Cognitive Stimulation Therapy

in mild to moderate

Alzheimer's Disease: an MRI study

Inaugural Dissertation

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Preface

Cognitive stimulation therapy (CST) for mild to moderated Alzheimer's dementia has been an amazing journey. Our journey began with the vision to test the potential benefits and underlying mechanism of CST as a non-pharmacological therapeutic approach for Alzheimer's disease (AD) in the absence of any cure for it.

CST is a type of rehabilitation intervention designed for individuals with mild to moderate dementia. It consists of a structured program of activities aimed at improving cognitive function and maintaining daily living skills. The therapy typically involves group sessions that last for one hour and are led by trained facilitators. The activities are based on a wide range of cognitive domains, including memory, language, attention, and perception, and are designed to be fun, stimulating, and challenging.

The rising quantity of research examining the effects of CST in AD dementia contrasts with the paucity of information regarding its neurobiological underpinnings and the lack of imaging studies. Functional magnetic resonance imaging (fMRI) offers experimental information on potential neuropsychological mechanisms underpinning non-pharmacological therapies like CST.

Research suggests that CST may lead to improvements in cognitive function by promoting neuroplasticity, the ability of the brain to adapt and reorganize in response to changes in the environment. The idea of neural plasticity or brain plasticity, began with the work of French physiologist Paul Broca in the late 19th century. He observed that after damage to certain areas of the brain, other areas of the brain could take over functions that were previously controlled by the damaged area. This observation led to the concept of brain compensation, which refers to the brain's ability to reorganize itself in response to injury or disease.

Implementing and customizing preventative and therapeutic therapies with the goals of maintaining general cognitive performance and delaying the clinical onset of dementia require the detection of the compensatory dynamics in healthy aging and prodromal AD.

Given this intertwined association of brain plasticity and potential positive effects of CST, we opted to speculate brain plasticity and compensation in healthy brain aging and prodromal AD in another cohort of ours, while we were investigating the effects of CST and its underpinning mechanism using fMRI.

And this is exactly what happened. Prof. Dr. Özgür A. Onur secured funding to perform the project of the CST for mild to moderate Alzheimer's and through a job

advertisement I was recruited as researcher and PhD student at the neurology department of Cologne university hospital.
Undertaking this project was a truly enriching experience, characterized by a blend of enjoyment and significant challenges. The enjoyable aspects stemmed from the opportunity to delve deep into a subject I'm passionate about, allowing me to explore creative solutions and innovative ideas. The satisfaction of making progress and achieving milestones was truly rewarding. However, it's important to acknowledge that this project also presented its fair share of challenges including:

Ethical Concerns and Informed Consent: Patients with AD may have impaired cognitive function, which raises ethical concerns about their ability to provide fully informed consent to participate in research. Special care and procedures are required to ensure their autonomy is respected.

Cognitive Impairment: The cognitive impairments caused by AD can affect a person's ability to understand the nature of the study, follow instructions, or provide accurate responses during assessments.

Caregiver Burden: Patients with AD often rely on family members or caregivers for support. Caregivers may already be burdened with providing care and may be hesitant to add the commitment of participating in research on top of their responsibilities.

Logistical Challenges: Alzheimer's patients may face transportation issues, mobility problems, or other logistical challenges that make it difficult for them to travel to research centers for assessments.

Comorbidities: Many AD patients also have other medical conditions. This can strict the eligibility criteria complicate the selection process for clinical trials and research studies, potentially limiting the pool of eligible participants.

Limited Sample Size: AD research often requires a large sample size to achieve statistically significant results. However, finding a sufficient number of eligible participants can be challenging, especially if researchers are looking for a specific demographic or stage of the disease.

Longitudinal Nature of Studies: Many Alzheimer's studies require participants to commit to long-term follow-ups, which can be difficult for patients and their families to maintain over time.

Public Mistrust: Concerns about privacy, data security, and how research findings will be used can contribute to public mistrust and reluctance to participate in research studies.

Apart from the above-mentioned challenges, our study encountered a formidable obstacle caused by the COVID-19 pandemic, which had a paralyzing effect on our patient recruitment efforts. The pandemic's widespread impact led to a series of unprecedented challenges that significantly hindered our ability to enroll participants in the trial, and delayed our project for more than two years.

Navigating complex technical requirements and tight deadlines required meticulous planning and a high level of adaptability. Overcoming unexpected hurdles demanded resourcefulness and a collaborative mindset. Despite these difficulties, the challenges were instrumental in fostering personal and professional growth, as they pushed me to think outside the box and develop new skills.

In retrospect, the combination of enjoyment and challenges made this project a valuable learning experience, demonstrating that the most fulfilling endeavors often arise from the synergy of both positive and demanding elements.

I am thrilled to see this project come to fruition and would like to particularly thank Prof. Dr. Özgür A. Onur for all his efforts, contributions and supports.

I am so grateful for the brilliant contribution from my colleagues, all participants in our study and their relatives. This, I believe, should be an illuminating neuroimaging-based evidence for the positive efficacy of CST for many years to come.

I hope readers of this dissertation will be inspired and encouraged to improve CST and innovate methods to unravel its underlying mechanism.

1. Introduction

1.1 Dementia

Dementia is a broad term used to describe a group of cognitive disorders that affect a person's ability to think, remember, reason, and perform everyday activities. It is not a specific disease but rather a syndrome characterized by a decline in cognitive function that is severe enough to interfere with a person's daily life and activities. A common symptom of dementia is memory loss. It frequently occurs as one of the initial signs and symptoms of the condition; however, depending on the cause of dementia, patients may experience the following symptoms with varying prevalence:

Cognitive symptoms:

- Memory loss, which is typically noticed by another person
- Difficulties in communicating or finding words
- Trouble with visual and spatial abilities, including getting disoriented while driving
- Reasoning and problem-solving issues
- Difficulty with complex tasks
- Difficulty with planning and organization
- Poor coordination and movement control
- Disorientation and confusion

Psychological Symptoms:

- Personality changes
- Depression
- Anxiety
- Agitation
- Inappropriate behavior
- Paranoia
- Hallucination

Diagnosing dementia is a complex process that often requires a multidisciplinary approach to ensure a thorough and accurate assessment. The diagnosis of dementia is made based on a combination of clinical assessment, cognitive testing, physical examination, laboratory tests, imaging studies, neuropsychological testing,

cerebrospinal fluid analysis, psychiatric evaluation, functional assessment and sometimes genetic testing. It is essential for healthcare professionals to consider all relevant information to determine the type and cause of dementia accurately, in order to tailor treatment, plan for the future, support individuals and their families, and even advance research, ultimately improve the quality of life for those affected by dementia.

1.1.1. Dementia types and burden

One of the main problems facing our societies is dementia, which affects 7% of Europeans over the age of 60 (OECD, 2014; Prince et al., 2013). Dementia is essentially a long-term, gradually destructive process in which a person's cognitive and functioning abilities decline. In Addition, the behavioral and psychological symptoms of dementia (BPSD), which commonly co-occur with dementia, exacerbate the patient's cognitive decline and functional impairment, intensifying the distress experienced by both the patient and their family.

The lack of current medications capable of curing dementia or significantly slowing its progression is largely due to the complex, diverse, and still poorly understood pathological mechanisms underlying the disease. Alzheimer's disease (AD) is the most common cause of dementia in the general population, followed by cerebrovascular disease, either occurring independently or in conjunction with AD.

Lewy body disease, which can present clinically with primarily motor symptoms (Parkinson's disease) or as a combination of cognitive and motor symptoms (Lewy body dementia), has garnered increased attention in recent years. Lewy body disease is now considered to be the third most common cause of dementia, even though AD is usually present in affected brains (80% of them) (Lewy body variant of AD).

Fourth on the list of dementia causes is frontotemporal lobar degeneration (FTLD). The term "executive dysfunction" describes a collection of pathologically and clinically diverse conditions that originate in the frontal and/or temporal lobes. Consequently, these conditions present clinically with impairments in executive functions (such as planning, sequencing, and control of thoughts or actions), language deficits, and/or behavioral disturbances.

Finally, there exists a heterogeneous group of conditions termed "minority dementias," which encompass rare neurodegenerative diseases (e.g., progressive supranuclear palsy, Huntington's disease), chronic infections (e.g., neurosyphilis, HIV infection), toxic or metabolic processes, nutritional deficiencies, and other secondary dementias

(e.g., normal pressure hydrocephalus, head trauma, multiple sclerosis) (Ames et al., 2010) (see **Table 1).**

Although there are several potential causes for dementia, AD, vascular disease, and Lewy body disease account for the great majority of cases in elderly adults. These three diseases have a common pathogenic mechanism and frequently manifest together (Iturria-Medina et al., 2016). In particularly elderly people, combined dementia is especially prevalent. Although it hasn't been proven, it has been hypothesized that the many pathologies would each contribute in some way to the clinical appearance. Only beta-amyloid plaques, neurofibrillary tangles (pathological indicators of AD), and vascular lesions have a consistent correlation between them and clinical signs of dementia. Indeed, significant amyloid-type AD pathology has been observed in the brains of individuals who did not exhibit dementia during their lifetime (Katzman et al., 1989), and the contrary observations have been documented wherein certain individuals afflicted with dementia exhibit an absence of pronounced pathological manifestations upon post-mortem examination of the brain (Boyle et al., 2013; Kawas et al., 2015). These counterintuitive discoveries may be elucidated by the limited sensitivity of detection methodologies; however, they also suggest that psychological and social variables could exert a notable influence on mitigating and potentially forestalling dementia and cognitive degradation.

Undoubtedly, the extensive, multifaceted, and intricate landscape of dementia necessitates exploration of therapeutic avenues beyond a strictly biological lens. Concepts such as cognitive reserve and brain reserve have been proposed to investigate potential compensatory mechanisms, which could be influenced by both pharmaceutical and non-pharmacological interventions (Stern et al., 2006). It is predictable that a combination of initiatives from various perspectives and disciplines will lead to the containment of the burden of dementia.

Table 1: Etiology of Dementia Types (Yates et al., 2019)

Dementia Type	Prevalence (%)
Primary (Degenerative) dementia	**55**
Alzheimer's disease dementia	35
Lewy body dementia	10
Frontotemporal dementia (FTD)	8
other types of primary dementias	2
Secondary (Non-degenerative) dementias	**5**
Cerebrovascular dementia (CVD)	3
other types of secondary dementias	2
Combined dementia	**40**
Mixed dementia (AD+CVD)	20
Lewy body variant of AD	15
other types of combined dementia	5

% indicates the prevalence across all types of dementia

1.1.2 Alzheimer's disease

AD, as the most common cause of dementia in the elderly, is a global health issue, affecting millions of people worldwide. The World Health Organization (WHO) estimates that dementia (including Alzheimer's) affects over 50 million people globally and is projected to increase with aging populations.

AD was first described by the German psychiatrist and neuropathologist, Alois Alzheimer in 1906. Alzheimer was working at the Royal Psychiatric Hospital in Frankfurt, Germany, where he was treating a patient with a rare form of dementia. After the patient passed away, Alzheimer conducted a post-mortem examination of her brain and discovered unusual deposits of protein, which are now known as amyloid plaques. He also observed abnormal tangles of fibers within the nerve cells, which are now known as neurofibrillary tangles. Alzheimer's findings marked the first scientific description of what is now known as AD.

The exact underlying causes of AD are not yet fully understood, but there are several factors that are believed to play a role in the development of the disease. These include:

Age: The risk of developing Alzheimer's increases with age, and the majority of people with the disease are over 65 years old.

Genetics: Certain genetic mutations have been identified that are associated with an increased risk of developing Alzheimer's. However, most cases of Alzheimer's occur in people without a known genetic risk factor.

Brain changes: Alzheimer's is characterized by a number of changes in the brain, including the formation of amyloid plaques and tau tangles, and the death of nerve cells and connections in the brain. The exact causes of these changes are not yet known, but they are thought to play a role in the development of the disease.

Inflammation: Chronic inflammation has been linked to the development of Alzheimer's, and some studies have suggested that this may contribute to the damage to the brain seen in the disease.

Lifestyle factors: Factors such as diet, physical activity, smoking, and alcohol consumption have been shown to influence the risk of developing Alzheimer's.

Other health conditions: Conditions such as high blood pressure, heart disease, and stroke have been linked to an increased risk of developing Alzheimer's.

It is likely that a combination of these and other factors contributes to the development of AD, and ongoing research is aimed at understanding the underlying causes of the disease in order to develop effective treatments and preventions.

1.1.3. Treatment options

While there is still no cure for AD, there are various treatments have been proposed to help manage the symptoms and improve quality of life for people with Alzheimer's. These treatments can be broadly categorized into the following:

Medications: The most commonly used medications for Alzheimer's, so far include cholinesterase inhibitors, N-methyl-D-Aspartate (NMDA) receptor antagonists, and memantine. Cholinesterase inhibitors are medications that work

by increasing the levels of a chemical called acetylcholine, which is important for memory and thinking.

NMDA receptor antagonists block the action of a certain neurotransmitter in the brain, which can help with symptoms such as agitation and aggression. Memantine regulates the activity of glutamate, a neurotransmitter that is involved in memory and learning. Recently, medical society has observed new developments in the medical treatment of AD. In June 2021, the U.S. Food and Drug Administration (FDA) granted accelerated approval to Aducanumab, a monoclonal antibody designed to target amyloid-beta plaques in the brain, which are a hallmark of AD. This approval was considered controversial due to mixed clinical trial results and concerns about the drug's effectiveness. Subsequent developments and ongoing research have further examined the drug's benefits and risks. In 2023, Lecanemab and Donanemab were added to medications regimens of patients with early stages of AD. They are intravenous (IV) antibodies that target and eliminate beta-amyloid from the brain. They have been granted conventional FDA approval for the treatment of early-stage AD, encompassing individuals with mild cognitive impairment (MCI) or mild dementia resulting from AD, who have verified evidence of elevated beta-amyloid levels in the brain. Lecanemab and Donanemab do not possess curative properties; rather, they are the first approved medications, which target the underlying biological mechanisms of AD and significantly alters its progression for individuals in the early stages (Sims et al., 2023; van Dyck et al., 2023).

Non-pharmacological therapies: These therapies focus on non-drug approaches to improve quality of life for individuals with Alzheimer's. Examples include CST, occupational therapy, exercise, and music therapy.

Lifestyle changes: Making changes to one's lifestyle, such as eating a healthy diet, engaging in regular physical activity, and maintaining social connections, can help manage the symptoms of Alzheimer's and improve overall health.

Experimental treatments: There are a number of experimental treatments that are being researched for Alzheimer's, including immunotherapy, gene therapy, and stem cell therapy. These treatments are still in the early stages of development

and are not yet widely available. Nevertheless, Lecanemab and Donanemab both belong to the category of immunotherapy for AD, and they have been already listed as effective medications for AD. In immunotherapy, the immune system is instructed to initiate an immunological response to exogenous cells or proteins, thereby eliminating them to prevent further complications. Lecanemab and Donanemab function by training the immune system to identify and eliminate the AD-associated amyloid protein. Lecanemab selectively interacts with amyloid at its early fibrillogenesis stage, while donanemab specifically binds to amyloid aggregates that have undergone clumping to form bigger cerebral plaques.

It's important to work closely with a healthcare provider to determine the best treatment plan for an individual with AD, as the specific treatment options will depend on the stage and severity of the disease, as well as individual factors such as overall health and medical history.

In terms of pharmaceutical treatment for AD, it is difficult to provide an exact number of medications for AD which have entered clinical trials, as this number is constantly changing as new compounds are developed and tested. Additionally, many compounds may be tested in early phase trials, but not continue to later stage trials if they do not show promising results.

However, it is known that there has been a significant effort to develop new treatments for AD, and many pharmaceutical companies and academic institutions have conducted clinical trials for drugs targeting various aspects of the disease. Despite this effort, the development of effective treatments for Alzheimer's has proven to be a challenging task, and many drugs that have entered clinical trials have not been successful in improving symptoms or slowing the progression of the disease.

As a result, there is a continued need for new treatments for AD, and many pharmaceutical companies and academic institutions are actively pursuing new pharmaceutical and non-pharmaceutical treatment approaches for the disease, with the goal of finding effective treatments to help manage the symptoms and improve quality of life for people with Alzheimer's.

1.2. Brain plasticity

The capacity of the brain to adapt to environmental stimulus or after suffering neurological impairment is known as neuroplasticity or brain plasticity (Wolf et al.,

2006). The concept of brain plasticity emerged from several key historical and scientific developments.

- **Early Neuroanatomical Observations**: In the 19th century, neuroanatomists like Santiago Ramón y Cajal made important observations about the structure of the brain, particularly with regard to the organization of neurons and their connections. These observations laid the foundation for understanding that the brain was not a static and fixed structure but could change over time.

- **Behavioral Studies**: Behavioral studies, particularly in the early to mid-20th century, provided evidence that the brain could adapt and reorganize in response to learning and experience. Pioneering research by psychologists such as Donald Hebb and Karl Lashley demonstrated that changes in behavior and learning were associated with changes in brain function and structure.

- **Functional Recovery After Brain Injuries**: Observations of individuals who had suffered brain injuries and were able to regain some lost functions contributed to the concept of neuroplasticity. These cases demonstrated the brain's ability to reorganize and compensate for damage, particularly in the context of stroke recovery and rehabilitation.

- **Animal Studies**: Experiments with animals, such as studies involving sensory deprivation, enriched environments, and brain lesions, provided further evidence of the brain's ability to adapt and rewire in response to changes in the environment or neurological conditions.

- **Advancements in Neuroimaging**: The development of advanced neuroimaging techniques, such as MRI and fMRI, allowed scientists to visualize and study the brain's structural and functional changes in response to various stimuli and experiences. These technologies provided more direct evidence of neuroplasticity in the human brain.

Brain plasticity is a broad concept that encompasses various forms of neural adaptation, nevertheless, there are other interconnected concepts in the field of

neuroscience including cognitive reserve, brain reserve, brain resilience, and compensation, which are all related to the brain's ability to adapt, recover, and maintain cognitive function under various circumstances.

1.2.1. Cognitive reserve, resilience and compensation

Brain plasticity, cognitive reserve, brain resilience, and compensation are all concepts related to how the brain functions and adapts to various challenges and changes. Although, they often overlap and interact in various ways, they have distinct definitions and implications. As these concepts are frequently used in the field of cognitive neuroscience, understanding their associations and differences are of great importance.

Brain plasticity plays a significant role in learning and memory, as well as in recovering from brain injuries or adapting to changing circumstances. It is closely related to the concept of brain resilience, as it enables the brain to bounce back from various challenges or injuries.

Cognitive reserve is a concept that suggests individuals with greater cognitive reserve have a buffer against cognitive decline or brain damage. It is the ability to use alternative neural networks or strategies to compensate for brain damage or decline. Cognitive reserve is associated with maintaining cognitive function in the face of age-related changes or diseases like Alzheimer's. It is often linked to factors like education, lifestyle, and intellectual engagement. Cognitive reserve can overlap with compensation, as it involves using alternative neural pathways to preserve cognitive function. However, it more focused on explaining individual differences in cognitive outcomes and the ability to withstand cognitive challenges.

Brain resilience refers to the brain's ability to withstand and recover from various stressors, including injuries, diseases, or emotional trauma. Resilience reflects the brain's capacity to adapt and maintain normal function under adverse conditions. It is often associated with the brain's ability to recover from trauma, adapt to changes, and maintain cognitive and emotional health in the face of adversity. Brain resilience can overlap with brain plasticity, as it involves the brain's ability to adapt and recover from injuries or stressors. Brain resilience is more concerned with the brain's capacity to withstand stressors and maintain function rather than the specific mechanisms of adaptation.

Compensation, in the context of brain function, refers to the brain's ability to adapt to cognitive deficits or changes by using alternative strategies or neural pathways. It involves the recruitment of additional brain regions to compensate for functional losses. Compensation is often seen in cases of brain injury or neurodegenerative diseases when the brain reorganizes to maintain cognitive function in the presence of damage. It can overlap with cognitive reserve, as cognitive reserve may facilitate compensation when the brain faces challenges.

In summary, brain plasticity and cognitive reserve are more general concepts, while brain resilience and compensation are more specific in terms of their focus on adaptability and functional preservation.

1.3. Enhancing brain functioning / plasticity

The etiology of AD is recognized as a process involving an amyloid cascade that ultimately results in neuronal death (Ballard et al., 2011). However, structural brain pathology, cannot fully explain the variability in clinical presentation and cognitive performance (STERN, 2002). The discrepancy brings up the concept of reserve, which includes both passive and active models, and offers a framework for comprehending the potential workings of psychological interventions that aim to improve cognitive functioning. Cognitive reserve and brain reserve are two types of reserve that are seen as complementary ways to deal with brain damage (STERN, 2002) (Yates et al., 2019). The concept of brain reserve can be understood as encompassing both passive and active coping mechanisms. In the passive aspect, brain reserve refers to an inherently larger capacity, allowing individuals to endure greater neural damage before cognitive deficits become apparent. This might involve having a higher number of neurons, more synapses, or redundant neural circuits (Yates et al., 2019). In contrast, the active component, often referred to as cognitive reserve, involves the efficient processing of tasks, enabling individuals to better withstand brain damage. This active mechanism may rely on either enhanced cognitive efficiency or the recruitment of compensatory processes to maintain function (Stern, 2012). A systematic review of 22 studies that followed 29,000 individuals over 7.1 years and used proxy measures of cognitive reserve (intelligence, occupation, and education) showed a decreased incidence of dementia (odds ratio [OR] = 0.54) (Yates et al., 2019). The study also identified complex mental activity in old age as a standalone indicator of a lower risk of dementia (MJ and P, 2006). Cognitive reserve is thought to manifest physiologically in synaptic organization or the utilization of brain networks, the latter of which may include the

capacity to recruit alternative networks or more effectively employ the same network (STERN, 2002). Neuroplasticity is an associated concept that describes our nervous system's capacity to change how it is organized in response to environmental pressure, physiological changes, and experience (Pascual-Leone et al., 2005). It can be seen structurally in changes to neuronal and synaptic structure, as well as functionally in changes to the activation pattern of various brain regions (Ganguly and Poo, 2013).
Development and learning rely on neuroplasticity mechanism (Pascual-Leone et al., 2005). During learning, the connectivity of brain networks, particularly those that are topologically complex or globally distributed, is reconfigured (Bassett et al., 2011).
As behaviorally relevant experience can remodel connectivity (activity-dependent plasticity) (Ganguly and Poo, 2013), we can propose that psychological interventions targeting the reinforcement of pre-existing neural connections, such as the recall of episodic memory in reminiscence therapy, may influence neuroplasticity and cognitive reserve differently compared to those that prioritize learning and novel experiences, such as cognitive training, cognitive stimulation, and cognitive rehabilitation (Yates et al., 2019).

1.3.1. Types of psychosocial interventions

When dementia first manifests clinically, episodic and prospective memory are typically the cognitive functions that are most severely impaired. The ability to mentally recreate past personal experiences is known as episodic memory, whereas the word "prospective memory" was more recently used to describe the ability to recall and complete tasks in a timely manner (McDaniel and Einstein, 2011). Prospective memory depends on medial temporal and frontal regions, whereas episodic memory relies on medial temporal structures (the hippocampus and parahippocampus). The parahippocampus and hippocampus serve as neuronal hubs or nodes and are intricately linked to cortical association areas. Perhaps the malfunctioning of the associated cortical areas over time leads to the deterioration of the hippocampus and parahippocampus.
Based on empirical research findings, it has been observed that individuals with dementia can still learn and retain some information and skills under appropriate conditions and with sufficient support and time, despite their memory challenges. Therefore, we can assume that cognitive assistance during memory construction would not only improve memory but also might prevent neuronal degeneration in light of the results that amyloid deposition in the association cortex precedes hippocampal

and parahippocampal degeneration. Interventions that follow the errorless learning principle and incorporate assistance during both encoding and retrieval tend to be particularly effective. Another key factor in achieving success is leveraging the relatively preserved cognitive functions, such as semantic memory and motor skills, to support impaired capacities. People with mild dementia exhibit learning capabilities in tasks related to explicit memory, reasoning, and other cognitive functions. However, for those with advanced dementia, the ability to learn is primarily limited to tasks involving implicit memory and motor skills (Bäckman, 1996; de Werd et al., 2013).

Psychological interventions aid people with dementia and cognitive decline in improving their cognitive abilities and preserving their functional autonomy. In addition, psychological interventions provide patients—and especially their caregivers—ways to avoid and handle behavioral issues as well as deal with the emotional and practical effects of the illness.

Any theoretically grounded, nonchemical, targeted, and reproducible intervention carried out with the patient or the caregiver and potentially resulting in some relevant benefit was operationally described as a non-pharmacological therapy. In essence, psychological interventions should include a justification for the intervention's design, a replication-safe process, and some empirical evidence proving the benefits that matter. Psychological interventions can concentrate on the dementia patient, the caregiver, or both.

