subsequent phase. The baseline conditions began at the same time for both patients, but treatment introduction was staggered across time and patients. The dotted red horizontal lines represent the average score in each phase. The dotted blue lines illustrate the trend lines for each baseline and treatment phase. The PCI, PND, PEM, and NAP indices have been calculated without the follow-up phase. PCI: Percentage change index; PND: Percentage of nonoverlapping data; PEM: Percentage of data exceeding the median; NAP: Nonoverlap of all pairs; ▲: Increase.

Figure 5.4 Visual illustration of immediacy of effect in immediate word recall



Note: Immediacy of the effect was calculated by comparing changes in the mean level of the last 3 data points (i.e., assessments) of the baseline conditions with the mean level of the last 3 data points of the treatment conditions. M: mean.

5.6.2 Episodic Memory: Delayed Word Recall & Recognition

Visual analysis and effect size indices did not provide evidence of differences between the patients' performance before compared to after treatment in the delayed word recall and recognition task.

5.7 Results: Single-Case Data-Secondary Outcomes

5.7.1 Trail Making Test A´

Phase characteristics are illustrated in Table 5.3. A schematic representation of patients' scores on TMT A′ during the A, B, and follow-up phases is illustrated in Figure 5.5.

Table 5.3 Phase characteristics for trail-making test A′

			Baseline		Treatment		
Patient	Baseline condition in weeks and (total assessments)	Number of assessments in the treatment phase	Mean (SD)	Median	Mean (SD)	Median	PCI%
#1	1 (3)	6	259 (59)	246	145(32)	142	▼44
#2	2 (4)	6	244(45)	242.5	221(110)	175	▼9
#3	3 (6)	6	300 (126)	300.5	122 (25)	125.5	▼59
#4	4 (8)	6	191 (109)	183	187 (49)	172.5	▼2
#5	5 (10)	6	224.5(73)	204.5	177.5 (43)	172	▼21

Note: PCI: Percentage of change. ▼: Decrease of behavior.

Within-phase examination. The stability criterion was not satisfied in any phase for all participants, indicating patients' unstable performance. The highest percentage of data falling within 15% of the phase mean was 50%, and the lowest was 33%, indicating a high variability in the single-case data. A visual inspection of the phases' trend lines showed highly unstable baseline conditions, making the investigation of a treatment effect difficult. However, a visual inspection of the graph data indicated a decrease in the mean levels after the introduction of the intervention, compared to the baseline conditions (Figure 5.5). Each patient's scores refer to the total time in seconds to complete the task; therefore, a decreased score after the intervention compared to baseline indicates faster

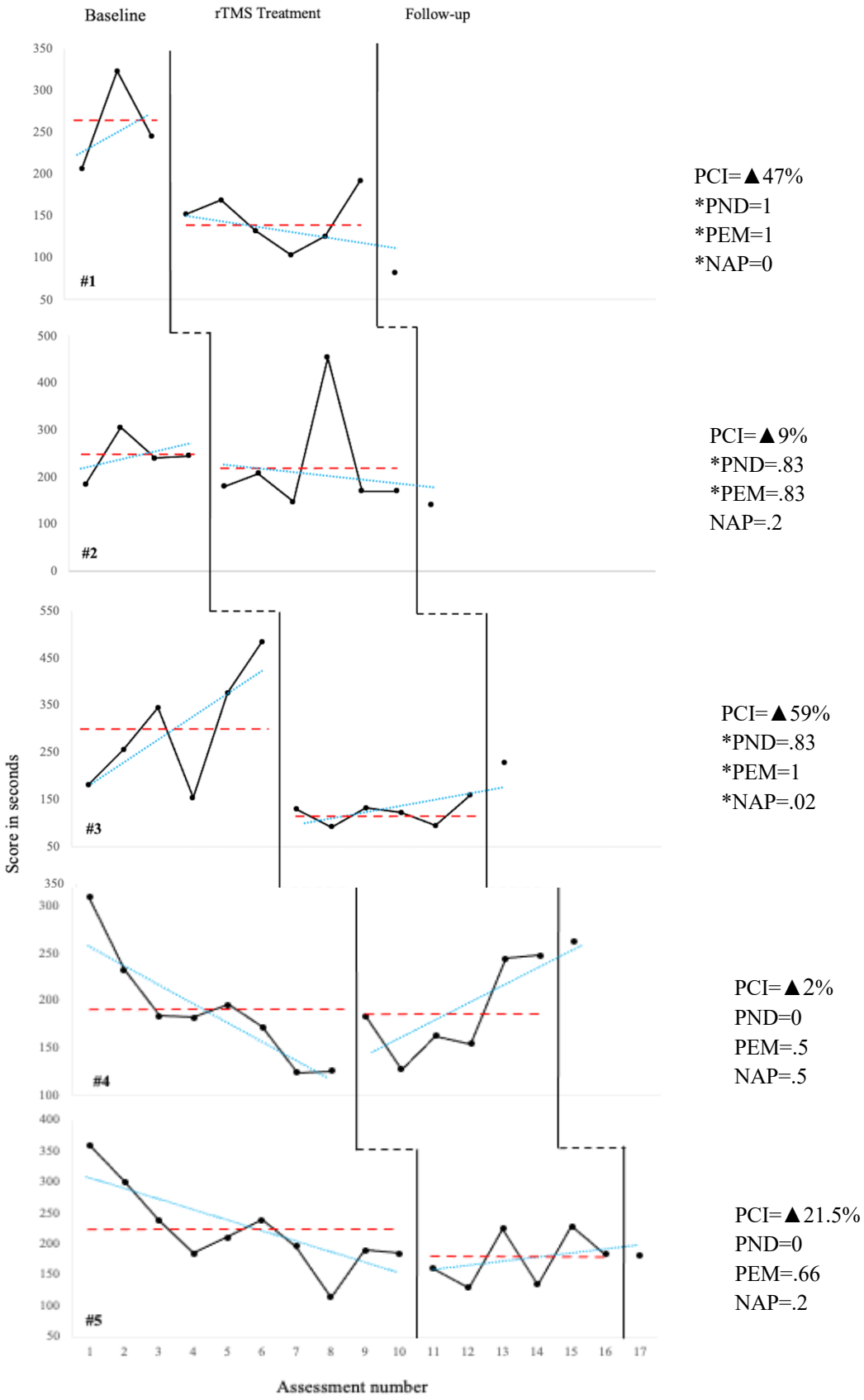
performance, which is considered a behavioral improvement due to the intervention. In contrast to the patients' scores during baseline, the PCI showed a decrease of 44% in Patient 1's total time, a decrease of 9% in Patient 2, a decrease of 59.3% in Patient 3, and a decrease of 21.4% in Patient 5. No difference was observed in Patient 4 (PCI=2.35).

Between-phase examination. An immediacy of the effect was observed in Patients 1 (45.6% improvement) and 3 (62% improvement). In contrast, no difference was observed in Patient 2, while Patients 4 and 5 presented increased treatment means by 54% and 9%, respectively (Figure 5.6). The PND index indicated a significant effect of the intervention in Patients 1 (PND=1, $p<.05$; all of the data points in the treatment phase did not overlap with those from the baseline phase), 2 (PND=.83, $p<.05$), and 3 (PND=.83, $p<.05$). No observed effect of the treatment was indicated for Patients 4 or 5 ($p>.05$). The PEM index showed the following:

- In Patient 1, all treatment data exceeded the baseline's median (PEM=1), indicating a highly effective treatment.
- In Patient 2, 83% of treatment data exceeded the baseline's median (PEM=.83), indicating a moderate treatment effect.
- In Patient 3, all treatment data exceeded the baseline's median (PEM=1), indicating a highly effective treatment.
- In Patients 4 and 5, 66.5% of treatment data exceeded the baseline's median (PEM=.66.5).

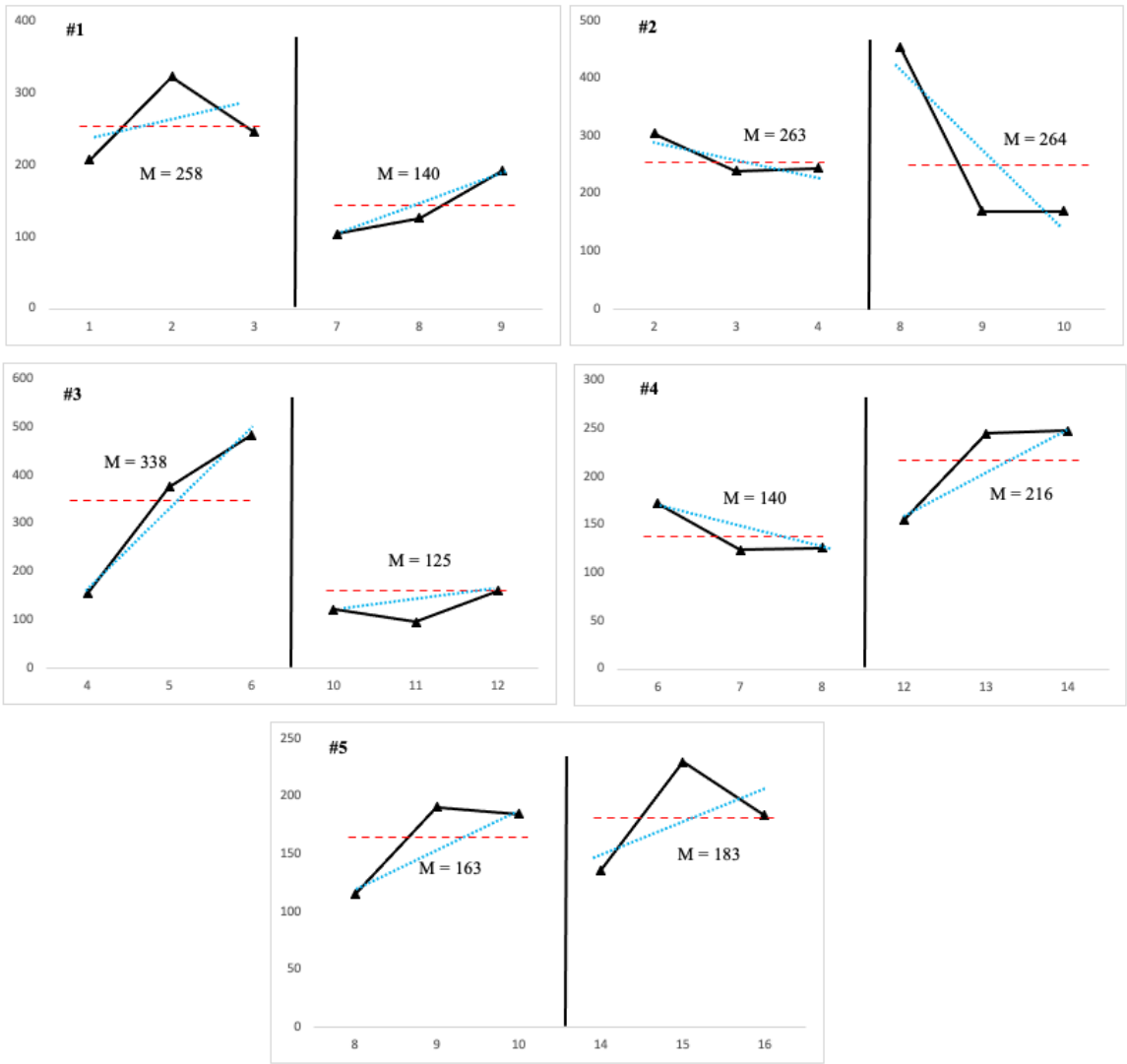
The calculated *p*-value for the NAP estimator provided evidence of a significant treatment effect on Patients 1 (NAP=0, $p<.05$) and 3 (NAP=.02, $p<.05$). Nonsignificant effects were observed for Patients 2 ($p=0.09$), 4 ($p=0.06$), and 5 ($p>.05$).

Figure 5.5 Schematic representation of observations on trail-making test A′ from baseline to follow-up between participants



Note: The vertical lines indicate the start of the subsequent phase. The baseline conditions began at the same time for both patients, but treatment introduction was staggered across time and patients. The dotted red horizontal lines represent the average score in each phase. The dotted blue lines illustrate the trend lines for each baseline and treatment phase. The PCI, PND, PEM, and NAP indices have been calculated without the follow-up phase. PCI: Percentage change index; PND: Percentage of nonoverlapping data; PEM: Percentage of data exceeding the median; NAP: Nonoverlap of all pairs; ▲: Increase; *: Significant treatment effect.

Figure 5.6 Visual illustration of immediacy of effect in trail-making test A′



Note: Immediacy of the effect was calculated by comparing changes in the mean level of the last 3 data points (i.e., assessments) of the baseline conditions with the mean level of the last 3 data points of the treatment conditions. M: mean.

5.7.2 Trail Making Test B´

The instructions of the test proved too complex for the patients to follow as instructed therefore, the data collection for this test stopped.

5.7.3 Corsi Block, Naming, Semantic Associations

Visual analysis and effect size indices did not provide evidence of differences between the patients' performance before compared to after the treatment in the Corsi block, naming, and semantic associations tasks.

5.8 Global Cognition

Patient scores on measures of global cognition are illustrated in Table 5.4. An immediate treatment effect was evident in all patients in both measures of global cognition (i.e., MMSE and ADAS-cog). Their performance was found to have further improved 3 months after the end of treatment.

Table 5.4 Patient performance on measures of general cognition

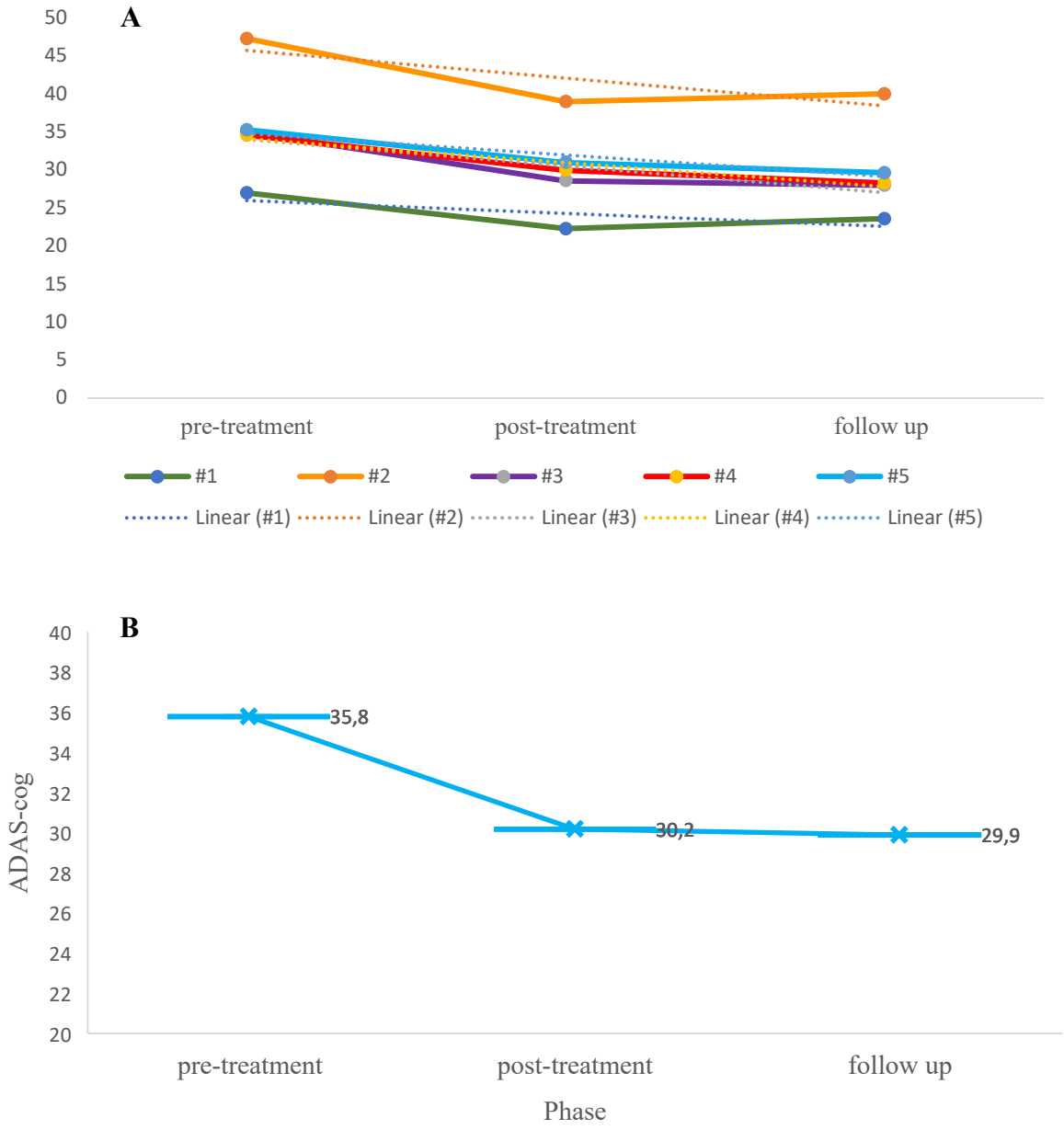
	MMSE				**ADAS-cog**			
Patients	*pre*	*immed*	*post*	*PCI %*	*pre*	*immed*	*post*	*PCI %*
#1	22	23	23	▲4.5	27	21.6	23.6	▲20
#2	13	15	16	▲15	47.3	39	40	▲17.5
#3	18	22	23	▲22	35	28.6	28	▲18
#4	21	21	20	0	34.6	30	28.3	▲13
#5	19	21	18	▲10.5	35.3	31	29.6	▲12

Note: The PCI refers to changes from pretreatment to immediately after the end of treatment. MMSE: Mini mental state examination; pre: Pretreatment; immed: Immediately after the end of treatment; port: Post-treatment. PCI: Percentage of change index; ADAS-cog: Alzheimer's disease assessment scale-cognitive subscale; ▲: Improvement in behavior.

All patients presented improvement immediately after the end of rTMS intervention in the ADAS-cog (average score=30.2), in relation to their pretreatment performance (average score=35.9; Figure 5.7 A). The effect was slightly higher in the follow-up phase, where the average reduction was 5.7 points (average score=29.9) in relation to

pretreatment and .3 in relation to immediately after the end of treatment (Figure 5.7 B). The rate of improvement ranged between 20% (Patient 1) and 12% (Patient 5), with a 16% average improvement in relation to immediately after the end of treatment and pretreatment. Four out of the five patients presented improvements in the MMSE, with improvements ranging between 4.5% (Patient 1) and 22% (Patient 3). Patient 4 presented approximately a 5% reduction in their performance.

Figure 5.7 Schematic representation of ADAS-cog scores from pretreatment to follow-up



Note: The ADAS-cog score is based on errors made in each subtest. The highest score (i.e., 80) indicates severe impairment, while the least impairment is indicated by the minimum score (i.e.,

0). Therefore, a drop in score indicates cognitive improvement. A. Patients' ADAS-cog total scores from pretreatment to follow-up; B. Differences in the average ADAS-cog scores of the five patients in each phase.

5.9 Neuropsychological Assessments

Cognitive function. Patients' average scores on the two neuropsychological evaluations are presented in Table 5.5. The PCI index was used to quantify the change between the two assessments. Patient performance was found to have improved 3 months after the intervention in the episodic memory task. The immediate recall of the logical memory test was improved by 1.5 items on average (75%; Figure 5.8 A), while the delayed recall improved by .5 items on average (Figure 5.8 B). In the immediate recall, Patient 1, in relation to the pretreatment assessment, remembered four more items, Patients 2 and 3 remembered 1 more item each, and Patient 5 improved their performance by 1.5 items. No difference was observed in Patient 4. The phonological verbal fluency increased from 16.8 average recalled words to 20.4 (22% improvement). The time needed to complete TMT A′ was reduced by 45 seconds (22% improvement). The effect was evident for Patients 1 (pretreatment: 132 sec, follow-up: 106 sec; 20% improvement), 2 (pretreatment: 237 sec, follow-up: 220 sec; 7% improvement), 3 (pretreatment: 104 sec, follow-up: 54 sec; 48% improvement), and 5 (pretreatment: 330 sec, follow-up: 201 sec; 39% improvement). No change was observed for Patient 4 (pretreatment: 252 sec, follow-up: 250 sec).

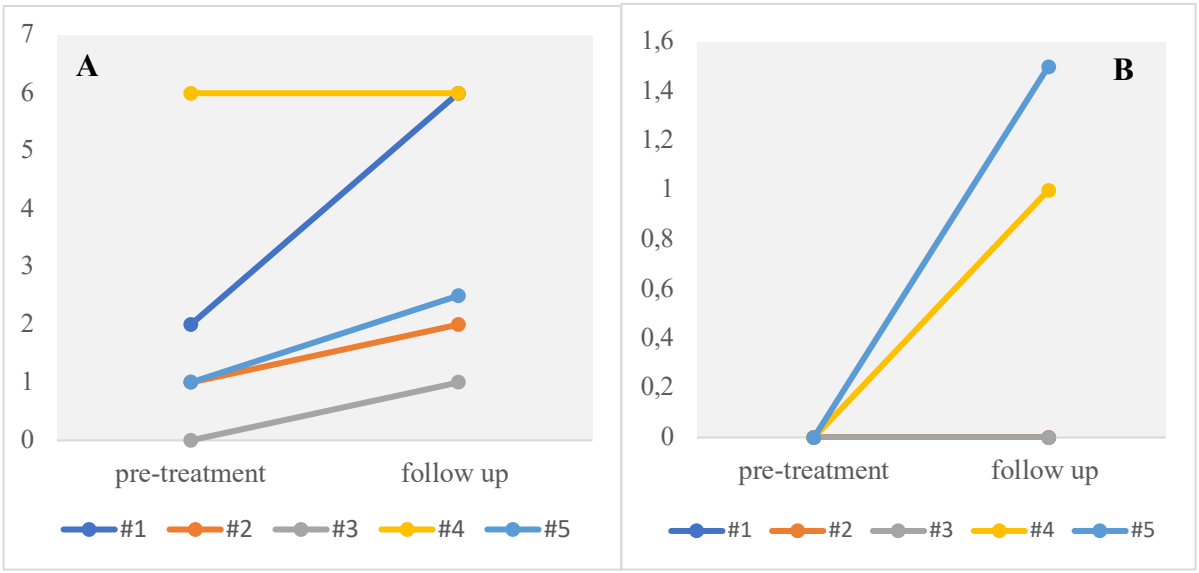
Mood and psychiatric symptoms. The neuropsychological evaluations indicated improvements in patients' mood and psychiatric symptoms 3 months after the end of rTMS intervention. The average score of the patients' performance on the GDS decreased between pretreatment (M=5.6) and follow-up (M=2.4) by 57%. The patients' performance on the BAI decreased between pretreatment average (M=3.8) and follow-up (M=1.2) by 68.5%. Patients' neuropsychiatric symptomatology decreased between pretreatment average (M=9) and follow-up (M=6) by 33% (Figure 5.9 A).

Table 5.5 Average scores on neuropsychological evaluations

Cognitive Domain	Neuropsychological test	Pre mean(SD)	Follow-up mean(SD)	PCI %
Memory	Logical memory			
	Immediate recall	2(2)	3.5(2)	75
	Delayed recall	0	.5(.3)	
	Rey Osterrieth complex figure			
	Immediate recall	2.6(5)	3(6)	15
	Delayed recall	1.9(4)	2(4)	5
Attention	Trail making test A´	211(87)	166(77)	21
	Digit span forward	6.6(1)	6.5(1)	1.5
Processing speed	Symbol digit modalities test	5.5(1)	6.7(3)	22
Working memory	Digit span backwards	3.4(2.5)	4(2)	17.5
Visuospatial abilities/praxis	Rey Osterrieth complex figure test - copy	27(8)	26(7)	3.7
Executive functions	Phonological verbal fluency	16.8(4)	20.5(4)	22
	Frontal assessment battery	11(4)	11.5(3)	4.5
	Trail making test B´	-	-	-
Mood/psychiatric symptoms	Geriatric depression scale – 30	5.6(4)	3.4(2.5)	39
	Beck anxiety inventory	3.8(5)	1.2(1.5)	68.5
	Neuropsychiatric inventory	9(2)	6(7)	33
Quality of life (QoL)	QoL in AD, patients' form	33(4)	40(6)	21
	QoL in AD, caregivers' form	32.4(5)	34.5(5)	4.5

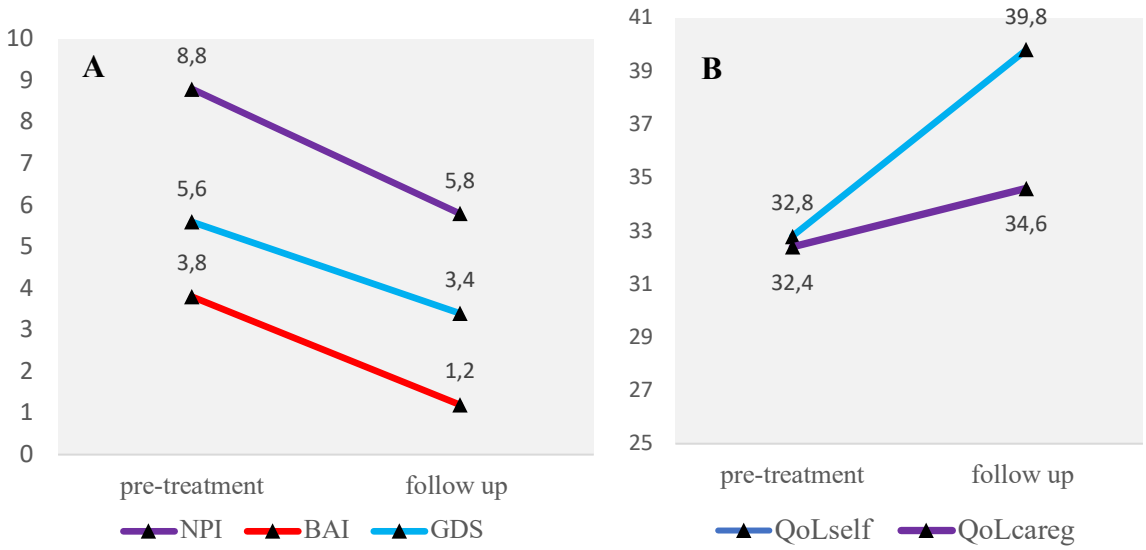
Note: The table shows the average scores and standard deviation of patients' performance, obtained by neuropsychological testing before the study and 3 months after the 2-week rTMS intervention. The interval between the two neuropsychological assessments was between 5 and 6 months, depending on the patient's baseline condition. The trail-making test B′ was not completed by any patient.

Figure 5.8 Schematic representation of patients' performance in episodic memory task



Note: A. Scores on the immediate recall of the logical memory task at pretreatment and follow-up. With exception of the Patient 5, whose performance presented no difference from pretreatment, all patients recalled more items from the stories immediately after their presentation; B. Scores on the delayed recall of the logical memory task at pretreatment and follow-up. Only Patients 4 and 5 improved their performance at follow-up. Patients 1, 2, and 3 were not able to recall any of the story's items after a 30-minute interval.

Figure 5.9 Schematic representation of patients' average scores in mood, neuropsychiatric symptoms, and quality-of-life measures at pretreatment and follow-up



Note: A. Average scores in depression, anxiety, and psychiatric symptom evaluation at pretreatment and follow-up. A drop in the total score in all three tests signifies symptom

alleviation. NPI: Neuropsychiatric inventory; BAI: Beck anxiety inventory; GDS: Geriatric depression scale. B. Average scores in quality-of-life evaluation. Increase in the total score signifies improvement in patients' quality of life. QoLself: Quality-of-life questionnaire, self-rated form; QoLcareg: Quality-of-life questionnaire, caregiver's form.

Quality of life. To evaluate whether the observed changes in patients' cognitive function, mood, and psychiatric symptoms had an effect on their daily living and function, the quality-of-life questionnaire was analyzed (Figure 5.9 B). The average score for self-rated quality of life improved from pretreatment (M=33) to follow-up (M=40) by 21%, indicating that patients perceived improvements in their overall quality of life. However, the patients' caregivers did not indicate the same extent of improvement. They reported improvement that did not exceed 4.5% in relation with their pretreatment quality of life.

Post-study interview. *Patient #1.* Mrs. M.X.'s family reported a significant improvement in her behavior. Her husband reported that she was happier and more active after her participation in the study. Specifically, he stated that she was keener to participate in social events, and generally, in leaving the house. In addition, she was able to follow a movie and remember some parts of it (in relation to before), and her everyday function was generally improved. Her daughter stated that she could remember things better than before (e.g., that they had arranged a family dinner) and that she was more eager to visit a relative's house or to go outside for a walk. From the clinical observation and evaluation, it became evident that her mood was improved, along with her reaction time and mental agility.

Patient #2. Mrs. P.K.'s son did not report any cognitive improvement. However, he observed a halt in the rate of decline in her function. His sensation was that his mother was stable after her participation in the study; however, she was in a better state than he was expecting based on the previous rate of decline. Mrs. P.K. did not report any observable changes in her function, nor were changes observed from clinical observation.

Patient #3. Mr. A.P.'s wife reported a significant improvement in his ability to remain calm under several everyday situations and to listen and discuss without anger and irritability. These observations were improvements in relation to his pre-study behavior. However, she reported a decline in relation to the period immediately after the end of treatment. She observed no changes in his cognitive function. Mr. A.P. himself, however,

reported significant changes in his cognitive function and mood. He stated that after the treatment and until the day of the reevaluation (i.e., 3 months later), he was better able to remember the things he wanted to do and he was able to go shopping without assistance (e.g., with a list). From the clinical observation, this was not evident.

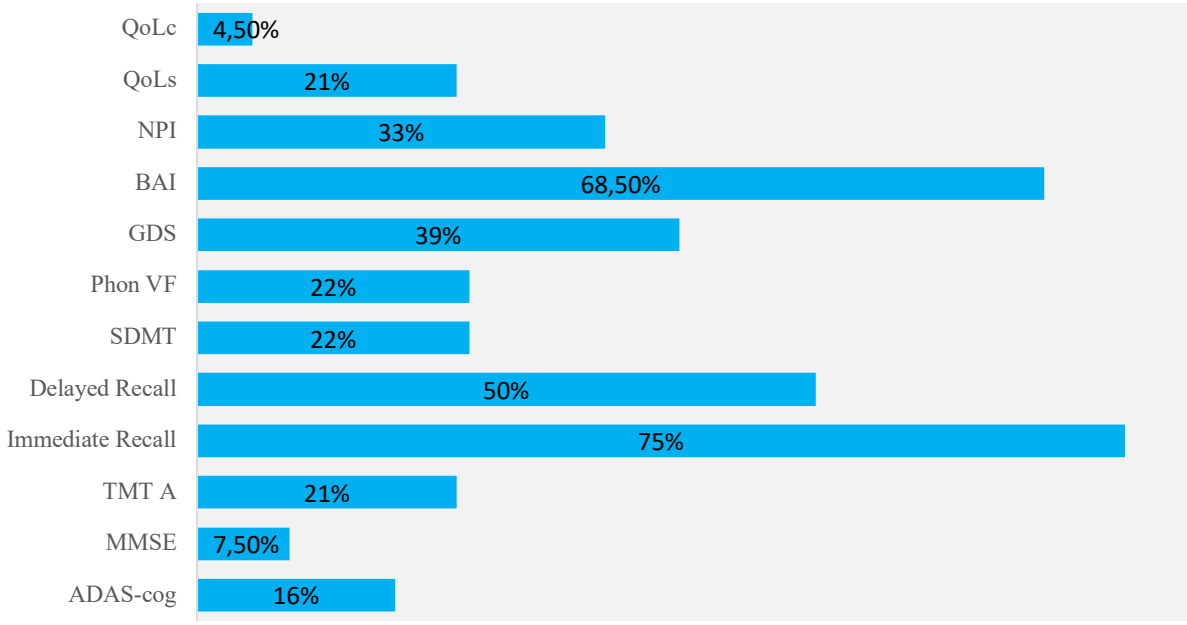
Patient #4. Mrs. T.P.'s husband reported no observable changes in her cognitive function. However, a significant improvement in her behavior was evident and maintained until reevaluation. Mrs. T.P. reported a significant improvement in her everyday life, a statement in accordance with her ratings in the quality-of-life questionnaire, where she rated most of the items higher in relation with her pretreatment evaluation. Her improved mood was evident from clinical observation.

Patient #5. Mr. A.I.'s wife reported no changes of any kind after the end of his participation in the study. In contrast, she reported a decline both in his cognitive function and his behavior. Mr. A.I. stated that he was feeling healthier.

Treatment fidelity. No variable that could affect patients' performance throughout the study was observed or indicated by the patients and/or their families.

Figure 5.10 demonstrates the overall percentage of change, from pretreatment neuropsychological evaluation to follow-up evaluation, on each task.

Figure 5.10 Overall percentage of change from pre-treatment to follow-up



Note*:* QoLc: Quality of life, caregivers' form; QoLs: Quality of life, self-rated form; NPI: Neuropsychiatric inventory; BAI: Beck anxiety inventory; GDS: Geriatric depression scale; SDMT: Symbol digit modalities test; TMT A: Trail-making test A; TMT B: Trail-making test B; MMSE: Mini mental state examination; ADAS-cog: Alzheimer 's disease assessment scale

5.10 Overall Treatment Effect in aMCI and AD Patients

To investigate the effect of the rTMS treatment in all patients who participated in the study and interpret the results in terms of statistical significance, a nonparametric paired-sample *t*-test (i.e., Wilcoxon *W*) was used, and the mean scores between pretreatment and follow-up neuropsychological evaluation data were compared. The analyses results are presented in Table 5.6.

Table 5.6 Statistical analyses results of key variables

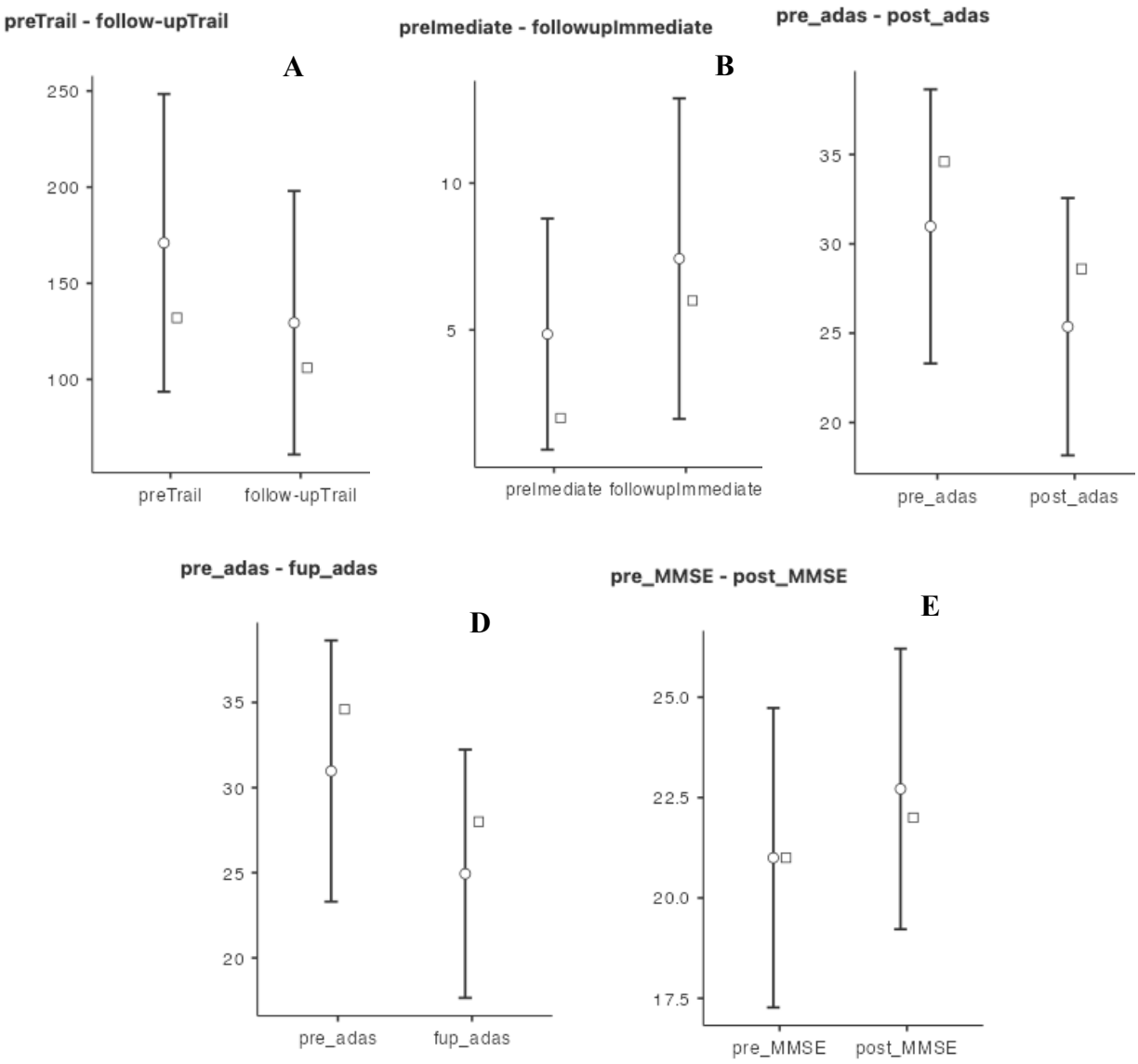
			Results			
Variables	MeanA (median)	MeanB (median)	Statistic (*W*)	*p* value	M.D.	Effect size Cohens *d*
ADAS/pre vs ADAS/immed	31 (34.6)	25.3 (28.6)	28	.016*	5.42	>2
ADAS/pre vs ADAS/fup	31 (34.6)	24.9 (28)	28	.016*	6.06	.7
MMSE/pre vs MMSE/immed	21 (21)	22.7 (22)	0	.034*	2	.5
MMSE/pre vs MMSE/post	21 (21)	22.6 (23)	4	.1	1.9	-
TrailA/pre vs TrailA/fup	171 (132)	129 (106)	28	.016*	33.5	>2
ImRecall/pre vs ImRecall/fup	4.8 (2)	7.4 (6)	0	.036*	2.25	1.3
DelRec/pre vs DelRec/fup	.8 (0)	1.6 (1)	1.5	.3	1.35	-
PhonFlu/pre vs PhonFlu/fup	22 (19)	24 (22)	6.5	.2	2.5	-
GDS/pre vs GDS/fup	7 (7)	4 (3)	15	0.05*	5	1.1
BAI/pre vs BAI/fup	5 (5)	1.8 (1)	10	.1	6	-
NPI/pre vs NPI/fup	8 (4)	4.7 (1)	21	.036*	4	.8
QoL/pre vs QoL/post (self)	34.5 (35)	40.5 (41)	0	.036*	7	1.2
QoL/pre vs QoL/post (careg)	33 (34)	36 (37)	0	.02*	2.5	1

Note: The degrees of freedom are 6 on each test. The asterisk (*) indicates statistically significant results. W: Wilcoxon W; M.D.: Mean difference; pre: Pretreatment scores; vs: Versus; immed: Immediately after the end of treatment evaluation; fup: Follow-up phase; TrailA: Trail-making test A′; ImRecall: Immediate recall of the logical memory test; DelRecall: Delayed recall of the

logical memory test; PhonFluency: Phonological verbal fluency; GDS: Geriatric depression scale; BAI: Beck's anxiety inventory; NPI: Neuropsychiatric inventory.

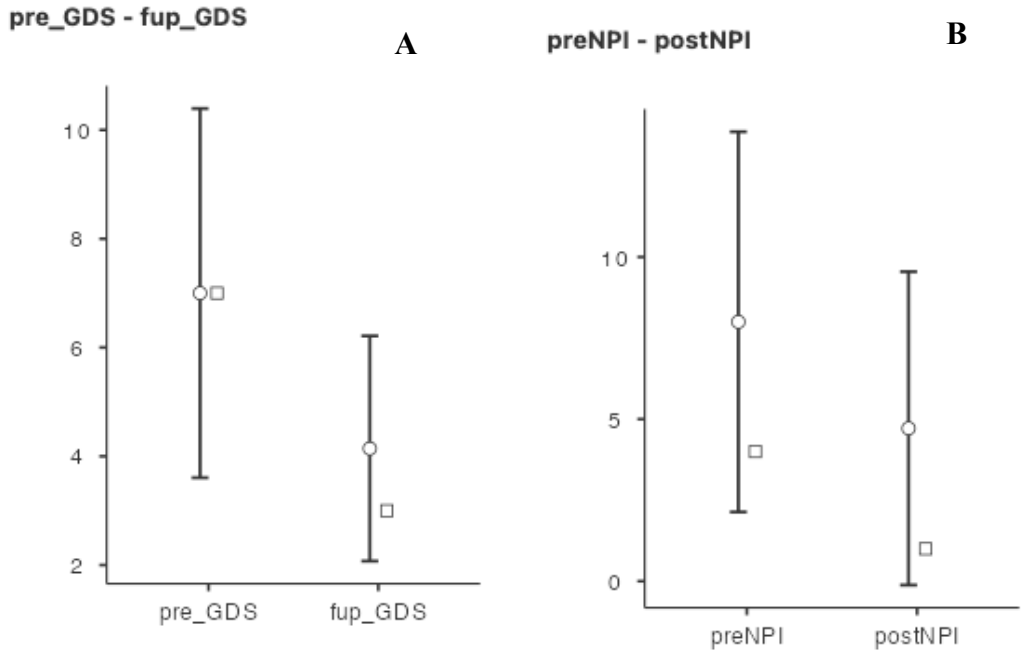
As illustrated in Table 5.6, significant differences between the mean scores at pretreatment and follow-up evaluation were found in TMT A′, the immediate recall of the logical memory task (Figure 5.11 A & B), the GDS, and the NPI (Figure 5.12 B). The patients' performance on the ADAS-cog was significantly improved from pretreatment to immediately after the end of treatment, by 5.2 points, and their performance was also statistically significant between pretreatment and follow-up (Figure 5.11 C & D). In the MMSE, a significant difference was observed among the patients' mean scores before the study and immediately after the end of treatment (Figure 5.11 E) The Cohen's *d* effect size index indicated a large effect in all aforementioned variables, with the exception the MMSE, which was found to be medium. The improvements in patients' delayed-recall scores and phonological verbal fluency and the observed reductions in the BAI were not found significant.

Figure 5.11 Graphical representation of average scores of all patients from pretreatment to follow-up for statistically significant variables.



Note: A. Mean scores on the ADAS-cog at pretreatment and immediately after the end of treatment; B. Mean scores on the ADAS-cog at pretreatment and follow-up; C. Mean scores on the MMSE at pretreatment and immediately after the end of treatment; D. Mean scores on TMT A′ at pretreatment and follow-up; E. Mean scores on the immediate recall of logical memory at pretreatment and follow-up. The ○ signifies each phase's mean score, and the □ signifies each phase's median.

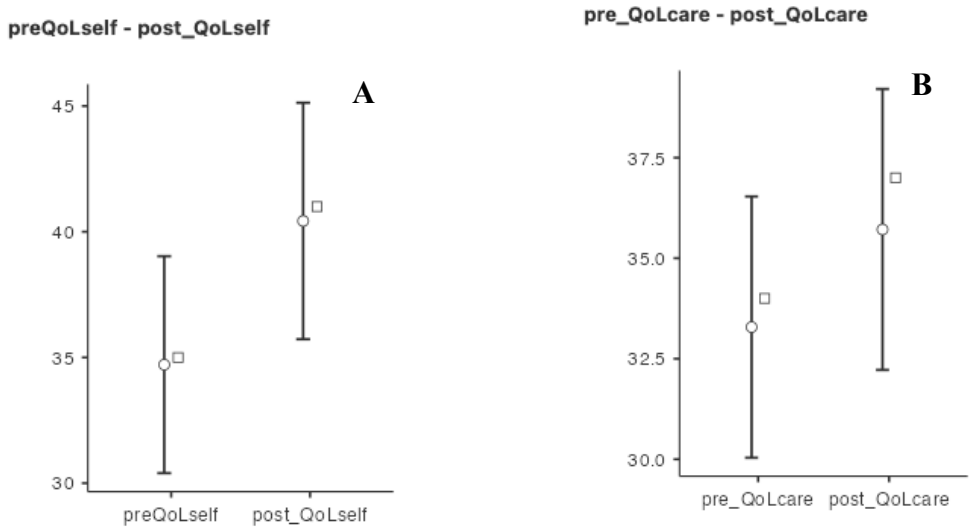
Figure 5.12 Graphical representation of all patients' average scores in evaluation of depression and neuropsychiatric symptoms at pretreatment and follow-up



Note: A. Mean scores on the geriatric depression scale at pretreatment and follow-up; B. Mean scores on the neuropsychiatric inventory at pretreatment and follow-up. The ○ signifies each phase's mean score, and the □ signifies each phase's median.