Combining numerous clinical target domains with multiple target receivers creates opportunities for varied treatment methods (patients and types of caregivers). Psychological interventions should be created to enhance or support person-centered care. It is crucial for implementation and likely for psychological interventions' effectiveness that the recipient (the patient, the caregiver, or both) agrees and cooperates with the intervention. Psychological interventions can end the vicious cycle of having cognitive challenges, its frequent negative psychological reaction, and the following social isolation if it is practiced within these presumptions. The alternative provided by properly customized and prescribed non-pharmacological therapy is a favorable dynamic of adaptability, social inclusion, emotional stability, and cognitive acceptance.

The idea that psychological interventions can ameliorate symptoms and alter the substrate of essentially biological processes has empirical support (see **Table 2**). The stimulation of cognitive abilities may help to strengthen those capacities or at the very

least slow down their decline, similar to how the appropriate usage of an injured limb favors its maintenance and function. For individuals with dementia to respond in a way that is adaptive, environmental modification and cognitive restructuring are essential. From the patient's perspective, psychosocial therapies should offer significant advantages in terms of promoting activity and involvement, maintaining or improving functional ability, and achieving personally important goals despite cognitive decline. Additionally, psychological treatments can assist the patient and his or her relative in positively responding to and "coming to terms" with the illness (WILSON, 1997).

Table 2: Key characteristics of cognitive rehabilitation, cognitive training, and cognitive stimulation

	Cognitive rehabilitation	**Cognitive training**	**Cognitive stimulation**
Goal	improvement of personal performance	improvement of specific cognitive functions	improvement of general cognitive performance
Structure	a series of individual sessions with a family caregiver is usually necessary	Individual or group sessions	mostly group sessions
Methods	environmental changes, external assistance, cognitive and emotional adaptation	repeated Guided practice	semantic associations, reality orientation, reminiscence
Components	comprehensive evaluation, identification of relevant objectives	standardized tasks, with a variety of difficulties (adaptive), and access to computer	social interaction, orientation board, pencil and paper exercises, sensorimotor activities

1.3.2. Cognitive Stimulation Therapy

CST was effectively ‘conceived’ almost three decades ago. A useful snapshot of the era was provided by a timely editorial headlined "Tacrine and psychological therapy in dementia - No contest?" (Orrell and Woods, 1996). Tacrine, a medication formerly used to treat dementia, and other possible therapeutic treatments were then assessed through robust, randomised controlled trials (RCTs). In sharp contrast, "psychological therapies," which comprised particular initiatives like reminiscence or environmental

modification, simply lacked the supporting data. There were no evidence-based treatments that also provided a reproducible treatment manual; research was mostly small-scale, uncontrolled, and full of methodological faults. Therefore, despite modest benefits and risks of adverse effects, clinicians and policy makers were concentrating on pharmacological therapies, claiming that "gold-standard" evidence was simply not available for "psychological therapy" and evaluating it in a trial adhering to the same methodological expectations of any drug trial.

The largest, most rigorous, and effective investigation at the time had a considerable impact on later works. A group from the Hospital Broca in Paris oversaw this randomized control experiment (Breuil et al., 1994), and they referred to their therapy approach as "Cognitive Stimulation." This was different from the Reality Orientation (RO), which is the more conventional approach and is defined as "the presentation and repetition of orientation-based information." RO previously dominated the literature. Breuil's Cognitive Stimulation technique appeared to have special qualities, intuitively involving individuals in fun group cognitive exercises more so than RO, which had a more repeated component. Their study involved 56 dementia patients, and they discovered that giving them tasks like word association and item categorization significantly improved their cognition.

The original CST trial, conducted by Spector et al. in 2003, involved 201 participants and was a single-blind, multi-center RCT. When compared to those receiving standard treatment, it showed that participants in the 14-session program significantly improved their cognition and quality of life. As a result, the UK's "National Institute of Clinical Excellence" (NICE) published dementia guidelines in 2006 that included references to the 2003 CST study. Importantly, there had previously been no suggestions for a non-pharmacological approach to treating dementia's cognitive symptoms.

The release of training manuals has been a crucial step in enabling the wider deployment of CST. Three UK manuals have been released since a manual called "Our time: an evidence based group program to promote cognitive stimulation to persons with dementia - manual for group leaders" was first published in the United States (Spector et al., 2005). The original, 14-session CST program is described in "Making a Difference" (Spector et al., 2006), and the maintenance CST program is included in "Making a Difference 2" (Aguirre et al., 2012).

Importantly, the second handbook more clearly introduced the "essential principals" of CST (see **Table 3**). Clinical feedback that suggested it was necessary to explain the CST procedures and how it differed from other therapies was what motivated this.

The use of CST seems to have grown continually since its inclusion in guidelines. CST was developed in the UK, and translation and adaptation of it started pretty quickly after that. Concurrently, work was being done in numerous nations. According to the World Alzheimer Report (2011), CST should be routinely administered to persons with early-stage dementia. This was a catalyst for further developments. Currently, CST is being studied or used clinically in a number of countries. Additionally, there is supporting evidence for CST's potential efficacy and cost-effectiveness. However, there is a lack of evidence for the underlying mechanism of potential efficacy. Moreover , a systematic study (Fossey et al., 2014) emphasized the typical disconnect between evidence and practice in dementia care, highlighting that while numerous training manuals are available without an evidence base, only a small number of evidence-based interventions have repeatable training manuals.

Table 3: Main principles of CST

	Main principle	Description	Example
1	Mental stimulation	Engage people's mind	ask participants to calculate their score in each played games.
2	New thoughts and association	Encourage new ideas and making semantic associations.	Ask participants to point out similarities and difference between the shown objects or persons.
3	Integrating orientation, but sensibly and implicitly	Incorporating place, time and individual-related information into discussion.	tasting local or seasonal foods and fruits.
4	Opinions	Ask for opinions rather than facts.	Ask for opinions about political and economical issues.
5	Reminiscence as a tool for living in the present	Besides promoting well-being reminiscence helps people orient to the present by making comparisons with the past.	Making comparison between the items and costs in the past and the present.

6	Providing hints to aid recall	Providing multisensory cues and hints aids recall.	During the discussion, provide information about the date and orientation.
7	Consistency and continuity between sessions	Memory is enhanced through features song such as keeping sessions in the same room with the same facilitator, and use of a theme.	Assign a routine to the group, for example, one person can serve tea, another could lead the song, another could help set up.
8	Implicit (instead of explicit) method of learning	The use of subtle tasks enables more implicit learning because they avoid direct questions, focus on facts, and place people on the spot.	The informal nature of the 'current affairs' session may allow people to learn new things, but the discussion doesn't explicitly emphasize it.
9	Linguistic stimulation	The development of language skills is stimulated through the naming of people and objects, the construction of words, and the association of words with other words.	In the 'word games' session, asking people to describe words without actually using them.
10	Stimulation of executive function	Executive function skills are stimulated through various tasks, including discussions of similarities and differences.	In the 'categorising objects' session, executive functioning is utilized through mental organization.
11	Person-oriented	CST should value people, treat them as individuals, and foster a positive social environment.	Maintaining interest and relevance in the group's activities.
12	Respectful attitude	Diversity of opinions and views should be respected.	Promoting a diversity of viewpoints that stimulates interesting debate.
13	Engagement	Everyone should be involved in sessions, given the opportunity to contribute, and their interests should be taken into consideration.	Describe the next session and allow the group to assist you in preparing materials that everyone will find useful.
14	Inclusion	It is important for everyone to be included, which may mean that quieter people need extra assistance.	Encourage everyone to share their opinions regularly without putting them on the spot.
15	Choiceness	During activities, choices should be offered based on interests and abilities.	During the session on 'Being Creative', people can choose an activity that appeals to them.

16	Fun	A fun and enjoyable learning environment should be provided by groups.	Competitive elements can be introduced to team games and quizzes.
17	Potential maximization	Lack of stimulation or opportunity prevents individuals from reaching their potential. Sessions should maximize potential instead.	Provide a task that is sufficiently challenging without feeling like people have failed. For example, include prices as part of the 'food' session if appropriate.
18	Developing and strengthening relationships	Sessions should be held in a supportive environment where group members and facilitators can strengthen their relationships.	Participants should be encouraged to meet socially or in another context once groups end, such as at the same lunch club.

1.3.3. CST in Germany

Dementia is a serious public health issue that is recognized on a global scale (World Health Organization and Alzheimer's disease International, 2012). The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, which is widely accepted throughout the world, take a biomedical definition of dementia. However, there are several ways that various societies and cultures view dementia (Blay and Peluso, 2010; Enjolras, 2005; Pollitt, 1996; Poveda, 2003; Werner, 2005; Whitehouse et al., 2005). The quality of life (QoL) of those with dementia may be impacted by social relationships with persons due to tolerance or stigma (Goffman, 1963). These factors may result in either social support or discrimination. However, there haven't been many studies done to determine how dementia is portrayed and perceived around the world (Jeste et al., 1999). To data, most frameworks that have been used to adapt therapies to different cultures have adopted a 'top-down' theoretical approach(Hwang, 2009), which involves starting with theoretical concepts of how best to culturally adapt the program. However, in order to tailor treatments that target people with dementia, frameworks must first take into account how dementia is viewed in the culture where the intervention will be implemented. Therefore, it was determined that a community-based developmental strategy taking into consideration how people from different cultures interpret dementia was the most appropriate approach to generate the given guidelines. It was anticipated that this method of adjusting CST would maximize its ecological validity. The Formative Method for

Adapting Psychotherapy (FMAP), a 'bottom-up' technique that entails working with service users as a first step to generate and promote ideas for therapy adaptation, served as the foundation for the framework used to construct the guidelines for the CST adaptation (Hwang, 2009). Because the chosen model and framework for CST adaptation were developed concurrently with other adaptation models, it contributes to the expanding body of literature on culturally responsive therapy development.

In order to create the guidelines, the community-based FMAP approach with evidence from existing international groups were merged. The guidelines' goal was to make it easier to develop new culturally appropriate CST programs around the world.

The FMAP approach has five phases that are focused on creating knowledge and working with stakeholders, integrating that knowledge with theory, empirical, and clinical knowledge, reviewing the initial culturally adapted clinical intervention with stakeholders and revising it, testing the culturally adapted intervention, and finalizing the culturally adapted version of intervention (see **Figure 1**).

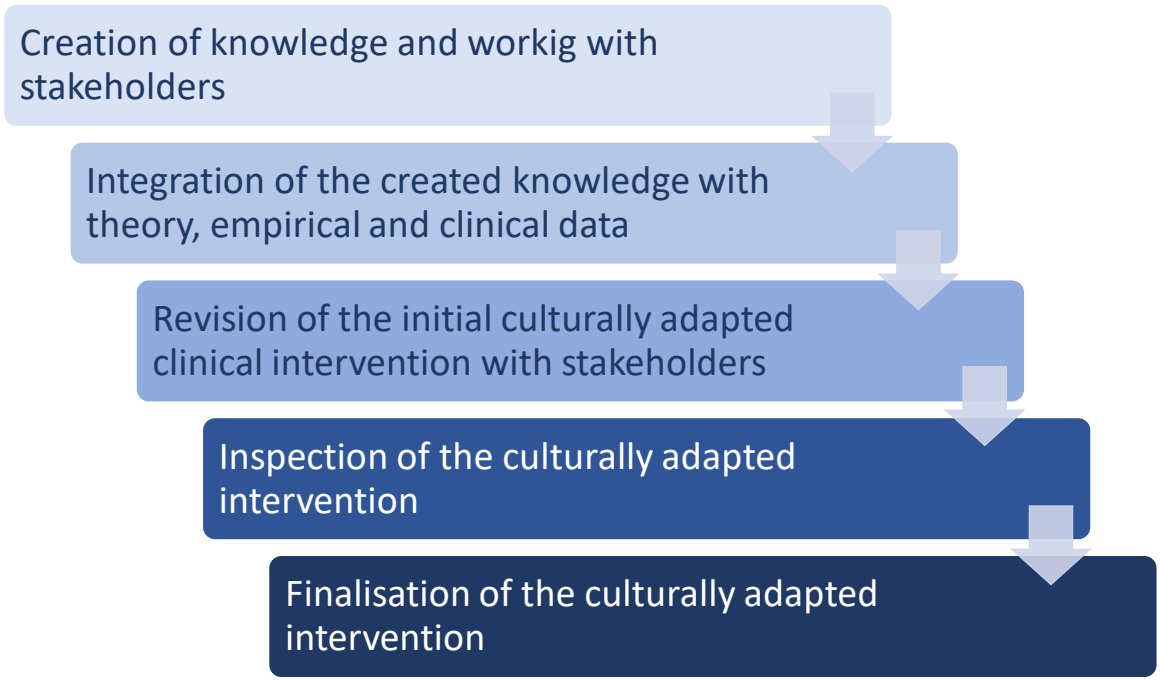


Figure 1: The five phases of the FMAP to other cultures (Hwang, 2006).

The FMAP model's phases can all be customized to fit the specific requirements of various projects. Additionally, examples from the past and present are used to explain how the FMAP is applied.

The initial phase to consider when adapting CST to a different culture is to choose which stakeholders to participate in the adaptation process and when to involve them.

Participants, mainstream health and mental healthcare practitioners, community-based organizations and agencies, traditional and indigenous healers, and spiritual and religious organizations are just a few examples of stakeholders included by the FMAP.

The information gathered from the focus groups held in the community will be combined in the second phase, and a new manual that has been culturally adjusted will be created.

In phase 3, it is advised that a second focus group be organized and held with the designated CST group facilitators after generating a draft of the culturally adapted CST manual. Initial reactions to the adapted intervention should be solicited at this focus group, along with suggestions for improvement. Special attention should be paid to the activities included in the revised and adapted manual. The guidebook will then be finalized before being put into use using this feedback.

In order to test the adapted program, the created CST manual from phase 3 should subsequently be piloted in phase 4 in various situations. This may entail implementing the entire program in two carefully chosen locations while testing its effectiveness using only the most basic outcomes, including cognitive and QoL measures.

In order to ensure sustainability and practicality (e.g., the frequency of sessions, number of participants, number of staff, duration of the sessions, transport, and financial constraints), the pilot should ideally be conducted in community centers that typically offer services for individuals with dementia.

Furthermore, gathering feedback from other staff and managers within the selected centers at this point will aid in their support and adaption of the CST program.

For phase 5 it is advised that participants and facilitators involved in the culturally adapted pilot in phase 4 are requested to participate in interviews or focus groups to elicit feedback regarding their experiences. For example what they liked, what they did not like, and their suggestions for program enhancement. Additional recommendations can be incorporated into the adapted program manual.

Issues pertaining to the development of the culturally appropriate German intervention for people with dementia were explored at two different gatherings. The lead for CST adaption in Germany fostered discussions.

1. At a workshop during the International CST Conference in London, July 2015, participants, including psychologists and occupational therapists from

Germany, the Netherlands, and Denmark, engaged in discussions. The workshop addressed two main topics: (i) the structure of the dementia healthcare system in Germany and (ii) the differences in health professional education between Germany and other European countries, with a focus on how these broader factors influence the implementation and accessibility of CST (Yates et al., 2019).

2. In January 2016, the National Dementia Guidelines Committee convened in Berlin, comprising professionals from dementia-related fields such as neurology, psychiatry, geriatrics, occupational therapy, speech therapy, physiotherapy, nursing, clinical psychology, and neuropsychology. The discussions focused on evidence-based recommendations for CST regarding specific outcomes. The Committee resolved to recommend CST as a psychosocial intervention aimed at enhancing cognitive function. Although improvements in QoL and depression observed in some RCTs were acknowledged, the guidelines would not specifically endorse CST as a primary intervention for these outcomes (Yates et al., 2019).

Findings from both events indicated that comprehensive materials are essential for the effective implementation of the modified program in Germany. This would enable medical professionals with limited preparation time, as well as nursing staff whose training is primarily focused on biomedical rather than psychosocial care, to efficiently organize CST sessions. For example, resources such as printable worksheets featuring word games, family trees, cognitive question cards, and images of artworks or advertisements would need to be readily accessible (Yates et al., 2019).

Results from the two events suggested that detailed materials would be necessary for the successful implementation of the modified program in Germany in order to allow medical professionals without scheduled preparation time or nursing staff with training that emphasizes biomedical care rather than psychosocial care to quickly prepare CST sessions. For instance, printable worksheets with word games, family trees, questions on thinking cards, images of works of art, or advertisements have to be available (Yates et al., 2019).

CST was strongly endorsed by the German Guidelines as the sole manual-based (and hence standardized and reproducible) psychosocial intervention. The use of outcome measures for both research and therapeutic evaluation was discussed. The CERAD-

NP (Consortium to Establish a Registry for Alzheimer's Disease, www.memoryclinic.ch) battery, which is more commonly employed, was recommended over the Alzheimer's Disease Assessment Scale (Mohs et al., 1997) due to its superior capacity to assess verbal episodic memory, particularly through delayed word list recall. It was proposed that the equivalence of these two measures be evaluated in the pilot study. QoL was considered a potential secondary outcome measure (Yates et al., 2019).

The severity of depressive symptoms, rather than a formal DSM diagnosis of major depression, was considered a relevant secondary outcome, as many patients exhibit depressive symptoms without meeting the full diagnostic criteria. However, at an individual level, CST may function similarly to a "pleasant activities" program, offering therapeutic benefits (Yates et al., 2019). Self-efficacy scores, which are also appropriate for non-depressed individuals and have been found to be responsive to various types of psychosocial therapies, were also taken into consideration as outcome measures in the pilot project (Kurz et al., 2012).

At the German Annual Meeting of Neuropsychologists in September 2016, the translation and adaptation of the CST program was introduced to a diverse audience of clinicians and researchers. During this presentation, activities within the CST program were mapped to specific cognitive functions. The repetitive, structured nature of the sessions was highlighted for its effectiveness in leveraging procedural memory, which tends to remain more intact in individuals with dementia compared to episodic memory. Additionally, the key CST principle of offering group members a variety of choices and encouraging decision-making was linked to the relatively better preservation of recognition memory over free recall in dementia patients. Although executive functions were consistently stimulated across sessions, they were particularly targeted in activities like Object Categorization and Thinking Cards. The presentation also included a comparison between CST and other therapeutic interventions available in Germany, as illustrated in **Table 4** (Yates et al., 2019).

The element of RO and its potential conflicts with a humanistic, person-centered approach were thoroughly examined. It was noted that individuals from the 1930s and 1940s in Germany, who grew up under authoritarian regimes, might have been subjected to a more rigid, sometimes violent, educational environment during their formative years. To avoid triggering negative associations or memory blocks, it was decided that questions related to the current date, time, and location, along with

specific word or number games, should be presented in a lighthearted and enjoyable manner. These activities would be framed as group quizzes rather than individual assessments to create a more supportive and engaging atmosphere (Yates et al., 2019).

Table 4: Available interventions for people with dementia in Germany (Yates et al., 2019)

Intervention	*Description*
Cognitive behavioral therapy (CBT)	Enjoyable activities and cognitive restructuring
Neurotransmitter stimulation	Pharmacological treatment approaches such as Acetylcholinesterase inhibitors (AChEI)
Person-centred, validating Dementia care approach	Focus on personal preferences and viewpoints, and discussion surrounding these
Reality Orientation (RO)	Using a whiteboard as a reality orientation board, reading and discussing real newspaper headlines at the beginning of each lesson

Following the workshop and subsequent meetings, the manual was translated into German utilizing the CST-recommended method of forward and reverse translation. The German adaptation team consulted closely with the original British authors of the CST manual to ensure the integrity of the intervention's core principles in the adapted version. Dementia care professionals were invited to participate in focus groups to assess the feasibility and acceptability of the adapted intervention in their specific settings. The translated manual underwent an initial review by two neuropsychologists, one psychology student, and a social worker, representing both community and residential care settings, to gather critical feedback on its practicality and potential for client acceptance (Yates et al., 2019). The following topics were recommended by the focus group:

- The manual's title should contain the term 'stimulation', similar to the English version, rather than a different German term used in previous translations, so that it is readily recognizable and associated with research reports (Yates et al., 2019).
- In this context, the title 'Making a Difference' was deemed to be unclear. Instead, the terms 'Basic course' and 'Advanced course' should distinguish Volumes 1 and 2 of the manual (Yates et al., 2019).

- To optimize the dual functionality of both manuals, a clear and comprehensive overview of corresponding sessions should be prominently featured. Additionally, the corresponding sessions from both the Basic and Advanced courses should be distinctly marked and highlighted throughout each manual to ensure ease of reference and integration (Yates et al., 2019).
- Session titles should prioritize emphasizing the thematic content (e.g., Words, Numbers, Money) rather than the concept of "gaming." In German, the term "gaming" is closely associated with "playing," which may evoke associations with children's activities. Therefore, reframing the titles to focus on the subject matter would ensure clarity and avoid unintended connotations (Yates et al., 2019).
- Several of the proposed activities, such as "Hangman" and bowling, are also well-known in Germany. However, some activities, like "thinking cards," were replaced by more familiar games, such as "Denk fix," which also uses cards with short, person-related or knowledge-based prompts (e.g., "Things that can fly" or "What adorns a person"). The first letter of the answer or the color of the box from which the card is selected is determined by a small turntable. Additionally, since Bingo is less popular in Germany compared to other European nations, it was substituted with the widely recognized "memory" game, where participants search for pairs of cards featuring famous faces, artworks, or household objects, either openly displayed or concealed (Yates et al., 2019).

Using the adapted manual, a feasibility assessment of the adapted CST intervention was conducted at both study sites. The fundamental CST sessions ran from May to July in 2016. A neuropsychologist led sessions with the assistance of a research associate. Patients were included if they had mild to moderate dementia (as determined by the DSM-IV criteria, were 65 years of age or older, were able to participate in group activities for up to one hour, could understand simple instructions, communicate verbally, and did not exhibit agitation or psychosis. The CST introductory course was evaluated in both a community and residential home setting (Yates et al., 2019).

Based on the results of the feasibility pilot study, the CST manual was modified further. The primary objectives of the feasibility study were as follows: (1) to evaluate the feasibility of conducting CST sessions in German settings; (2) to evaluate the

acceptability of the adapted CST sessions for persons with dementia and their caregivers; and (3) to identify any areas for further adaptation.

Following each session, feedback was gathered from clinicians, patients, and caregivers. Key outcome measures for the pilot study were administered, including the ADAS-Cog, the Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Battery (CERAD-NP), which also incorporates the Mini-Mental State Examination (Folstein et al., 1975), the Quality of Life in Alzheimer's Disease Scale (QoL-AD) (Logsdon et al., 1999), the Center for Epidemiological Studies Depression Scale (CES-D) (Eaton et al., 2004), and the General Self-Efficacy Scale (GSE) (Schwarzer, R., & Jerusalem, 1995). Despite the limited sample size, notable improvements were observed, particularly on the ADAS-Cog and GSE scales (Yates et al., 2019).

The guidelines outlined in this chapter offer a structured framework for the cultural adaptation of CST, ensuring that the adapted program upholds the same foundational principles, effectiveness, and impact on clinical outcomes for individuals with dementia as the original CST intervention (Orrell et al., 2014; Spector et al., 2003). These guidelines enable a systematic approach to ensuring cultural relevance and acceptability, while maintaining therapeutic efficacy scales (Yates et al., 2019).

The World Alzheimer's Report 2014 emphasizes that CST should be routinely administered to individuals with early-stage dementia worldwide. It highlights CST's potential as a cost-effective intervention to enhance cognitive function and quality of life, especially in developing nations where resources may be limited. These guidelines, therefore, play a crucial role in facilitating future adaptations of CST across diverse cultural and geographical contexts, ensuring its global applicability and effectiveness (Yates et al., 2019).

These recommendations provide guidance on how to culturally adapt the content and structure of CST without compromising its efficacy. The recommendations were founded on clinical and practical experience, as well as evidence from a review of the most commonly used frameworks for adapting therapy to other cultures. Specifically, the guidelines are based on the FMAP framework and its five stages. The evidence available from small investigations of the adapted programs indicates that they are also advantageous (Mkenda et al., 2018; Yamanaka et al., 2013). Despite the fact that guidelines have been developed and CST continues to be adapted for various cultures, additional research is required to investigate the cultural influences as a critical factor.

Previous research underscores the impact of culture on the understanding of dementia, the use of related services, and the experiences of both family and formal caregivers (Janevic and Connell, 2001; Yamanaka et al., 2013). As such, interventions tailored through culturally and linguistically informed, community-based methodologies are expected to align more closely with the specific norms, needs, and expectations of the culture and belief systems in question. This is important because attitudes and beliefs regarding aging and dementia are influenced by these cultural frameworks (Mukadam et al., 2011). Future research should therefore examine how culturally grounded interpretations of aging and dementia within different societal contexts may shape and affect the overall effectiveness of CST interventions (Yates et al., 2019).

Despite the establishment of a European consensus on outcome measures for evaluating psychosocial interventions in dementia care (Moniz-Cook et al., 2008), there remains a lack of robust evidence regarding the optimal outcome measures to assess intervention effectiveness. This gap hinders the ability to perform meaningful comparisons between studies and different interventions, thereby limiting the standardization and generalizability of research findings across the field (Yates et al., 2019). To gain a greater understanding of the efficacy of adapted interventions such as CST, additional research and consensus will be required, which is one of the main question in our research and will be mainly addressed from the next chapter onwards.

1.3.4. *Neurovitalis Senseful*

NEUROvitalis senseful was our CST of choice, which represents a cognitive stimulation intervention developed on the basis of the *NEUROvitalis* cognitive training program (Middelstädt et al., 2016). Independent from the adaptation route of cognitive simulation therapy in Germany, *NEUROvitalis* was developed in 2010 by Dr. Gisa Baller and the team of Prof. Elke Kalbe in 2010 at Cologne University hospital in Germany. *NEUROvitalis* cognitive training program is aimed at healthy older people as well as individuals with MCI or mild dementia (Baller, Kalbe, Kaesberg, & Kessler, 2009). *NEUROvitalis senseful* was modified for use with patients with mild to moderate dementia in that overly demanding elements were removed and those for multisensory stimulation and relaxation were added. The program consists of 16 sessions held twice a week for 60 minutes. The sessions take place in a group setting, optimally consisting of groups of between three and five participants. The structure of all sessions is the same and is as follows: At the beginning, a welcoming ritual takes place in which the mood of the participants is addressed. This is followed by the first of three phases,

which focus on practicing a cognitive area - executive functions, memory, language or social cognition. Afterwards, concentration and mental receptivity are to be strengthened by a short phase of relaxation. Elements of progressive muscle relaxation, mindfulness exercises and short movement sequences are used for this purpose. In the third phase of the intervention, sensory stimulation takes place, focusing on either the tactile, olfactory or auditory senses. Body language is also part of multisensory stimulation. Typical exercises include describing and matching scents or tactile materials and reading aloud a short story to which participants are asked to respond with appropriate light movements. Each session concludes with a closing ritual, which, like the welcoming ritual, relates to the psychological state of the participants. The main focus of the intervention is on the stimulation of cognitive functions. The activation of the memory is aimed at the treatment of meaningful images that refer to relevant past events and developments, such as the fall of the Berlin Wall or the introduction of the euro. The active recollection of the participants of the presented contents and an exchange about personal experiences is promoted. The category memory game also serves to activate the memory by assigning subordinate terms to the corresponding superordinate terms. The game format is similar to memory in that revealed cards can either be paired up or must be covered again for the next player. Executive functions are particularly enhanced by the use of two games (lateral thinking and city map game). Cross-thinking is an activation game in which color, shape and size combinations are to be assigned on a game plan according to partly interfering criteria and changing rules. Selective and divided attention are also stimulated. By means of the city map game, a city map is to be put together with individual route maps. Then selected target positions on the map are to be reached with a game piece and the shortest way between two positions is to be found or walked. With regard to language, word finding is to be stimulated by means of a dice game in which the participants are to find suitable terms for a given category. The terms should start with a randomly chosen letter. By discussing everyday pictures, common social interactions (e.g., a couple's walk in the woods, a mother and child arguing), and basic emotions in various exercises, the participants' social cognition is to be strengthened. In the other two phases of the intervention, cognitive functions are addressed and promoted at least indirectly. For example, during multisensory stimulation, procedural memory (movement history) or recognition (smelling and feeling) are also activated. When appropriate, an attempt is made to connect to the participants' biography and

engage them in conversations about personal experiences and opinions. Most exercises can be adapted to the patient's individual level of functioning by, for example, asking open-ended questions or providing response options. Compared to other stimulation interventions, *NEUROvitalis* senseful is characterized by complete standardization and manualization. In addition, a basic set of materials is provided, which makes the procedure additionally time-efficient in application.

The ADAS-Cog (Ihl & Weyer, 1993; Rosen et al., 1984), which was briefly mentioned above, was used in this study to assess global cognitive status and thus to test the hypotheses. Due in part to its sensitivity to change in moderately severe dementia, the test battery is very commonly used in studies examining the effects of pharmacological or psychosocial interventions in dementia patients (Benge, Balsis, Geraci, Massman, & Doody, 2009; Bond et al., 2012; Robert et al., 2010; Woods et al., 2012). Thus, the use of the established measurement instrument provides good comparability across different studies. The internal consistency is α = .82 and the scale correlates to r = -.81 with the MMST. The ADAS-Cog consists of 11 subtests that map the cognitive domains of memory, language, orientation, and perceptual-motor skills, such as praxia. The individual subtests, which are actively worked on by the patient in paper-pencil format, are shown below:

1. **Free reproduction**: A word list consisting of 10 words is presented and is to be learned in the process. Subsequently, the recalled words are to be named.

2. **Orientation**: Questions about spatial, temporal and personal orientation (name, place, time, date, day of the week, year, month, season) are to be answered.

3. **Imagination:** The patient is to perform individual steps necessary to make a letter ready for mailing. First, fold a piece of paper and put it in an envelope. Then this is to be taped shut, an address added, and a stamp stuck on it.

4. **Drawing:** Geometric figures (circle, intersecting rectangles, rhombus, cube) are to be traced.

5. **Instructions:** First, a fist should be made and then pointed first to the ceiling and then to the floor. Then three objects placed on the table (pencil, wristwatch, postcard) are to be placed in position according to the instructions.

6. **Naming**: Each finger of a hand is to be named. Then, 12 pictured objects are to be named correctly.

7. **Word recognition**: 12 words are presented to be learned. Then both the learned words and 12 new words are shown. It is to be decided which words are from the learned list.

The test administrator answers the four other items based on behavioral observation.

8. **Test instruction forgetting**: The test administrator indicates how often the patient had to be reminded of the test instruction in the word recognition subtest.

9. **Verbal fluency**: The test administrator indicates the extent to which the patient had difficulty making himself understood during the examination period.

10. **Comprehension of spoken language**: The test administrator indicates the extent to which the patient had difficulty in understanding spoken language during the examination period.

11. **Word-finding difficulties in spontaneous speech**: The test administrator indicates to what extent the patient showed problems in word finding during the examination.

The test battery takes approximately 40 minutes to complete. A maximum of 70 points can be achieved, which corresponds to the greatest possible impairment. A lower score accordingly indicates lower cognitive deficits.

1.3.5 Current evidence for CST effects

Cognitive therapies may be able to counteract the diseased foundation and mechanism of dementia in light of discoveries of neuroplasticity in the brains of people

with blindness and other disorders (Vemuri et al., 2016). CST has been shown to improve cognition in persons with mild-to-moderate AD (Woods et al., 2023, 2012). However, the precise cognitive and neurobiological mechanisms underlying its effects remain largely unidentified. To date, only a limited number of studies have explored the neuropsychological pathways involved in these changes. Gaining a deeper understanding of how non-pharmacological interventions produce cognitive and neural modifications will be crucial for refining intervention design. This could have significant implications for optimizing participant selection, including determining the most appropriate intervention time frames or stages of the disease to maximize therapeutic benefits (Yates et al., 2019).

CST entails engaging the person in enjoyable cognitive tasks that do not primarily involve practicing particular cognitive areas. It was developed based on the documented cognitive benefits of RO, with an added social component (Spector et al., 2010). These features of CST are consistent with the theoretical frameworks of general cognitive reserve, neuroplasticity, and current advances in understanding brain functioning from a large-scale brain network perspective. In the next chapter, we briefly outline the previous evidence of cognitive therapies' mechanisms (Yates et al., 2019).

1.3.5.1 Neuorpsychological evidence of CST mechanisms

Few studies have explored the neuropsychological mechanisms underpinning CST. In a previous randomized controlled trial (RCT) involving 56 participants, Breuil et al. (1994) examined the effects of a general cognitive stimulation approach and found improvements in memory and learning following 10 sessions conducted over five weeks. These improvements were measured using the Word List Memory Test (WLMT) within the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery (Morris et al., 1989). The cognitive benefits observed were notably linked to a higher baseline cognitive score and a lower level of education (Yates et al., 2019).

Using the standard CST protocol defined by Spector et al. (2003), two more recent studies have investigated mechanisms of action. In an RCT involving 201 individuals with dementia (Spector et al., 2010), generalized cognitive improvements were observed, particularly on the cognitive subscale of the ADAS-Cog (Rosen et al., 1984). Notably, improvements were found in the language subscale, though no significant changes were observed in other subscales. The authors concluded that CST may enhance general cognition by improving language function, possibly through the

formation of new semantic connections (Spector et al., 2010). Hall et al. (2013) reached similar conclusions using a different set of neuropsychological tests. In a smaller sample of 34 dementia patients, they observed post-intervention changes in memory, syntactic comprehension, and orientation. The authors hypothesized that CST's language-based components might enhance syntactic processing and facilitate verbal recall by creating new semantic links, leading to broader cognitive benefits (Yates et al., 2019).

1.3.5.2 Findings from neuroimaging studies

Studies using positron emission tomography (PET), single-photon emission tomography (SPECT), and fMRI have revealed changes in the brains of healthy volunteers, MCI patients, and AD patients who underwent cognitive-focused psychological therapies (Hosseini et al., 2014; van Os et al., 2015). When doing previously trained memory tasks, healthy older adults showed an increase in hippocampal perfusion and a decrease in frontal cortex activation compared to baseline perfusion (van Os et al., 2015). These findings imply that the hippocampus is neuroplastic, resulting in higher neuronal efficiency.

Activation of several frontal and parietal cortical regions, unrelated principally to the trained cognitive tasks, was also consistently seen in participants with MCI after memory training, and this activation was connected with clinical improvement. These adjustments imply that memory training may trigger compensation mechanisms and reallocate cognitive functions in mildly brain-damaged individuals to restore the affected functions (Hosseini et al., 2014; van Os et al., 2015).

Evidence from functional MRI in dementia patients is also encouraging. 60 individuals with mild to moderate AD participated in a RCT, in which Baglio et al. examined the outcomes of a 10-week, rigorous multi-component stimulation program. The superior temporal gyrus, the right insular cortex, and the thalamus were all activated in the experimental group, along with improvements in language, memory, and neuropsychiatric symptoms; however, no changes were seen in the control group, which received standard medical treatment. Additionally, there were strong connections between the changes in cognitive function and the level of increased activity in the left superior temporal gyrus, the precuneus, and the left thalamus (Baglio et al., 2015).

In a study employing MRI spectroscopy (H-MRI), several chemicals were assessed before and after memory training in a cohort of 11 adults with mild cognitive impairment (MCI) (mean age 68). Post-intervention analysis revealed a significant reduction in choline-containing compounds within the hippocampus (Yang et al., 2016). These findings were regarded as evidence of the existence of brain alterations brought on by memory training because hippocampal choline is often increased in aging and AD (i.e. neuroplasticity) (Yates et al., 2019).

The evidence derived from clinical, neuroimaging, and biological studies supports a model in which psychosocial interventions in neurodegenerative dementia lead to a delay in cognitive and functional decline. This delay is attributed to the reallocation of neural resources involved in various cognitive functions, without altering the lesional load or the overall duration of the disease. From both personal and societal perspectives, this treatment response is currently considered relevant and adequate for managing neurodegenerative disorders (Pouryamout et al., 2012).

1.4. Scope of the thesis

Our primary objective is to unravel the intricate mechanisms underpinning the potential efficacy of CST in addressing the cognitive challenges associated with AD. Leveraging the promising capabilities of MRI in discerning subtle structural and functional alterations in the brain, we have embarked on a pioneering research endeavor. This study, conducted at the Neurology Department of Cologne University Hospital, involves a group of mild to moderate AD patients who have undergone our CST program. By utilizing MRI, we aspire to shed light on the neural transformations that may underlie the cognitive benefits observed in patients participating in our therapy, thus advancing our understanding of CST's therapeutic potential for individuals afflicted by AD.

Building upon the current wealth of knowledge concerning the pivotal role of neuroplasticity as the proposed underlying mechanism of CST, and the fact that brain plasticity may appear as compensatory effects in brain imaging studies, we have first taken a pioneering step in establishing a comprehensive framework to detect resting-state compensatory effect in healthy aging and MCI. Having ascertained the presence of brain plasticity-driven compensational effects in the context of both healthy aging and MCI, our research endeavors were directed toward unraveling the remarkable capacity of CST in mitigating cognitive decline in mild to moderate AD patients. Importantly, our study was designed to delve into the underlying mechanisms

responsible for the putative positive impact of CST, and we harnessed the power of MRI to help us unveil the intricate neural transformations at play.

1.4.1 Revealing compensatory mechanisms in aging and prodromal AD (RIMCAD-study)

Brain plasticity refers to the ability of the brain to change and reorganize itself in response to experience and injury. This process allows the brain to compensate for damage or dysfunction by forming new connections and pathways. As a result, compensation through brain plasticity plays a crucial role in recovering lost functions and maintaining normal brain function.

Brain plasticity allows for the formation of new neural connections, which can support the development of new skills and the improvement of cognitive function. CST is designed to enhance brain plasticity and promote compensatory mechanisms in individuals with cognitive decline or impairment. Thus, individuals with higher levels of brain plasticity may be more likely to show positive efficacy from CST. However, other factors such as the type and severity of cognitive impairment, the intensity and duration of therapy, and individual differences in motivation and engagement can also impact the outcome of CST.

Prior to beginning with our research on CST, in the first section of my study, we opted to detect traces of compensation in healthy brain aging and prodromal AD.

There have been reports indicating divergent effects of aging on brain functions: elderly individuals demonstrate decreased activity in certain brain regions while exhibiting increased activity in others (Cabeza et al. 2012). These findings, which are backed by a body of research showing a general deterioration in structural and functional brain integrity in AD, cast doubt on the conventional wisdom that aging is exclusively associated with a straightforward pattern of cognitive and neurological decline.

Several studies have investigated how the brains of AD patients remodel themselves, attributing these changes to brain plasticity (delEtoile et al. 2017). Contrary to the primary assumption, these and other studies have demonstrated that neuroplasticity is not exclusive to children (Dennis et al. 2013) but is also observed in the healthy brain aging (Fuchs et al. 2014) and even in the context of neurodegeneration (Enciu et al. 2011), including AD (delEtoile et al. 2017) (Behfar et al., 2020).

The latter findings led to the development of the 'neuronal compensation' concept. Despite its widespread use, the concept of compensation remains somewhat ambiguous due to the poorly understood underlying neurological mechanisms (Behfar et al., 2020). This ambiguity is partly attributable to the difficulty in defining the characteristics of compensation and the challenge in assessing these characteristics in vivo (Gregory et al. 2017). Consequently, several theoretical models of compensation in healthy aging and in the context of neurodegeneration have been proposed (Gregory et al. 2017) (Behfar et al., 2020).

The majority of existing compensation theories were developed within task-based contexts, while compensatory processes in resting-state networks in healthy brain aging and early neurodegeneration have rarely been discussed. Resting-state studies, however, offer several advantages over task-based studies, as they impose fewer demands on experimental design, participant compliance, instructions, and training requirements. Cabeza et al. proposed essential criteria for an observed enhanced connectivity to be considered compensatory (Cabeza et al. 2018). For instance, increased connectivity should be directly or indirectly associated with a neural resource deficiency or a supply-demand imbalance (Cabeza et al. 2012; Lövdén et al. 2010) (Behfar et al., 2020).

These changes may result from brain atrophy, decreased cerebral perfusion, or neurotransmitter deficiency (Cabeza et al. 2018). Within the framework of resting-state network connectivity, we proposed four criteria to identify compensatory mechanisms: First, the brain area must exhibit a significant enhanced functional connectivity. Second, this increase in functional connectivity must coexist with a loss of brain integrity in that region, such as volume reduction (Cabeza et al. 2012; Seeley et al.2010). Third, to exclude nonselective neuronal recruitment, the region must be specifically associated with cognitive processing (Cabeza, 2002; Logan et al., 2002). Finally, the increase in connectivity in that region must be positively correlated with cognitive performance, thereby differentiating compensation from nonspecific and maladaptive recruitment, where higher connectivity is not linked to improved cognitive performance (Cabeza et al. 2012) or is even associated with worse performance (Bakker et al., 2012) (Behfar et al., 2020).

We employed graph theory analysis within our novel criterion-oriented paradigm to investigate resting-state compensation in healthy brain aging and prodromal AD. We postulated that during both healthy aging and MCI with biomarkers indicative of AD,

brain areas would exhibit compensatory mechanisms characterized by a significant enhancement in degree centrality (DC), despite the presence of atrophy. Furthermore, we posited that higher DC in these brain regions would be positively correlated with better cognitive performance, signaling effective compensation (Behfar et al., 2020).

1.4.2 Yielding brain plasticity by CST in early and moderate AD (CogStim-study)

The most frequent cause of dementia is AD, a neurodegenerative condition that progresses over time. Patients with AD experience BPSD (Lyketsos et al., 2000), which affect the overwhelming majority (80-90%) of them. As these clinical symptoms negatively impact the patients' quality of life, they often require ongoing supervision and assistance for their activities of daily living. Prolonged hospitalization, elevated healthcare costs, morbidity, and mortality are significant consequences of behavioral and psychological symptoms of dementia (BPSD) (Brodaty et al., 2015; Laganà et al., 2022; Peters et al., 2015).These outcomes lead to considerable suffering for patients and their caregivers, and impose a substantial burden on society (Behfar et al., 2023). In the absence of a definitive cure, the primary pharmacological treatments for Alzheimer's disease (AD) consist of cholinesterase inhibitors and excitatory amino acid receptor antagonists. However, both classes of drugs demonstrate limited efficacy in addressing the cognitive and memory-related symptoms associated with AD (Ballard et al., 2005; Campbell et al., 2008; Massoud and Léger, 2011; Sato et al., 2011; Sink et al., 2005). Behavioral and psychological symptoms of dementia (BPSD), which can exacerbate cognitive and functional impairments, are frequently managed with antipsychotics and anticonvulsants; however, these medications are associated with a higher incidence of adverse events (Seibert et al., 2021) (Behfar et al., 2023).

Recently approved anti-amyloid medications such as Aducanumab and Lecanemab demonstrated only a restricted clinical impact, despite the robust and convincing alterations observed in amyloid-imaging results (Budd Haeberlein et al., 2022). Moreover, the existing anti-amyloid medications are difficult to adopt in clinics due to increased administrative and financial burden, and their potential efficacy is limited to patients with MCI. Given the current limits in pharmacological options, the study of non-pharmacological therapies gains increasing interest (Behfar et al., 2023).

A non-pharmacological treatment strategy aims to counteract cognitive decline and potentially alleviate the severity of BPSD symptoms with efficacy comparable to pharmacological approaches (Brodaty and Arasaratnam, 2012). Various non-pharmacological interventions have been proposed for managing cognitive impairment and BPSD in AD patients, including non-invasive brain stimulation, physical therapy, reminiscence therapy, cognitive training, and cognitive stimulation (Abraha et al., 2017; Berg-Weger and Stewart, 2017). Consequently, current dementia treatment guidelines predominantly advocate for non-pharmacological interventions such as CST as the primary treatment approach (Li et al., 2022) (Behfar et al., 2023).

CST is one of the most widely endorsed non-pharmacological interventions, incorporating a range of group activities, exercises, and discussions to improve overall cognitive and social functioning (Woods et al., 2023, 2012). Systematic reviews and meta-analyses have demonstrated significant cognitive improvement induced by CST in patients with mild to moderate stages of Alzheimer's disease dementia (Aguirre et al., 2013; Alves et al., 2013; Buschert et al., 2010; Chen, 2022; Huntley et al., 2015; Woods et al., 2023, 2012). Additionally, although based on a relatively smaller number of studies, CST has shown clinically promising effects on several outcome measures, including quality of life (Aguirre et al., 2013; Buschert et al., 2010; Woods et al., 2023, 2012) (Behfar et al., 2023).

Language has been identified as a primary domain of change in CST, owing to the verbal stimulation activities involved (Lobbia et al., 2019; Spector et al., 2010). However, the literature remains fragmented and inconclusive regarding the mechanisms underlying these changes. Early research on the effects of CST in AD did not provide evidence on its neurobiological mechanisms (Buschert et al., 2010) (Behfar et al., 2023).

Recent studies and theoretical frameworks suggest that CST-induced cognitive improvements in individuals with dementia may be associated with brain and cognitive reserve (Liu et al., 2018). The concept of cognitive reserve, which has gained attention in AD research, posits that compensatory cognitive strategies, more common among individuals with higher education and cognitively demanding lifestyles, help maintain cognitive performance despite brain pathology. Consequently, the duration of formal education has been widely proposed as a robust indicator of cognitive reserve in both early and recent studies (Farfel et al., 2013; Jefferson et al., 2011; Roe et al., 2007; Wilson et al., 2019). Another approach, on the other hand, is the concept of brain

reserve, which claims that greater efficiency and capacity of the networks involved in cognition, for example, through more neurons, synapses, or additional neural networks, allows individuals to sustain superior levels of cognitive functioning despite brain damage (Marques et al., 2016; Serra et al., 2017; Steffener and Stern, 2012)(Behfar et al., 2023).

Neuroimaging studies indicate that prolonged maintenance of cognitive performance is associated with enhanced functional connectivity and increased efficiency across various cortical regions (Vuoksimaa et al., 2013). Additionally, it has been suggested that CST can modify neuronal excitability, inducing brain plasticity and compensatory mechanisms (Cespón et al., 2018). Despite the available evidence and its potential cognitive benefits, the specific mechanisms underlying CST remain unknown. Due to the complex nature of CST, understanding its mechanisms without insights into brain-level activities has proven challenging (Behfar et al., 2023).

Brain connectivity analysis provides an opportunity to enhance our understanding of the underlying mechanisms of non-pharmacological approaches such as CST. Despite a growing body of research on the effects of CST in Alzheimer's disease dementia, there is a notable lack of imaging studies, even though such studies often reveal greater effects compared to purely cognitive investigations (Rose and Donohoe, 2013). fMRI-based brain network connectivity analysis could offer experimental data on the potential neuropsychological mechanisms underlying CST. Brain network connectivity can be altered by behaviorally relevant activities, a phenomenon known as activity-dependent plasticity (Ganguly and Poo, 2013). Learning can lead to the restructuring of topologically complex or widely distributed brain networks (Bassett et al., 2011). Therefore, combining CST with fMRI could provide innovative insights into the fundamental brain plasticity mechanisms involved in CST. Additionally, follow-up studies investigating the extent and sustainability of potential CST effects are warranted (Behfar et al., 2023).

This study investigated (i) the effectiveness of a CST program, consisting of sixteen 60-minute sessions administered twice weekly over an eight-week period, with a follow-up assessment after three months, and (ii) the underlying neural correlates using MRI. We hypothesized that CST would improve global cognition, Behavioral and Psychological BPSD, and QoL in individuals with mild to moderate Alzheimer's disease dementia. Additionally, we examined whether cognitive improvements following CST were associated with enhanced brain connectivity supporting memory and cognition.

We assessed the correlation between pre- and post-intervention imaging findings and the neuropsychological outcomes of the intervention compared to a no-intervention control group (Behfar et al., 2023).

2. Materials and methods

2.1.1 Participants of RIMCAD-study

This study was conducted as part of the RIMCAD-study (Retroactive Interference during Memory Consolidation in Aging and Dementia) undertaken by the Memory Clinic Köln Jülich. The RIMCAD-study received approval from the ethics committee of the medical school at the University of Cologne. From the larger participant pool of the RIMCAD trial, three experimental groups were established for the current study: (i) fifteen young healthy controls (young HC), (ii) fifteen elderly healthy controls (senior HC), and (iii) fifteen patients with MCI (Behfar et al., 2020) (see **Table 5**).

Given that MCI encompasses a diverse population (Petersen et al. 2001), we exclusively enrolled participants with prodromal AD according to the IWG-2 criteria (Dubois et al., 2016, 2014), requiring at least one positive AD biomarker. Biomarkers indicative of AD included amyloid deposition, as determined by positron-emission tomography (PET), or abnormal concentrations of cerebrospinal fluid (CSF) amyloid-42, abnormal concentrations of phospho-tau, or a total tau/amyloid-42 ratio greater than 0.52 in CSF samples (Duits et al. 2015) (Behfar et al., 2020).

All patients with MCI exhibited amnestic symptoms, with 40% also displaying impairments in executive function. Informed written consent was obtained from all participants, who received financial compensation upon completion of the study. All participants had normal or corrected-to-normal vision and were right-handed, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971) (Behfar et al., 2020).

Regarding the exclusion criteria, participants were screened for neurological and psychiatric conditions such as epilepsy, Parkinson's disease, multiple sclerosis, traumatic brain injury, depression, mania, or schizophrenia (Behfar et al., 2020). Additionally, respiratory, cardiovascular, gastrointestinal, and kidney-related disorders, as well as past and present drug or alcohol addiction, were exclusion criteria (Behfar et al., 2020). Potential MRI contraindications, including claustrophobia, non-removable piercings, pacemakers, and magnetic implants, were also assessed beforehand. The

sample size was determined through a post-hoc analysis using G*Power 3.1 (Faul et al., 2007) and IBM SPSS, version 23.0 (Behfar et al., 2020).