Finally, the treatment effect was found statistically significant on patients quality of life as was rated by the patients (Figure 5.13 A) and their caregivers (Figure 5.13 B).

Figure 5.13 Graphical representation of patients and caregivers' average rates on Quality of Life measure at pre-treatment and follow-up



Note: A. Mean scores of the patients self-rates in the Quality of Life in AD scale at pre-treatment and follow-up; B. Mean scores of the caregivers' rates in the Quality of Life in AD scale at pre-treatment and follow-up. The ○ signifies each phase's mean score, and the □ signifies each phase's median.

5.11 Chapter Summary

The main purpose of this study was to investigate the efficacy of gamma-band precuneus stimulation in mitigating cognitive dysfunction in patients with mild-to-moderate AD. The findings suggested that 40 Hz rTMS treatment is an effective, safe, and tolerable intervention for alleviating cognitive dysfunction and psychiatric symptoms in AD patients. Specifically, the obtained single-case data revealed a positive treatment effect in four out of the five patients, in their immediate word recall and attention skills. No effects were observed in the delayed word recall, word recognition, visual memory, naming, and semantic associations. An immediate treatment effect was observed in all patients' ADAS-cog scores, which was maintained and further improved at 3 months post-treatment. The neuropsychological data revealed a wide and long lasting treatment effect. Three-months post-treatment four patients presented improvements in immediate word recall, attention, and phonemic verbal fluency. Finally, a remarkable alleviation of the patients' depressive, anxiety and neuropsychiatric symptoms was observed. This study provides preliminary evidence that 40 Hz rTMS might represent a promising and effective non-invasive intervention in the rehabilitation of AD. Overall, this novel approach was found to have a statistically significant effect in cognitive and psychiatric variables, both in MCI and AD.

Chapter 6 Discussion

The aim of this thesis was to investigate whether 40 Hz transcranial magnetic stimulation, delivered bilaterally to the precuneus, is effective in mitigating cognitive dysfunction in patients with aMCI and AD. To answer this question, neurophysiological, normative, and experimental studies were conducted. Initially, a neurophysiological study investigating the effects of a newly developed 40 Hz rTMS protocol was conducted by stimulating the primary motor cortex of healthy participants. The results indicated that the specific protocol induced inhibitory physiological aftereffects that outlasted the stimulation period. The stimulation was found well-tolerated and safe. Subsequently, standardization and normative studies were conducted, aiming to develop alternative and equally difficult neuropsychological tests for the Greek-Cypriot population. In this work the Cypriot word pool, a list of approximately 2,850 standardized words was created. This word pool was used as a reference in the development of two alternative and equally difficult forms of the ADAS-cog-12, as well as in the development of 17 alternative forms of the neuropsychological tests, that were used in the final study of this research. Finally, a randomized, concurrent, multiple baseline design study was conducted, to investigate the effects of 40 Hz rTMS in patients with aMCI and AD. This chapter summarizes and discusses the results of these studies. The limitations of these studies are addressed, and recommendations and future directions are outlined.

6.1 Neurophysiological Effects of 40 Hz rTMS in the Human Motor Cortex

Chapter 2 presented the development of a novel 40 Hz rTMS protocol and reported the results of a study aiming to investigate its feasibility, safety, and the aftereffects on participants' cortical excitability. The developed 40 Hz rTMS protocol was applied over the primary motor cortex of 15 healthy participants. The influence on cortical excitability was assessed by comparing resting motor threshold before stimulation, with resting motor threshold immediately after and up to 45 minutes post stimulation. A neuronavigation system was used to ensure stable coil position and same stimulation parameters (e.g., hotspot coordinates). The results indicated that 40 Hz rTMS stimulation was well tolerated by all participants and no side effects were reported. The stimulation was found

to significantly influence cortical excitability by inducing suppression on the stimulated networks. Specifically, the inhibitory effect was observed immediately after the stimulation and reached the highest point at 45 minutes after the stimulation.

While rTMS has been widely used in rehabilitation of neurological and psychiatric disorders it is only recently that the scientific attention shifted towards the effects and the potential of gamma frequency brain stimulation. In a recent study, the feasibility and safety of 40 Hz audiovisual brain stimulation was assessed (Suk et al., 2020), indicating the safety of such an intervention as well as its ability to induce gamma brain activity. Further, previous studies have used 40 Hz protocols, through sensory or other non-invasive techniques, to explore their disease-modifying effect in AD, reporting cognitive amelioration and possible delay in disease progression (Chan et al., 2021; Liu et al., 2021). To our knowledge, the present study is the first to investigate the consequences of 40 Hz stimulation through the non-invasive TMS on neuronal excitability on the human motor cortex.

rTMS effects on corticospinal excitability depend on specific parameters, the so-called TMS protocols as well as coil geometry (Habib et al., 2018). It is also well accepted that low-frequency stimulation, defined as stimulation of $1 \leqq$ Hz, leads to a decrease of cortical excitability whereas stimulation in high frequencies, defined as stimulation of $\geqq$ 5 Hz, increases excitability (Iglesias, 2020; Somaa et al., 2022). However, there are only a few well established rTMS protocols for which their underlying effects have been investigated not only behaviorally but at neurophysiological level as well. In a prominent physiological study, Huang et al. (2005) investigated the effects of different theta burst stimulation (TBS) paradigms in corticospinal excitability. This study led to the establishment of the suppressive effect of, the well-used since then, cTBS protocol (i.e., continuous TBS) and the excitatory effect of the iTBS (i.e., intermittent TBS). A triggering question, however, is whether by stimulating in specific frequencies it is possible to drive brain wave activity. An evidence-based answer to this question might hold the potential for the development of frequency-based treatment stimulation protocols for diseases for which brain wave dysfunctions have been identified and even been associated with the observed cognitive and/or behavioral deficits (e.g., Cho et al., 2020; Mably & Colgin, 2018).

Previous studies have reported an association between brain stimulation and brain wave entrainment. For instance, Koch et al. (2018) stimulated the precuneus of AD patients at 20 Hz (i.e., a frequency that falls within the range of beta oscillations) using TMS, and through a TMS-EEG analysis indicated entrainment of beta brain activity, not only locally at the precuneus but at network level as well. The authors reported that the observed patients' cognitive improvement could be explained by the long-lasting increase of beta-rhythm that resulted from 20 Hz rTMS. In a more recent study, Liu et al. (2021) delivered 40 Hz rTMS over the angular gyrus of AD patients and through a variety of techniques and analysis (e.g., resting state EEG, MRI, power spectral density analysis, long-range functional integration analysis, dynamic connectivity analysis of TMS-EEG) indicated entrainment of gamma-band oscillations in the left posterior temporoparietal regions. The same results have been observed in healthy participants and epilepsy patients, where 40 Hz audiovisual stimulation increased gamma-rhythm oscillations which were found to be increasing over time (Suk et al., 2020). Whether our developed gamma-band rTMS protocol can entrain gamma brain waves remains to be seen.

6.1.1 Significance of the Results, Limitations and Future Directions

This study provides preliminary evidence about the efficacy of the specific 40 Hz rTMS protocol in inducing long-lasting effects in cortical excitability. By using the specific petameters cortical excitability can be suppressed for up to 45′ minutes. An important limitation of this study is that brain wave activity was not evaluated before and post stimulation, therefore, the effects on gamma-rhythms are unspecified. This is important issue that needs to be addressed as if the stimulation can induce gamma wave supersession, then it could be a useful technique in neurorehabilitation of diseases characterized by increased gamma brain activity (e.g., May et al., 2019; Mussigmann et al., 2021). On the contrary, if the underling suppressive effect can still entrain gamma brain activity, as has already been observed in previous studies (e.g., Liu et al., 2021), then this protocol might be used safely in diseases in which gamma-rhythms are known to be disrupted (e.g., Traikapi & Konstantinou, 2021; Wang et al., 2017). Future research needs to investigate the effects of this 40 Hz rTMS protocol on gamma brain activity as well as the connection between the observed suppressive effect with known neuronal mechanisms such as long term depression. Further, the addition of a sham stimulation

condition in future replication studies will be beneficial to improve the accuracy of our findings.

6.2 Normative Studies and Test Development

Chapter 3 presented the normative studies conducted in this thesis. As described in detail in Chapter 4, to investigate the effects of 40 Hz rTMS through a single case design study in aMCI and AD patients, repeated cognitive evaluations separated by only a few days were conducted for the assessment of primary and secondary outcomes. Repeated neuropsychological evaluations result to practice effects, that prevent identifying whether the noticed changes in test scores are attributable to the study's intervention, or to increased familiarity with the assessment tests (Wesnes & Pincock, 2002). To avoid misleading results in our study, alternative cognitive forms were created for each neuropsychological test, before the beginning of the single-case design study.

For the development of the necessary neuropsychological material, initially two Cypriot dialect-based corpora were created. Subsequently, the CWP, a list of approximately 2,850 words (selected from the Cypriot dialect-based corpora), was created. Normative data were collected for the included in the CWP words for the three most important words' characteristics, namely (1) frequency, (2) imageability, and (3) concreteness. The CWP was used as a reference for selecting stimuli during the alternative forms development. The ADAS-cog was translated in Greek and adapted for the Greek-Cypriot population and two alternative and equal in difficulty forms were created. Finally, 17 alternative forms were created for the neuropsychological tests that were used to evaluate primary and secondary outcomes during the multiple baseline study.

6.2.1 Cypriot Dialect-Based Corpora

The lack of standardized word lists built upon the Cypriot dialect was a major obstacle for the development of cognitive tests targeting Greek-Cypriot participants. The aim of this study was to overcome this obstacle by developing Cypriot dialect-based databases accompanied by words' frequency measures. Word frequency is among the most important variables in experimental psychology in general, and in memory research, in particular (Brysbaert et al., 2011), as it affects the accuracy and speed with which each

word can be recognized and recalled (Balota et al., 2004; Hulme et al., 2003; Roodenrys et al., 1994; Whaley, 1978). Two corpora were created, the NEWSLEX-CY and the DIALEX-CY. Both corpora include frequency measures calculated for the most well established standardized indices: (1) frequency per million words, (2) occurrence per million words, and (3) the Zipf scale. The three alternative frequency estimators provide researchers with the opportunity to decide which one best fits their needs.

The NEWSLEX-CY database was created from the analysis of the electronic forms of the Cypriot newspapers and magazines. In the absence of other electronic materials (e.g., subtitles or open access Cypriot books) the news and magazines were found to represent the only available recourses to extract language materials that Greek-Cypriots are exposed to. The advantage of this corpus is that it includes more than 10,000,000 tokens, which is of paramount importance for the extraction of reliable word frequency statistics. However, Cypriot journalists write mostly in standard Greek, and even though the audience is Greek-Cypriots, the language might not be representative of the dialect as it is spoken in everyday life. This raises the concern of whether the NEWSLEX-CY can be used reliably with Greek-Cypriot participants. As Brysbaert and New (2009) have suggested, newspapers are a valuable source to be used to extract reliable language materials. People are exposed to the news, and therefore it is expected that they are familiar with the language. Importantly, newspapers include general columns, such as cooking or traveling, where the language is less formal, and dialect representative words are used. For instance, the words *αιγινό; αγρινό; κουπέπια; αϊράνι; αναρή; αρτυσιά; αφέλια; βαζανάκι etc.,* which are used in the Cypriot dialect, were found in the corpus. Even if the NEWSLEX-CY is not entirely representative of the Cypriot dialect, provides reliable statistics for common words that Greek-Cypriots are exposed to and are using in their everyday communication.

The DIALEX-CY corpus was created with the aim to capture the non-formal language as it is used in both spoken and written expression of the Cypriot dialect. This database was created by the analysis of internet sources (personal blogs, discussion groups, websites) and by data collected by a survey. In the survey, 141 healthy participants were recruited and asked to recall as many words as they could from specific categories, similar to the categories where data from the internet sources were collected. The data collected from the internet sources and the survey were then used to develop the DIALEX-CY, which

was considered dialect representative. This process allowed as to develop an acceptable in length corpus for the calculation of frequency statistics.

The advantage of this corpus is that it captures the Cypriot dialect as it is used in everyday life. Words such as *αγρέλι; αγρινό; πιθκιάβλι; αθάσι; αίγα; αιγινό; ασημόκολλα; αυκωτές; λαψάνα; λίμπουρας; λουβί; κουφί; μοσχοκάρφι; κάλαθος; ρίγα* etc., which are used in the Cypriot dialect, were observed in the corpus. The major disadvantage of the DIALEX-CY is that it is comprised approximately by 1,100,000 tokens, which is close to the minimum required length for the extraction of reliable frequency statistics. It is well indicated that the size of the corpus plays a crucial role in the development of quality frequency measures, especially for the very low-frequency words (Brysbaert et al., 2011). However, the criteria under which the internet and verbal sources were selected during the corpus collection, were extremely strict to have only Cypriot-Greek based sources. Therefore, since every available electronic source related to our desired categories and every available discussion group has been included in the analysis, the generated corpus is believed to be representative of the words that are used when talking about these categories.

Another concern about the DIALEX-CY, is whether the merge of the internet sources with the verbally obtained data through the survey, affected the frequency statistics. Still, the investigation of the reliability of the frequency estimates (by comparing the calculated estimators for the words appearing in both corpora), indicated that the words were characterized as high, medium, or low frequency words in the same manner in both corpora. The selected words had common categorization according to not only the three levels of taxonomy (i.e., high, medium, low) but also according to the more strict six levels of taxonomy (i.e., high-high, high-low; medium-high, medium-low; low-high, low-low). This observation indicates that each word is represented similarly in both corpora, which provides comfort on the reliability of the calculated estimates.

It is important to note that both databases were created from the analysis of written material which might lead to potential bias in favor of those with higher educational level compromising the reliability of the estimated frequency statistics. Researchers and clinicians must consider these limitations when using the databases and frequency statistics.

Overall, this work provides researchers who work with Greek-Cypriot participants, with the necessary material to be used in cognitive and psycholinguistic research and set the basis for the development of Cypriot based standardized word pools.

Future Directions

Considering the above mentioned limitations of each corpora, the development of one Cypriot-based corpus, created by the analysis of materials based purely on Greek-Cypriot sources, such as poetry books, songs, or subtitles, will be of great importance for research and clinical application. This corpus will allow the extraction of frequency estimates that will reliably capture the frequency with which each word is used in the dialect. As the available sources are scarce for the creation of such a corpus (10,000,000-20,000,000 words are required for reliable estimators—eg., Brysbaert et al., 2011), development of norms for words' subjective frequency (i.e., the estimation of times that individuals come across a word in spoken and written language, e.g., Balota et al., 2001), could be a more feasible way to control this variable in research. It is important that future studies will be focused on further developing the NEWSLEX-CY and DIALEX-CY to achieve to the greatest possible extent, reliability of their context and provide researchers with a powerful tool for conducting cognitive research with Greek-Cypriot participants.

6.2.2 Cypriot Word Pool

The CWP was developed by selecting words from the NEWSLEX and DIALEX corpora, according to criteria that best suited the needs of this thesis (i.e., words that could be used as stimuli in the neuropsychological tests). Initially, 3,250 words were included in the pool and a normative study was conducted aiming to create subjective norms for imageability and concreteness. These variables are well known to affect one's ability to recognize and recall words (Stadthagen-Gonzalez & Davis, 2006). Seven hundred and forty nine healthy participants were recruited and participated either in the imageability or the concreteness normative study. Each participant was given a booklet with 250 words and was asked to rate each word in terms of its ability to arouse mental images (imageability study) or whether they think it was an abstract or concrete word (concreteness study).

The adopted methodology was rigorous, to ensure the creation of reliable norms and was guided by similar well-known normative studies (Friendly et al., 1982; Soares et al., 2017; Scott et al., 2019). This strict methodology allowed us to deeply investigate participants' commitment in the study, as the completion of the questionnaire/booklet was demanding; as such, the norms were created using only the responses of participants who truly engaged in the study. The analyses indicated high internal reliability and validity. Imagery norms were created for 2,852 words and concreteness norms for 2,844 words. These norms were considered reliable for use in the alternative forms' development. For both imagery and concreteness, the CWP provides values for (1) the mean rating of each item, (2) standard deviation, (3) median, and (4) number of participants who rated each item. Normative data were also collected for the objective variables of number of letters, number of syllables, and part of speech for the 2,850 words included in the pool. Overall, the CWP is a powerful tool for conducting cognitive research with Greek-Cypriot participants and provides subjective and objective normative data for 2.850 words.

Future Directions

The creation of the CWP was the first step towards the development of sensitive tools for research with Greek-Cypriot participants, as it provides normative data for frequency, imageability and concreteness estimates. However, there are other word properties that depend on the experiences that individuals have with the use of each word in their language, and they also affect the accuracy and speed with which they can be recognized and recalled (Soares et al., 2017). These among others are *subjective frequency* (i.e., the estimation of the number of times that individuals come across a word in spoken and written language—e.g., Balota et al., 2001) and *experiential familiarity* (i.e., the extent that individuals know and use the words in their everyday life—e.g., Cordier & Le Ny, 2005). *Age of acquisition* is also one of the most important variables in word recognition. Early-acquired words are processed more efficiently than late-acquired words, even when word frequency and word length are controlled for (Baayen et al., 2016; Brysbaert et al., 2016; Brysbaert & Biemiller, 2017; Johnston & Barry, 2007). Therefore, it is important that future studies will concentrate on the development of normative data for these variables. Then, the CWP would be a highly reliable tool in cognitive and psycholinguistic research, as well as in clinical practice in Cyprus.

6.2.3 Cypriot Alzheimer's Disease Assessment Scale-Cognitive Subscale

The ADAS-cog is considered the gold standard for the evaluation of antidementia treatment efficacy (Skinner et al., 2012), as it is the most widely used neuropsychological test in AD clinical trials (Ihl et al., 2012; Rabey & Dobronevsky, 2016; Rozzini et al., 2007). The aim of this study was to develop two alternative and equally difficult forms of the ADAS-cog-12 for the Greek-Cypriot population. This allowed us to minimize as much as possible the practice effect and truly investigate the rTMS effect on the patients' behavior. Moreover, the implementation of the ADAS-cog in our study allowed us to have results that are comparable with other relevant studies.

Two alternative forms for the word recall, naming, and word recognition were created (these subtests are known to be affected by repeated and close in time assessments; Mohs et al., 1997), and the complete tests were administered to healthy and demented participants at an interval of 2 weeks. The statistical analyses indicated that when the two forms were administered with at least a 2-week interval, there was no evidence of practice effect. Participants' total scores were identical in both forms. No significant differences were observed between the two forms in any specific subtest. Hence, the forms were considered reliable for use in the assessment of the primary outcomes of this thesis experimental work.

Significance of the Study

To our knowledge, this is the first attempt for the standardization of this valuable tool for the Greek-Cypriot population. Due to practice effects, use of the same form of the test more frequently that every six months, is not recommended (Mohs et al., 1997). Therefore, the significance of this study lies in providing AD researchers with two tests of similar psychometric properties to be used for the evaluation of an AD treatment efficacy (pre- and post-treatment), with an interval of less than six months. On that basis, misleading results that might stem from patients' increased familiarity can be significantly minimized, reducing therefore the likelihood of misinterpretation of clinical trials outcomes.

Limitations

An important limitation of this study is the small sample size. Even though the results indicated that neither healthy nor demented participants improved their performance in the second form, when administered with a time interval of two weeks from the first one, a larger sample size would allow additional certainty about the absence of practice effect. It is important to note that two improved versions of the ADAS-cog-12 have been created, the ADAS-cog-14 forms A′ and B′. These include improvements relating to the replacement of problematic stimuli (e.g., the word *coconut* was removed from the object naming task as it was observed that it was problematic to be found as well as to be carried by the investigators—in the naming task real objects are presented to participants). In addition, the cancelation and maze subtests were included to allow for more thorough patients' assessment both in clinical and research settings. This study is currently running for both the cognitive and non-cognitive subscales (ADAS-14-noncog).

6.2.4 Alternative Neuropsychological Test Forms

The aim of this study was the development of alternative forms of neuropsychological tests for the evaluation of the primary and secondary outcomes during the single-case design study. The standardized words from the CWP were used as reference and 17 alternative word learning lists, naming tasks, and semantic association tasks were created. For each stimulus that was used, 16 alternative stimuli with identical subjective and objective statistics were selected, during the forms development process. Consequently, each of the 17 alternative forms was created to have identical properties with the other 16. In addition, using an algorithm for the generation of random numbers, alternative forms were also created for the Corsi block-tapping task (forward subtest) and the Trail Making Tests A' and B'.

The use of alternative forms in repeated testing is a common practice in correcting for practice effects and it has been shown that even though they cannot completely eliminate these practice effects, they can significantly minimize them (Beglinger et al., 2005; Benedict & Zgaljardic, 1998; Watson et al., 1994; Zgaljardic & Benedict, 2001). Other potential methodological procedures for reducing the impact of practice effects in research settings have been proposed, such as the *prebaseline massed practice* approach. This method involves the intense practice (i.e., repeated administration of the tests) before the introduction of any independent variables. However, numerous administrations might be needed before establishing a baseline score in which the practice effect will have been

minimized (McCaffrey & Westervelt, 1995). In the case of our study, the adopted design already involved several evaluations within a small period of time, making each patient's schedule exhausting both for the families and participants. In addition, the participation of MCI patients raised concerns about a possible ceiling effect associated with intense practice, that could prevent further improvement in performance as a result of the treatment (Goldberg et al., 2015). Other approaches to attenuate practice effects have been proposed, such as the reliable change index and the use of control groups (Goldberg et al., 2015). Even though each of these methods have their own strengths, they are both dependent on untreated cases and therefore require larger sample size, which in our study was not feasible.