Table 5: demographic data of MCI, senior HC and young groups (Behfar et al., 2020).

	Young HC	Senior HC	MCI
sample size (n)	15	15	15
Sex(%male)	60	60	60
Age	24.4±2.85	67.26±8.11	71.13± 5.76
Education (years)	15.53±4.44	14.6±3.62	12.46±3.65
MMSE	N/A	29.53±0.61	25.14±3.18

Abbreviation: MMSE, Mini-Mental State Examination.

2.1.2 MRI acquisition and preprocessing

At the Research Center Jülich, MR imaging was performed on each participant in the study. Structural MRI and resting-state fMRI data were acquired using a 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany). T1-weighted structural images were collected with a rapid gradient echo sequence using the following parameters: repetition time (TR) = 2250 ms, echo time (TE) = 3.03 ms, flip angle (FA) = 9°, field of view (FOV) = 256 × 256 mm², voxel size = 1 mm isotropic, and 176 gapless interleaved sagittal slices. During the 7-minute resting-state image acquisition, patients were instructed to remain awake and alert, with their eyes open and not focused on anything specific. Functional images were obtained using echo planar imaging (EPI) with the following parameters: TR = 3000 ms, TE = 30 ms, FA = 90°, FOV = 200 × 200 mm², voxel size = 2.5 × 2.5 × 2.8 mm, interleaved oblique slices parallel to the infra-supratentorial line, and a gap of 0.28 mm (Behfar et al., 2020).

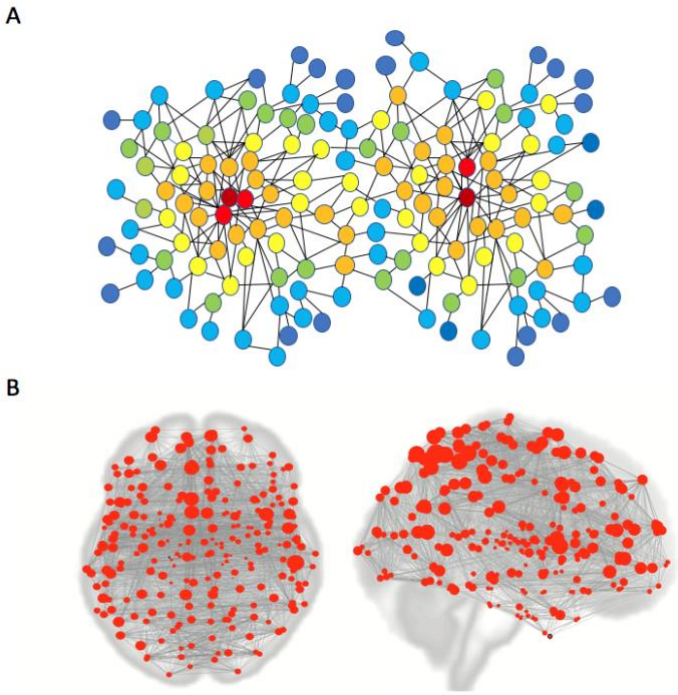
Data were preprocessed using the default preprocessing workflow of the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). The first four images of the 155 volumes were discarded to allow the signal to reach equilibrium. Functional images were realigned to the first acquired volume of the session. EPIs were co-registered to the high-resolution T1 structural image, normalized to the Montreal Neurological Institute (MNI) stereotactic space, and resampled to a voxel size of 2 × 2 × 2 mm³. To address motion-related artifacts (Conwell et al., 2018), frame-wise displacement (FD) was included as a covariate of no interest in our models, estimated according to the method suggested by (Jenkinson et al. 2002). This method is preferred for FD

estimation due to its consideration of voxel-wise differences (Yan et al. 2013) (Behfar et al., 2020).

2.1.3 Graph theory analysis

Graph theory is a standard paradigm for the mathematical modelling of networks. The graph G(N, K) can be used to depict a network, where N denotes the number of nodes and K is the number of edges. DC is a straightforward indicator of a node's relevance in a network by measuring its connectedness to all other nodes. The degree of node *i* is defined as the number of edges connected to it and is computed *by* $k_i=\sum_{j\in G}a_{ij}$ (a_{ij} is the i^{th} row & j^{th} column element of adjacency matrix *A)* (Wang, 2010). In graph theory and network analysis, indicators of centrality identify hub nodes, which have more edges than the average in a network (Behfar et al., 2020) (see **Figure 2**).

Figure 2: Network and the concept of degree centrality (Behfar et al., 2020).



(A) in the illustrated network, the red nodes have the highest degree centrality, and the color spectrum from red to blue represents the gradual reduction of degree centrality (B) Red circles represent the nodes in a brain network, composed of 246 nodes. In this network, each node is one of the 246 ROIs of the Brainnetome Atlas.

In order to apply graph theory analysis to fMRI scans, BOLD (blood oxygen level dependent) time series of brain activity was employed, and Brainnetome Atlas with 246 ROIs was imported as the nodes of the network (Behfar et al., 2020).

We utilized the Brainnetome Atlas (Fan et al., 2016) in conjunction with the CONN toolbox (Whitfield-Gabrieli et al. 2012) to generate connectivity matrices. This was achieved by averaging the time series of the BOLD signals for all voxels within each ROI and computing the Pearson's correlation of these average signals between ROIs. The ratio of the remaining robust connections to the total number of connections is defined as cost, ranging from 0 to 1. Setting extremely large values for cost retains weaker edges and noisy connections, whereas assigning very small values removes too many edges, resulting in a disconnected graph. By setting the cost as a threshold in a network of n nodes (N), one can maximize the global cost efficiency (GCE) of the network (Bassett et al., 2009) , which is computed as (Behfar et al., 2020):

$$GCE = GE - Cost \quad (1)$$

$$GE = \frac{1}{n}\sum_{i\epsilon N} E_i = \frac{1}{n}\sum_{i\epsilon N} \frac{\sum_{j\epsilon N, j\neq i} {d_{ij}}^{-1}}{n-1} \quad (2)$$

Where G*E* and E_i denote the global efficiency and the efficiency of node *i*, respectively, while d_{ij} represents the shortest path length between nodes i and j. Additionally, weighted connectivity matrices can be binarized using an optimal threshold on connectivity matrices (Bassett et al., 2009; Dimitriadis et al., 2010). The CONN toolbox facilitates the computation of global and nodal graph metrics on both binary and weighted networks. At the individual subject level, we performed a ROI-to-ROI analysis incorporating all regions defined by the Brainnetome Atlas (Fan et al., 2016), determining the optimal cost that maximizes the global efficiency for each group. The optimal cost was respectively 17.5% ± 2.5% (mean ± SD), 18% ± 3% and 18.5 ± 2.5 % across young HC, senior HC and MCI groups, where the average maximum GCE of 0.36 ± 0.03 in all groups were obtained. Then, the generated weighted connectivity matrices were converted into binary matrices using a cost of %18 on positive correlations, which was the average of the optimal cost among all three groups (Behfar et al., 2020).

Graph theory analyses were performed on three distinct groups: young HC, senior HC, and subjects diagnosed with MCI. Adjacency matrices and network measures were computed for each ROI. Between-group differences in DC were assessed using two-tailed t-tests with a significance threshold adjusted for false discovery rate (FDR) to $p < 0.05$. This analysis encompassed two separate comparisons: (1) young HC versus senior HC and MCI, and (2) senior HC versus MCI. For the first comparison, sex and

education were included as covariates of no interest, while for the second comparison, age, sex, and education were considered, with age additionally serving as a covariate of interest (Behfar et al., 2020).

2.1.4 Brainnetome Atlas

The Brainnetome Atlas (Fan et al., 2016), comprising 246 regions of interest (ROIs)—including 210 cortical and 36 subcortical subregions (see **Figure *2***)—is delineated based on meta-analyses of task-based functional imaging studies (Fan et al., 2016), This atlas provides fine-grained parcellations and extensive coverage of functional connectivity, features typically lacking in other human brain atlases (Behfar et al., 2020).

The Brainnetome Atlas was developed using noninvasive multimodal imaging techniques to establish a connectivity-based parcellation framework that defines the subdivisions of the human brain, thereby unveiling novel aspects of its connectivity architecture. This atlas integrates brain connectivity data with cytoarchitecture and other microscale information. The delineated structures in the Brainnetome Atlas are correlated with mental processes using the BrainMap database (Balsters et al. 2014; Fox et al. 2014a; Laird et al. 2009), provide an initial estimation of the mental processes associated with each cortical and subcortical region (Fan et al., 2016). The functional properties of each subregion in the Brainnetome Atlas are derived from the behavioral domains and paradigm class metadata labels of the BrainMap database (www.brainmap.org/taxonomy), utilizing both forward and reverse inferences (Cieslik et al., 2013; Clos et al., 2013; Eickhoff et al., 2011; Fan et al., 2016; Fox et al., 2014) (Behfar et al., 2020).

2.1.5 Volumetric analysis

To identify regions that meet the criteria for compensation, as defined in the introduction, and to distinguish regions of interest (ROIs) exhibiting significant atrophy, a volumetric analysis was conducted using the Computational Anatomy Toolbox (CAT12, Version 12.1, http://dbm.neuro.uni-jena.de/cat/). This toolbox is an extension of Statistical Parametric Mapping (SPM12; Wellcome Centre for Human Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and is implemented in MATLAB R2015b (The MathWorks, Natick, USA) (Behfar et al., 2020).

Following segmentation of all T1 images into gray matter (GM), white matter (WM), and cerebrospinal fluid, all images were normalized to MNI space using DARTEL with six iterations and the integrated DARTEL template in MNI space (Ashburner et al. 2009; Mechelli et al.2005). During the registration step, local GM and WM volumes were preserved by adjusting their Jacobian determinants. Subsequently, the normalized GM images were smoothed with a Gaussian filter (FWHM = 8 x 8 x 8 mm). The GM volumes of the ROIs with significantly higher measures of DC identified in the group contrast were then extracted for statistical analysis (Behfar et al., 2020).

2.1.6 Neuropsychological tests

From the comprehensive set of neuropsychological assessments conducted in the RIMCAD study (for detailed methodology, see (Conwell et al. 2018) two specific tests were selected: the Verbal Learning and Memory Test (VLMT), a German adaptation of the Rey Auditory Verbal Learning Test (RAVLT) (Lux et al. 1999) to evaluate memory performance (Zhao et al. 2015), and the Trail Making Test (TMT) (Rodewald et al. 2012) to assess cognitive flexibility (Kinsella et al., 2007) (Behfar et al., 2020).
To refine and standardize the test results, we generated a composite VLMT score by averaging the standardized z-scores of the VLMT trials I–V (total learning), VI (recall after interference), and VII (delayed recall). Additionally, a delta TMT value was calculated by subtracting the TMT-A score from the TMT-B score (Behfar et al., 2020).

2.1.7 Correlation analysis between compensatory ROIs and neuropsychological tests

To evaluate the hypothesis that higher connectivity is associated with improved performance, as proposed in the fourth criterion of the introduction, we conducted a correlation analysis. Initially, all graph measures obtained from the graph theory analysis in the group-level results section of the CONN toolbox were exported. We specifically extracted the DC measures of the compensatory ROIs. Subsequently, we examined the relationship between DC in compensatory ROIs and the neuropsychological test outcomes in senior HC and subjects with MCI using a linear regression analysis with least squares fitting, implemented in MATLAB R2015b (The MathWorks, Natick, USA), and corrected for multiple comparisons. Visualization was performed using R (R Core Team, 2013) along with the ggplot2 package (Wickham, 2016) (Behfar et al., 2020).

2.1.8 Seed-to-ROI Analysis

Seed-to-ROI analysis was conducted using the compensatory ROIs as seeds and all 246 ROIs of the Brainnetome Atlas as target ROIs. The bivariate Fisher-transformed correlation coefficients between two ROIs' BOLD signals were used to define the seed-to-ROI correlation matrices (https://web.conn-toolbox.org/measures/roi-to-roi).

$$r(i,j) = \frac{\sum_t R_i(t)R_j(t)}{\sqrt{\sum_t R_i(t)^2 \sum_t R_j(t)^2}}$$

$$Z(i,j) = tanh^{-1}r(i,j)$$

Ri(t) = BOLD signals within i^{th} ROI, centered to zero mean

r(i,j) = correlation coefficients between i^{th} and j^{th} ROIs

Z(i,j) = Fisher-transformed correlation coefficient

The CONN toolbox's single-subject level was used to conduct seed-to-ROI correlation analyses as bivariate correlations without weighting.

2.2.1 CogStim Study design

Initially, potential participants' eligibility was assessed over the phone. Then, they were invited over to review inclusion and exclusion criteria. The study's objectives and procedures were explained to the participants and their relatives. After receiving written consent, the pre-stimulation baseline neuropsychological assessment was carried out. The intervention group then had CST for 8 weeks, but the control group had no appointments during this time. According to the recommended criteria by Breuil et al. (1994), all pre- and post-stimulation assessments, including neuropsychological tests and neuroimaging, were conducted within one week prior to the inception of the stimulation period or following the final session of the stimulation program (see **Figure 3**). Following the post-stimulation examination by three months, a neuropsychological follow-up was conducted.

Figure 3: Study flow (Behfar et al., 2023).

Schematic illustration of the study flow.

Abbreviation: ADAS-Cog, the Alzheimer's Disease Assessment Scale, cognitive subsection, MMSE, Mini-Mental State Examination.

2.2.2 Participants of CogStim study

This study (ID:16-298) was authorized by the ethics committee of the University of Cologne, Germany, and it was carried out in accordance with the 1975 Declaration of Helsinki. Each patient or their authorized representative provided informed written consent prior to the begin of the study. At the conclusion of the study, control group participants were offered to take part in the intervention program. The University Hospital in Cologne, Germany, recruited patients with mild to moderate AD dementia. Participants and their care givers were interviewed to obtain required information on their demographics, including precise length of education as a proxy measure for cognitive reserve. The study was divided into an intervention and a control group, and all recruited participants in both groups met the Jack et al. (2018) criteria for Alzheimer's continuum (see **Table 6**) with at least CSF or PET-based amyloid positive. At the neurology division of the university hospital in Cologne, certified neurologists assessed the severity of dementia and operationalized it using the Mini-Mental State Examination (MMSE) score, which ranged from 10 to 26 points (Folstein et al., 1975). Additional recruitment criteria included being over the age of 60, possessing normal or corrected-to-normal vision and hearing, and being a native German speaker or having an excellent command of the German language. Patients with life-threatening illnesses or other concurrent neurological or psychological disorders were excluded. To avoid selection bias and ensure timely initiation of the intervention, patients who consented to participate in the study and met the inclusion criteria were sequentially recruited for the intervention group. Following this, the control group was recruited in the same sequential manner. No compensation was given to the participants. All MRI scans were performed at the Research Center Jülich, and all participants either had transportation provided to and from the facility or were reimbursed for their travel expenses (Behfar et al., 2023).

2.2.3 Intervention group

As described above, participants in the intervention group attended the multi-domain CST program *NEUROvitalis senseful*, which was especially created for AD dementia patients, based on the previously released standardized cognitive training program *NEUROvitalis* (Baller et al., 2009). Liesk et al. (2015) previously came to the conclusion

that the original *NEUROvitalis* cognitive training program included components, such as psychoeducational elements and training of cognitive strategies, that are too challenging for AD dementia patients. As a result, the challenging sections were eliminated from the modified version while keeping the group games. To ensure thorough stimulation, the CST program also addresses a wider range of cognitive domains. The adjusted program also included tasks for sensory stimulation and relaxation (Behfar et al., 2023).

Each session adheres to a predetermined structure, which is succinctly described in **Table 7**. With a focus on social and information processing, the conventional group CST protocol calls for 14 sessions to be delivered twice weekly for seven weeks (Spector et al., 2003), recommending minimal efficacy comparable to pharmaceutical therapies (Onder et al., 2005; Spector et al., 2003). *NEUROvitalis Senseful* was developed based on insights from the most established CST programs. It features a median session length of 45 minutes, a median frequency of two sessions per week, a median total of 20 sessions, and a median follow-up period of 10 weeks (Woods et al., 2023). The program is designed to provide the optimal "dose" of cognitive stimulation needed to combat cognitive decline. All stimulating interventions were carried out by certified neuropsychologists during an eight-week period with a maximum of four participants per group, two sessions each week. Each of the 16 sessions was done for 60 minutes and included a variety of group activities. Each session begins with a brief ritual called the "mood scale," where participants share their current mood. The initial main phase includes a task focused on one of four cognitive domains—memory, language, executive functions, or social cognition—followed by a brief relaxation exercise from one of the remaining three domains. This section's activities are inspired by well-established techniques such as progressive muscle relaxation (Jacobson et al., 1990) and mindfulness (Bishop et al., 2004). The second phase consists of sensory-stimulating exercises, such as short narratives paired with light movement tasks or sensory stimulation through auditory, tactile, or olfactory means. These cognitive and sensory exercises aim to create a personal connection to the group members' biographies and encourage discussions about their experiences (Werheid and Thöne-Otto, 2006). Most tasks can be tailored to the individual abilities of dementia patients. For example, varying the number of cues or options available allows for adjusting the difficulty level in the word-finding, memory, and sensory stimulation sections. Tasks are evenly distributed across the 16 intervention sessions

to ensure all domains receive equal stimulation during the intervention period. Overall, our CST program emphasizes enhancing cognitive functions while incorporating additional elements to further boost cognition. Therefore, cognitive functions are stimulated by sensory stimulation tasks that demand thorough recognition and verbalization of haptic and olfactory information. Movement exercises also focus on procedural memory. Every session includes a relaxing segment that could improve memory, mental receptivity, and focus (Schloffer et al., 2010). The detail description of the stimulating interventions was provided by Middelstadt (Middelstadt et al., 2016) (Behfar et al., 2023).

Importantly, participants were also instructed to refrain from altering in their medication regimen, participation in any other interventional research or starting any new therapies. Additionally, the participants' compliance to the provided instructions were verified with the participants and their care givers at the end of the CST (Behfar et al., 2023).

Table 6: CSF and imaging biomarkers of AD (Behfar et al., 2023).

Aβ42 (pg/ml)	pTAU(pg/ml)	tTAU(pg/ml)	Aβ42 /40	tTAU/Aβ42	FDG-PET (metaROI)	18F-AV-45 (SUVR)	AT(N)-profile
Intervention Group							
869.5	121	506.7	0.07	0.58	N/A	N/A	A+T+(N)+
399.5	62	293.1	0.08	0.73	N/A	N/A	A+T+(N)-
516.6	123	522.1	0.06	1.01	N/A	N/A	A+T+(N)+
205.1	80	287.7	0.05	1.40	N/A	N/A	A+T+(N)-
372.9	72	464.3	0.05	1.25	N/A	N/A	A+T+(N)-
408.8	38	210.4	0.08	0.51	N/A	N/A	A+T-(N)-
491	82	202	0.07	0.41	N/A	N/A	A+T+(N)-
680.3	100	687.2	0.06	1.01	N/A	N/A	A+T+(N)+
313.9	112	911.1	0.05	2.90	N/A	N/A	A+T+(N)+
721.3	119	1662.8	0.05	2.31	N/A	N/A	A+T+(N)+
529	78	660.8	0.05	1.25	N/A	N/A	A+T+(N)+
427	123	811	N/A	1.90	N/A	N/A	A+T+(N)+
715.3	174	511.4	0.05	0.71	N/A	N/A	A+T+(N)+
368.7	92	424.1	0.05	1.14	N/A	N/A	A+T+(N)-
752.9	121	722.2	0.06	0.99	N/A	N/A	A+T+(N)+
Control Group (recruitment at study site)							
361.5	67	292	0.05	0.81	N/A	N/A	A+T+(N)-
545.6	116	1164.6	0.04	2.13	N/A	N/A	A+T+(N)+
527	N/A	335	0.06	0.64	N/A	N/A	A+T?(N)+
474.6	71	293.2	0.07	0.62	N/A	N/A	A+T+(N)-

517.6	83	562.1	0.06	1.09	N/A	N/A	A+T+(N)+
340	48	365	N/A	1.07	N/A	N/A	A+T-(N)-
566.3	67	219.1	0.07	0.38	N/A	N/A	A+T+(N)-
426.2	99	409.6	0.08	0.88	N/A	N/A	A+T+(N)-
Control Group (ADNI)							
564.5	21.54	224.6	N/A	0.4	1.03	1.45	A+T-(N)+
523.9	24.81	266.2	N/A	0.51	1.04	1.67	A+T+(N)+
801.1	17.29	211.7	N/A	0.26	0.91	N/A	A+T-(N)+
805.3	24.39	268.1	N/A	0.33	0.90	1.22	A+T+(N)+
624.1	37.72	365.8	N/A	0.59	1.02	1.45	A+T+(N)+
760	63.4	606.6	N/A	0.8	1.2	1.59	A+T+(N)+
461.2	23	247.1	N/A	0.05	1.22	1.38	A+T+(N)+

Biomarkers indicative of AD were assessed for all participants. The reference values for the intervention and local-recruitment control groups are as follows: Aβ42 > 650 pg/ml, pTAU < 61 pg/ml, tTAU < 466 pg/ml; Aβ42/40 ratio > 0.1; tTAU/Aβ42 < 0.52. For the control group (ADNI), the reference values are: Aβ42 > 880 pg/ml; pTAU < 23 pg/ml; tTAU < 93 pg/ml; tTAU/Aβ42 < 0.33; FDG-PET > 1.21 metaROI; and ^{18}F-AV-45 < 1.11 SUVR.

Abbreviations: Aβ42: amyloid-beta 42; pTAU: phosphorylated tau-Protein; tTAU: Total Tau-Protein; FDG-PET: ^{18}F-fluorodeoxyglucose-positron emission tomography; ^{18}F-AV-45: Florbetapir F 18 for amyloid-beta plaques positron emission tomography imaging.

Table 7: Structure, sessions and phases of the cognitive stimulation program NEUROvitalis senseful(Behfar et al., 2023).

Duration	5 min	20 min					10 min				20 min					5 min
Session number	Mood scale	Exercises for cognitive functions	Executive functions	Memory	Language	Social cognition	Relaxation period	Progressive muscle relaxation	Slight movement	Mindfulness	Sensory stimulation	Tactile	Olfactory	Auditory	Body language	Mood scale
1	✓	Everyday situations				✓	Hands	✓			Describe fragrances		✓			✓
2	✓	Think differently	✓				Pass it forward!		✓		Describe fragrances		✓			✓
3	✓	Think differently	✓				Seeing			✓	Movement story				✓	✓
4	✓	Meaningful pictures		✓			Arms, shoulders, neck	✓			Describe sounds			✓		✓
5	✓	Finding words			✓		Finger gymnastics		✓		Describe sounds			✓		✓
6	✓	Everyday situations				✓	Tasting			✓	Feeling exercises	✓				✓
7	✓	City map game	✓				Hands	✓			Feeling exercises	✓				✓
8	✓	Finding words			✓		Cups and balls		✓		Movement story				✓	✓
9	✓	Finding words			✓		Seeing and feeling			✓	Movement story				✓	✓
10	✓	Meaningful pictures		✓			Stomach, back, buttock	✓			Describe fragrances		✓			✓
11	✓	Basic emotions				✓	Finger gymnastics		✓		Describe sounds			✓		✓
12	✓	Basic emotions				✓	Seeing and feeling			✓	Feeling exercises	✓				✓
13	✓	Finding words			✓		Legs and feet	✓			Movement story				✓	✓
14	✓	Category memory game		✓			Pass it forward!		✓		Describe fragrances		✓			✓
15	✓	Category memory game		✓			Tasting			✓	Describe sounds			✓		✓
16	✓	City map game	✓				Hands	✓			Feeling exercises	✓				✓

2.2.4 Control group

The controls did not receive any intervention and were instructed to carry on with their usual daily routines and refrain from any concurrent medical or any other therapeutic procedures. By the second scan, the participants and their care givers had attested to the participants' commitment to these requirements. Due to the COVID-19 pandemic and subsequent contact restrictions beginning in 2020, we were unable to continue enrolling patients for the control group. To ensure comparable participant numbers in both the control and intervention groups, we utilized the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). AD patients (n=7) from the ADNI database were carefully selected to match our enrollment and study design criteria, thereby minimizing differences between the intervention and control groups. Selection criteria included demographic and diagnostic measures, type of MRI scanner, time interval between two imaging sessions, and any changes in concurrent medication (see **Table 8**). For the ADNI participants, however, the only accessible scores were MMSE and ADAS-Cog. International labs (Hansson et al., 2018; Jagust et al., 2009; Landau et al., 2012; Ou et al., 2019) provided the cut-off points for each of the ADNI database's examined biomarkers, and each participant's AT(N)-profile was established in accordance with Jack et. al. (2018) (Behfar et al., 2023) (see **Table 6**).

Table 8: Demographic data (Behfar et al., 2023).

	Intervention group	Control group	Control group (self)	Control group (ADNI)	*Intervention vs. Control p*-value
Number of patients	15	15	8	7	_
Sex (%male)	60	60	62	57	1
Age (yrs)	72.5±2.2	73.7±1.6	72±0.5	75.6±1.3	0.8
MMSE	19.6±1	22.8±1	21.2±1.6	24.5±0.6	0.16
Education (yrs)	13.6±0.7	14.7±0.8	13.3±0.8	16.2±1.4	0.6

Abbreviations: ADNI: Alzheimer's Disease Neuroimaging Initiative; MMSE: Mini-Mental Status Examination

2.2.5 Neuropsychological assessments

Identical neuropsychological tests were administered during both pre- and post-stimulation assessments for each participant in the intervention and control groups. All neuropsychological tests employed are widely used in international research studies (E. Moniz-Cook et al., 2008). The participants' cognitive abilities were assessed using the MMSE (Folstein et al., 1975) and the Alzheimer's Disease Assessment Scale, cognitive subsection (ADAS-Cog) (Rosen et al., 1984). Early cognitive stimulation research (Orrell et al., 2014; Spector et al., 2003; Werheid et al., 2021) used these

well-established measurements, which enhances the results' comparability and reproducibility. Furthermore, these measurements encompass several domains, providing a comprehensive evaluation of cognitive and memory functioning while reducing the likelihood of false positives. The ADAS-Cog, consisting of 11 items assessing memory, orientation/praxis, and language, is frequently utilized in clinical studies involving AD patients (Hobart et al., 2013). The ADAS-Cog scores range from 0 to 74 points, with higher scores indicating more severe cognitive impairment. QoL was assessed both subjectively and objectively using the European Quality of Life Five Dimension Five Level (EQ-5D-5L) questionnaire, a widely used multi-attribute utility tool for evaluating health-related quality of life (EuroQol Research Foundation, 2019). This instrument includes five items—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—to evaluate various life aspects. The total score ranges from 0 to 100 points, with higher scores indicating a higher QoL level (Behfar et al., 2023).

The Neuropsychiatric Inventory (NPI) (Cummings, 1997) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) were primarily focused on BPSD (Galasko et al., 2006). The NPI consists of twelve items designed to assess a range of neuropsychiatric symptoms, including anxiety, apathy/indifference, agitation/aggression, aberrant motor behavior, appetite/eating disturbances, delusions, depression/dysphoria, disinhibition, euphoria/elation, hallucinations, irritability/lability, and nocturnal behavioral disturbances. Each domain is scored by multiplying the frequency and severity of the symptoms, resulting in a composite score ranging from 0 (no behavioral symptoms) to 144 points (maximum severity of all symptoms). The ADCS-ADL assesses activities of daily living (ADL) performed over the past four weeks. The total score for all items ranges from 0 (indicating lowest functional ability) to 78 (indicating highest functional ability) (Behfar et al., 2023).
The neuropsychological assessments were conducted as a formal interview. Along with a self-rated section, the EQ-5F-5L and NPI assessments also included a proxy-rated section for which each patient's spouse was questioned (Behfar et al., 2023).
In the control group, seven participants were chosen form the ADNI database, matching our recruiting and research methodology. Notably, as for the cognitive and neuropsychological assessments, only MMSE and ADAS-Cog scores were provided for the ADNI participants (Behfar et al., 2023).

2.2.6 MRI data acquisition and preprocessing

The Research Centre Jülich performed MRI scans on research participants who did not have any MRI contraindications. Structural MRI and resting-state functional MRI data were acquired using a 3T MAGNETOM Trio scanner (Siemens, Erlangen, Germany) (Behfar et al., 2023).

A rapid gradient-echo sequence with the following parameters was used to acquire T1 structural images: TR = 2250 ms, TE = 3.03 ms, FA = 9°, FOV = 256 mm × 256 mm, voxel size = 1 mm isotropic, and 176 gapless interleaved sagittal slices. Patients were advised to remain awake, focus on a projected cross, and avoid specific thoughts during the 7-minute resting-state image acquisition. Functional images were acquired using EPI with the following parameters: TR = 3000 ms, TE = 30 ms, FA = 90°, FOV = 200 mm × 200 mm, voxel size = 2.5 mm × 2.5 mm × 2.8 mm, with interleaved oblique slices parallel to the infra-supratentorial line and a gap of 0.28 mm. The seven control group participants, whose data were obtained from the ADNI database, also underwent 3T Siemens MR scanning. T1 structural images were acquired using a rapid gradient-echo sequence with a slice thickness of 1.0 mm and a matrix Z of 176.0. Functional images were obtained using EPI with the following settings: slice thickness of 2.5–3.4 mm, TR = 3000 ms, and TE = 30 ms (Behfar et al., 2023).

MR images were preprocessed using the default pipeline of the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Of 155 volumes, the first four images were discarded to allow the signal to stabilize. Functional images were realigned to the first volume acquired in the session. EPIs were then co-registered to the high-resolution T1 structural image, normalized to the MNI stereotactic space, and resampled to a voxel size of 2 × 2 × 2 mm^3 (Behfar et al., 2023).

After normalization, an 8-mm full-width at half maximum (FWHM) isotropic Gaussian kernel was used to spatially smooth the images. Individual head motion parameters were controlled and eliminated at relative displacement criterion of +/- 3 mm (Behfar et al., 2023).

To take consider motion-related artifacts into account (Conwell et al., 2018), we included FD, calculated according to Jenkinson et al. (2002), used in our models as a covariate of no interest. The proposed method by Jenkinson et al. (2002) is favored to other FD methods as it incorporates voxel-wise differences into its derivation (Yan et al. 2013).

2.2.7 Brainnetome Atlas

The extended Brainnetome Atlas includes 274 ROIs (210 cortical, 36 subcortical, and 28 cerebellar subregions), which are assigned to brain functions based on many meta-analyses of task-based functional imaging studies. This version of the Atlas additionally covers the cerebellum (Fan et al., 2016). The majority of the current brain atlases lack fine-grained parcellation and do not include all of the functional information for the various brain regions. Using a variety of multimodal imaging modalities, the Brainnetome Atlas was created to provide a connectivity-based parcellation framework, that identifies the subsections of the human brain, revealing new aspects of connectivity architecture. The Brainnetome Atlas, in particular, combines brain connectivity with microscale details like cytoarchitecture of various brain areas. Through the use of the BrainMap database, the structures in the Brainnetome Atlas are connected to mental processes (Balsters et al., 2014; Fox et al., 2014; Laird et al., 2009), enabling an assessment of the mental functions supported by each cortical and subcortical region of the Brainnetome Atlas (Fan et al., 2016). Based on the behavioral domains and paradigm class metadata labels of the BrainMap database (www.brainmap.org/taxonomy), the functions of each subarea in the Brainnetome Atlas are described using forward and reverse inferences (Cieslik et al., 2013; Clos et al., 2013; Eickhoff et al., 2011; Fan et al., 2016; Fox et al., 2014) (Behfar et al., 2022).

2.2.8 Structural analysis

Structural MRI data were analyzed using the voxel-based morphometry (VBM) technique on CAT12 toolbox and SPM12 software, which provides comprehensive details on morphometric properties while avoiding biases brought by structural changes (Ashburner and Friston, 2000). Using CAT12 toolbox, structural images were first segmented and smoothed. GM and WM volumes were added to obtain the total brain volume. Total intracranial volume (TIV) was calculated as the summation of GM, WM and CSF quantities. Then, to investigate within-group and between group comparisons, paired-sample t-test and ANCOVA were carried out using SPM12 software while adding TIV as a nuisance covariate (Behfar et al., 2023).

2.2.9 Functional connectivity analyses

Two methods were applied: atlas-based ROI-to-ROI functional connectivity analysis and seed-to-voxel analysis utilizing a priori selections from the ROI-to-ROI results. For the atlas-based ROI-to-ROI analysis, we used the Brainnetome Atlas (Fan et al., 2016)

with 274 ROIs in the CONN toolbox v.19.c (Whitfield-Gabrieli et al. 2012) to create connectivity matrices for each subject. The time series of the BOLD signals from all voxels in each ROI of the Brainnetome Atlas were averaged, and Pearson's correlations of these average signals were calculated and z-transformed. In a similar manner, in the seed-to-voxel analysis, correlation maps of the entire brain were created by extracting the BOLD signal from the seed ROI and calculating the z-transformed correlation coefficient between that signal and the signals from all other brain voxels. General linear models were fitted utilizing all related within-subject pairwise z-transformed correlation coefficient measurements following the ROI-to-ROI and voxel-based analyses at the subject level (Behfar et al., 2023).

Subsequently, seed-to-voxel analysis was performed with a voxel-wise threshold of $p<0.001$ and a cluster-level threshold of $p<0.05$ (FDR-corrected). Additionally, group-level ROI-to-ROI analysis was carried out with a threshold of $p<0.05$, FDR-corrected at the seed level. For all within-group and between-group comparisons, FD was included as a covariate of no interest (Behfar et al., 2023).

Following group comparisons, the z-transformed correlation coefficients for each subject from the ROI-to-ROI analysis, as well as the Fisher z-transformed correlation coefficients averaged over all voxels within the cluster from the seed-to-voxel analysis, were extracted for subsequent correlation analysis with the neuropsychological test scores (Behfar et al., 2023).

2.2.10 Association between connectivity changes and neuropsychological tests

We explored the association between connectivity alterations observed in ROI-to-ROI and seed-to-voxel analyses and cognitive measures among participants in the intervention groups following CST. To achieve this, we extracted Fisher z-transformed correlation coefficients from the resting-state MR images as connectivity measures. For the ROI-to-ROI analysis, these coefficients were obtained for each subject, while for the seed-to-voxel analysis, the coefficients were averaged over all voxels within the cluster. We then estimated the association between these connectivity measures and changes in MMSE and ADAS-Cog scores post-CST using linear regression models, adjusting for age and sex (Behfar et al., 2023).

To achieve this, connectivity measures were extracted from resting-state MR images for each subject in both the ROI-to-ROI and seed-to-voxel analyses. The Fisher z-transformed correlation coefficients were used, averaged over all voxels within the cluster for the seed-to-voxel analysis. The associations between these connectivity measures and changes in MMSE and ADAS-Cog scores post-CST were then estimated using linear regression models, with adjustments for age and sex (Behfar et al., 2023).

2.2.11 Statistical analyses

Statistical analyses were conducted using IBM SPSS, version 23.0, MATLAB R2017b (The MathWorks, Natick, USA), and R (R Core Team, 2013). The reliability of changes in the MMSE, ADAS-Cog, and EQ-5D-5L measures was assessed using the reliable change index (RCI) within the intervention group (post-to-pre-stimulation and follow-up to post-stimulation) and the control group (2^{nd} test to 1^{st} test) prior to applying statistical analyses to the data. Additionally, the Shapiro-Wilk test was used for each group to validate that the data from the evaluations were distributed normally. With the use of IBM SPSS and G*Power 3.1, a post-hoc estimation of our sample size was also carried out (Behfar et al., 2023).

Based on our hypotheses, we conducted a two-tiered analysis to assess the impact of stimulation on the intervention group relative to any changes observed in the control group. First, within-group alterations were evaluated using multifactorial ANOVA for each group. To account for batch effects in the statistical models, we included a covariate indicating whether the participant was initially enrolled in the study or if the data was imported from ADNI. Next, to evaluate between-group differences, we compared the within-group changes in the intervention group (post-stimulation > pre-stimulation) with the within-group changes in the control group (2^{nd} > 1^{st}). Given the relatively modest sample size, the between-group comparison was conducted using the Wilcoxon test, a non-parametric method. The significance threshold was set at 0.05 for all within- and between-group comparisons (Behfar et al., 2023).

3. Results

3.1.1 Initial evaluation of RIMCAD data

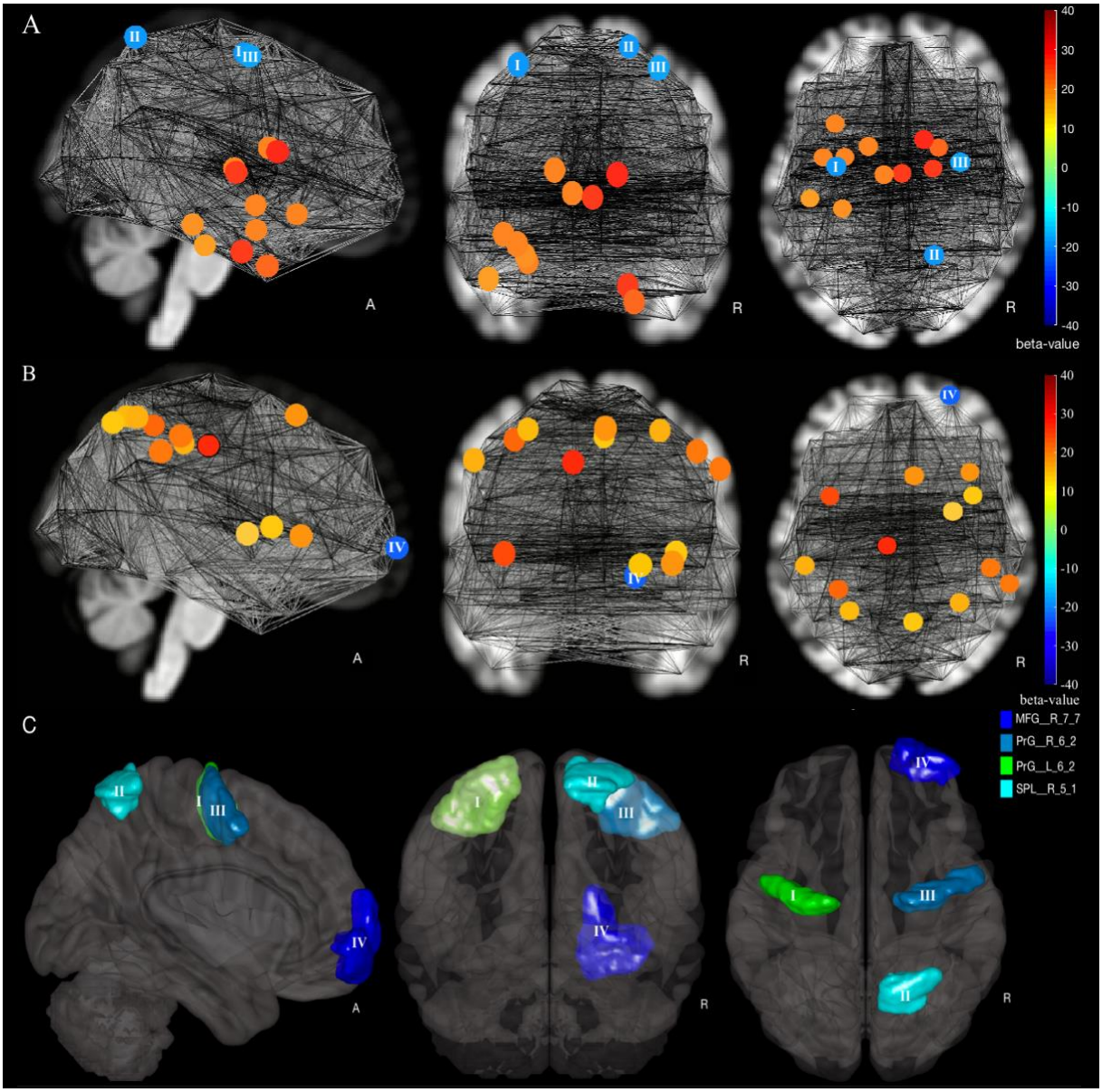
In all 45 participants from RIMCAD study, we evaluated imaging and neuropsychological data in three groups: young HC, older HC, and MCI. The three groups did not differ significantly in sex and level of education. The senior HC and MCI groups' ages did not differ significantly from one another ($p > 0.05$). The Shapiro-Wilk test in R was used in each step of the subsequent analysis to confirm that the data had a normal distribution.

3.1.2 Graph theory analysis and the ROIs with a significant increase of DC

In the comparison between the senior healthy control (HC) and mild cognitive impairment (MCI) group versus the younger HC group, we observed elevated DC measures in three ROIs: the right superior parietal lobule, specifically rostral area 7 (Brainnetome label: SPL_R_5_1), as well as the right and left precentral gyri in caudal dorsolateral area 6 (Brainnetome labels: PrG_R_6_2 and PrG_L_6_2) (**Figure 4 & Figure 5**), higher DC measures depicted in circles of blue shades, lower measures in red shades; see also **Table 9**). Moreover, the contrast between the senior HC and the MCI group revealed higher DC measures in the right middle frontal gyrus, lateral areal 10 (Brainnetome label: MFG_R_7_7) (Behfar et al., 2020) (**Figure 4 & Figure 5**, and **Table 9**).

A post-hoc power analysis was conducted using G*Power 3.1 and IBM SPSS, with $\alpha = 0.05$ and an effect size of 0.39, derived from a multivariate analysis of variance (MANOVA; $F(4,40) = 6.5$, $p = 0.0001$, partial $\eta^2 = 0.39$). The results indicated a statistical power (1-β) of 0.80 for the sample size used in the study, based on the outcomes of the graph theory analysis (Behfar et al., 2020).

Figure 4: Increase and Decrease of degree centrality in intergroup contrasts (Behfar et al., 2020).



(A) In the contrast between young HC and senior HC & MCI subjects, blue-shaded circles indicate a significant increase in DC, while red-shaded circles denote a significant decrease in DC in senior HC and MCI subjects compared to young HC ($p<0.05$, FDR-corrected). (B) In the contrast between senior HC and MCI subjects, blue-shaded circles highlight a significant increase in DC in MCI subjects compared to senior HC ($p<0.05$, FDR-corrected). The significant regions of interest (ROIs), as labeled by the Brainnetome atlas, are (I) PrG_L_6_2, (II) SPL_R_5_1, (III) PrG_R_6_2, and (IV) MFG_R_7_7. (C) All four compensatory ROIs are derived from the two intergroup contrasts.

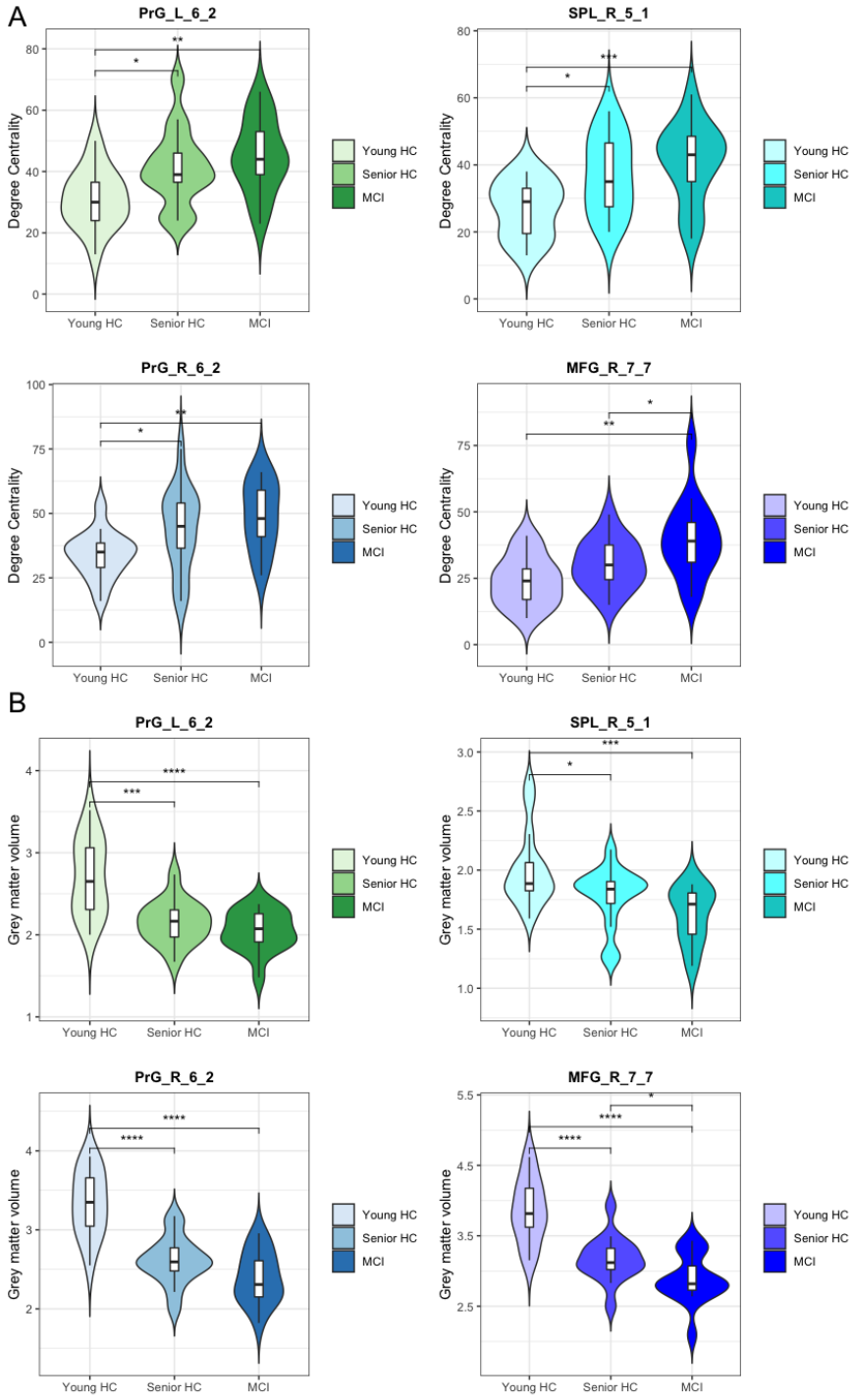
Table 9: The coordinates of the ROIs with significant higher degree centrality in the intergroup contrasts (Behfar et al., 2020).

Contrast	Brainnetome atlas label	Region	behavioral domain according to the Brainnetome atlas
senior HC + MCI > young HC (p<0.05, FDR-corrected)	PrG_L_6_2	left precentral gyrus, caudal dorsolateral area 6	spatial cognition, action execution
senior HC + MCI > young HC (p<0.05, FDR-corrected)	SPL_R_5_1	right superior parietal gyrus, rostral area 7	working memory, somatic & spatial cognition, attention, action execution
senior HC + MCI > young HC (p<0.05, FDR-corrected)	PrG_R_6_2	right precentral gyrus, caudal dorsolateral area 6	somatic & spatial cognition, action execution
MCI > senior HC (p<0.05, FDR-corrected)	MFG_R_7_7	right middle frontal gyrus, lateral area 10	Cognition, explicit memory

3.1.3 Volumetric analysis of the compensatory ROIs

As stated in our criteria for compensatory mechanisms, the respective ROIs must have concurrent higher measures of DC with lower GM volumes. After correcting for TIV, volumetric analysis revealed significant lower GM volume of the compensatory ROIs. In contrast to the young HC group, the senior HC and MCI group showed significantly lower volume in all four compensatory ROIs (**Table 9**), as shown in **Figure 5** (p<0.05, FDR-corrected). Even though further lower volumes were detected in the MCI group compared to the senior HC in all four compensatory ROIs, this reached significance level only in the right middle frontal gyrus (p<0.05, FDR-corrected).

Figure 5: Degree centrality and grey matter volume of compensatory ROIs (Behfar et al., 2020).



Depiction of (A) DC and (B) grey matter volume in the right and left precentral gyri (caudal dorsolateral area 6; Brainnetome labels: PrG_R_6_2 and PrG_L_6_2), the superior parietal lobe (rostral area 7; Brainnetome label: SPL_R_5_1), and the right middle frontal gyrus (lateral area 10; Brainnetome label: MFG_R_7_7). Statistical significance is denoted as follows: (*) p<0.05 (FDR-corrected), ***(**)*** *p<0.01 (FDR-corrected),* ***(***)*** *p<0.005 (FDR-corrected), and (****) p<0.001 (FDR-corrected).*

3.1.4 Correlation analysis between DC, total VLMT, and delta TMT values

As depicted in **Table 10** and **Figure 6**, the DC measures of the right superior parietal lobule, rostral area 7 (Brainnetome label: SPL_R_5_1), the right middle frontal gyrus, lateral area 10 (Brainnetome label: MFG_R_7_7), and the right precentral gyrus, caudal dorsolateral area 6 (Brainnetome label: PrG_R_6_2) were significantly associated with total VLMT scores in the MCI group ($p < 0.05$, corrected for multiple tests) (Behfar et al., 2020).

After accounting for multiple comparisons, the correlation between the DC measurements of the compensatory ROIs, total VLMT, and delta TMT values revealed no significant link in senior HC (Behfar et al., 2020) (see **Table 11**).