Limitations and Future Directions

The major limitation of this study is that the created alternative forms were not administered to healthy population to establish that all forms had a similar level of difficulty. Therefore, even though several objective and subjective variables relating to the selected stimuli (i.e., words) were considered when developing the forms, there are still no data to confirm that none of the forms is easier or more difficult from the others.

The evaluation of cognitive domains, such as verbal and visual memory, attention, and semantic knowledge (cognitive domains that these tests evaluate), is common in research. Hence, these forms could be used for the creation of a database to be used by researchers who work with Greek-Cypriot participants. Accordingly, future work could be focused on establishing the difficulty levels of these forms. This will be an important step for the implementation of single-case design studies in Cyprus, which will allow the evidence-based investigation of scientific questions, when a large sample size is not feasible or available.

6.3 Effects of 40 Hz rTMS in aMCI and AD

Chapters 4 and 5 presented the results of a single experimental design study aiming to investigate whether gamma-band magnetic stimulation, delivered bilaterally for 10 days to the precuneus, improves cognitive function in patients with aMCI and mild-to-moderate probable AD. The hypothesis was that 40 Hz precuneus stimulation for 10 days would lead to alleviation of patients' cognitive dysfunction. The efficacy of the gamma

stimulation was evaluated by the analysis of the single-case data, by neuropsychological evaluations, and through the adapted to the Greek–Cypriot population ADAS-cog-12, immediately after the end of the stimulation and 3 months post-stimulation. Moreover, to deeply capture the treatment's effect on the patients' function, qualitative data were obtained through patient and caregiver interviews. Results indicated that gamma stimulation had a wide effect on patients' cognitive and emotional function, which was evident immediately after the end of the intervention and was sustained for up to 3 months post-treatment. Importantly, gamma stimulation was found safe, and none of the participants reported side effects.

6.3.1 Feasibility of Gamma Magnetic Stimulation

The aim of this study was to investigate the safety, tolerability, and feasibility of exposure to five daily sessions of 40 Hz rTMS and 10 sessions in total, with an interval of 2 days (i.e., Monday to Friday: investigation of safety, tolerability, and feasibility; two days with no stimulation and then exposure to five more sessions: investigation of safety, tolerability, and feasibility). The study provided evidence that the specific 40 Hz rTMS protocol was well tolerated, safe, and feasible. All patients, regardless of their AD stage, adhered excellently to magnetic stimulation for 2 consecutive weeks. The stimulation was rated as painless and well tolerable. No severe or even mild adverse events related to magnetic stimulation were reported.

Recent evidence has demonstrated that gamma light and sound stimulation can drive gamma neuronal activity in several brain areas and decrease the accumulated amyloid and tau pathology in mice models of AD. Furthermore, these changes coincide with the transformation of glial cells, the primary immune cells of the brain, and cognitive improvements (Adaikkan et al., 2019; Iaccarino et al., 2016; Martorell et al., 2019; Singer et al., 2018). These findings led to the development of the new and pioneering approach, which targets gamma oscillations as a potential disease-modifying intervention in AD. Although the feasibility of gamma sensory stimulation has been previously investigated (He et al., 2021), determining whether such a high-frequency stimulation is safe, tolerable, and feasible in AD human patients, through other non-invasive stimulation techniques, is required to advance new gamma-based therapeutic approaches for AD. The current findings strongly support safety, tolerability, and feasibility of the applied protocol, to perform daily over five consecutive days, or 10 days with a small interval, as

a potential intervention for aMCI and AD. Patients were compliant during the study, and the absence of any adverse events is quite reassuring about its safety. Accordingly, this protocol can serve as a basis for an even more aggressive protocol to be developed (e.g., increasing the number of applied trains or decreasing the inter-train intervals) and investigating whether it could maximize the outcome on patients' cognition and everyday function.

To the best of our knowledge, this is only the second study to provide evidence about 40 Hz rTMS feasibility. Liu et al. (2021) delivered 40 Hz rTMS over the bilateral angular gyrus of patients with probable AD and found that the intervention was safe when applied three times a week for up to 4 consecutive weeks. That study, along with the results of the present thesis, addresses potential concerns about gamma-band magnetic stimulation and provides the foundation to further advance this newly developed approach.

6.3.2 Effects of 40 Hz Magnetic Stimulation in Patients with aMCI – Summary of Results

A noteworthy observation is that the single-case data obtained throughout the baseline phases presented great variability, making the visual inspection and detection of the treatment effect difficult. Stability during the baseline phases is a crucial criterion in single-case designs, as it allows for the separation of intervention effects from those of maturation, experience, learning, and practice (Lobo et al., 2017). In addition, a stable performance at baseline, with a minor or no trend, allows the comparison with a new pattern of behavior following intervention (Kratochwill et al., 2010). The implementation of sensitivity analysis (i.e., the calculation of different effect size indices) allowed the in-depth observation of the obtained single-case data without failing to indicate the effect due to instability (e.g., the PND index is highly affected by outliers, while the PEM uses a baseline median and is thus less affected by outliers and more suitable for unstable performance at the baseline; Alresheed et al., 2013). Therefore, even in the absence of stability within or between phases, the implementation of effect size indices made the comparison across phases achievable.

Regarding patients' episodic memory performance, the analysis of the obtained single-case data from the baseline to treatment phases indicated that both aMCI patients improved their immediate word recall by approximately 11% after the intervention. The

effect, however, was not significant. An immediate effect was found on both patients' delayed word recall. The effect was moderate in the first patient, observable by the PEM, while a highly effective and statistically significant effect was observed in the second patient, evidenced by both the PEM and NAP indices. The greatest treatment effect, which was statistically significant in both patients, was found in TMT A′, indicating improvements in patients' psychomotor speed, visual search abilities, and attention. Moreover, both patients improved in TMT B′, where the effect was moderate for the first patient and high and statistically significant for the second, indicating improvements in their executive functions. Finally, the treatment was found highly effective and statistically significant in the naming ability of the second patient. No treatment effects were found on patients' recognition, visual memory, or semantic associations.

The results demonstrated an effective immediate treatment effect in both patients' ADAS-cog scores, which was maintained and further improved at 3 months post-treatment. This rate of improvement suggests an effective and lasting treatment effect (Schrag & Schott, 2012). The data from the neuropsychological evaluations suggest that gamma-band stimulation had a wide effect on both patients' cognitive and emotional functions. With the exception of episodic memory, the patients presented identical improvement profiles. Regarding episodic memory, the first patient recalled immediately one more item in relation to pretreatment but recalled one less item at delayed recall. The effect was high on the second patient, who recalled four more items immediately and two more items after an interval of 25 minutes, in relation to pretreatment. Both patients presented improvements in their recognition ability, an observation which was also evident in their ADAS-cog performance. As observed in the single-case data, the patients significantly improved in TMT A′ and B′. A remarkable observation, which was identical in both patients, was reductions by an average of 43% of their depressive symptomatology, reductions by an average of 51% of their anxiety symptoms, and accordingly, a reduction of nearly 70% of their neuropsychiatric symptoms.

The first patient reported more positive improvements regarding their quality of life, rating most of the aspects of their life as excellent at post-treatment. The caregiver also reported significant improvements. The second patient rated a slight improvement in their quality of life, a rating that was greater than that observed by their caregiver. Finally, a treatment effect was reported by both the patients and their families, who reported observable changes in their behavior and mood after treatment.

6.3.3 Effects of 40 Hz Magnetic Stimulation in Patients with Probable AD - Summary of the Results

As observed with the aMCI patients, single-case data obtained throughout the baseline phases presented great variability, making the visual inspection and detection of the treatment effect difficult. The effect size and PCI indices were used to evaluate possible changes from baseline to treatment phases. Accordingly, even in the absence of stability, improved immediate recall was observed for four participants in the increased mean level, PCI, and NAP indices. Specifically, on average, the four patients improved their immediate recall by 40% after the end of treatment. The effect was moderate in two patients and high in the other two. The NAP indicated a significant effect on one of the patients. A visual inspection of the graphed data indicated a treatment effect in four patients, while Patient 4 did not present any improvement. In the same manner, the single-case data provided evidence of improvements in patients' attention skills as evaluated by TMT A′. Specifically, PND scores indicated statistically significant treatment effects in three patients. The NAP estimator provided evidence of a significant treatment effect in two of the five patients. Despite not being statistically significant in all the patients, the treatment effect was visually evident on the graphed data in four out of the five patients. Again, Patient 4 did not present improvements.

Furthermore, the results demonstrated an immediate, effective treatment effect in all patients' ADAS-cog scores, which was further maintained and improved at 3 months post-treatment. Four patients presented improvements in MMSE scores immediately after the end of treatment, which were maintained and further improved 3 months post-treatment in three patients.

The neuropsychological data indicated that at 3 months post-treatment, gamma rTMS intervention induced a 75% improvement on average in the immediately recalled items in the logical memory test. At the same time, on average, 0.5 more items were recalled after an interval of 25 minutes. Patients' attention improvement was also evident in the neuropsychological evaluation, as indicated by time reductions in the TMS A′ in four of the patients. On average, four patients improved their performance by 20%. Finally, gamma rTMS improved patients' phonemic verbal fluency (an average improvement of 22%) and led to anxiety, depressive, and neuropsychiatric symptom alleviation. Overall,

the results of the study show a wide and long-lasting positive effect of precuneus gamma stimulation on AD patients' cognitive function.

Regarding patients' self-reported quality of life, an overall improvement of 21% was evident, indicating that the patients perceived an improvement in their functioning after treatment. The patients' caregivers reported improvements, albeit of a smaller magnitude. The qualitative data obtained through the interviews indicated that both patients and caregivers observed behavioral changes after treatment. The changes were related mostly with depressive symptomatology alleviation and in general with improvements in mood. Two patients reported improvements in their memory, while one caregiver reported a halt in the rate of their mother's cognitive decline. One caregiver reported no observed difference after the treatment.

A noteworthy observation was the response of Patient 4 in the TMS treatment in comparison with the other four patients. Specifically, Patient 4 presented limited signs of improvement in both the neuropsychological evaluations and the assessments during the single-case phases. As Patient 4 had similar clinical characteristics to the other four AD patients, a possible explanation is that the TMS protocol was applied at a lower intensity in this patient (i.e., 65% of the maximal machine output—80% of their RMT). It is possible that the stimulation was not strong enough to stimulate the precuneus at the same extent as for the other three patients. This observation raises a concern, given the absence of universal golden standard protocols in the application of TMS for neurorehabilitation, even small deviations in some parameters may have significant impacts on the therapy's effectiveness.

6.3.4 Overall Treatment Effect in aMCI and AD Patients

As previously indicated by the single-case analysis and the neuropsychological data, a statistically significant overall treatment effect was found in both cognitive and psychiatric variables. Specifically, statistically significant improvements 3 months after the 40 Hz rTMS were observed in the patients' (1) attentional and psychomotor speed (i.e., TMT A′); (2) immediate story recall; (3) depressive symptomatology; (4) neuropsychiatric symptomatology; and (5) quality of life, as rated by both the patients and their caregivers. In the same manner, the patients' global cognition was significantly improved immediately after the end of treatment and remained statistically significant 3

months post-treatment. The treatment effect was large in all aforementioned variables, with only the effect on the MMSE and ADAS-cog (pretreatment in comparison with follow-up) measured as medium.

6.3.5 Interpretation of Findings

The results of this thesis have provided significant preliminary evidence demonstrating that 40 Hz precuneus rTMS might be an effective and side effect-free intervention in the neurorehabilitation of aMCI and AD. The rTMS improved all patients' global cognition, which was maintained for at least 3 months post-treatment. The ADAS-cog is the gold standard for the evaluation of antidementia interventions and has been widely used in clinical trials (e.g., Andrade et al., 2018; Bentwich et al., 2011b; Seltzer et al., 2004; Solomon et al., 1996). The observed magnitude of improvement, a reduction of 5.7 points immediately after the end of treatment and 6.1 points 3 months post-treatment, is an improvement that signifies a clinically relevant change, and it is associated with one stage of change on the clinical dementia rating-global (CDR; Schrag & Schott, 2012).

The results of this study are in accordance with Liu et al. (2021), who found that 40 Hz rTMS over the bilateral angular gyrus of patients with probable AD led to an average reduction of 5 points on the ADAS-cog immediately after the end of 12 sessions. This improvement was maintained and slightly further improved 8 weeks post-treatment. Importantly, these findings were not observed in the patients who received sham stimulation, indicating that gamma angular gyrus magnetic stimulation was able to alleviate and sustain the patients' cognitive decline. It is worth noting that the observed reduction in the ADAS-cog, as reported by these two gamma-band rTMS studies, is larger than that reported for a recently accepted drug for AD. Specifically, the drug lecanemab (brand name Leqembi)—a humanized IgG1 monoclonal antibody treatment that intends to tackle the root of the disease and slow cognitive decline—which was recently approved by the U.S. Food and Drug Administration (FDA), has resulted in pathology decrease, which in turn, led to a reduction of 1.44 in the ADAS-cog after 18 months of treatment (van Dyck et al., 2023). However, due to reported complications in patients who received the treatment, whether the benefit is worth the risk is currently under discussion (Reardon, 2023).

Regarding the effect of the approved medications for AD on patients' cognitive function, in a randomized control trial, the effect of donepezil treatment on patients with MCI was evaluated. The patients who received donepezil for 6 weeks presented small but significant improvements in their ADAS-cog performance. However, 18.4% of the participants were withdrawn from treatment due to adverse side effects (Doody et al., 2009). Imbimbo et al. (2000) implemented a 6-month, double blind, placebo-controlled trial to investigate the effect of eptastigmine—a centrally acting cholinesterase inhibitor drug—in mild-to-moderate AD. They found that in relation to placebo, patients who received the drug presented a reduction of 1.56 points on the ADAS-cog. The effect has been slightly higher in clinical trials with other cholinesterase inhibitors, such as tactrine (Knapp et al., 1994; Solomon et al., 1996), donepezil (Rogers et al., 1998; Seltzer et al., 2004), and other drugs such as memantine and rivastigmine (for a review see Li et al., 2019). The reported adverse effects in these studies ranged from nausea, vomiting, diarrhea, anxiety, and depression (50% of patients in Imbimbo et al., 2000 suffered from one or more symptoms) to liver transaminase elevation (28% of patients in Knapp et al., 1994).

Considering the small efficacy of the approved treatment for AD (i.e., cholinergic, and glutamatergic drugs), observed severe adverse side effects, and general absence of a disease-modifying treatment (Anderson et al., 2017; Cummings et al., 2014; Kim et al., 2022; Yaari & Hake, 2015; Yiannopoulou et al., 2019), the need for identifying non-pharmacological, safe, and at the same time effective techniques in the rehabilitation of MCI and AD is paramount. Gamma-band stimulation is a novel approach whose potential therapeutic role and disease-modifying effect is being investigating, with preliminary evidence to provide support for its efficacy (e.g., Liu et al., 2021; Chan et al., 2021). The results of this study, along with Liu et al. (2021), support the effect of gamma-band rTMS in alleviating and maintaining patients' cognitive decline. To our best knowledge, no other gamma-band magnetic stimulation studies have been done; however, the beneficial effect of rTMS has been demonstrated at other frequencies. For instance, Rabey and Dobronevsky (2016) reported an ADAS-cog reduction of 2.4 points after 6 weeks of 10 Hz rTMS combined with cognitive training. In the same manner, Nguyen et al. (2017) reported a reduction of 2.9 points in the ADAS-cog of patients with probable AD, after a combination of cognitive training and 10 Hz rTMS over six brain areas thought to be dysfunctional in AD, for a 5-week period.

It is evident that TMS has the potential to improve patients' cognitive function, with the 40 Hz protocols reporting the utmost effect. An interesting question still to be addressed is whether the reported significant effects on patients' cognitive function result from disease pathology reduction or are the consequence of the alleviation of depressive symptomatology. In any case, as several clinical trials have suggested that conventional antidepressants are ineffective for the treatment of AD-related depression (Cassano et al., 2019; Insel & Wang, 2009; Pomara & Sidtis, 2007; Sepehry et al., 2012)—it has even been called a *treatment-resistant depressive disorder* (Lozupone et al., 2018)—improvements in this symptomology can be considered a step forward.

6.3.6 Does Gamma-Band rTMS Alleviate AD Neuropathology or Just Improve Depression?

The results of this study indicated that 40 Hz rTMS significantly alleviated patients' depressive and neuropsychiatric symptomatology, an observation apparent in all patients. Although not significant, a reduction of patients' anxiety symptoms was also observed. Depression and anxiety are prominent neuropsychiatric features of AD (Galts et al., 2019; Kaiser et al., 2014; Zhao et al., 2016). In MCI, the presence of depression and anxiety represent risk factors for cognitive decline and progression to dementia and have also been linked to functional decline in daily activities (Ma, 2020). The pathogenic mechanisms underlying depression in the early stages of AD represent an emotional reaction to the progressive cognitive decline, and anxiety can appear as an initial compensating behavior. In these stages, the symptoms are more intense, as the disease has a major impact on patients' functioning (Botto et al., 2022). At the same time, even from the MCI, anxiety has been associated with positive amyloid scans, mesial temporal changes with atrophy and hypometabolism in the entorhinal region (Mendez, 2021). Several biological factors have been suggested as causes in the later stages, such as cortical and limbic atrophy, lower resting cortical metabolism, and the overall neurodegeneration of areas and circuits dealing with emotions (Botto et al., 2022). The question of whether gamma-band stimulation has a disease-modifying effect or simply leads to alleviation of neuropsychiatric symptoms—and therefore the observed cognitive improvement is a consequence of the improved mood—must be addressed.

While the exact mechanisms underlying TMS-induced cognitive changes in the patients' function were not investigated in this thesis, recent evidence suggests that gamma stimulation through TMS has the potential to modify the observed neuropathology of AD. Specifically, Liu et al. (2021) found that 12 sessions of 40 Hz angular gyrus rTMS modulated the affected gamma-band oscillations in the left posterior temporoparietal region. Furthermore, the stimulation prevented gray matter volume loss; enhanced local functional integration within the bilateral angular gyrus, as well as global functional integration in the bilateral angular gyrus and left middle frontal gyrus; strengthened information flow from the left posterior temporoparietal region to the frontal areas; and strengthened the dynamic connectivity between anterior and posterior brain regions. The authors suggested that the administered gamma-band rTMS protocol led to the modulation of gamma-band oscillations, which effectively improved patients' cognition by promoting local, long-range, and dynamic connectivity within the brain.

Similar findings have been reported recently by He and colleagues (2021), who investigated the efficacy of audiovisual 40 Hz stimulation in AD patients. In this study, 8 weeks of flicker stimulation significantly increased default mode network's functional connectivity and led to changes in the patients' immune profile in CSF, which showed trends toward the down regulation of immune factors, suggesting an engagement of the neuroimmune system after exposure to audiovisual stimulation. Similarly, Chan et al. (2022) demonstrated that AD patients who received 3 months of daily 40 Hz audiovisual stimulation presented (1) lesser ventricular dilation and hippocampal atrophy, (2) increased functional connectivity in the DMN as well as with the medial visual network, (3) better performance on the face–name association delayed-recall test, and (4) improved measures of daily activity rhythmicity compared to those who received sham stimulation.

It is evident that gamma entrainment therapy studies have provided evidence suggesting that the modulation of gamma brain activity may have the potential to reduce hippocampal atrophy; improve gamma brain activity and functional connectivity; and promote local, long-range, and dynamic connectivity, leading to alleviation of cognitive dysfunction in AD patients. This evidence provides support for the notion that the observed improvements in patients' cognitive functions are a consequence of the underling pathology mitigation and not merely the consequence of mood enhancement.

Regarding the improvements in patients' neuropsychiatric symptoms, a possible underling mechanism is the enhancement of functional connectivity of the DMN. Functional studies of the neural networks identified in the brain's resting state and its relationship with neuropsychiatric disorders have been growing over the last decade. Among the resting state networks, the DMN has gained particular attention due to its involvement in self-referential processes, often affected in conditions such as depression and anxiety (Beauregard et al., 2006). It has been recognized that major depression and anxiety are associated with altered functional connectivity in the DMN (Beauregard et al., 2006; Coutinho et al., 2016; Liao et al., 2010; Wise et al., 2017; Zhao et al., 2007; Zhu et al., 2012). The observed changes transcend connectivity strength alterations and extend to reduced connectivity stability within key DMN nodes, such as the mPFC and PCC (Wise et al., 2017). As previous gamma-band brain stimulation studies indicated enhancement in the patients' DMN (Chan et al., 2022; Liu et al., 2022; He et al., 2021), the hypothesis is that precuneus (a key node of the DMN) gamma stimulation may reinforce or even stabilize functional connectivity in the DMN, thus strengthening dynamic connectivity between other important nodes of the network. Even though this mechanism could provide an explanation regarding neuropsychiatric symptomatology alleviation, evidence from functional studies is needed to investigate the effect of gamma-band stimulation in the DMN.

6.3.7 Study Limitations

This study was subject to some limitations. First, the clinical diagnosis of MCI and AD was not supported using well-known biomarkers, making the diagnosis of the disease in the enrolled participants uncertain. Second, while alternative forms of equal difficulty were developed for patients' assessments during the baseline and treatment phases, the exact level of difficulty was not assessed. Therefore, it is possible that patients' performance was affected by some difficulty deviations. However, the alternative forms of ADAS-cog used were adapted, and their equality in difficulty had been examined and established before the study. Third, the obtained single-case data failed to establish stable patient performance during the baseline conditions, making the comparison between phases uncertain. With this possibility in mind, the study's protocol involved neuropsychological evaluations, with a relatively acceptable interval between them. Furthermore, the variability of patients' severity together with the lack of sham

stimulation condition, prevent the extraction of safe conclusions regarding the effects of the intervention on each stage and further limit the generalization of the results. Finally, neuroimaging techniques were not employed post-treatment to detect the underling neurophysiological changes caused by the TMS treatment. Therefore, there is no evidence to support any brain physiological changes caused by the stimulation, and hence, the extent to which the observed cognitive improvements were affected by factors such as practice effect or anxiety and/or psychiatric symptom alleviation cannot be determined. Despite these limitations, the findings support a positive effect of 40 Hz TMS over the precuneus on AD patients' cognitive function.