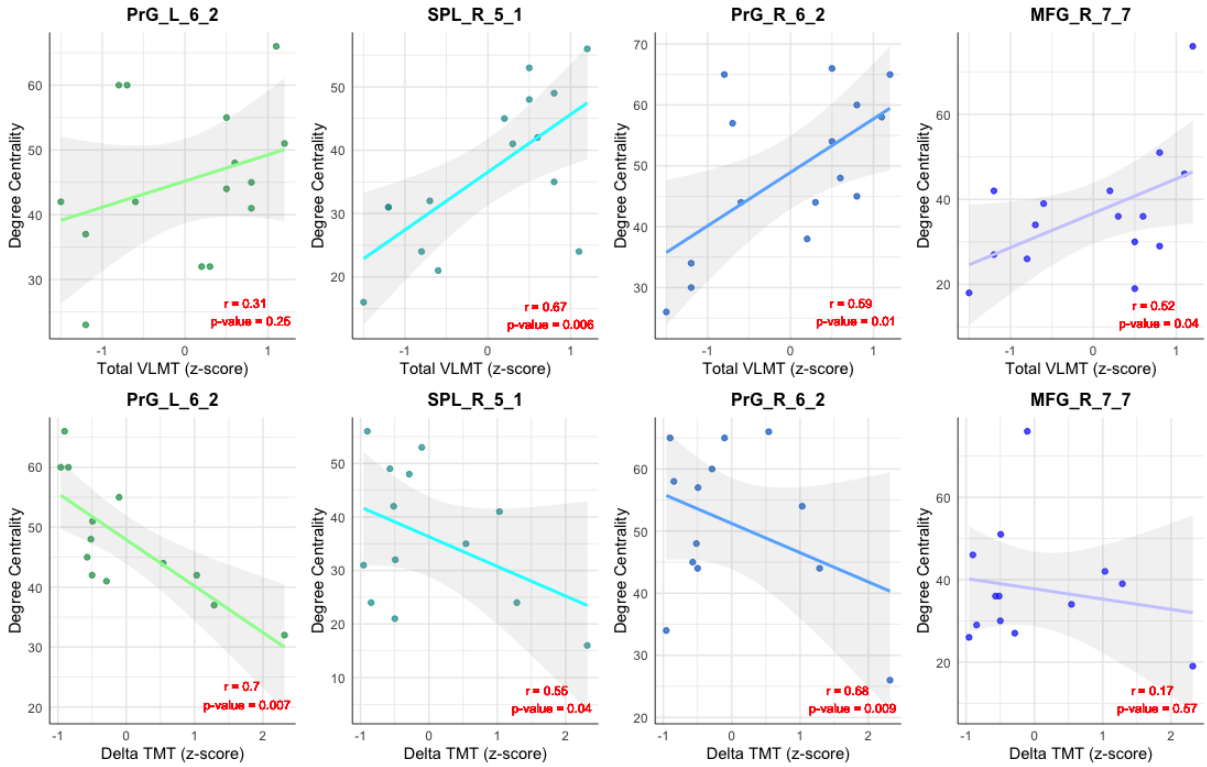
Table 10: Association between DC measures of cognition-correlated compensatory ROIs, total VLMT, and delta TMT scores in MCI patients. Correlation with significant p-values are highlighted in bold. All p-values are adjusted for multiple comparisons (Behfar et al., 2020).

Score / **ROI**	**Total VLMT**		**Delta TMT**		**behavioral domain according to the Brainnetome atlas**
	r	***p-value***	***r***	***p-value***	
PrG_L_6_2	0.312	0.258	0.701	**0.007**	spatial cognition, action execution
PrG_R_6_2	0.599	**0.018**	0.689	**0.009**	somatic & spatial cognition, action execution
SPL_R_5_1	0.670	**0.006**	0.555	**0.048**	working memory, somatic & spatial cognition, attention
MFG_R_7_7	0.522	**0.046**	0.173	0.571	explicit memory

Table 11: Association between DC measures of cognition-related compensatory ROIs, total VLMT, and delta TMT scores in senior HC. All p-values are adjusted for multiple comparisons (Behfar et al., 2020).

Score / **ROI**	**Total VLMT**		**Delta TMT**		**behavioral domain according to the Brainnetome atlas**
	r	***p-value***	***r***	***p-value***	
PrG_L_6_2	0.286	0.301	0.368	0.178	spatial cognition, action execution
PrG_R_6_2	0.260	0.350	0.464	0.082	somatic & spatial cognition, action execution
SPL_R_5_1	0.274	0.322	0.002	0.995	working memory, somatic & spatial cognition, attention
MFG_R_7_7	0.396	0.144	0.002	0.995	explicit memory

Figure 6: Association between DC measure and neuropsychological tests (Behfar et al., 2020).

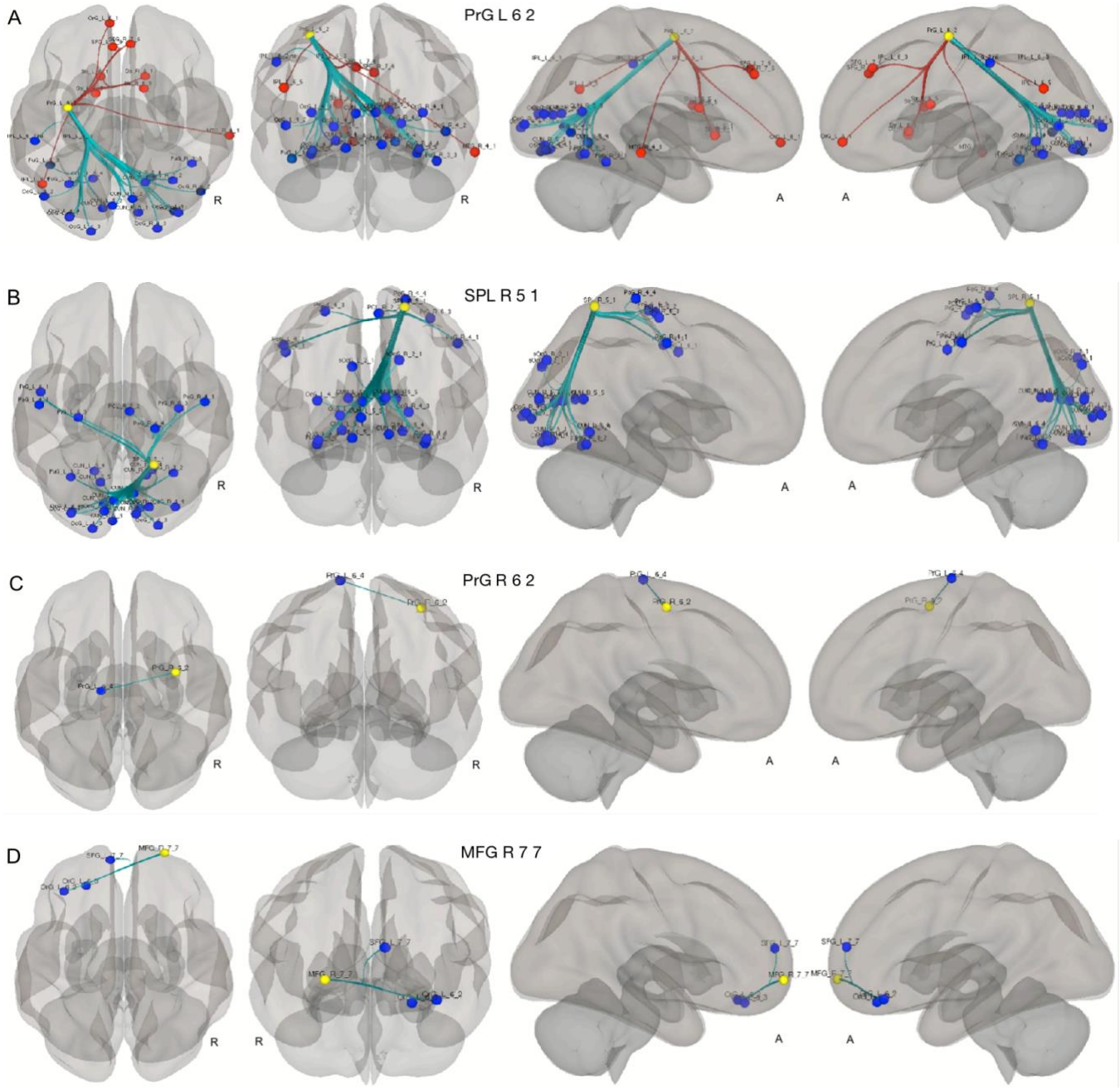


The association between DC measures of compensatory ROIs—including the right and left precentral gyri (caudal dorsolateral area 6), the superior parietal lobe (rostral area 7), and the right middle frontal gyrus (lateral area 10) [Brainnetome labels: PrG_R_6_2, PrG_L_6_2, SPL_R_5_1, and MFG_R_7_7]—and cognitive performance is depicted by the total VLMT score (upper row) and ΔTMT score (lower row) in MCI patients.

3.1.5 Seed-to-ROI Analysis

As illustrated in **Figure 7,** the compensatory ROIs in the right superior parietal lobe (Brainnetome label: SPL_R_5_1) and the right and left precentral gyri (Brainnetome labels: PrG_R_6_2 and PrG_L_6_2) demonstrated significantly higher associations with cognition-related areas, including multiple ROIs in the occipital lobes, cuneus, fusiform gyri, and pre- and postcentral gyri. Likewise, the compensatory ROI in the right middle frontal gyrus (Brainnetome label: MFG_R_7_7) exhibited significantly increased correlations with cognition-related ROIs in the left superior frontal gyrus and the left orbital gyrus (Behfar et al., 2020).

Figure 7: Seed to ROI analysis of the compensatory ROIs (Behfar et al., 2020).



Yellow circles denote compensatory ROIs, while colored circles indicate ROIs with significant alterations in connectivity relative to the compensatory ROIs. Specifically, blue circles signify an increase, and red circles signify a decrease in connectivity within the following comparisons: (A-C) young HC versus senior HC and MCI, and (D) senior HC versus MCI ($p < 0.05$, FDR-corrected).

3.2.1 Initial evaluation of CogStim data

The neuropsychological and the imaging data of all participants in the intervention and the control groups were evaluated. With a 17% (n=3) drop-out rate in the intervention group, 83% (n=15) of individuals successfully finished the program, and of those, 72% (n=13) had MR imaging. %75 (n=6) of the individuals in the locally recruited subgroup of controls (n=8) who met our MR safety criteria had received scans. Only imaging data, MMSE scores, and ADAS-Cog scores were provided for the data collected from ADNI (n=7).

The outcome of psychological interventions such as CST have been seen to be affected by individual attributes especially age and education (Carbone et al., 2021). Therefore, we determined that there was no difference in the baseline MMSE, age, or education between the intervention and control groups—the latter of which acted as a proxy for cognitive reserve (see **Table 8**).

3.2.2 Neuropsychological assessments

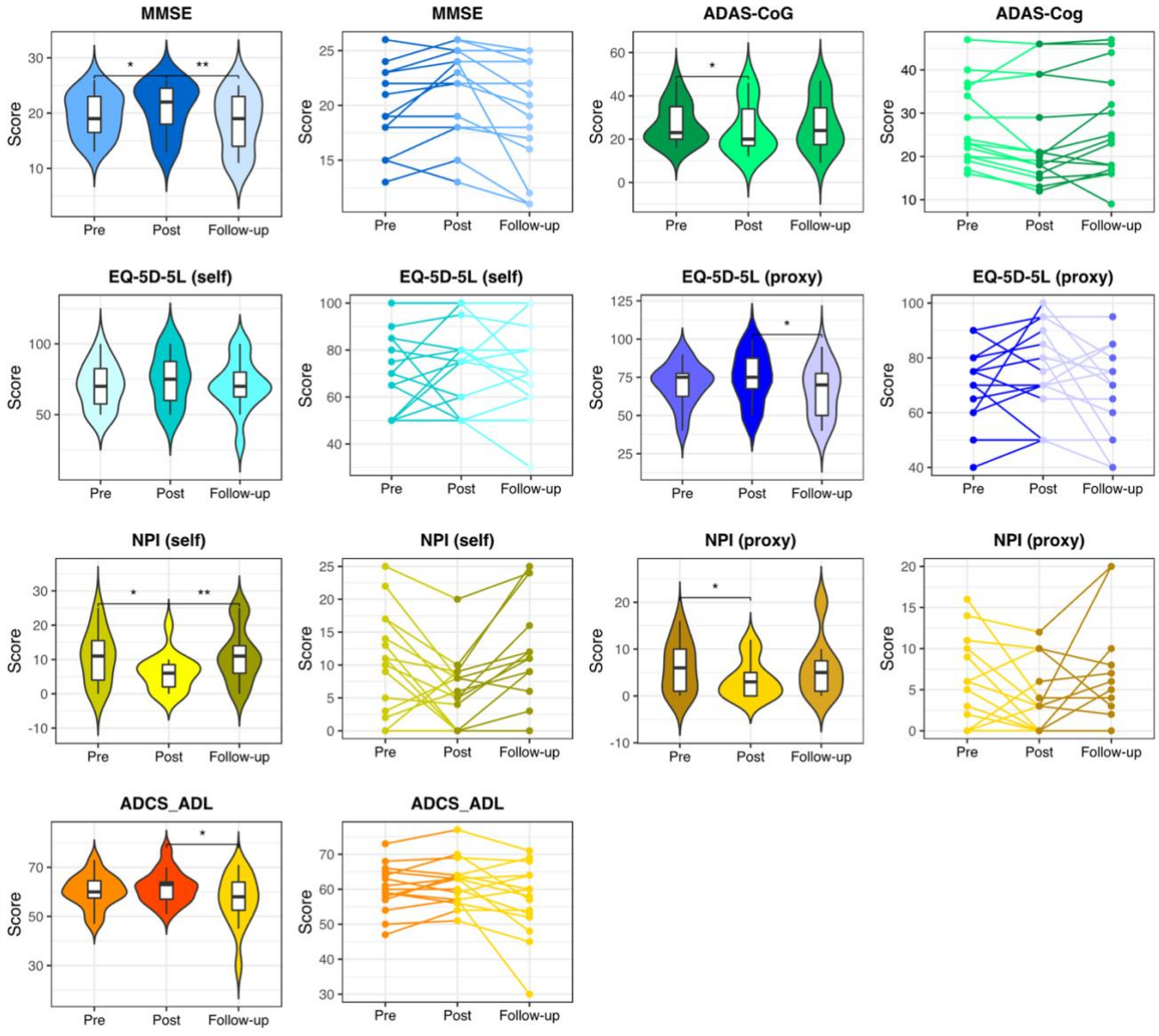
In the intervention group, significant changes were observed in the MMSE, ADAS-Cog, NPI (self), and NPI (proxy) measures in the pre- versus post-stimulation comparison, indicating improvement from baseline. Additionally, follow-up assessments indicated a significant return to baseline values. Although the self- and proxy-rated EQ-5D-5L and ADCS-ADL scores showed no significant improvement immediately following the stimulation period, the follow-up revealed a substantial decline in the proxy-rated EQ-5D-5L and ADCS-ADL scores compared to the post-stimulation assessment (see **Figure 8** and **Table 12**) (Behfar et al., 2023).

In the control group, no significant alterations were observed, except for the self-rated EQ-5D-5L, which indicated a substantial decline in quality of life (see **Figure 9** and **Table 12**) (Behfar et al., 2023).

The MMSE, EQ-5D-5L (self), and NPI (self) assessments exhibited a significant difference favoring the intervention group when comparing the within-group changes (post-stimulation vs. pre-stimulation) in the intervention group to the within-group changes (second assessment vs. first assessment) in the control group (see **Table 13**) (Behfar et al., 2023).

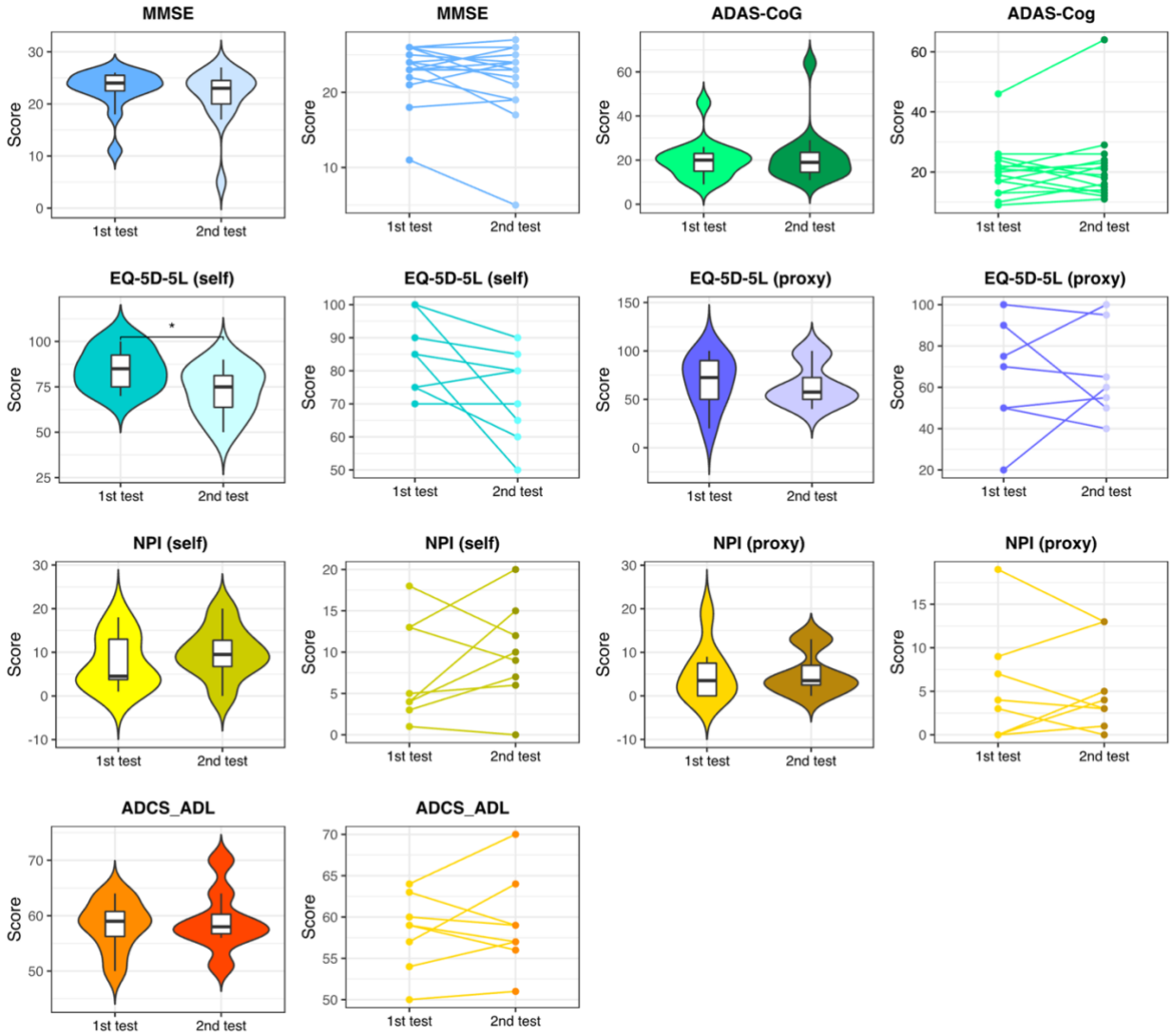
We assessed the correlation between years of education, as a proxy for cognitive reserve, and changes in MMSE, ADAS-Cog, NPI (self), and NPI (proxy) scores that showed significant improvement following CST. This evaluation was based on the debated premise that cognitive reserve is a predictor of intervention response in CST. As illustrated in **Figure 10**, of the measures that improved after CST (MMSE, ADAS-Cog, NPI self-reported, and NPI reported by proxy), MMSE was significantly correlated with years of education. This finding suggests that cognitive reserve, as indicated by years of education, may predict cognitive gains following CST (Behfar et al., 2023).

Figure 8: Neuropsychological assessments in the intervention group (Behfar et al., 2023).



*Neuropsychological assessment outcomes for participants in the intervention group, measured at pre-stimulation, post-stimulation, and follow-up intervals. Abbreviations: ADAS-Cog: the Alzheimer's Disease Assessment Scale, cognitive subsection; ADCS-ADL: the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; EQ-5D-5L: the European Quality of Life Five Dimension with Five Levels; MMSE: Mini-Mental Status Examination; NPI: The Neuropsychiatric Inventory. * and ** respectively represent p<0.05, p<0.01.*

Figure 9: Neuropsychological assessments in the control group (Behfar et al., 2023).



*Outcomes of the first and second neuropsychological assessments, conducted approximately 10 weeks apart, within the control group. Abbreviations: ADAS-Cog: the Alzheimer's Disease Assessment Scale, cognitive subsection; ADCS-ADL: the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; EQ-5D-5L: the European Quality of Life Five Dimension with Five Levels; MMSE: Mini-Mental Status Examination; NPI: The Neuropsychiatric Inventory. * represents p<0.05.*

Table 12: Outcomes of neuropsychological assessments (Behfar et al., 2023).

Intervention Group					
Assessment	Pre-stim.	Post-stim.	Follow-up	pre- vs. Post-stim *(p-value)*	Post-stim vs. Follow-up *(p-value)*
MMSE	19.6±1	20.8±1.2	18.4±1.3	**0.02**	**3.4×10^{-3}**
ADAS-Cog	27.1±2.4	24.8±3.1	26.8±3.1	**0.04**	0.06
EQ-5D-5L (self)	70.3±4.1	75.3±4.7	71±4.7	0.15	0.15
EQ-5D-5L (proxy)	70.3±3.5	75±4.3	66±4.4	0.11	**0.02**
NPI (self)	10.6±2	6.1±1.4	11.2±2.1	**0.01**	**1.6×10^{-3}**
NPI (proxy)	6.1±1.4	3.6±1.1	6.1±1.7	**0.03**	0.05
ADCS-ADL	60.3±1.7	61.8±1.7	56.8±2.7	0.06	**0.01**

Control Group			
Assessment	1st test	2nd test	1st vs. 2nd test (*p-value*)
MMSE	22.8±1.0	21.6±1.4	0.09
ADAS-Cog	20.2±2.3	21.8±3.3	0.2
EQ-5D-5L (self)	85 ± 4.0	72.5 ± 4.8	**0.02**
EQ-5D-5L (proxy)	68.1 ± 9.4	64.4 ± 7.7	0.3
NPI (self)	7.6±2.2	9.9±2.1	0.1
NPI (proxy)	5.2±2.3	5.3±1.7	0.5
ADCS-ADL	57±4.1	57.4±5.4	0.4

Abbreviations: ADAS-Cog: the Alzheimer's Disease Assessment Scale, cognitive subsection; ADCS-ADL: the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; EQ-5D-5L: the European Quality of Life Five Dimension with Five Levels; MMSE: Mini-Mental Status Examination; NPI: The Neuropsychiatric Inventory.
Statistically significant p-values are bolded

Table 13: Outcomes of neuropsychological assessments (Behfar et al., 2023).

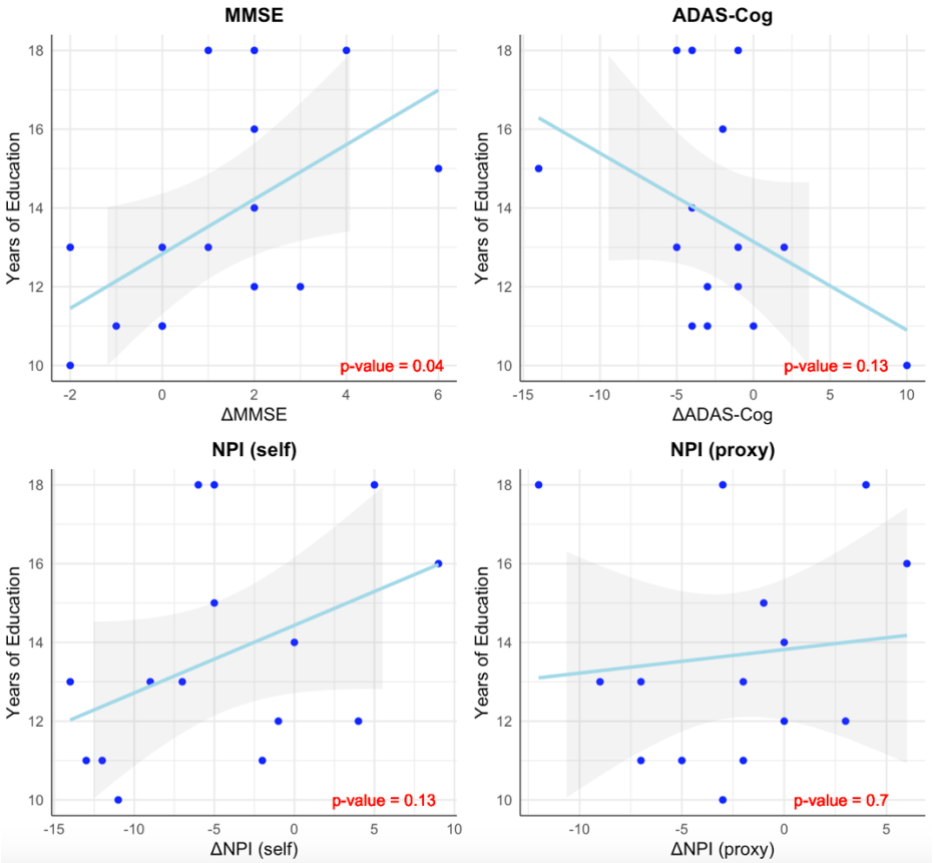
Intervention vs. Control		
Assessment	$\text{Intervention}_{\text{post-pre}}$ vs. $\text{Control}_{\text{2nd-1st}}$ Wilcoxon test	
	Effect size	(*p*-value)
MMSE	0.38	**0.04**
ADAS-Cog	0.24	0.1
EQ-5D-5L (self)	0.44	**0.03**
EQ-5D-5L (proxy)	0.23	0.2
NPI (self)	0.45	**0.03**
NPI (proxy)	0.28	0.1
ADCS-ADL	0.03	0.9

Abbreviations:ADAS-Cog: the Alzheimer's Disease Assessment Scale, cognitive subsection;
ADCS-ADL: the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory;
EQ-5D-5L: the European Quality of Life Five Dimension with Five Levels;
MMSE: Mini-Mental State Examination; NPI: The Neuropsychiatric Inventory.
Statistically significant p-values are bolded.

3.2.3 VBM analysis

Paired t-tests in neither group revealed any significant structural changes over time, and ANCOVA did not demonstrate any significant contrast between the two groups. Next, we speculated whether the total brain volume at baseline could predict the outcome of intervention in CST. Herein, we evaluated the correlation between the total brain volume at baseline, a marker of brain reserve, and changes in MMSE, ADAS-Cog, NPI (self) and NPI (proxy) measures, all of which significantly improved following CST. In the intervention group, improvement in MMSE, ADAS-Cog, NPI (self) and NPI (proxy) measure after CST did not demonstrate any significant association with the baseline brain volume, as shown in **Figure 11** (Behfar et al., 2023).

Figure 10: Association between years of education and significant outcomes of CST (Behfar et al., 2023).

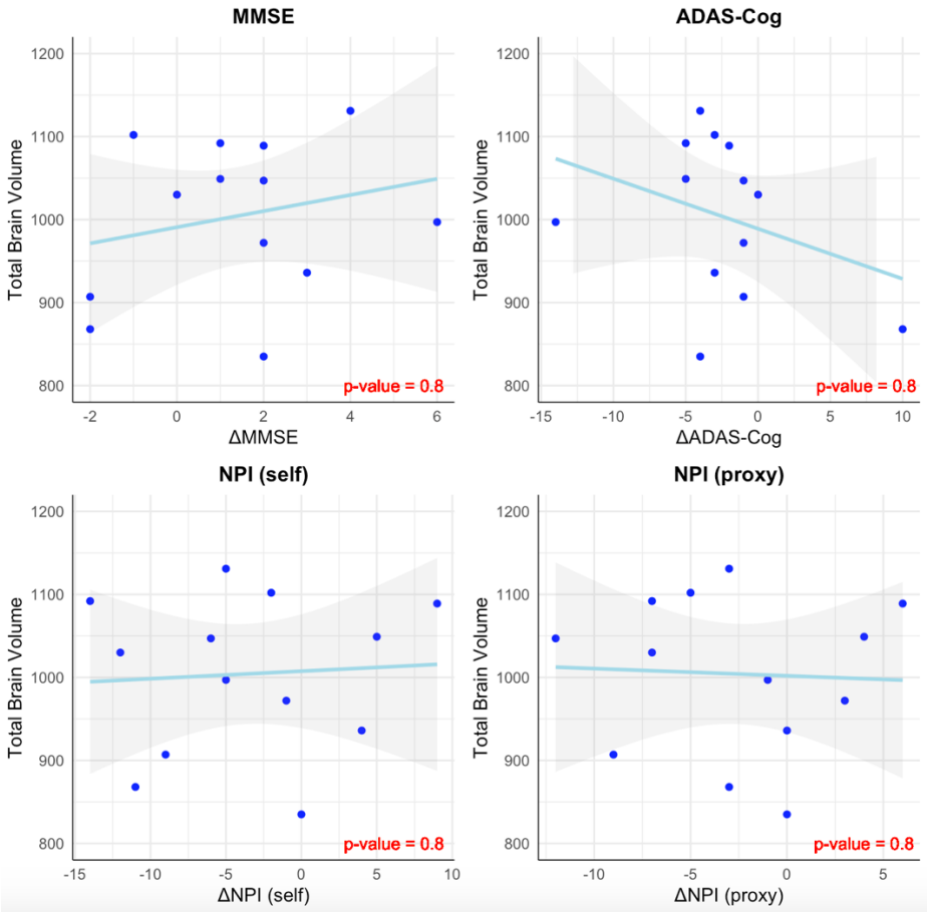


Years of Education	ΔMMSE			ΔADAS-Cog		
	Estimate	*Adj. R2*	*p-value*	*Estimate*	*Adj. R2*	*p-value*
	0.43	0.24	**0.04**	-0.72	0.09	0.13
	ΔNPI (self)			**ΔNPI (proxy)**		
	Estimate	*Adj. R2*	*p-value*	*Estimate*	*Adj. R2*	*p-value*
	1.1	0.12	0.13	0.19	-0.06	0.7

The association between years of education, as a proxy for cognitive reserve, and the post- versus pre-stimulation changes in MMSE, ADAS-Cog, NPI (self), and NPI (proxy) scores within the

intervention group is assessed. The changes following stimulation are represented by ΔMMSE, ΔADAS-Cog, ΔNPI (self), and ΔNPI (proxy). All p-values are Bonferroni-corrected for multiple comparisons, with statistically significant p-values highlighted in bold.

Figure 11: Association between the total brain volume and significant outcomes of CST (Behfar et al., 2023).



Total Brain Volume	ΔMMSE			ΔADAS-Cog		
	Estimate	*Adj. R2*	*p-value*	*Estimate*	*Adj. R2*	*p-value*
	5×10^{-3}	-0.03	0.8	-0.01	0.02	0.8
	ΔNPI (self)			**ΔNPI (proxy)**		
	Estimate	*Adj. R2*	*p-value*	*Estimate*	*Adj. R2*	*p-value*
	4×10^{-3}	-0.08	0.8	-2×10^{-3}	-0.08	0.8

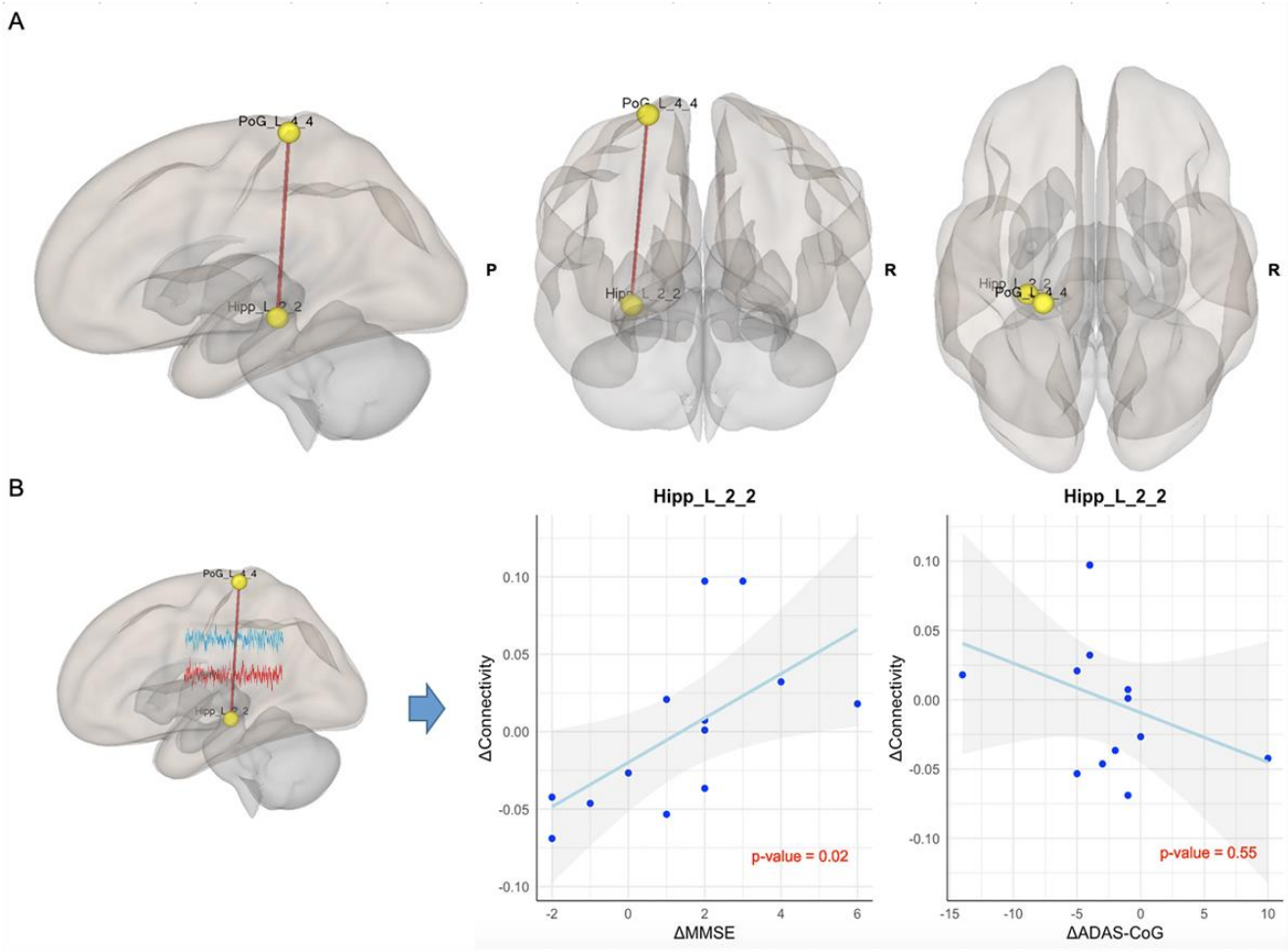
The association between total brain volume, as a proxy for brain reserve, and the post- versus pre-stimulation changes in MMSE, ADAS-Cog, NPI (self), and NPI (proxy) scores in the intervention group is examined. The changes following stimulation are represented by ΔMMSE, ΔADAS-Cog, ΔNPI (self), and ΔNPI (proxy). All p-values are Bonferroni-corrected for multiple comparisons.

3.2.4 ROI-to-ROI Analysis

Across all ROIs of the Brainnetome atlas, ROI-to-ROI analysis was conducted for both the intervention and control groups, with FD accounted for in the models. In the intervention group, we descovered a significant increase in functional connectivity between the left caudal hippocampus (Brainnetome label: Hipp_L_2_2) and the trunk region of the left postcentral gyrus (Brainnetome label: PoG_L_4_4) from pre- to post-stimulation (p<0.05, p-FDR seed-level corrected and Bonferroni-corrected for multiple comparisons) (Behfar et al., 2023) (see **Figure 12**).

No significant changes in ROI-based functional connectivity were observed in the control group. A repeated measure ANOVA test was used to examine the post- vs. pre-stimulation period comparisons between the groups in order to ascertain the effects of CST in the intervention group as compared to the control group. In the comparison between the alterations of the Hipp_L_2_2 ~ PoG_L_4_4 correlation in the intervention and the control group ($\Delta Connectivity_{Intervention-Control} = \Delta Connectivity_{Intervention} - \Delta Connectivity_{Control}$), we observed a significant increase of functional connectivity in the intervention group in contrast to the control group ($F(2,23)$=3.9, p=0.029, partial η^2 =0.27). Importantly, the *post-hoc* assessment of our sample size using G*Power 3.1 and IBM SPSS for α=0.05 revealed a power (1-ß) of 0.7 (Behfar et al., 2023).

Figure 12: ROI-to-ROI analysis in the intervention group, Contrast: post-stimulation > pre-stimulation (Behfar et al., 2023).



C

Contrast	Brainnetome atlas label	Region	Paradigm Brainnetome atlas
Post- > Pre-stimulation *(p<0.05, p-FDR seed-level corrected, & corrected for multiple comparisons)*	Hipp_L_2_2	left caudal-hippocampus	recognition & associate recall
	PoG_L_4_4	trunk region of left postcentral gyrus	Sequence recall & learning

D

	ΔMMSE			ΔADAS-Cog		
	Estimate	*Adj. R2*	*p-value*	*Estimate*	*Adj. R2*	*p-value*
ROI-to-ROI connectivity (*Post- > Pre-stimulation*)	26.14	0.56	**0.02**	-31.12	0.16	0.55

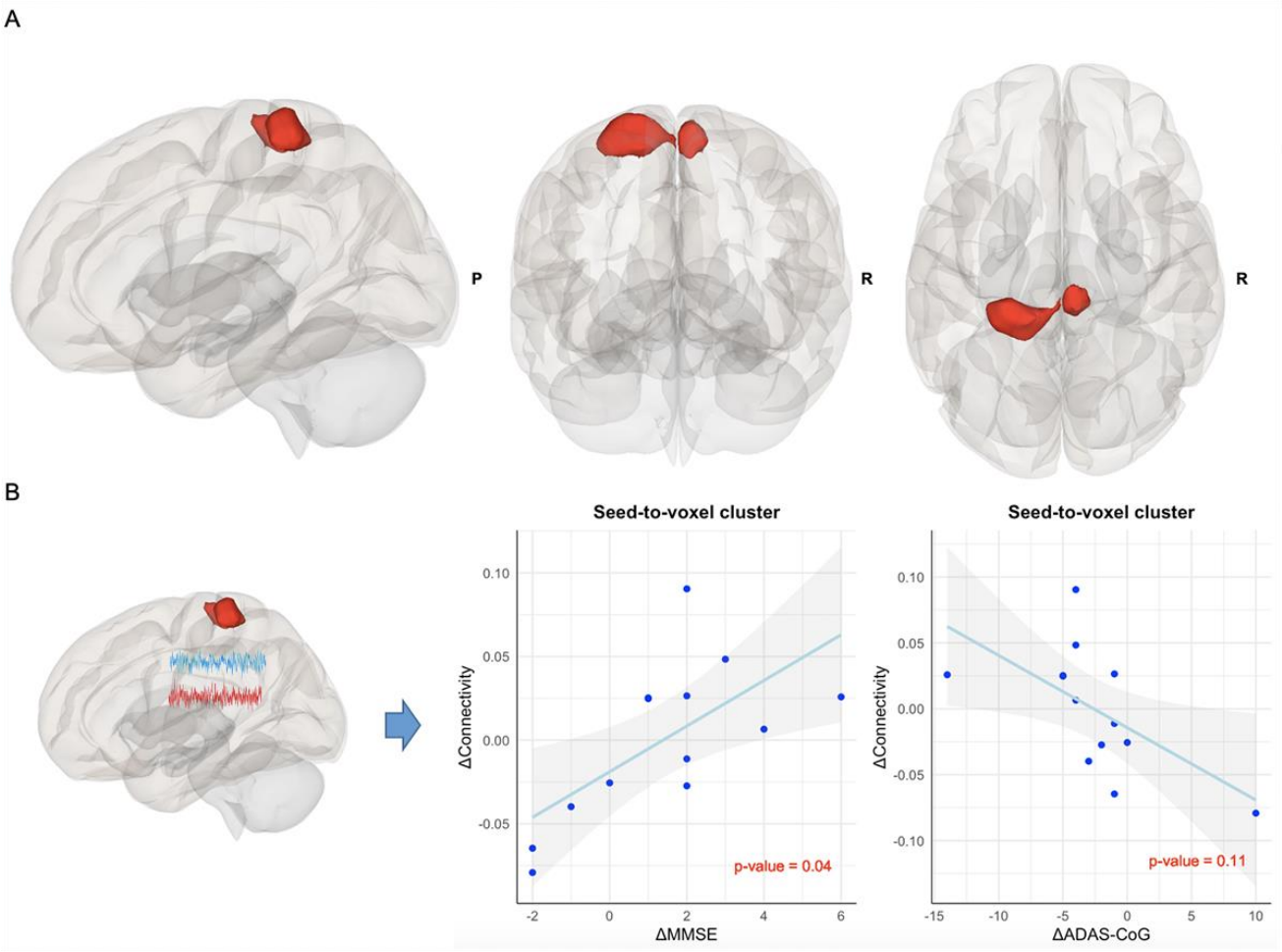
(A) The results of the ROI-to-ROI analysis comparing post-stimulation versus pre-stimulation conditions across 274 ROIs in the Brainnetome Atlas within the intervention group (p<0.05, p-FDR seed-level corrected, and adjusted for multiple comparisons) indicate an increase in ROI-to-ROI functional connectivity, denoted by the red line. (B) The left panel illustrates the correlation between the increase in functional connectivity between Hipp_L_2_2 and PoG_L_4_4 and MMSE scores, while the right panel shows the correlation with ADAS-Cog scores. These associations are adjusted for age and sex, with p-values Bonferroni-corrected for multiple comparisons. (C) The coordinates of ROIs exhibiting a significant increase in functional connectivity in the intervention group are provided. (D) The correlation between up-regulated connectivity and changes in cognitive measures, including ΔMMSE and ΔADAS-Cog scores, is presented. All associations are adjusted for age and sex, with p-values Bonferroni-corrected for multiple comparisons. Statistically significant p-values are highlighted in bold.

3.2.5 Seed-to-voxel Analysis

The findings of the ROI-to-ROI analysis were further explored. The left caudal hippocampus (Brainnetome label: Hipp_L_2_2) was used as the seed in a seed-to-voxel analysis, which revealed significant increases in functional connectivity following the CST program. Overlaps of several regions including the left and the right superior frontal gyri, the left and the right superior parietal lobules, the left and the right postcentral gyri and the left and the right precentral gyri were seen (voxel-wise threshold $p<0.001$, cluster threshold p-FWE<0.05, two-tailed) (Behfar et al., 2023) (see

Figure *13*).

Figure 13: Seed-to-voxel analysis in the intervention group, Contrast: post-stimulation > pre-stimulation (Behfar et al., 2023).



C

Contrast	Region	Cluster size (voxels)	Coordinates (x,y,z)	Peak *t* value
Post- > Pre-stimulation	precentral gyrus (left/right), postcentral gyrus (left/right),	582	-22 -36 +72	4.44

(voxel-wise threshold p<0.001, cluster threshold p-FWE<0.05, two-tailed)	Superior frontal gyrus (left/right), superior pariatal lobule (left/right)

D

	ΔMMSE			**ΔADAS-Cog**		
	Estimate	*Adj. R2*	*p-value*	*Estimate*	*Adj. R2*	*p-value*
Seed-to-Voxel connectivity (*Post- > Pre-stimulation*)	29.18	0.52	**0.04**	-59.67	0.37	0.11

(A) The seed-to-voxel analysis results using the left caudal hippocampus (Brainnetome label: Hipp_L_2_2) as the seed, comparing post- versus pre-stimulation conditions in the intervention group, reveal a significant increase in functional connectivity (height threshold p<0.001, cluster threshold p-FWE<0.05, two-tailed), indicated by the red cluster. (B) The correlation between the increase in functional connectivity within this cluster and the MMSE scores (left panel) and ADAS-Cog scores (right panel) is depicted. These associations are adjusted for age and sex, with p-values Bonferroni-corrected for multiple comparisons. (C) The coordinates of clusters exhibiting a significant increase in functional connectivity in the seed-to-voxel analysis within the intervention group are provided. (D) The correlation between the up-regulation of connectivity and changes in cognitive measures, including ΔMMSE and ΔADAS-Cog scores, is presented. All associations are adjusted for age and sex, with Bonferroni-corrected p-values. Statistically significant p-values are highlighted in bold.

3.2.6 Association between connectivity changes and neuropsychological tests

As depicted in **Figure 12**, the enhanced of connectivity between the left caudal hippocampus (Brainnetome label: Hipp_L_2_2) and the trunk region of the left postcentral gyrus (Brainnetome label : PoG_L_4_4), with learning and memory as classes of testing paradigm, significantly associated with improved MMSE scores (p<0.05, Bonferroni-corrected for multiple comparison). Participants in the intervention group showed a negative, albeit non-significant, correlation with ADAS-Cog scores (Behfar et al., 2023) (see **Figure 12**).

In the seed-to-voxel analysis, the enhanced connectivity in the cluster was significantly associated with the improvement of the MMSE score (see

Figure *13*). Although there was a nominally significant negative association between the enhanced of connectivity in the cluster and the ADAS-Cog scores, this correlation did not hold up after Bonferroni-correction for multiple comparisons (Behfar et al., 2023) (see

Figure *13*).

4. Discussion

4.1 Neuroplasticity and novel characteristics of compensation in healthy brain aging and early neurodegeneration

Our first study utilizing RIMCAD data significantly contributed to the ongoing discourse on compensatory mechanisms in neurodegenerative diseases. The main aim was to offer new insights into the dynamics and dimensions of compensation in healthy brain aging and MCI with AD biomarkers, particularly through the lens of resting-state connectivity derived from graph theory. To our knowledge, graph theory analysis has seldom been employed to detect compensatory effects in the AD continuum. We identified four cognition-related ROIs exhibiting compensatory features in a resting-state fMRI design, using graph measures. These compensatory ROIs included the right superior parietal gyrus (rostral area 7), the right middle frontal gyrus (lateral area 10), and the right and left precentral gyri (caudal dorsolateral area 6). In these ROIs, we observed higher DC measures, indicating stronger connectivity, despite the presence of regional atrophy. These findings suggest that regional structural deterioration of the brain may not necessarily correspond to regional brain function. Although the DC measure of the compensatory ROIs was well correlated with cognitive performance in MCI patients, this correlation was not observed in elderly healthy controls. This aligns with the concept of compensation, which posits that the brain attempts to offset cognitive decline by enhancing neural activity or connectivity. In subsequent seed-to-ROI analyses, using the aforementioned compensatory ROIs as seeds or hubs, we observed significantly higher connectivity between these ROIs and cognition- and memory-related ROIs in the fusiform gyrus, caudal cuneus, occipital polar cortex, pre- and postcentral gyri, and middle occipital gyrus. The cognitive domains encompassed by the compensatory ROIs include language, semantic, and spatial cognition (Fan et al., 2016). Importantly, in the context of dementia, some of these ROIs are linked to learning and sequence recall (Fan et al., 2016). This is

consistent with our observation that the DC measure of the compensatory ROIs showed a significant association with memory, cognitive flexibility, and executive functioning, as inferred from VLMT and TMT values (Behfar et al., 2020).

In task-based fMRI investigations, various compensatory activity enhancement patterns associated with brain aging have been suggested. One report indicated that the hemispheric asymmetry of the prefrontal lobes observed in younger individuals decreases in older adults, a pattern termed "Hemispheric Asymmetry Reduction in Older Adults" (HAROLD) (Cabeza et al. 2002). Subsequent research proposed that this mechanism might also occur in the parietal lobe (Piefke et al. 2012). Another report proposed increased prefrontal cortex activity in elderly individuals alongside decreased occipital lobe activity, referred to as "Posterior-Anterior Shift with Aging" (PASA) (Davis et al. 2008). Furthermore, a compensatory mechanism in healthy brain aging and AD was proposed, involving enhanced functional connectivity in the prefrontal cortex (Gregory et al. 2017), despite evidence from postmortem, in vivo, and brain imaging studies indicating atrophy in this region. This led to the frontal lobe theory, which posits that cognitive inefficiencies in aging are primarily associated with structural and functional deterioration of the frontal lobes (Cabeza et al. 2012). The CRUNCH model (Compensatory-Related Utilization of Neural Circuits Hypothesis) expands these models by describing typical aging-related activity changes associated with compensation without limiting it to specific cerebral regions (Reuter-Lorenz et al. 2008) (Behfar et al., 2020).