6.3.8 Future Directions

Gamma-band transcranial magnetic stimulation has been only recently introduced in neurorehabilitation on MCI and AD. Preliminary evidence supports its efficacy in modifying the underling pathology and improving patients' cognitive function and psychiatric symptomatology. However, well-designed randomized clinical trials with large samples are needed to advance this new gamma-based therapeutic approach and establish its efficacy in MCI and AD. It is important for future studies to focus on the earliest stage of AD (i.e., MCI and early AD), as the clinical significance of 40 Hz TMS seems to be more beneficial at these stages. As concerns about feasibility, safety, and tolerability have been addressed, it would be important to investigate whether new modified protocols could maximize the outcome. The protocol modifications could involve an increase in the total applied pulses, higher intensity, or even the stimulation of more than one brain region, such as the precuneus and angular gyrus, simultaneously. At the same time, the effects of these protocols on the accumulated pathology must be investigated and established. Another important question that must be addressed in future studies is whether gamma-band stimulation in key nodes of the default mode network can modify the observed alterations on its functional connectivity to improve depression and anxiety symptoms in AD, symptoms that are resistant to conventional antidepressants.

6.4 Conclusion

Neurophysiological, normative, and experimental studies were conducted in this thesis. A 40 Hz rTMS protocol was developed and its neurophysiological effects, when applied

on the motor cortex of healthy participants, were evaluated. This study provided evidence that the application of the specific protocol is feasible, safe, well-tolerated and can induce long-lasting effects on neural plasticity. Specifically, the stimulation found to induce suppression on cortical excitability for up to 45 minutes. This study was the first to investigate the consequences of 40 Hz stimulation, through non-invasive transcranial magnetic stimulation, on neuronal excitability on the human motor cortex.

Normative studies were conducted aiming to develop alternative and equally difficult neuropsychological tests for the Greek-Cypriot population. These studies led to the creation of the first standardized Cypriot word pool, a list of 2,850 words, a valuable tool for conducting research with Greek-Cypriot participants. The ADAS-cog-12, the gold standard neuropsychological test for assessing the effectiveness of AD interventions, was adapted for the Greek-Cypriots and two equally difficult alternative forms were developed. Therefore, this study provides AD researchers with two alternative forms of similar psychometric properties to be used for the evaluation of AD interventions. On that basis, misleading results that might stem from patients' increased familiarity can be significantly minimized, reducing therefore the likelihood of misinterpretation of clinical trials outcomes. Finally, alternative forms were created for some of the most widely used neuropsychological tests, such as the word learning list, naming, semantic associations, Corsi block-tapping test and trail making test A′ and B′. The evaluation of verbal and visual memory, semantic knowledge, attention, and executive functions (cognitive domains that the created forms evaluate) is common in cognitive research. Therefore, these forms could be used for the creation of a database to be used by researchers who work with Greek-Cypriot participants. This will be an important step for the implementation of single-case design studies in Cyprus, which will allow the evidence-based investigation of scientific questions with relatively small sample size.

The final aim of this thesis was to investigate the efficacy of 40 Hz transcranial magnetic stimulation, applied bilaterally to the precuneus, in mitigating cognitive dysfunction in aMCI and mild-to-moderate AD. The results provided preliminary evidence that gamma brain stimulation, through TMS, may have the potential to alleviate cognitive dysfunction in patients with aMCI and AD. Stimulating bilaterally the precuneus at 40 Hz, can improve patients' cognitive function and neuropsychiatric symptoms for up to 3 months.

Specifically, this study indicated a high and significant improvement in all patients' global cognition, regardless of disease stage. In addition, an identical profile of improvement was evident in patients' neuropsychiatric symptoms. In general, a wide effect on patients' cognitive function was observed in both the aMCI the AD patients that was accompanied by significant improvements in their quality of life, as rated by both the patients and their caregivers. These results align with previous studies reporting patients' improvements in global cognition, but we further investigated in more depth the effects on patients' cognitive function, which indicated a wider positive effect. The results of this thesis reinforce the evidence that TMS at gamma frequency is safe and tolerable and provide further evidence and support of the view that TMS could represent a promising and effective non-pharmacological intervention for improving cognitive impairment in AD. In conclusion, this study offers preliminary evidence regarding the efficacy of gamma-band TMS as an effective non-invasive technique in MCI and AD neurorehabilitation.

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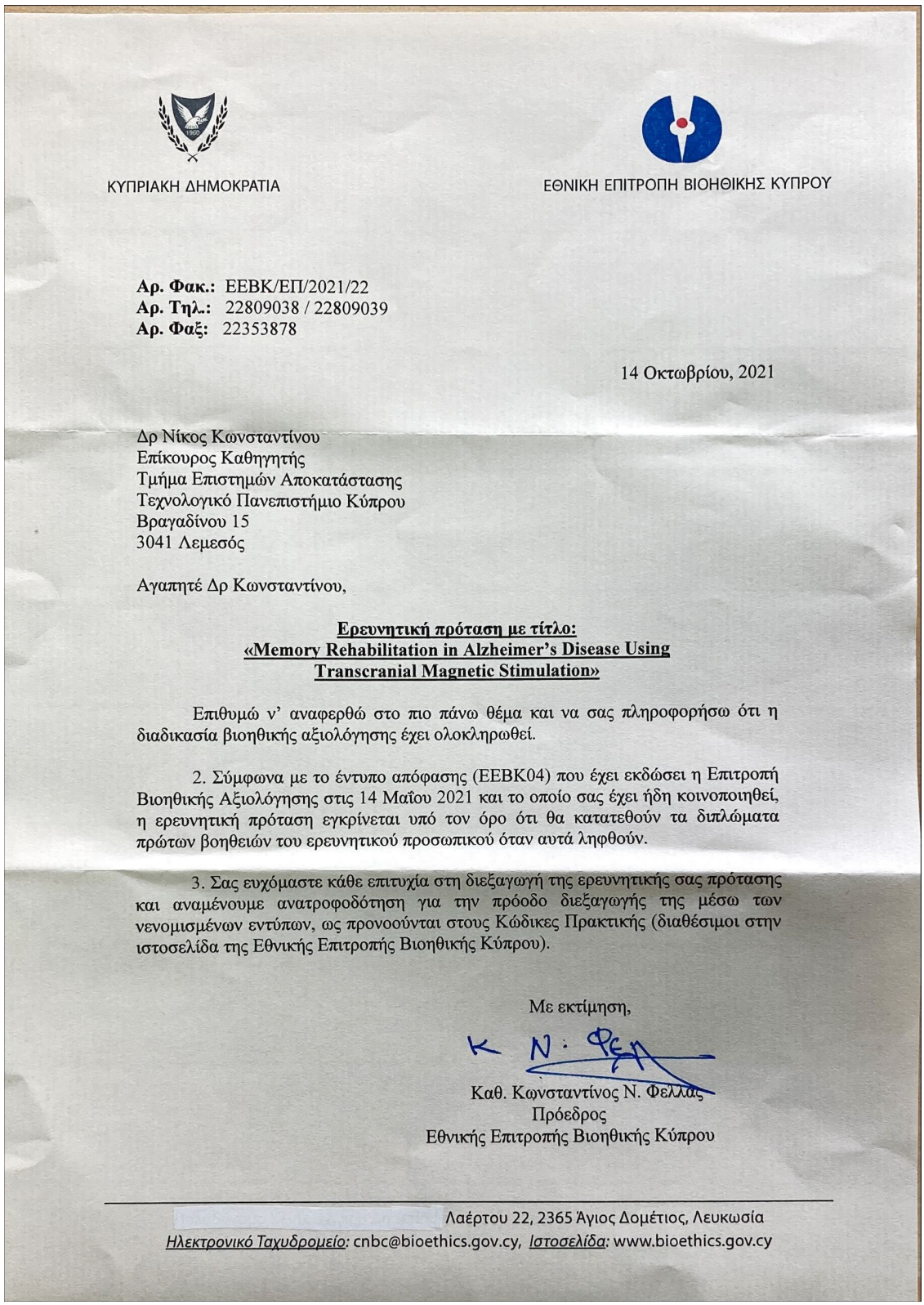
Appendix 1: Ethical Committee Approval

The approval involves the study described in chapter 2, the study for the development of the Cypriot word pool which described in chapter 4 and the primary investigation of this thesis that described in chapter 3.



ΚΥΠΡΙΑΚΗ ΔΗΜΟΚΡΑΤΙΑ

ΕΘΝΙΚΗ ΕΠΙΤΡΟΠΗ ΒΙΟΗΘΙΚΗΣ ΚΥΠΡΟΥ

Αρ. Φακ.: ΕΕΒΚ/ΕΠ/2021/22
Αρ. Τηλ.: 22809038 / 22809039
Αρ. Φαξ: 22353878

14 Οκτωβρίου, 2021

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Αγαπητέ Δρ Κωνσταντίνου,

Ερευνητική πρόταση με τίτλο:
«Memory Rehabilitation in Alzheimer's Disease Using Transcranial Magnetic Stimulation»

Επιθυμώ ν' αναφερθώ στο πιο πάνω θέμα και να σας πληροφορήσω ότι η διαδικασία βιοηθικής αξιολόγησης έχει ολοκληρωθεί.

2. Σύμφωνα με το έντυπο απόφασης (ΕΕΒΚ04) που έχει εκδώσει η Επιτροπή Βιοηθικής Αξιολόγησης στις 14 Μαΐου 2021 και το οποίο σας έχει ήδη κοινοποιηθεί, η ερευνητική πρόταση εγκρίνεται υπό τον όρο ότι θα κατατεθούν τα διπλώματα πρώτων βοηθειών του ερευνητικού προσωπικού όταν αυτά ληφθούν.

3. Σας ευχόμαστε κάθε επιτυχία στη διεξαγωγή της ερευνητικής σας πρότασης και αναμένουμε ανατροφοδότηση για την πρόοδο διεξαγωγής της μέσω των νενομισμένων εντύπων, ως προνοούνται στους Κώδικες Πρακτικής (διαθέσιμοι στην ιστοσελίδα της Εθνικής Επιτροπής Βιοηθικής Κύπρου).

Με εκτίμηση,

Καθ. Κωνσταντίνος Ν. Φελλάς
Πρόεδρος
Εθνικής Επιτροπής Βιοηθικής Κύπρου

Λαέρτου 22, 2365 Άγιος Δομέτιος, Λευκωσία
Ηλεκτρονικό Ταχυδρομείο: cnbc@bioethics.gov.cy, *Ιστοσελίδα:* www.bioethics.gov.cy

Appendix 2: Safety Screening for TMS Eligibility

ΕΝΤΥΠΟ ΑΝΙΧΝΕΥΤΙΚΟΥ ΕΛΕΓΧΟΥ ΓΙΑ ΔΙΑΚΡΑΝΙΑΚΗ ΜΑΓΝΗΤΙΚΗ ΔΙΕΓΕΡΣΗ (ΔΜΔ)

Παρακάτω είναι ένα ερωτηματολόγιο που χρησιμοποιείται για να καθορίσει αν οι πιθανοί συμμετέχοντες είναι κατάλληλοι για ΔΜΔ.

ΠΑΡΑΚΑΛΩ ΣΥΜΠΛΗΡΩΣΤΕ ΤΟ ΠΑΡΑΚΑΤΩ ΕΝΤΥΠΟ:

Δημογραφικά Στοιχεία

Ημερ. γέννησης: .....

Τόπος γέννησης: .....

Μητρική/ές γλώσσα/ες: Κυπριακή Άλλη

(ονομάστε την άλλη γλώσσα) .....

Μόρφωση: Δημοτικό / Γυμνάσιο / Λύκειο / Κολλέγιο /

Πανεπιστήμιο / Μεταπτυχιακό / Διδακτορικό

Άλλο: .....

Επάγγελμα: .....

Διεύθυνση: .....

.....

Τηλ. επικοινωνίας: .....

_____ _____

Υπογραφή Συμμετέχοντα Ημερομηνία

_____ _____

Υπογραφή Μάρτυρα Ημερομηνία

ΟΝΟΜΑ ΑΣΘΕΝΟΥΣ ή/και ΕΘΕΛΟΝΤΗ:

Παρακαλώ σημειώστε ό,τι ισχύει:

Νευρολογική ή Ψυχιατρική διαταραχή	ΝΑΙ	ΟΧΙ
Τραύμα στο κεφάλι	ΝΑΙ	ΟΧΙ
Εγκεφαλικό επεισόδιο	ΝΑΙ	ΟΧΙ
Χειρουργική επέμβαση στον εγκέφαλο	ΝΑΙ	ΟΧΙ
Μέταλλο ή μεταλλικά ρινίσματα στο κρανίο ή στα μάτια	ΝΑΙ	ΟΧΙ
Εγκεφαλική βλάβη	ΝΑΙ	ΟΧΙ
Βηματοδότη	ΝΑΙ	ΟΧΙ
Ιστορικό με σπασμούς ή/και επιληπτικές κρίσεις	ΝΑΙ	ΟΧΙ
Οικογενειακό ιστορικό επεισοδίων επιληψίας	ΝΑΙ	ΟΧΙ
Εμφυτευμένες ηλεκτρονικές συσκευές (π.χ. κοχλιακό εμφύτευμα)	ΝΑΙ	ΟΧΙ
Ενδοκρανιακές γραμμές	ΝΑΙ	ΟΧΙ
Σκλήρυνση κατά Πλάκας	ΝΑΙ	ΟΧΙ
Κατάθλιψη	ΝΑΙ	ΟΧΙ
Θεραπεία με Αντικαταθλιπτικά (π.χ. Αμιτρυπτιλήνη, Αλοπεριδόλη)	ΝΑΙ	ΟΧΙ
Εμφυτευμένη αντλία παροχής φαρμακευτικής αγωγής	ΝΑΙ	ΟΧΙ
Ενδοκρανιακή πάθηση	ΝΑΙ	ΟΧΙ
Αλφισμός (λευκοπάθεια)	ΝΑΙ	ΟΧΙ
Έντονο άγχος/ανησυχία	ΝΑΙ	ΟΧΙ
Κυοφορούσα αυτή την περίοδο	ΝΑΙ	ΟΧΙ
Χρόνιοι πονοκέφαλοι	ΝΑΙ	ΟΧΙ
Συχνές τάσεις λιποθυμίας	ΝΑΙ	ΟΧΙ
Έχετε πιει αλκοόλ τις τελευταίες 24 ώρες;	ΝΑΙ	ΟΧΙ
Έχετε κάνει χρήση ναρκωτικών ουσιών τον τελευταίο μήνα;	ΝΑΙ	ΟΧΙ
Είχατε ικανοποιητικό βραδινό ύπνο το βράδυ πριν το πείραμα;	ΝΑΙ	ΟΧΙ

Δηλώνω υπεύθυνα ότι όλες οι πληροφορίες που παρέχονται στο παρόν έντυπο ελέγχου ΔΜΔ είναι αληθείς και πλήρεις από κάθε άποψη.

_____ _____

Υπογραφή Συμμετέχοντα Ημερομηνία

_____ _____

Υπογραφή Μάρτυρα Ημερομηνία

Appendix 3: Research Flyer

Γνωρίζετε κάποιον με ήπια ή μέτρια συμπτώματα που οφείλονται στη

Νόσο Αλτσχάιμερ;

Αν ναι, το άτομο αυτό μπορεί να πληροί τα κριτήρια συμμετοχής σε κλινική έρευνα που διεξάγεται από το Τεχνολογικό Πανεπιστήμιο Κύπρου στη Λεμεσό.

Η έρευνα αποσκοπεί στη βελτίωση της νοητικής λειτουργίας των ασθενών μέσω Μη-Παρεμβατικής και Μη-Φαρμακευτικής Θεραπείας.

Η έρευνα αυτή έχει την έγκριση της Εθνικής Βιοηθικής Κύπρου (Αρ. Φακ.: ΕΕΒΚ/ΕΠ/2021/22)

Τεχνολογικό Πανεπιστήμιο Κύπρου

Brain and Cognitive Science Lab

Ενημερωθείτε για την έρευνα:
+357 99571290 & ag.traikapi@edu.cut.ac.cy

Appendix 4: Patients Screening Documents for the Single Case Data Collection 'Form 1'

Phase	Data Point Number	Subject Number	Examiner Initials	Examination Date
				Μέρα

CONFIDENTIAL

"Episodic Memory Effects of Precuneus Gamma Frequency Transcranial Magnetic Stimulation in Alzheimer's Disease: A Multiple Baseline Study"

Patients Screening Documents

Form 1

Word Learning List
(Immediate recall, delayed recall & recognition)

Trail Making Test A' & B'

Corsi Block Tapping test

Naming Test

Semantic Association Test Visuoperceptual

Semantic Association Test Verbal

Cyprus University of Technology

GFinADStudy

Phase	Data Point Number	Subject Number	Examiner Initials	Examination Date
				Μέρα Μήνας Έτος

Word Learning List
Recall

Λέξεις	1	2	3
ελιά			
απόγευμα			
αεροπλάνο			
καρπούζι			
σινί			
ακτή			
αλιγάτορας			
γραμματέας			
τζάκι			
γλάστρα			
γέφυρα			
μαχλέπι			
δίπλωμα			
εξάγωνο			
Total:			
Total of 3 trials:			
Total Intrusions:			

f1

GFinADStudy

Phase	Data Point Number	Subject Number	Examiner Initials	Examination Date
				Μέρα Μήνας Έτος

Word Learning List
Delayed Recall

Λέξεις	
ελιά	
απόγευμα	
αεροπλάνο	
καρπούζι	
σινί	
ακτή	
αλιγάτορας	
γραμματέας	
τζάκι	
γλάστρα	
γέφυρα	
μαχλέπι	
δίπλωμα	
εξάγωνο	
Total:	
Total Intrusions:	

f1

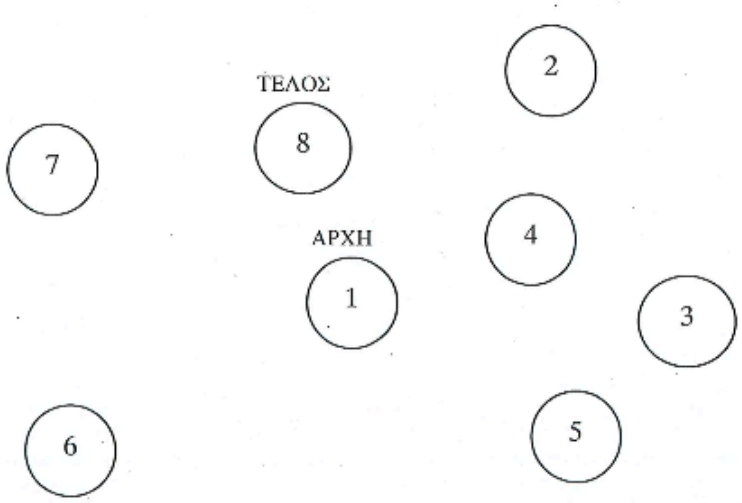
GFinADStudy

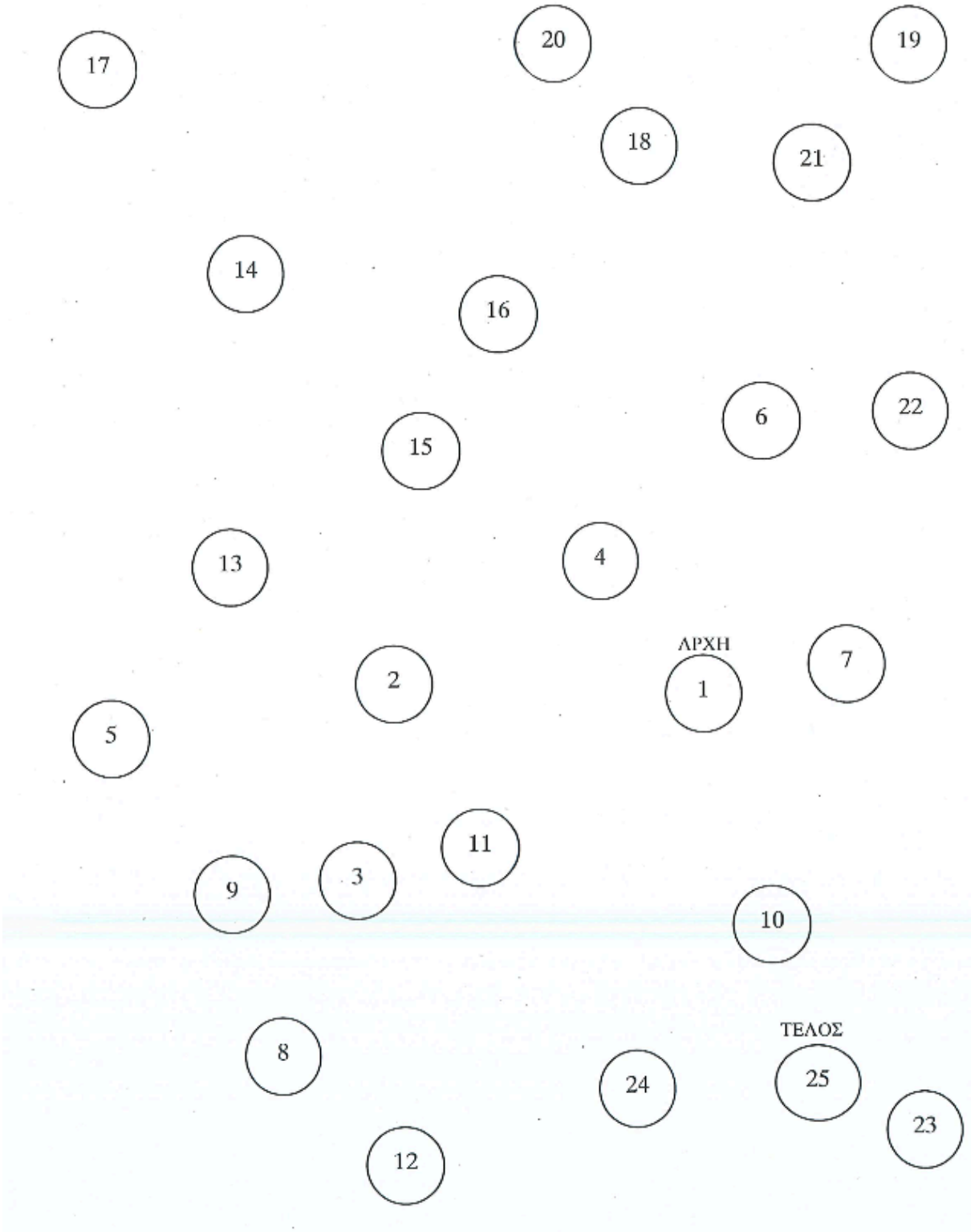
Phase	Data Point Number	Subject Number	Examiner Initials	Examination Date
				Μέρα Μήνας Έτος

Word Learning List
Recognition

	Λέξεις	ΝΑΙ	ΟΧΙ	Semantically related	Not related
1	**ελιά**				
2	ζυμάρι				
3	**απόγευμα**				
4	ερευνητής				
5	λεωφορείο				
6	αγγουράκι				
7	**αεροπλάνο**				
8	**καρπούζι**				
9	φλυτζάνι				
10	άμμος				
11	**σινί**				
12	βάτραχος				
13	αφρός				
14	**ακτή**				
15	**αλιγάτορας**				
16	καλάθι				
17	**γραμματέας**				
18	αρμάρι				
19	**τζάκι**				
20	λαβίδα				
21	σφηνάκι				
22	**γλάστρα**				
23	**γέφυρα**				
24	βρώμη				
25	μπεγλέρι				
26	**μαχλέπι**				
27	**δίπλωμα**				
28	**εξάγωνο**				
	Σύνολο:				

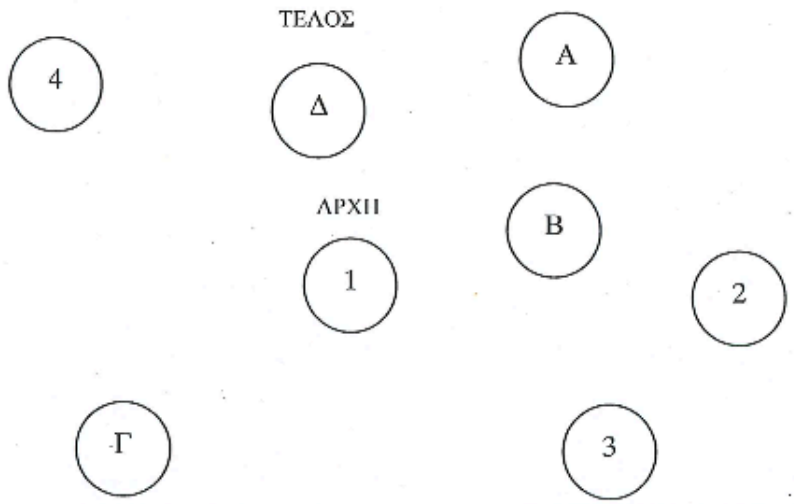
Trail Making Test A'

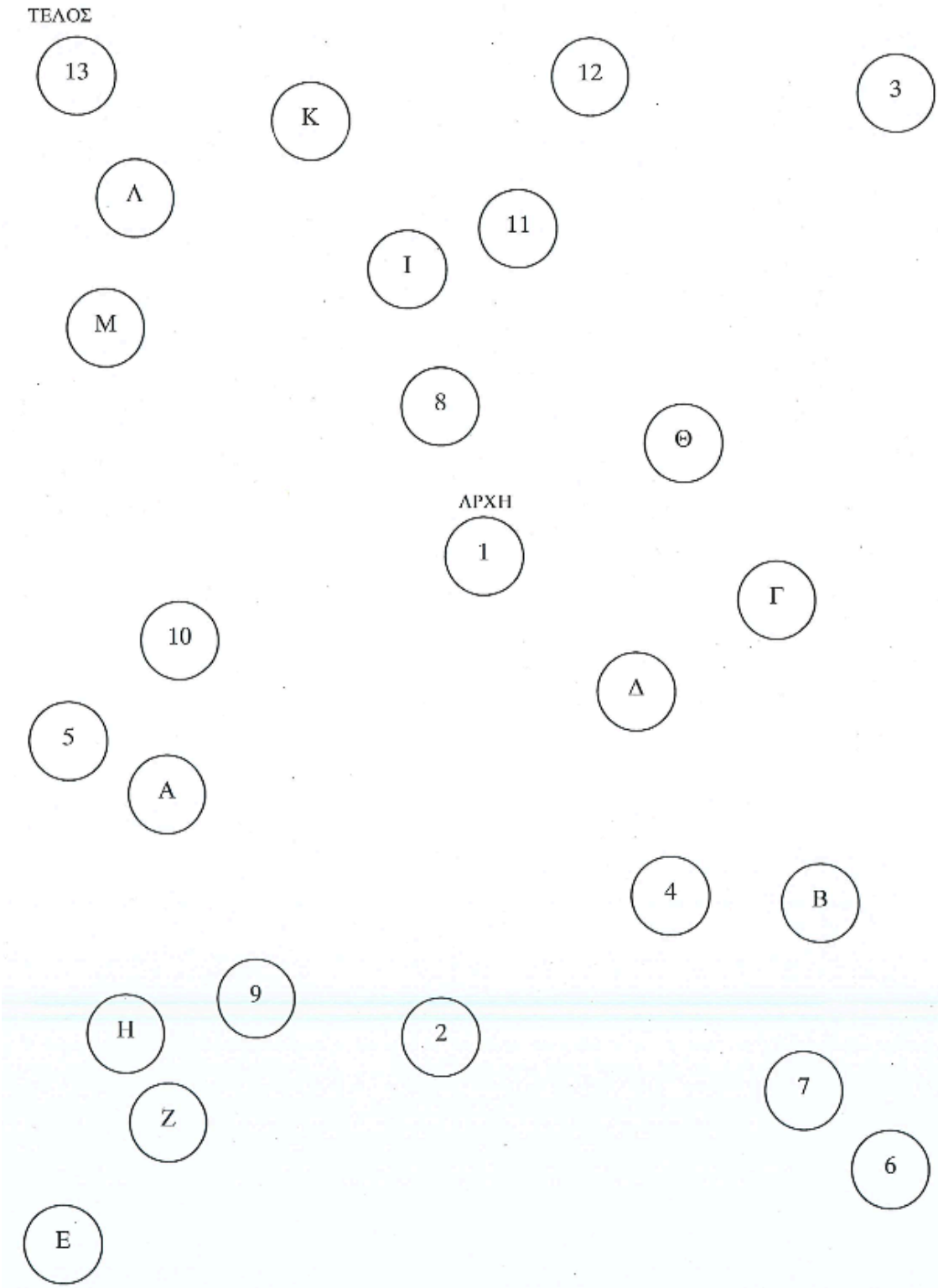



17
20
19
18
21
14
16
6
22
15
13
4
ΑΡΧΗ
7
2
1
5
11
9
3
10
ΤΕΛΟΣ
8
24
25
23
12

f1

Trail Making B'




ΤΕΛΟΣ
13
12
3
Κ
Λ
11
Ι
Μ
8
Θ
ΑΡΧΗ
1
Γ
10
Δ
5
Α
4
Β
9
Η
2
7
Ζ
6
Ε

GFinADStudy f1

Phase	Data Point Number	Subject Number	Examiner Initials	Examination Date
				Μέρα Μήνας Έτος

Corsi Block-Tapping Test
Forward

			Σ	Λ
1	a	5 7		
	b	1 4		
2	a	3 9 4		
	b	4 1 7		
3	a	6 5 3 9		
	b	7 9 3 1		
4	a	8 4 5 2 7		
	b	4 8 6 7 3		
5	a	9 7 5 4 3 6		
	b	4 3 7 6 4 6		
6	a	5 1 2 3 4 8 5		
	b	3 5 4 2 9 5 1		
7	a	4 7 4 1 3 9 4 5		
	b	5 4 3 2 5 6 4 5		
8	a	4 9 2 5 7 6 8 6 9		
	b	3 6 1 8 5 7 1 6 5		

Σύνολο:	
Span:	

GFinADStudy f1

Phase	Data Point Number	Subject Number	Examiner Initials	Examination Date
				Μέρα Μήνας Έτος

Corsi Block-Tapping Test
Backwards

			Σ	Λ
1	a	7 8		
	b	2 3		
2	a	9 8 1		
	b	5 9 8		
3	a	6 2 5 1		
	b	9 1 3 5		
4	a	6 8 3 5 6		
	b	1 4 5 9 7		
5	a	2 4 6 3 7 9		
	b	3 1 4 2 5 8		
6	a	1 8 2 4 3 6 9		
	b	7 4 1 9 5 8 6		
7	a	1 6 5 4 7 6 3 6		
	b	5 3 9 4 2 1 7 3		
8	a	4 2 6 1 3 7 9 4 5		
	b	9 1 2 9 4 2 7 3 2		

Σύνολο:	
Span:	

GFinADStudy

Phase	Data Point Number	Subject Number	Examiner Initials	Examination Date
				Μέρα Μήνας Έτος

Naming

	Εικόνες	ΣΒ	ΦΒ	Απάντηση	Σωστό	Λάθος
1	βιβλίο					
2	δώρο					
3	αλεπού					
4	γάιδαρος					
5	πλιγούρι					
6	ανεμιστήρας					
7	γλώσσα					
8	αλουμινόχαρτο					
9	αγρότης					
10	λάμπα					
11	αερόστατο					
12	καπετάνιος					
13	ενυδρείο					
14	παντζάρι					
15	φελλός					
	Total (αυθόρμητα):					
	Total με ΣΒ:					
	Total με ΦΒ:					

GFinADStudy

Phase	Data Point Number	Subject Number	Examiner Initials	Examination Date
				Μέρα Μήνας Έτος

Semantic Associations / Verbal and Visuoperceptual

Verbal		Superordinate (class membership)		Contiguity (its complement)		Part-whole (its single part)		Function (its use)	
non-living items		Σωστό	Σ/Λ	Σωστό	Σ/Λ	Σωστό	Σ/Λ	Σωστό	Σ/Λ
1	βιβλίο	υλικό διαβάσ		τετράδιο		σελίδα		διαβάζω	
2	ανεμιστήρας	κλιματισμός		σόμπα		καλώδιο		δροσίζομαι	
3	γλώσσα	στόμα		χείλη		σάλιο		γεύομαι	
4	παντζάρι	λαχανικό		χώρια		φύλλα		τρώω	
	ΣΥΝΟΛΟ								
living items		Σωστό	Σ/Λ	Σωστό	Σ/Λ	Σωστό	Σ/Λ		
1	αλεπού	ζώο		σκίουρος		ουρά			
2	γάιδαρος	θηλαστικό		άλογο		αυτιά			
3	αγρότης	επάγγελμα		γεωργός		χωράφι			
4	καπετάνιος	ναυτικό		πλοίο		στολή			
	ΣΥΝΟΛΟ								

Visuoperceptual		Superordinate (class membership)		Contiguity (its complement)		Part-whole (its single part)		Function (its use)	
1	βιβλίο	υλικό διαβάσ		σημειωματάριο		σελίδα		διαβάζω	
2	πλιγούρι	τρόφιμο		ρύζι		μακαρονάκι		τρώω	
3	παντζάρι	λαχανικό		λάχανο		φύλλα		τρώω	
4	γάιδαρος	ζώο		άλογο		αυτιά			
5	αλεπού	ζώο		σκίουρος		ουρά			
	ΣΥΝΟΛΟ								

Appendix 5: Imagery Booklet 1

Τεχνολογικό Πανεπιστήμιο Κύπρου

Έρευνα για τη
Νοητική Απεικόνιση των Λέξεων
Φόρμα 1

Πληροφορίες για την έρευνα: Οι λέξεις διαφέρουν ως προς την ικανότητά τους να προκαλούν νοητικές εικόνες πραγμάτων ή γεγονότων. Ορισμένες λέξεις προκαλούν μία αισθητηριακή εμπειρία, όπως μία νοητική εικόνα ή έναν ήχο πολύ γρήγορα και εύκολα, ενώ άλλες μπορεί να το κάνουν με δυσκολία μετά από καθυστέρηση ή καθόλου. **Σκοπός αυτής της έρευνας είναι να βαθμολογήσετε μία λίστα λέξεων ως προς την ευκολία με την οποία σας προκαλούν νοητικές εικόνες.**

Επικεφαλής Ερευνητές: Δρ Νίκος Κωνσταντίνου και Άρτεμις Τραϊκάπη, Τεχνολογικό Πανεπιστήμιο Κύπρου.

Κίνδυνοι συμμετοχής: Δεν προκύπτει κανένας κίνδυνος και καμία επιπλοκή από τη συμμετοχή σας σε αυτή την έρευνα.

Εμπιστευτικότητα: Τα δεδομένα που συλλέγονται είναι ανώνυμα και δε χρειάζεται να παρέχετε καμία πληροφορία για την ταυτότητά σας. Τα δεδομένα θα διατηρηθούν από τους ερευνητές και μπορεί να χρησιμοποιηθούν στο μέλλον για μελέτες εγκεκριμένες από τον αρμόδιο, προαναφερθέντα φορέα. Καμία ληφθείσα πληροφορία δε θα μπορεί να οδηγήσει στην ταυτοποίησή σας.

Μπορείτε να επικοινωνήσετε μαζί μας για οποιαδήποτε περαιτέρω πληροφορία σχετικά με την παρούσα μελέτη στην ηλεκτρονική διεύθυνση: nikos.konstantinou@cut.ac.cy & ag.traikapi@edu.cut.ac.cy.

Η έρευνα αυτή έχει την έγκριση της Εθνικής Βιοηθικής Κύπρου (Αρ. Φακ.: ΕΕΒΚ/ΕΠ/2021/22)

Έχω διαβάσει τις παραπάνω πληροφορίες και έχω κατανοήσει ότι η συμμετοχή μου στην έρευνα είναι εθελοντική και ότι μπορώ να διακόψω όποτε το επιθυμώ. Συμφωνείτε να συμμετάσχετε στην έρευνα (και επιβεβαιώνετε ότι είστε άνω των 18 ετών);

☐ ΝΑΙ

☐ ΟΧΙ

<u>Οδηγίες για την Συμπλήρωση του Ερωτηματολογίου:</u>

Η βαθμολόγηση θα γίνει σε κλίμακα επτά σημείων όπου το -1- είναι το χαμηλό άκρο της κλίμακας και το -7- το υψηλό άκρο. Βαθμολογήστε κάθε λέξη κυκλώνοντας τον αριθμό αυτό που αντιπροσωπεύει καλύτερα την κρίση σας **ως προς την ΕΥΚΟΛΙΑ και την ΤΑΧΥΤΗΤΑ που η κάθε λέξη σας προκαλεί νοητικές εικόνες.** Οι λέξεις που προκαλούν εικόνες γρήγορα και εύκολα πρέπει να βαθμολογούνται με -7-; οι λέξεις που προκαλούν εικόνες δύσκολα ή καθόλου πρέπει να βαθμολογούνται με -1-; λέξεις που βρίσκονται ενδιάμεσα στην ευκολία και δυσκολία πρέπει να βαθμολογούνται κατάλληλα μεταξύ των δύο άκρων. Μη διστάσετε να χρησιμοποιήσετε όλο το εύρος αριθμών μεταξύ -1- και -7-. Ταυτόχρονα μην ανησυχείτε για το πόσο συχνά χρησιμοποιείτε έναν συγκεκριμένο αριθμό αρκεί να αντιπροσωπεύει πραγματικά την κρίση σας. Εργαστείτε αρκετά γρήγορα ωστόσο, σας παρακαλούμε να είστε προσεκτικοί στις αξιολογήσεις σας. ΜΗ ΒΑΘΜΟΛΟΓΕΙΤΕ λέξεις που δε γνωρίζετε.

Παράδειγμα:

ΔΕΔΟΜΕΝΟ	(1)	2	3	4	5	6	7
	Χαμηλή νοητική απεικόνιση						Υψηλή νοητική απεικόνιση
ΜΟΛΥΒΙ	1	2	3	4	5	6	(7)
	Χαμηλή νοητική απεικόνιση						Υψηλή νοητική απεικόνιση

Τεχνολογικό Πανεπιστήμιο Κύπρου

Δημογραφικά Δεδομένα

Φύλο

- ☐ Θήλυ
- ☐ Άρρεν
- ☐ Άλλο

Ηλικία

……..

Υπηκοότητα

- ☐ Κυπριακή
- ☐ Ελληνική
- ☐ Άλλο

Τόπος Καταγωγής

- ☐ Λεμεσός
- ☐ Λευκωσία
- ☐ Λάρνακα
- ☐ Πάφος
- ☐ Αμμόχωστος
- ☐ Κερύνεια

Επίπεδο Εκπαίδευσης

- ☐ Δημοτικό
- ☐ Γυμνάσιο
- ☐ Λύκειο
- ☐ Βασικό Πτυχίο
- ☐ Μεταπτυχιακό
- ☐ Διδακτορικό

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΛΥΚΟΣ	1	2	3	4	5	6	7	☐
ΤΙΓΡΗΣ	1	2	3	4	5	6	7	☐
ΛΙΟΝΤΑΡΙ	1	2	3	4	5	6	7	☐
ΑΡΚΟΥΔΑ	1	2	3	4	5	6	7	☐
ΞΙΦΙΑΣ	1	2	3	4	5	6	7	☐
ΦΑΛΑΙΝΑ	1	2	3	4	5	6	7	☐
ΚΑΜΗΛΟΠΑΡΔΑΛΗ	1	2	3	4	5	6	7	☐
ΓΑΤΟΣ	1	2	3	4	5	6	7	☐
ΓΑΪΔΑΡΟΣ	1	2	3	4	5	6	7	☐
ΣΚΙΟΥΡΟΣ	1	2	3	4	5	6	7	☐
ΚΑΤΣΙΚΑ	1	2	3	4	5	6	7	☐
ΑΡΝΙ	1	2	3	4	5	6	7	☐
ΑΓΕΛΑΔΑ	1	2	3	4	5	6	7	☐
ΓΟΥΡΟΥΝΙ	1	2	3	4	5	6	7	☐
ΠΕΡΙΣΤΕΡΙ	1	2	3	4	5	6	7	☐
ΠΑΠΑΓΑΛΟΣ	1	2	3	4	5	6	7	☐
ΚΑΝΑΡΙΝΙ	1	2	3	4	5	6	7	☐
ΕΛΑΦΙ	1	2	3	4	5	6	7	☐
ΧΡΥΣΟΨΑΡΟ	1	2	3	4	5	6	7	☐
ΧΑΜΣΤΕΡ	1	2	3	4	5	6	7	☐
ΚΟΥΝΕΛΙ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΠΑΝΘΗΡΑΣ	1	2	3	4	5	6	7	☐
ΚΑΡΧΑΡΙΑΣ	1	2	3	4	5	6	7	☐
ΛΕΟΠΑΡΔΑΛΗ	1	2	3	4	5	6	7	☐
ΤΣΙΤΑ	1	2	3	4	5	6	7	☐
ΜΠΑΡΜΠΟΥΝΙ	1	2	3	4	5	6	7	☐
ΓΑΥΡΟΣ	1	2	3	4	5	6	7	☐
ΓΟΠΑ	1	2	3	4	5	6	7	☐
ΜΑΡΙΔΑ	1	2	3	4	5	6	7	☐
ΠΕΣΚΑΝΔΡΙΤΣΑ	1	2	3	4	5	6	7	☐
ΣΑΛΑΧΙ	1	2	3	4	5	6	7	☐
ΤΣΙΠΟΥΡΑ	1	2	3	4	5	6	7	☐
ΛΑΒΡΑΚΙ	1	2	3	4	5	6	7	☐
ΣΟΛΟΜΟΣ	1	2	3	4	5	6	7	☐
ΤΟΝΟΣ	1	2	3	4	5	6	7	☐
ΧΕΛΙΔΟΝΟΨΑΡΟ	1	2	3	4	5	6	7	☐
ΣΑΡΔΕΛΑ	1	2	3	4	5	6	7	☐
ΚΟΥΚΟΥΒΑΓΙΑ	1	2	3	4	5	6	7	☐
ΑΕΤΟΣ	1	2	3	4	5	6	7	☐
ΧΕΛΙΔΟΝΙ	1	2	3	4	5	6	7	☐
ΣΠΟΥΡΓΙΤΙ	1	2	3	4	5	6	7	☐
ΑΗΔΟΝΙ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΤΡΙΖΟΝΙ	1	2	3	4	5	6	7	☐
ΓΥΠΑΣ	1	2	3	4	5	6	7	☐
ΓΕΡΑΚΙ	1	2	3	4	5	6	7	☐
ΚΟΡΑΚΙ	1	2	3	4	5	6	7	☐
ΠΑΠΙΑ	1	2	3	4	5	6	7	☐
ΧΗΝΑ	1	2	3	4	5	6	7	☐
ΛΕΛΕΚΙ	1	2	3	4	5	6	7	☐
ΠΕΛΑΡΓΟΣ	1	2	3	4	5	6	7	☐
ΓΛΑΡΟΣ	1	2	3	4	5	6	7	☐
ΜΕΛΙΣΣΑ	1	2	3	4	5	6	7	☐
ΠΕΤΑΛΟΥΔΑ	1	2	3	4	5	6	7	☐
ΜΥΓΑ	1	2	3	4	5	6	7	☐
ΚΟΥΝΟΥΠΙ	1	2	3	4	5	6	7	☐
ΠΑΠΑΡΟΥΝΑ	1	2	3	4	5	6	7	☐
ΤΕΡΜΙΤΗΣ	1	2	3	4	5	6	7	☐
ΣΚΑΘΑΡΙ	1	2	3	4	5	6	7	☐
ΑΚΡΙΔΑ	1	2	3	4	5	6	7	☐
ΚΑΤΣΑΡΙΔΑ	1	2	3	4	5	6	7	☐
ΚΑΜΠΙΑ	1	2	3	4	5	6	7	☐
ΣΚΟΥΛΗΚΙ	1	2	3	4	5	6	7	☐
ΣΦΗΚΑ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΨΩΜΙ	1	2	3	4	5	6	7	☐
ΜΑΚΑΡΟΝΙΑ	1	2	3	4	5	6	7	☐
ΜΟΥΣΑΚΑΣ	1	2	3	4	5	6	7	☐
ΦΑΣΟΛΙΑ	1	2	3	4	5	6	7	☐
ΦΑΚΗ	1	2	3	4	5	6	7	☐
ΛΟΥΒΙ	1	2	3	4	5	6	7	☐
ΛΟΥΚΑΝΙΚΟ	1	2	3	4	5	6	7	☐
ΣΑΛΑΜΙ	1	2	3	4	5	6	7	☐
ΚΑΡΟΤΟ	1	2	3	4	5	6	7	☐
ΚΟΥΛΟΥΡΙ	1	2	3	4	5	6	7	☐
ΜΠΙΣΚΟΤΑ	1	2	3	4	5	6	7	☐
ΝΤΟΜΑΤΑ	1	2	3	4	5	6	7	☐
ΤΥΡΙ	1	2	3	4	5	6	7	☐
ΓΑΡΙΔΑ	1	2	3	4	5	6	7	☐
ΚΑΣΤΑΝΟ	1	2	3	4	5	6	7	☐
ΠΑΞΙΜΑΔΙ	1	2	3	4	5	6	7	☐
ΚΟΤΟΠΟΥΛΟ	1	2	3	4	5	6	7	☐
ΓΑΛΟΠΟΥΛΑ	1	2	3	4	5	6	7	☐
ΠΑΤΑΤΑ	1	2	3	4	5	6	7	☐
ΡΥΖΙ	1	2	3	4	5	6	7	☐
ΣΑΛΑΤΑ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΠΟΥΡΓΟΥΡΙ	1	2	3	4	5	6	7	☐
ΣΟΥΒΛΑΚΙ	1	2	3	4	5	6	7	☐
ΜΠΙΦΤΕΚΙ	1	2	3	4	5	6	7	☐
ΑΥΓΑ	1	2	3	4	5	6	7	☐
ΔΟΥΚΙΣΣΑ	1	2	3	4	5	6	7	☐
ΚΑΡΥΔΑ	1	2	3	4	5	6	7	☐
ΚΑΛΑΜΠΟΚΙ	1	2	3	4	5	6	7	☐
ΤΑΡΤΑ	1	2	3	4	5	6	7	☐
ΣΟΚΟΛΑΤΙΝΑ	1	2	3	4	5	6	7	☐
ΜΙΛΦΕΙ	1	2	3	4	5	6	7	☐
ΠΡΟΦΙΤΕΡΟΛ	1	2	3	4	5	6	7	☐
ΠΙΣΤΑΤΣΙΟ	1	2	3	4	5	6	7	☐
ΠΑΓΩΤΟ	1	2	3	4	5	6	7	☐
ΚΟΚ	1	2	3	4	5	6	7	☐
ΚΡΕΠΑ	1	2	3	4	5	6	7	☐
ΒΑΦΛΑ	1	2	3	4	5	6	7	☐
ΝΤΟΝΑΤ	1	2	3	4	5	6	7	☐
ΠΑΚΛΑΒΑΣ	1	2	3	4	5	6	7	☐
ΚΑΤΕΪΦΙ	1	2	3	4	5	6	7	☐
ΓΑΛΑΚΤΟΠΟΥΡΕΚΟ	1	2	3	4	5	6	7	☐
ΠΟΥΡΕΚΙΑ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΑΝΑΡΟΚΡΕΜΑ	1	2	3	4	5	6	7	☐
ΣΑΜΑΛΙ	1	2	3	4	5	6	7	☐
ΡΑΒΑΝΙ	1	2	3	4	5	6	7	☐
ΤΣΙΖΚΕΙΚ	1	2	3	4	5	6	7	☐
ΜΗΛΟΠΙΤΑ	1	2	3	4	5	6	7	☐
ΚΟΥΡΑΜΠΙΕΣ	1	2	3	4	5	6	7	☐
ΜΕΛΟΜΑΚΑΡΟΝΟ	1	2	3	4	5	6	7	☐
ΠΙΠΕΡΙ	1	2	3	4	5	6	7	☐
ΚΑΝΕΛΑ	1	2	3	4	5	6	7	☐
ΚΑΡΔΑΜΟ	1	2	3	4	5	6	7	☐
ΠΑΠΡΙΚΑ	1	2	3	4	5	6	7	☐
ΓΛΥΚΑΝΙΣΟΣ	1	2	3	4	5	6	7	☐
ΤΟΥΡΜΕΡΙΚ	1	2	3	4	5	6	7	☐
ΣΑΦΡΑΝ	1	2	3	4	5	6	7	☐
ΧΑΛΟΥΜΙ	1	2	3	4	5	6	7	☐
ΑΝΑΡΗ	1	2	3	4	5	6	7	☐
ΜΥΖΗΘΡΑ	1	2	3	4	5	6	7	☐
ΓΡΑΒΙΕΡΑ	1	2	3	4	5	6	7	☐
ΚΕΦΑΛΟΤΥΡΙ	1	2	3	4	5	6	7	☐
ΠΑΡΜΕΖΑΝΑ	1	2	3	4	5	6	7	☐
ΜΟΤΣΑΡΕΛΑ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΕΝΤΑΜ	1	2	3	4	5	6	7	☐
ΚΑΣΕΡΙ	1	2	3	4	5	6	7	☐
ΓΚΟΥΝΤΑ	1	2	3	4	5	6	7	☐
ΛΑΧΑΝΟ	1	2	3	4	5	6	7	☐
ΑΓΓΟΥΡΑΚΙ	1	2	3	4	5	6	7	☐
ΜΑΡΟΥΛΙ	1	2	3	4	5	6	7	☐
ΣΠΑΝΑΚΙ	1	2	3	4	5	6	7	☐
ΡΟΚΑ	1	2	3	4	5	6	7	☐
ΣΕΣΚΟΥΛΟ	1	2	3	4	5	6	7	☐
ΡΑΠΑΝΑΚΙ	1	2	3	4	5	6	7	☐
ΠΑΝΤΖΑΡΙ	1	2	3	4	5	6	7	☐
ΑΓΚΙΝΑΡΑ	1	2	3	4	5	6	7	☐
ΚΟΥΛΟΥΜΠΡΑ	1	2	3	4	5	6	7	☐
ΚΡΕΜΜΥΔΙ	1	2	3	4	5	6	7	☐
ΜΑΪΝΤΑΝΟΣ	1	2	3	4	5	6	7	☐
ΚΟΛΙΑΝΔΡΟΣ	1	2	3	4	5	6	7	☐
ΚΟΛΟΚΥΘΙ	1	2	3	4	5	6	7	☐
ΚΟΛΟΚΑΣΙ	1	2	3	4	5	6	7	☐
ΝΕΡΟ	1	2	3	4	5	6	7	☐
ΑΝΑΨΥΚΤΙΚΟ	1	2	3	4	5	6	7	☐
ΟΔΟΝΤΟΚΡΕΜΑ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΧΑΡΤΙ	1	2	3	4	5	6	7	☐
ΚΑΘΑΡΙΣΤΙΚΟ	1	2	3	4	5	6	7	☐
ΦΡΟΥΤΟ	1	2	3	4	5	6	7	☐
ΛΑΧΑΝΙΚΟ	1	2	3	4	5	6	7	☐
ΜΟΥΣΤΑΡΔΑ	1	2	3	4	5	6	7	☐
ΚΕΤΣΑΠ	1	2	3	4	5	6	7	☐
ΜΑΓΙΟΝΕΖΑ	1	2	3	4	5	6	7	☐
ΔΗΜΗΤΡΙΑΚΑ	1	2	3	4	5	6	7	☐
ΣΟΚΟΛΑΤΑ	1	2	3	4	5	6	7	☐
ΛΕΜΟΝΑΔΑ	1	2	3	4	5	6	7	☐
ΨΑΡΙ	1	2	3	4	5	6	7	☐
ΚΑΤΕΨΥΓΜΕΝΑ	1	2	3	4	5	6	7	☐
ΟΔΟΝΤΟΓΛΥΦΙΔΑ	1	2	3	4	5	6	7	☐
ΠΛΥΝΤΗΡΙΟ	1	2	3	4	5	6	7	☐
ΜΑΛΑΚΤΙΚΟ	1	2	3	4	5	6	7	☐
ΤΣΑΙ	1	2	3	4	5	6	7	☐
ΚΑΦΕΣ	1	2	3	4	5	6	7	☐
ΚΑΚΑΟ	1	2	3	4	5	6	7	☐
ΒΟΤΑΝΟ	1	2	3	4	5	6	7	☐
ΜΠΑΧΑΡΙΚΟ	1	2	3	4	5	6	7	☐
ΚΡΕΑΣ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΑΛΛΑΝΤΙΚΟ	1	2	3	4	5	6	7	☐
ΚΡΑΣΙ	1	2	3	4	5	6	7	☐
ΜΠΥΡΑ	1	2	3	4	5	6	7	☐
ΓΑΛΑ	1	2	3	4	5	6	7	☐
ΓΙΑΟΥΡΤΙ	1	2	3	4	5	6	7	☐
ΜΠΛΟΥΖΑ	1	2	3	4	5	6	7	☐
ΠΑΝΤΕΛΟΝΙ	1	2	3	4	5	6	7	☐
ΦΟΥΣΤΑ	1	2	3	4	5	6	7	☐
ΦΟΡΕΜΑ	1	2	3	4	5	6	7	☐
ΚΛΑΤΣΕΣ	1	2	3	4	5	6	7	☐
ΠΟΥΚΑΜΙΣΟ	1	2	3	4	5	6	7	☐
ΓΡΑΒΑΤΑ	1	2	3	4	5	6	7	☐
ΒΡΑΚΙ	1	2	3	4	5	6	7	☐
ΕΣΩΡΟΥΧΑ	1	2	3	4	5	6	7	☐
ΣΙΑΡΠΑ	1	2	3	4	5	6	7	☐
ΚΑΣΚΟΛ	1	2	3	4	5	6	7	☐
ΣΑΚΑΚΙ	1	2	3	4	5	6	7	☐
ΠΑΛΤΟ	1	2	3	4	5	6	7	☐
ΣΟΥΤΙΕΝ	1	2	3	4	5	6	7	☐
ΖΙΒΑΓΚΟ	1	2	3	4	5	6	7	☐
ΦΑΝΕΛΑ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΚΛΑΤΣΟΔΕΤΑ	1	2	3	4	5	6	7	☐
ΓΙΛΕΚΟ	1	2	3	4	5	6	7	☐
ΣΩΒΡΑΚΟ	1	2	3	4	5	6	7	☐
ΜΠΟΞΕΡΑΚΙ	1	2	3	4	5	6	7	☐
ΚΟΣΤΟΥΜΙ	1	2	3	4	5	6	7	☐
ΠΑΠΙΓΙΟΝ	1	2	3	4	5	6	7	☐
ΜΠΟΤΕΣ	1	2	3	4	5	6	7	☐
ΠΑΝΤΟΦΛΕΣ	1	2	3	4	5	6	7	☐
ΓΡΑΦΕΙΟ	1	2	3	4	5	6	7	☐
ΚΑΡΕΚΛΑ	1	2	3	4	5	6	7	☐
ΠΕΝΑ	1	2	3	4	5	6	7	☐
ΜΟΛΥΒΙ	1	2	3	4	5	6	7	☐
ΠΛΗΚΤΡΟΛΟΓΙΟ	1	2	3	4	5	6	7	☐
ΜΟΛΥΒΟΘΗΚΗ	1	2	3	4	5	6	7	☐
ΑΥΤΟΚΙΝΗΤΟ	1	2	3	4	5	6	7	☐
ΤΗΛΕΦΩΝΟ	1	2	3	4	5	6	7	☐
ΟΘΟΝΗ	1	2	3	4	5	6	7	☐
ΜΠΟΥΚΑΛΙ	1	2	3	4	5	6	7	☐
ΨΑΛΙΔΙ	1	2	3	4	5	6	7	☐
ΤΕΤΡΑΔΙΟ	1	2	3	4	5	6	7	☐
ΒΙΒΛΙΟ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΚΑΘΡΕΦΤΗΣ	1	2	3	4	5	6	7	☐
ΚΑΛΑΘΟΣ	1	2	3	4	5	6	7	☐
ΜΑΝΤΗΛΙ	1	2	3	4	5	6	7	☐
ΛΑΜΠΑ	1	2	3	4	5	6	7	☐
ΠΑΠΟΥΤΣΙΑ	1	2	3	4	5	6	7	☐
ΤΗΛΕΟΡΑΣΗ	1	2	3	4	5	6	7	☐
ΤΡΑΠΕΖΙ	1	2	3	4	5	6	7	☐
ΠΙΑΤΟ	1	2	3	4	5	6	7	☐
ΠΟΤΗΡΙ	1	2	3	4	5	6	7	☐
ΠΙΡΟΥΝΙ	1	2	3	4	5	6	7	☐
ΜΑΧΑΙΡΙ	1	2	3	4	5	6	7	☐
ΣΧΑΡΑ	1	2	3	4	5	6	7	☐
ΝΤΟΥΛΑΠΙ	1	2	3	4	5	6	7	☐
ΕΡΜΑΡΙ	1	2	3	4	5	6	7	☐
ΚΡΕΒΑΤΙ	1	2	3	4	5	6	7	☐
ΕΤΑΖΙΕΡΑ	1	2	3	4	5	6	7	☐
ΚΟΜΟΔΙΝΟ	1	2	3	4	5	6	7	☐
ΠΟΛΥΘΡΟΝΑ	1	2	3	4	5	6	7	☐
ΚΑΝΑΠΕΣ	1	2	3	4	5	6	7	☐
ΑΝΑΚΛΙΝΔΡΟ	1	2	3	4	5	6	7	☐
ΣΚΑΜΠΟ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΜΠΟΥΦΕΣ	1	2	3	4	5	6	7	☐
ΒΙΒΛΙΟΘΗΚΗ	1	2	3	4	5	6	7	☐
ΥΠΟΛΟΓΙΣΤΗΣ	1	2	3	4	5	6	7	☐
ΨΥΓΕΙΟ	1	2	3	4	5	6	7	☐
ΦΟΥΡΝΟΣ	1	2	3	4	5	6	7	☐
ΚΟΥΡΤΙΝΑ	1	2	3	4	5	6	7	☐
ΤΟΥΑΛΕΤΑ	1	2	3	4	5	6	7	☐
ΜΠΑΝΙΟ	1	2	3	4	5	6	7	☐
ΑΜΠΑΖΟΥΡ	1	2	3	4	5	6	7	☐
ΣΑΠΟΥΝΙ	1	2	3	4	5	6	7	☐
ΦΤΥΑΡΙ	1	2	3	4	5	6	7	☐
ΣΦΥΡΙ	1	2	3	4	5	6	7	☐
ΣΟΥΓΙΑΣ	1	2	3	4	5	6	7	☐
ΠΕΣΣΑ	1	2	3	4	5	6	7	☐
ΚΛΕΙΔΙ	1	2	3	4	5	6	7	☐
ΚΑΒΟΥΡΑΣ	1	2	3	4	5	6	7	☐
ΤΡΥΠΑΝΙ	1	2	3	4	5	6	7	☐
ΚΑΤΣΑΒΙΔΙ	1	2	3	4	5	6	7	☐
ΤΕΚΙΛΑ	1	2	3	4	5	6	7	☐
ΛΥΚΟΣ	1	2	3	4	5	6	7	☐
ΤΙΓΡΗΣ	1	2	3	4	5	6	7	☐

	Νοητική Απεικόνιση							Δε γνωρίζω τη λέξη
	χαμηλή						υψηλή	
ΛΙΟΝΤΑΡΙ	1	2	3	4	5	6	7	☐
ΑΡΚΟΥΔΑ	1	2	3	4	5	6	7	☐
ΞΙΦΙΑΣ	1	2	3	4	5	6	7	☐

Appendix 6: Concreteness Booklet 1

Τεχνολογικό Πανεπιστήμιο Κύπρου

Έρευνα για την
Αφαιρετικότητα των Λέξεων
Φόρμα 1

Πληροφορίες για την έρευνα: Οι λέξεις διαφέρουν ως προς το επίπεδο της αφαιρετικότητάς τους. Ορισμένες λέξεις αναφέρονται σε απτά αντικείμενα, υλικά ή άτομα που μπορούν εύκολα να γίνουν αντιληπτά με τις αισθήσεις. Τέτοιες λέξεις μπορούν να θεωρηθούν ως συγκεκριμένες λέξεις (concrete words). Άλλες λέξεις αναφέρονται σε αφηρημένες έννοιες που δεν είναι εύκολα αντιληπτές με τις αισθήσεις. **Ο σκοπός της έρευνας αυτής είναι η βαθμολόγηση μίας λίστας λέξεων ως προς το επίπεδο της αφαιρετικότητάς τους.**

Επικεφαλής Ερευνητές: Δρ Νίκος Κωνσταντίνου και Άρτεμις Τραϊκάπη, Τεχνολογικό Πανεπιστήμιο Κύπρου.

Κίνδυνοι συμμετοχής: Δεν προκύπτει κανένας κίνδυνος και καμία επιπλοκή από τη συμμετοχή σας σε αυτή την έρευνα.

Εμπιστευτικότητα: Τα δεδομένα που συλλέγονται είναι ανώνυμα και δε χρειάζεται να παρέχετε καμία πληροφορία για την ταυτότητά σας. Τα δεδομένα θα διατηρηθούν από τους ερευνητές και μπορεί να χρησιμοποιηθούν στο μέλλον για μελέτες εγκεκριμένες από τον αρμόδιο, προαναφερθέντα φορέα. Καμία ληφθείσα πληροφορία δε θα μπορεί να οδηγήσει στην ταυτοποίησή σας.

Μπορείτε να επικοινωνήσετε μαζί μας για οποιαδήποτε περαιτέρω πληροφορία σχετικά με την παρούσα μελέτη στην ηλεκτρονική διεύθυνση: nikos.konstantinou@cut.ac.cy & ag.traikapi@edu.cut.ac.cy.

Η έρευνα αυτή έχει την έγκριση της Εθνικής Βιοηθικής Κύπρου (Αρ. Φακ.: ΕΕΒΚ/ΕΠ/2021/22)

Έχω διαβάσει τις παραπάνω πληροφορίες και έχω κατανοήσει ότι η συμμετοχή μου στην έρευνα είναι εθελοντική και ότι μπορώ να διακόψω όποτε το επιθυμώ. Συμφωνείτε να συμμετάσχετε στην έρευνα (και επιβεβαιώνετε ότι είστε άνω των 18 ετών);

☐ ΝΑΙ

☐ ΟΧΙ

Οδηγίες για την Συμπλήρωση του Ερωτηματολογίου:

Η βαθμολόγηση θα γίνει σε κλίμακα επτά σημείων όπου το -1- είναι το χαμηλό άκρο της κλίμακας (αφηρημένη λέξη) και το -7- το υψηλό άκρο (συγκεκριμένη λέξη). Βαθμολογήστε κάθε λέξη κυκλώνοντας τον αριθμό αυτό που αντιπροσωπεύει καλύτερα την κρίση σας ως προς το επίπεδο της αφαιρετικότητάς της. Οι λέξεις που μπορούν εύκολα να γίνουν αντιληπτές με τις αισθήσεις πρέπει να βαθμολογούνται με -7-; οι λέξεις που αναφέρονται σε αφηρημένες έννοιες που δεν είναι εύκολα αντιληπτές με τις αισθήσεις πρέπει να βαθμολογούνται με -1-; λέξεις που βρίσκονται ενδιάμεσα στην αφαιρετικότητά τους πρέπει να βαθμολογούνται κατάλληλα μεταξύ των δύο άκρων. Μη διστάσετε να χρησιμοποιήσετε όλο το εύρος αριθμών μεταξύ -1- και -7-. Ταυτόχρονα μην ανησυχείτε για το πόσο συχνά χρησιμοποιείτε έναν συγκεκριμένο αριθμό αρκεί να αντιπροσωπεύει πραγματικά την κρίση σας. Εργαστείτε αρκετά γρήγορα ωστόσο, σας παρακαλούμε να είστε προσεκτικοί στις αξιολογήσεις σας'. ΜΗ ΒΑΘΜΟΛΟΓΕΙΤΕ λέξεις που δε γνωρίζετε.

Παράδειγμα:

ΔΗΜΟΚΡΑΤΙΑ	(1)	2	3	4	5	6	7
	Αφηρημένη						Συγκεκριμένη
ΚΑΡΕΚΛΑ	1	2	3	4	5	6	(7)
	Αφηρημένη						Συγκεκριμένη

Τεχνολογικό Πανεπιστήμιο Κύπρου

Δημογραφικά Δεδομένα

Φύλο

- ☐ Θήλυ
- ☐ Άρρεν
- ☐ Άλλο

Ηλικία

.....

Υπηκοότητα

- ☐ Κυπριακή
- ☐ Ελληνική
- ☐ Άλλο

Τόπος Καταγωγής

- ☐ Λεμεσός
- ☐ Λευκωσία
- ☐ Λάρνακα
- ☐ Πάφος
- ☐ Αμμόχωστος
- ☐ Κερύνεια

Επίπεδο Εκπαίδευσης

- ☐ Δημοτικό
- ☐ Γυμνάσιο
- ☐ Λύκειο
- ☐ Βασικό Πτυχίο
- ☐ Μεταπτυχιακό
- ☐ Διδακτορικό

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

αφηρημένη συγκεκριμένη

ΛΥΚΟΣ	1	2	3	4	5	6	7	☐
ΤΙΓΡΗΣ	1	2	3	4	5	6	7	☐
ΛΙΟΝΤΑΡΙ	1	2	3	4	5	6	7	☐
ΑΡΚΟΥΔΑ	1	2	3	4	5	6	7	☐
ΞΙΦΙΑΣ	1	2	3	4	5	6	7	☐
ΦΑΛΑΙΝΑ	1	2	3	4	5	6	7	☐
ΚΑΜΗΛΟΠΑΡΔΑΛΗ	1	2	3	4	5	6	7	☐
ΓΑΤΟΣ	1	2	3	4	5	6	7	☐
ΓΑΪΔΑΡΟΣ	1	2	3	4	5	6	7	☐
ΣΚΙΟΥΡΟΣ	1	2	3	4	5	6	7	☐
ΚΑΤΣΙΚΑ	1	2	3	4	5	6	7	☐
ΑΡΝΙ	1	2	3	4	5	6	7	☐
ΑΓΕΛΑΔΑ	1	2	3	4	5	6	7	☐
ΓΟΥΡΟΥΝΙ	1	2	3	4	5	6	7	☐
ΠΕΡΙΣΤΕΡΙ	1	2	3	4	5	6	7	☐
ΠΑΠΑΓΑΛΟΣ	1	2	3	4	5	6	7	☐
ΚΑΝΑΡΙΝΙ	1	2	3	4	5	6	7	☐
ΕΛΑΦΙ	1	2	3	4	5	6	7	☐
ΧΡΥΣΟΨΑΡΟ	1	2	3	4	5	6	7	☐
ΧΑΜΣΤΕΡ	1	2	3	4	5	6	7	☐
ΚΟΥΝΕΛΙ	1	2	3	4	5	6	7	☐

4

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΠΑΝΘΗΡΑΣ	1	2	3	4	5	6	7	☐
ΚΑΡΧΑΡΙΑΣ	1	2	3	4	5	6	7	☐
ΛΕΟΠΑΡΔΑΛΗ	1	2	3	4	5	6	7	☐
ΤΣΙΤΑ	1	2	3	4	5	6	7	☐
ΜΠΑΡΜΠΟΥΝΙ	1	2	3	4	5	6	7	☐
ΓΑΥΡΟΣ	1	2	3	4	5	6	7	☐
ΓΟΠΑ	1	2	3	4	5	6	7	☐
ΜΑΡΙΔΑ	1	2	3	4	5	6	7	☐
ΠΕΣΚΑΝΔΡΙΤΣΑ	1	2	3	4	5	6	7	☐
ΣΑΛΑΧΙ	1	2	3	4	5	6	7	☐
ΤΣΙΠΟΥΡΑ	1	2	3	4	5	6	7	☐
ΛΑΒΡΑΚΙ	1	2	3	4	5	6	7	☐
ΣΟΛΟΜΟΣ	1	2	3	4	5	6	7	☐
ΤΟΝΟΣ	1	2	3	4	5	6	7	☐
ΧΕΛΙΔΟΝΟΨΑΡΟ	1	2	3	4	5	6	7	☐
ΣΑΡΔΕΛΑ	1	2	3	4	5	6	7	☐
ΚΟΥΚΟΥΒΑΓΙΑ	1	2	3	4	5	6	7	☐
ΑΕΤΟΣ	1	2	3	4	5	6	7	☐
ΧΕΛΙΔΟΝΙ	1	2	3	4	5	6	7	☐
ΣΠΟΥΡΓΙΤΙ	1	2	3	4	5	6	7	☐
ΑΗΔΟΝΙ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΤΡΙΖΟΝΙ	1	2	3	4	5	6	7	☐
ΓΥΠΑΣ	1	2	3	4	5	6	7	☐
ΓΕΡΑΚΙ	1	2	3	4	5	6	7	☐
ΚΟΡΑΚΙ	1	2	3	4	5	6	7	☐
ΠΑΠΙΑ	1	2	3	4	5	6	7	☐
ΧΗΝΑ	1	2	3	4	5	6	7	☐
ΛΕΛΕΚΙ	1	2	3	4	5	6	7	☐
ΠΕΛΑΡΓΟΣ	1	2	3	4	5	6	7	☐
ΓΛΑΡΟΣ	1	2	3	4	5	6	7	☐
ΜΕΛΙΣΣΑ	1	2	3	4	5	6	7	☐
ΠΕΤΑΛΟΥΔΑ	1	2	3	4	5	6	7	☐
ΜΥΓΑ	1	2	3	4	5	6	7	☐
ΚΟΥΝΟΥΠΙ	1	2	3	4	5	6	7	☐
ΠΑΠΑΡΟΥΝΑ	1	2	3	4	5	6	7	☐
ΤΕΡΜΙΤΗΣ	1	2	3	4	5	6	7	☐
ΣΚΑΘΑΡΙ	1	2	3	4	5	6	7	☐
ΑΚΡΙΔΑ	1	2	3	4	5	6	7	☐
ΚΑΤΣΑΡΙΔΑ	1	2	3	4	5	6	7	☐
ΚΑΜΠΙΑ	1	2	3	4	5	6	7	☐
ΣΚΟΥΛΗΚΙ	1	2	3	4	5	6	7	☐
ΣΦΗΚΑ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΨΩΜΙ	1	2	3	4	5	6	7	☐
ΜΑΚΑΡΟΝΙΑ	1	2	3	4	5	6	7	☐
ΜΟΥΣΑΚΑΣ	1	2	3	4	5	6	7	☐
ΦΑΣΟΛΙΑ	1	2	3	4	5	6	7	☐
ΦΑΚΗ	1	2	3	4	5	6	7	☐
ΛΟΥΒΙ	1	2	3	4	5	6	7	☐
ΛΟΥΚΑΝΙΚΟ	1	2	3	4	5	6	7	☐
ΣΑΛΑΜΙ	1	2	3	4	5	6	7	☐
ΚΑΡΟΤΟ	1	2	3	4	5	6	7	☐
ΚΟΥΛΟΥΡΙ	1	2	3	4	5	6	7	☐
ΜΠΙΣΚΟΤΑ	1	2	3	4	5	6	7	☐
ΝΤΟΜΑΤΑ	1	2	3	4	5	6	7	☐
ΤΥΡΙ	1	2	3	4	5	6	7	☐
ΓΑΡΙΔΑ	1	2	3	4	5	6	7	☐
ΚΑΣΤΑΝΟ	1	2	3	4	5	6	7	☐
ΠΑΞΙΜΑΔΙ	1	2	3	4	5	6	7	☐
ΚΟΤΟΠΟΥΛΟ	1	2	3	4	5	6	7	☐
ΓΑΛΟΠΟΥΛΑ	1	2	3	4	5	6	7	☐
ΠΑΤΑΤΑ	1	2	3	4	5	6	7	☐
ΡΥΖΙ	1	2	3	4	5	6	7	☐
ΣΑΛΑΤΑ	1	2	3	4	5	6	7	☐

	Αφαιρετικότητα							Δε γνωρίζω τη λέξη
	αφηρημένη						συγκεκριμένη	
ΠΟΥΡΓΟΥΡΙ	1	2	3	4	5	6	7	☐
ΣΟΥΒΛΑΚΙ	1	2	3	4	5	6	7	☐
ΜΠΙΦΤΕΚΙ	1	2	3	4	5	6	7	☐
ΑΥΓΑ	1	2	3	4	5	6	7	☐
ΔΟΥΚΙΣΣΑ	1	2	3	4	5	6	7	☐
ΚΑΡΥΔΑ	1	2	3	4	5	6	7	☐
ΚΑΛΑΜΠΟΚΙ	1	2	3	4	5	6	7	☐
ΤΑΡΤΑ	1	2	3	4	5	6	7	☐
ΣΟΚΟΛΑΤΙΝΑ	1	2	3	4	5	6	7	☐
ΜΙΛΦΕΙ	1	2	3	4	5	6	7	☐
ΠΡΟΦΙΤΕΡΟΛ	1	2	3	4	5	6	7	☐
ΠΙΣΤΑΤΣΙΟ	1	2	3	4	5	6	7	☐
ΠΑΓΩΤΟ	1	2	3	4	5	6	7	☐
ΚΟΚ	1	2	3	4	5	6	7	☐
ΚΡΕΠΑ	1	2	3	4	5	6	7	☐
ΒΑΦΛΑ	1	2	3	4	5	6	7	☐
ΝΤΟΝΑΤ	1	2	3	4	5	6	7	☐
ΠΑΚΛΑΒΑΣ	1	2	3	4	5	6	7	☐
ΚΑΤΕΪΦΙ	1	2	3	4	5	6	7	☐
ΓΑΛΑΚΤΟΠΟΥΡΕΚΟ	1	2	3	4	5	6	7	☐
ΠΟΥΡΕΚΙΑ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΑΝΑΡΟΚΡΕΜΑ	1	2	3	4	5	6	7	☐
ΣΑΜΑΛΙ	1	2	3	4	5	6	7	☐
ΡΑΒΑΝΙ	1	2	3	4	5	6	7	☐
ΤΣΙΖΚΕΙΚ	1	2	3	4	5	6	7	☐
ΜΗΛΟΠΙΤΑ	1	2	3	4	5	6	7	☐
ΚΟΥΡΑΜΠΙΕΣ	1	2	3	4	5	6	7	☐
ΜΕΛΟΜΑΚΑΡΟΝΟ	1	2	3	4	5	6	7	☐
ΠΙΠΕΡΙ	1	2	3	4	5	6	7	☐
ΚΑΝΕΛΑ	1	2	3	4	5	6	7	☐
ΚΑΡΔΑΜΟ	1	2	3	4	5	6	7	☐
ΠΑΠΡΙΚΑ	1	2	3	4	5	6	7	☐
ΓΛΥΚΑΝΙΣΟΣ	1	2	3	4	5	6	7	☐
ΤΟΥΡΜΕΡΙΚ	1	2	3	4	5	6	7	☐
ΣΑΦΡΑΝ	1	2	3	4	5	6	7	☐
ΧΑΛΟΥΜΙ	1	2	3	4	5	6	7	☐
ΑΝΑΡΗ	1	2	3	4	5	6	7	☐
ΜΥΖΗΘΡΑ	1	2	3	4	5	6	7	☐
ΓΡΑΒΙΕΡΑ	1	2	3	4	5	6	7	☐
ΚΕΦΑΛΟΤΥΡΙ	1	2	3	4	5	6	7	☐
ΠΑΡΜΕΖΑΝΑ	1	2	3	4	5	6	7	☐
ΜΟΤΣΑΡΕΛΑ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΕΝΤΑΜ	1	2	3	4	5	6	7	☐
ΚΑΣΕΡΙ	1	2	3	4	5	6	7	☐
ΓΚΟΥΝΤΑ	1	2	3	4	5	6	7	☐
ΛΑΧΑΝΟ	1	2	3	4	5	6	7	☐
ΑΓΓΟΥΡΑΚΙ	1	2	3	4	5	6	7	☐
ΜΑΡΟΥΛΙ	1	2	3	4	5	6	7	☐
ΣΠΑΝΑΚΙ	1	2	3	4	5	6	7	☐
ΡΟΚΑ	1	2	3	4	5	6	7	☐
ΣΕΣΚΟΥΛΟ	1	2	3	4	5	6	7	☐
ΡΑΠΑΝΑΚΙ	1	2	3	4	5	6	7	☐
ΠΑΝΤΖΑΡΙ	1	2	3	4	5	6	7	☐
ΑΓΚΙΝΑΡΑ	1	2	3	4	5	6	7	☐
ΚΟΥΛΟΥΜΠΡΑ	1	2	3	4	5	6	7	☐
ΚΡΕΜΜΥΔΙ	1	2	3	4	5	6	7	☐
ΜΑΪΝΤΑΝΟΣ	1	2	3	4	5	6	7	☐
ΚΟΛΙΑΝΔΡΟΣ	1	2	3	4	5	6	7	☐
ΚΟΛΟΚΥΘΙ	1	2	3	4	5	6	7	☐
ΚΟΛΟΚΑΣΙ	1	2	3	4	5	6	7	☐
ΝΕΡΟ	1	2	3	4	5	6	7	☐
ΑΝΑΨΥΚΤΙΚΟ	1	2	3	4	5	6	7	☐
ΟΔΟΝΤΟΚΡΕΜΑ	1	2	3	4	5	6	7	☐

10

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΧΑΡΤΙ	1	2	3	4	5	6	7	☐
ΚΑΘΑΡΙΣΤΙΚΟ	1	2	3	4	5	6	7	☐
ΦΡΟΥΤΟ	1	2	3	4	5	6	7	☐
ΛΑΧΑΝΙΚΟ	1	2	3	4	5	6	7	☐
ΜΟΥΣΤΑΡΔΑ	1	2	3	4	5	6	7	☐
ΚΕΤΣΑΠ	1	2	3	4	5	6	7	☐
ΜΑΓΙΟΝΕΖΑ	1	2	3	4	5	6	7	☐
ΔΗΜΗΤΡΙΑΚΑ	1	2	3	4	5	6	7	☐
ΣΟΚΟΛΑΤΑ	1	2	3	4	5	6	7	☐
ΛΕΜΟΝΑΔΑ	1	2	3	4	5	6	7	☐
ΨΑΡΙ	1	2	3	4	5	6	7	☐
ΚΑΤΕΨΥΓΜΕΝΑ	1	2	3	4	5	6	7	☐
ΟΔΟΝΤΟΓΛΥΦΙΔΑ	1	2	3	4	5	6	7	☐
ΠΛΥΝΤΗΡΙΟ	1	2	3	4	5	6	7	☐
ΜΑΛΑΚΤΙΚΟ	1	2	3	4	5	6	7	☐
ΤΣΑΙ	1	2	3	4	5	6	7	☐
ΚΑΦΕΣ	1	2	3	4	5	6	7	☐
ΚΑΚΑΟ	1	2	3	4	5	6	7	☐
ΒΟΤΑΝΟ	1	2	3	4	5	6	7	☐
ΜΠΑΧΑΡΙΚΟ	1	2	3	4	5	6	7	☐
ΚΡΕΑΣ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΑΛΛΑΝΤΙΚΟ	1	2	3	4	5	6	7	☐
ΚΡΑΣΙ	1	2	3	4	5	6	7	☐
ΜΠΥΡΑ	1	2	3	4	5	6	7	☐
ΓΑΛΑ	1	2	3	4	5	6	7	☐
ΓΙΑΟΥΡΤΙ	1	2	3	4	5	6	7	☐
ΜΠΛΟΥΖΑ	1	2	3	4	5	6	7	☐
ΠΑΝΤΕΛΟΝΙ	1	2	3	4	5	6	7	☐
ΦΟΥΣΤΑ	1	2	3	4	5	6	7	☐
ΦΟΡΕΜΑ	1	2	3	4	5	6	7	☐
ΚΛΑΤΣΕΣ	1	2	3	4	5	6	7	☐
ΠΟΥΚΑΜΙΣΟ	1	2	3	4	5	6	7	☐
ΓΡΑΒΑΤΑ	1	2	3	4	5	6	7	☐
ΒΡΑΚΙ	1	2	3	4	5	6	7	☐
ΕΣΩΡΟΥΧΑ	1	2	3	4	5	6	7	☐
ΣΙΑΡΠΑ	1	2	3	4	5	6	7	☐
ΚΑΣΚΟΛ	1	2	3	4	5	6	7	☐
ΣΑΚΑΚΙ	1	2	3	4	5	6	7	☐
ΠΑΛΤΟ	1	2	3	4	5	6	7	☐
ΣΟΥΤΙΕΝ	1	2	3	4	5	6	7	☐
ΖΙΒΑΓΚΟ	1	2	3	4	5	6	7	☐
ΦΑΝΕΛΑ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΚΛΑΤΣΟΔΕΤΑ	1	2	3	4	5	6	7	☐
ΠΛΕΚΟ	1	2	3	4	5	6	7	☐
ΣΩΒΡΑΚΟ	1	2	3	4	5	6	7	☐
ΜΠΟΞΕΡΑΚΙ	1	2	3	4	5	6	7	☐
ΚΟΣΤΟΥΜΙ	1	2	3	4	5	6	7	☐
ΠΑΠΙΓΙΟΝ	1	2	3	4	5	6	7	☐
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ΠΑΝΤΟΦΛΕΣ	1	2	3	4	5	6	7	☐
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ΚΑΡΕΚΛΑ	1	2	3	4	5	6	7	☐
ΠΕΝΑ	1	2	3	4	5	6	7	☐
ΜΟΛΥΒΙ	1	2	3	4	5	6	7	☐
ΠΛΗΚΤΡΟΛΟΓΙΟ	1	2	3	4	5	6	7	☐
ΜΟΛΥΒΟΘΗΚΗ	1	2	3	4	5	6	7	☐
ΑΥΤΟΚΙΝΗΤΟ	1	2	3	4	5	6	7	☐
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ΨΑΛΙΔΙ	1	2	3	4	5	6	7	☐
ΤΕΤΡΑΔΙΟ	1	2	3	4	5	6	7	☐
ΒΙΒΛΙΟ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΚΑΘΡΕΦΤΗΣ	1	2	3	4	5	6	7	☐
ΚΑΛΑΘΟΣ	1	2	3	4	5	6	7	☐
ΜΑΝΤΗΛΙ	1	2	3	4	5	6	7	☐
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ΠΑΠΟΥΤΣΙΑ	1	2	3	4	5	6	7	☐
ΤΗΛΕΟΡΑΣΗ	1	2	3	4	5	6	7	☐
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ΕΤΑΖΙΕΡΑ	1	2	3	4	5	6	7	☐
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ΚΑΝΑΠΕΣ	1	2	3	4	5	6	7	☐
ΑΝΑΚΛΙΝΔΡΟ	1	2	3	4	5	6	7	☐
ΣΚΑΜΠΟ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΜΠΟΥΦΕΣ	1	2	3	4	5	6	7	☐
ΒΙΒΛΙΟΘΗΚΗ	1	2	3	4	5	6	7	☐
ΥΠΟΛΟΓΙΣΤΗΣ	1	2	3	4	5	6	7	☐
ΨΥΓΕΙΟ	1	2	3	4	5	6	7	☐
ΦΟΥΡΝΟΣ	1	2	3	4	5	6	7	☐
ΚΟΥΡΤΙΝΑ	1	2	3	4	5	6	7	☐
ΤΟΥΑΛΕΤΑ	1	2	3	4	5	6	7	☐
ΜΠΑΝΙΟ	1	2	3	4	5	6	7	☐
ΑΜΠΑΖΟΥΡ	1	2	3	4	5	6	7	☐
ΣΑΠΟΥΝΙ	1	2	3	4	5	6	7	☐
ΦΤΥΑΡΙ	1	2	3	4	5	6	7	☐
ΣΦΥΡΙ	1	2	3	4	5	6	7	☐
ΣΟΥΓΙΑΣ	1	2	3	4	5	6	7	☐
ΠΕΣΣΑ	1	2	3	4	5	6	7	☐
ΚΛΕΙΔΙ	1	2	3	4	5	6	7	☐
ΚΑΒΟΥΡΑΣ	1	2	3	4	5	6	7	☐
ΤΡΥΠΑΝΙ	1	2	3	4	5	6	7	☐
ΚΑΤΣΑΒΙΔΙ	1	2	3	4	5	6	7	☐
ΤΕΚΙΛΑ	1	2	3	4	5	6	7	☐
ΛΥΚΟΣ	1	2	3	4	5	6	7	☐
ΤΙΓΡΗΣ	1	2	3	4	5	6	7	☐

Δε γνωρίζω τη λέξη

Αφαιρετικότητα

	αφηρημένη						συγκεκριμένη	
ΛΙΟΝΤΑΡΙ	1	2	3	4	5	6	7	☐
ΑΡΚΟΥΔΑ	1	2	3	4	5	6	7	☐
ΞΙΦΙΑΣ	1	2	3	4	5	6	7	☐

Appendix 7: Inclusion Criteria Checklist

GFinADStudy

Inclusion Criteria Checkbox

Patient's Name: _____

Criteria	Inclusion Rates		
Mini Mental State Examination Score (MMSE)	17-24	AT	
Global Deterioration Scale (GDS)	4 or 5	AT	
Instrumental Activities of Daily Living (IADL)	10-20	AT	
Activities of Daily Living (ADL)	<5	AT	
Geriatric Depression Scale-30 (GDS-30)	<15	AT	
MRI		clinic	
Visual abilities	within normal range	AT	
Hearing abilities	within normal range	AT	
TMS safety Screening	pass	AT	
Caregiver who agree to be responsible throughout the study		AT	
Stable Medical & Pharmacological condition	for at least 2 months prior to the study	doctor	
Cholinesterase inhibitors medication	if they are taking the medication for more that 2 months prior to the study	doctor	
Psychoactive medication within the last 2 months	absent	doctor	
Under drugs with anticholinergic properties	absent	doctor	
Absence of any clinically significant medical history that may induce cognitive deterioration	absent	doctor	
Diagnosis of epilepsy	absent	doctor	
Medical implants in the head or pacemaker	absent	doctor	
Brain injury history	absent	doctor	
Surgery to the heart or stroke	absent	doctor	
DIAGNOSIS OF PROBABLE ALZHEIMER'S DISEASE		DOCTOR	

Appendix 8: Developed Neuropsychological Material & Thesis Publications

Links to the developed material:

- Unique word lists
- The Cypriot Word Pool
- Alzheimer's Disease Assessment Scale-cognitive subscale-12 / Form A΄
- Alzheimer's Disease Assessment Scale-cognitive subscale-12 / Form B΄

Thesis publications:

Traikapi, A., Kalli, I., Kyriakou, A., Stylianou, E., Symeou, R. T., Kardama, A., Christou, Y. P., Phylactou, P., & Konstantinou, N. (2022). Episodic memory effects of gamma frequency precuneus transcranial magnetic stimulation in Alzheimer's disease: A randomized multiple baseline study. *Journal of Neuropsychology*, 00, 1– 23. https://doi.org/10.1111/jnp.12299

Traikapi, A., & Konstantinou, N. (2021). Gamma oscillations in Alzheimer's disease and their potential therapeutic role. *Frontiers in Systems Neuroscience*, 154. https://doi.org/10.3389/FNSYS.2021.782399

Traikapi, A., Phylactou, P., & Konstantinou, N. (2022). Repetitive transcranial magnetic stimulation of the human motor cortex in the gamma band reduces cortical excitability. *Neurophysiologie clinique= Clinical neurophysiology*, *52*(5), 407-409. https://doi.org/10.1016/j.neucli.2022.09.005