Our connectivity-based findings exhibited patterns comparable to those observed in task-based fMRI studies and analyses emphasizing regional activation. In particular, we identified successful compensation in the right middle frontal gyrus (lateral area 10) among MCI patients. Moreover, we found that during the transition from healthy aging to MCI, volume reduction is notably pronounced in this prefrontal region, which indirectly supports the frontal lobe hypothesis. Successful compensation was also demonstrated in the right and left precentral gyri (caudal dorsolateral area 6), which have consistently been implicated in working memory tasks (Howard et al., 2003; Huang et al., 2013; Kambara et al., 2017; Kirschen et al., 2010; Meltzer et al., 2008; Narayanan et al., 2005; Noy et al., 2015). These findings align with evidence

suggesting that increased resting-state nodal centrality in the right middle frontal gyrus and right precentral gyrus may function as a compensatory mechanism, aiding MCI patients in recruiting additional cognitive resources to regain normal cognitive levels (Yao et al. 2010). Moreover, prior research has shown that the parietal lobe is recruited in a task-specific manner to compensate for brain aging (Huang et al. 2012; Piefke et al. 2012). In MCI patients, a resting-state compensatory recruitment of the right superior parietal gyrus (rostral area 7) was identified. These findings on compensatory connectivity changes in the frontal and parietal lobes can be viewed as resting-state counterparts to the HAROLD (Cabeza et al. 2002; Piefke et al. 2012) and/or CRUNCH (Reuter-Lorenz et al. 2008) models of task-based compensation, extending links between our results and previous studies. McCarthy et al. used graph metrics to investigate the PASA phenomenon in task-based and resting-state networks, finding a bilateral increase in DC in the superior parietal gyrus and pre- and post-central gyri in early AD and healthy aging (McCarthy et al. 2014). These results are consistent with our observations in the right superior parietal gyrus and the left and right precentral gyri (caudal dorsolateral region). McCarthy et al. also noted a distinct pattern of decreased DC in the posterior regions in older individuals compared to younger ones, supporting our seed-to-ROI analysis findings of an anterior-to-posterior trend in the right superior parietal gyrus (rostral area 7) and left precentral gyrus (caudal dorsolateral area 6). The clinical and interventional relevance of these findings is significant. Non-invasive stimulation techniques, such as transcranial magnetic stimulation (TMS), may enhance neuronal performance in various brain regions. The identified compensatory ROIs could serve as targets for non-invasive stimulation interventions (Cotelli et al. 2008; Solé-Padullés et al. 2006) (Behfar et al., 2020).

There are a number of limitations to take into account in our current study: Firstly, our dataset consists of a relatively modest number of MCI patients categorized by beta-amyloid and tau biomarkers. Therefore, research with a larger patient cohort is necessary to corroborate these findings. Secondly, we utilized the earlier version of the A/T/N categorization framework (Jack et al. 2016) as the diagnostic criteria for our study participants. In the earlier version, an isolated positive beta-amyloid (A+) biomarker status was sufficient for AD classification, whereas the most recent version (Jack et al. 2018) requires both beta-amyloid (A+) and phospho-tau (T+) biomarker statuses for an AD diagnosis. Thirdly, CSF biomarkers were not available for the senior HC group in our cohort. Including the biomarker status of healthy elderly individuals,

who might already have AD pathologies, would have been advantageous for interpreting the results. Fourthly, we limited our comparisons in this study to those at the group level. However, putting these criteria to the test on an individual basis reveals concrete preferences for the use of personalized medicine in clinical settings, therefore this is a topic that deserves further studies. Group comparison fMRI studies are frequently utilized to understand general brain function, typically by averaging individual effects to maximize the signal-to-noise ratio (SNR). While this approach offers statistical benefits in group comparisons, it fails to sufficiently describe individual-level brain activity. The most commonly employed strategy to interpret fMRI-derived results on an individual level involves relating and comparing them to other individual measures, such as test scores or behavioral measures (Dubois et al., 2016), which has also been our method of choice. Nonetheless, another suggested method is to transit from association analysis to a predictive, machine-learning inspired framework to optimize the generalizability and interpretability of fMRI-derived findings at the individual level (Gabrieli et al., 2015; Linden et al., 2012; Yarkoni et al., 2017). Fifthly, in our current research, we specifically explored the applicability of our proposed compensation framework utilizing the Brainnetome atlas across all cerebral regions. However, the cerebellum's role in cognition, memory, and learning (Schmahmann et al., 2010) suggests that cognitive compensation may extend beyond the cerebrum. Consequently, it will be essential to investigate the compensatory mechanisms within the cerebellum using functional brain atlases that encompass this region (Behfar et al., 2020).

In conclusion, we presented a novel framework for characterizing compensation in healthy brain aging and early neurodegeneration by integrating graph theory analysis of resting-state fMRI data with volumetric analyses of structural MRI. The identified compensatory effect in healthy elderly individuals and MCI patients provided evidence on neuroplasticity in brain aging and the early stages of AD continuum. Furthermore, utilizing an ROI-based atlas with exquisite parcellation allowed for a more accurate mapping of compensatory zones. These regions were significantly correlated with cognitive performance scores in MCI participants, offering new insights into the mechanisms of memory and executive function compensation. Based on these findings, longitudinal studies encompassing a broader range of cognitive impairment categories and stages—such as subjective cognitive decline (SCD), early MCI, late MCI, amnestic versus non-amnestic MCI, and mild to severe AD—are necessary to

further enlighten the dynamics and dimensions of resting-state compensatory mechanisms in neurodegenerative processes associated with cognitive decline. Future research seems to favor individual-level analyses based on a predictive machine-learning framework to better understand the compensating mechanisms (Behfar et al., 2020).

4.2 AD patients retain sufficient neuroplasticity to benefit from CST

In this study, we examined the effects of our eight-week CST program on patients with mild to moderate AD, comparing them to a no-intervention control group both immediately after the intervention and at a three-month follow-up. The primary parameters of interest were cognitive outcomes, QoL, and associated alterations in brain connectivity. We hypothesized that CST, in comparison to the no-intervention control, would (i) promote cognitive performance and QoL and (ii) enhance cognition-related brain connectivity (Behfar et al., 2023).

As anticipated, no significant changes were observed in the neuropsychological assessments within the control group, whereas the self-rated QoL evaluation showed a considerable decline. In contrast, the intervention group revealed significant improvements in cognitive function, QoL, and neuropsychiatric measures immediately following the CST period, pointing to the program's beneficial effects. The positive impact of the CST program was further reinforced by a significant deterioration in most evaluated measures at the follow-ups, suggesting that the observed immediate post-CST effects are unlikely due to repeated testing. Notably, self- and proxy-rated QoL and neuropsychiatric measures were relatively consistent across both groups, confirming the reliability of patients' self-evaluations. These findings align with published reviews and meta-analyses, which assert that CST effectively enhances cognition and QoL in dementia patients (Aguirre et al., 2013; Buschert et al., 2010; Chen, 2022; Spector et al., 2012; Woods et al., 2023, 2012) (Behfar et al., 2023).

The between-group comparison was significant on the MMSE and self-rated EQ-5D-5L and NPI measures, in agreement with the substantial research reinforcing the short-term cognitive benefits of CST programs for patients with mild to moderate dementia (Woods et al., 2023) (Behfar et al., 2023).

The impact of cognitive reserve on the outcomes of neuropsychological techniques has been examined in earlier and more recent research of healthy aged people and patients with mild dementia (Liu et al., 2021; Wang et al., 2020). The body of research

in this area is scattered and not yet clear, but earlier findings point to the importance of cognitive reserve as a predictor of therapeutic response in CST (Behfar et al., 2023). In our study, the improvement in MMSE scores was significantly correlated with years of education, providing further evidence for the utility of cognitive reserve as a predictor of response to CST in patients with mild to moderate AD. This finding supports the hypothesis that patients with higher cognitive reserve may experience greater benefits from CST. Conversely, the absence of a correlation between baseline total brain volume and CST outcomes suggests that the efficacy of CST may not be reliant on brain reserve in this patient population (Behfar et al., 2023).

To date, limited research has examined the effects of CST for dementia on structural or functional brain alterations. Consistent with a recent study evaluating the neural mechanisms of CST in dementia patients (Liu et al., 2021), our study did not observe any structural changes in the intervention group post-CST. However, given that structural changes may require months or years to become evident, it is necessary to conduct structural analyses within long-term CST maintenance programs (Behfar et al., 2023).

Subsequently, we investigated CST-induced alterations in brain connectivity using fMRI. CST enhanced connectivity between the memory-associated left hippocampus (Brainnetome label: Hipp_L_2_2) and a learning- and memory-related sub-region of the left postcentral gyrus (Brainnetome label: PoG_L_4_4). The hippocampus is a highly plastic brain region, facilitating the formation of new neuronal connections, which is essential for cognitive development and advanced cognitive processes (Wenger and Lövdén, 2016). Environmental enrichment paradigms, comprise of physical activity, cognitive stimulation, and social interaction, have been demonstrated to induce hippocampal neurogenesis and enhance synaptic plasticity (Lu et al., 2003). Moreover, a recent study reported increased intrinsic functional connectivity within the default mode network (DMN) following CST, which supports ongoing cognitive processes (Liu et al., 2021)(Behfar et al., 2023).

Previous research has demonstrated that mental activities in older adults enhance functional connectivity within resting-state brain networks (Chapman et al., 2013). Studies investigating the effect of non-pharmacological interventions for dementia on structural and functional brain changes indicate that aging brains, regardless of dementia status, possess the capacity for plasticity (Pieramico et al., 2012; Shigihara et al., 2020). It has been suggested that increased brain connectivity may either reflect

neuroplastic alterations in the structural substrate triggered by cognitive training or a more flexible utilization of pre-existing neural networks through cognitive training, independent of structural alterations (Lövdén et al., 2010). Consequently, it seems plausible that the significant enhancement of connectivity in a neuroplastic region such as the hippocampus was driven by CST. Despite the presumed hippocampal damage associated with AD, the hippocampus retains enough neuroplasticity to benefit from CST (Rosen et al., 2011) (Behfar et al., 2023).

Moreover, seed-to-voxel analysis showed extensive up-regulation of connectivity encompassing the left superior parietal lobule, as well as the right and left precentral and postcentral gyri. These regions have previously been identified as playing compensatory roles in healthy aging and prodromal Alzheimer's disease (Behfar et al., 2020). In line with our findings of up-regualted connectivity in the parietal lobes following CST, Liu et al.(2021) reported enhanced resting-state connectivity in the medial and bilateral parietal cortices after a CST program in patients with mild dementia (Behfar et al., 2023).

Subsequently, we conducted an in-depth analysis of the correlation between the enhancement of functional connectivity and the improvement of cognitive performance, which confirmed a statistically significant association with MMSE scores. This association substantiates the reliability of both neuroimaging and cognitive assessment outcomes and suggests a potential neurobiological mechanism underlying the CST-induced cognitive improvements. Notably, the correlation further demonstrated that changes in hippocampal functional connectivity were consistent with individual-level variations in cognitive performance across participants. The observed concordance between increased connectivity and cognitive enhancement provides evidence supporting hippocampal hyperactivation as a possible compensatory response (Dickerson et al., 2008). Additionally, the marked upregulation of connectivity between the hippocampus and parietal regions, along with its correlation with improved MMSE scores, may implicate the lateral parietal cortex in episodic memory processes (Davidson et al., 2008) (Behfar et al., 2023).

The precise mechanisms underpinning the CST-induced enhancement of functional connectivity remain elusive, largely due to a paucity of imaging studies that dissect these effects. Consequently, we draw parallels between our observations and those from cognitive training studies, where an increase in hippocampal perfusion during memory tasks has been documented in cognitively trained older adults (van Os et al.,

2015). In patients with MCI, hippocampal activation is consistently observed following memory training, along with the recruitment of various frontal and parietal cortical regions that are not directly related to the trained cognitive functions. This suggests that memory training in individuals with mild brain injury may facilitate compensatory mechanisms, reallocating cognitive resources to regain impaired functions (Hosseini et al., 2014; van Os et al., 2015). A analogous mechanism may be applicable to CST, which encompasses a broader range of cognitive domains compared to traditional cognitive training. Chapman et al. (2013) proposed an alternative biological pathway, suggesting that strategy-based cognitive training could leave a neural “footprint” on intrinsic signals, such as spontaneous neural activity. This neural imprint may reflect the accumulation of neurotransmitter-specific receptors in the stimulated regions, along with an enhanced synthesis of essential intra-neuronal molecules required for synaptic function. Furthermore, Valenzuela et al. (2003) demonstrated, through the use of MR spectroscopy, that prolonged cognitive training in healthy elderly individuals modified the neurochemistry of the medial temporal lobe (Behfar et al., 2023).

The observed enhancement in connectivity between the posterior hippocampus and the postcentral gyrus may signify a transition from short- to long-range functional connections. In the early stages of AD, the hippocampi exhibit functional disconnection from adjacent structures involved in learning and memory, such as the entorhinal cortex (DeKosky et al., 2002). Conversely, in the mild to moderate stages of AD, hippocampal connections to several distant regions associated with learning and memory, including the postcentral gyrus, remain relatively intact both structurally and functionally (Buckner et al., 2000; Kim et al., 2013). Consequently, CST may have stimulated neuronal activity within the hippocampus, and the observed upregulation of connectivity between the left posterior hippocampus and the trunk region of the left postcentral gyrus may indicate an intact neuroplasticity reserve in the postcentral gyrus. This reserve may facilitate the formation of new compensatory connections during the mild to moderate stages of AD. Earlier studies have also claimed that the enhanced outcomes observed following cognitive interventions may be attributed to the activation and integration of complementary neuroplasticity mechanisms (Cespón et al., 2018), wherein neurons and synapses are recruited into pre-existing neural networks (Bamidis et al., 2014) (Behfar et al., 2023).

Given the multi-domain character of the interventions, identifying the specific 'active components' of CST is necessary for enhancing its therapeutic efficacy. In this context, the observed upregulation of intrinsic connectivity following CST offers valuable insights. The up-ragulated connectivity within the medial parietal cortices supports the notion of its involvement in the representation of the mental self (Liu et al., 2021). Previous research has identified the medial parietal regions as key nodes in self-representation (Lou et al., 2004), and it has been demonstrated that episodic memory may be supported by the lateral parietal cortex (Davidson et al., 2008) (Behfar et al., 2023).

Recent dementia studies have further explored the role of self in memory processes, highlighting the decline in episodic memory expression and future planning as a consequence of disruptions in self-continuity (Strikwerda-Brown et al., 2019). Our CST program integrated cognitive and sensory exercises aimed at fostering a personal connection with participants' biographies and encouraging dialogue about personal experiences and perspectives. The cognitive and sensory tasks, along with the continuity and consistency maintained across sessions, may play a role in facilitating and restoring self-continuity. A recent study by Zhang et al. (2020), demonstrated that both autobiographical recall and narrative conditions can enhance memory, particularly in amnestic MCI patients, by investigating the impact of self-referential thinking on memory. The study concluded that linking information to the "self" provides a valuable cognitive schema for individuals with cognitive impairments, contingent upon the accuracy of autobiographical memory. In this context, our findings suggest that the memory domain is primarily influenced by the CST, indicating that the relevant tasks may have a potentiating effect on memory functions. By focusing on these potential "active ingredients," CST could offer a valuable refinement for intervention design (Behfar et al., 2023).

Due to the fact that CST is a brief intervention, it is necessary to determine if its benefits can be extended over a prolonged period of time. Maintenance cognitive stimulation therapy (MCST) is a longer course of CST, that aims to maintain or slow down the decline of cognitive function in people with dementia. It is typically provided to people who have completed an initial course of CST and have shown some improvement in their cognitive function. The goal of MCST is to maintain the gains made during the initial course of CST and to prevent further decline in cognitive function.

MCST typically involves a reduced frequency of sessions compared to the initial course of CST. The sessions may also be less structured and more flexible, to better suit the needs and abilities of the individual. The sessions may also include activities that are more tailored to the individual's interests and hobbies, in order to keep them engaged and motivated.

Continuing CST has shown an improvement of quality of life; and an enhancement of cognition for those taking acetylcholinesterase inhibitors (AChEIs) (Orrell et al., 2014). In a more recent MCST study exploring the effectiveness and cost-effectiveness of MCST in 236 participants, modest outcome gains over 6 months were observed and MCST appeared cost-effective CST for people with mild-to-moderate dementia (D'Amico et al., 2015). However, there are overall some limitations to MCST that should be considered:

- **Limited research**: There is limited research on the effectiveness of MCST, and more studies are needed to fully understand its long-term benefits for maintaining cognitive function in people with dementia.

- **Requires regular participation**: MCST requires regular participation and engagement, which may be difficult for some people with dementia to maintain over time.

- **Limited effect on global cognitive function**: MCST is primarily focused on specific cognitive domains, and it may not be effective in improving global cognitive function in some people.

- **Difficulty in implementation**: MCST can be difficult to implement in some settings, such as long-term care facilities, due to staffing and resource constraints.

- **Not suitable for people with severe dementia**: MCST may not be suitable for people with severe dementia, as they may have difficulty participating in the activities.

- **Cost-effective**: MCST might not be cost-effective for some individuals and/or organizations.

Our findings must be interpreted with caution due to some potential limitations. Firstly, our study sample size was relatively small, and a larger sample size is needed to confirm the results. However, with two stimulation sessions per week for eight weeks, as well as baseline, post-intervention, and follow-up sessions, this study is already quite laborious for a single center. A multi-center approach with a significantly larger patient sample is recommended to prove the validity of the presented results. Secondly, participants were unable to be blinded. Nevertheless, this is a prevalent issue with non-pharmaceutical interventions (Behfar et al., 2023).

Thirdly, the design of our study does not allow for the precise attribution of post-intervention effects to specific components of the CST program, or to the social aspects of the sessions to which patients were indirectly exposed. Fourthly, due to the SARS-CoV-2 pandemic, it was ethically unjustifiable to continue data collection from patients at risk for COVID-19. Consequently, data acquisition was halted, and we relied on matched imaging and neuropsychological datasets from seven AD patients within the ADNI database, for whom only MMSE and ADAS-Cog test results were available. Fifthly, the environmental enrichment paradigm encompasses also social and lifestyle factors that can influence structural and functional brain changes (Colavitta et al., 2023). Despite instructing participants not to initiate any new activities during the CST period, our findings may have been affected by their adherence to such unmeasured yet impactful environmental variables, as well as the absence of comparable data for the ADNI patients. Finally, while the study was adequately powered to detect large effects, it may have been underpowered to identify smaller effects, such as those related to cognitive reserve, due to the relatively small sample size (Behfar et al., 2023).

In light of the potential influence of cognitive reserve on the outcomes of CST, we decided to control for any significant differences in years of education—used as a proxy for cognitive reserve—between the intervention and control groups. A larger stratifiable cohort would be necessary to accurately assess the impact of cognitive reserve on CST outcomes. The primary limitations of our study stem from common challenges associated with geriatric trials, such as difficulties in recruitment, high dropout rates, issues with intervention fidelity, and compliance challenges. These

obstacles could be resolved by implementing an internet-based CST program via digital platforms, which could address time, cost, and location-related barriers inherent in traditional in-person CST programs. Large-scale multi-center initiatives, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (Kivipelto et al., 2013) and extensive internet-based trials like "Maintain Your Brain (MYB)" (Heffernan et al., 2019), may offer valuable insights by evaluating multi-domain interventions within larger cohorts (Behfar et al., 2023).

4.3 Future of cognition-focused non-pharmacological therapies in AD

In light of the cost effectiveness of CST, it is broadly recommended as a non-pharmacological treatment approach in AD (Woods et al., 2023, 2012) and ought to be widely accessible in all settings, including communities and institutions. It is challenging to make such programs practical for people with physical limitations or for communities who are difficult to reach, and it could be necessary to incorporate regional healthcare services.

The deployment of well-designed e-health platforms in homes and aged-care institutions might be a field worth developing.

To solidify cognition-focused non-pharmacological therapies as the primary treatment for patients with dementia, a number of concerns still need to be resolved in further studies. To comprehend the time-course of CST benefits and the suitable procedures for maintaining effects, significant study is already being conducted. However, long-term studies should continue to focus on how CST affects non-cognitive areas (such as functional autonomy, mood, and behavior), as well as how the CST may be able to treat certain diseases (i.e. effect beyond symptomatic improvement).

Further research is also required to determine how to balance the frequency and strength of different intervention components over time, especially those that aim to stimulate advanced cognitive performance. An RCT (Muñiz et al., 2015), which reports the three-year outcomes of the initial one-year study (Olazarán et al., 2004) , demonstrated sustained improvements in activities of daily living performance over the three-year intervention period. Unexpectedly, cognition improved after the first year, but fell below usual care control group performance after the third year (Yates et al., 2019).

A significant problem is creating a CST program that is both reproducible and economical. It may be necessary to adopt highly individualized interventions, focusing on a small number of personally relevant requirements and utilizing the largely unaltered capacities, in order to achieve clinically meaningful therapy results.

Treatment should be given in real-world circumstances with just enough automation. Additionally, repeated follow-up visits or booster sessions should be used to ensure persistence in the day-to-day setting. Ability-based evaluations should be supplemented by patient-centered outcome measurements since personally relevant goals can be accomplished in a variety of ways (Clare et al., 2010; Kurz et al., 2012).

Clearly, non-pharmacological therapies must put out an imaginative effort and methodological improvement in order to improve dementia care globally. Interventions must be highly individualized in a setting of ideal social care, which makes it difficult to create interventions that can be repeated and have predictable outcomes. It is desirable that cognitive rehabilitation programs be created, which can be made easily accessible to citizens.

Studies using functional neuroimaging have shown reallocation of neural resources in dementia patients following cognitive training and cognitive rehabilitation, indicating neuroplasticity and the effectiveness of interventions (van Os et al., 2015).

Neuroimaging studies are costly and frequently uncomfortable for the patient, which raises questions regarding their importance. Clinical and personally meaningful outcomes continue to be the benchmark for evaluating the outcomes of non-pharmacological therapies, in our opinion. Because of this, clinical assessments should always be used in conjunction with neuroimaging and other biological data to assess the effectiveness of interventions and to better understand the clinical significance of the detected neurological changes (Clare et al., 2009).

Another concern is the makeup of the control groups, especially in light of the advantages of conducting lengthy trials. Recently, it has been proposed to switch from active control circumstances to control conditions that correspond to treatment groups in terms of improvement expectations (Boot et al., 2013).

However, since expectations are evoked and adjusted not only prior to but also throughout therapy, it seems impractical to disentangle expectations of cognitive improvement from the cognitive effects themselves. We posit that long-term studies with large samples of well-defined patients—such as those characterized by clinical features and Alzheimer's disease biomarkers that predict a consistent rate of cognitive

decline—should be adequate to demonstrate the overall efficacy of cognitive interventions, even when using usual care or historical control groups (Olazarán and Muñiz, 2017).

New strategies that go beyond the cognition-focused non-pharmacological therapies taken into account here merit study and additional research. A recent study examined CST, mindfulness, muscular relaxation, and standard care. The research findings over a two-year period revealed that the improvements in general cognitive measures were most pronounced with mindfulness interventions, moderate with relaxation techniques, and minimal with CST (Quintana-Hernández et al., 2016).

Although they both aim to improve general cognition, mindfulness and CST take very distinct techniques and engage various cognitive processes. It is obvious that the impact of new and traditional non-pharmacological therapies on general cognition as well as any potential differences in effect on particular cognitive functions should be directly compared. For these next studies to be valid, the therapists working with the various experimental groups must be independent and motivated similarly.

As multiple medications with distinct modes of action are frequently combined to treat complicated illnesses such as AD, it is important to look into any potential additive effects between other types of non-pharmacological therapies and cognition-focused non-pharmacological therapies. It is generally recognized that AD is associated with an increase in cortisol levels because the hypothalamus-hypophysis-adrenal axis is functioning better. Exercise may reduce cortisol levels, enhance BDNF, and improve neuronal regeneration, thus decreasing that hyperactivation and giving a physiologic basis for the neural alterations induced by cognition-focused non-pharmacological therapies (Adlard and Cotman, 2004).

A trial combining physical activity, diet, CT, and vascular risk monitoring in older persons who were at risk of dementia due to limited or slightly impaired cognitive ability recently showed promising outcomes (Ngandu et al., 2015).

Recent reports of a decline in dementia incidence show that some vascular risk factors may now be better controlled, but they also point to the positive effects of stimulating environments and intellectual pursuits (Doblhammer et al., 2015; Satizabal et al., 2016). Despite the fact, that this is positive, a gradual rise in dementia prevalence is predicted over the coming decades due to population aging, therefore, breakthroughs in the treatment of comorbidities associated with aging may lead to improvements in dementia care. The hoped-for biological therapies may stabilize the illness in its early

clinical phases, but the number of elderly persons with mild to moderate dementia will continue to rise, typically with a pathological foundation of mixed or even poorly characterized dementia. Highly individualized, cognition-focused non-pharmacological therapies will continue to be thoroughly adjusted in this situation to improve relevant symptoms and limitations of persons with dementia and to lessen the burden of their caretakers.

5. Conclusion

Neuroplasticity is a concept that refers to the brain's ability to reorganize itself by forming new neural connections throughout life. In the first part of our research we provided supporting evidence on the previous knowledge that neuroplasticity which emerges as compensatory effect is not just limited to the developing brain; and even in old age and early neurodegeneration, the brain retains some capacity for plasticity. Herein, we structured a novel framework to characterize compensatory effect in healthy brain aging and AD continuum.

Our findings in the second part of our research demonstrated positive impacts of CST on cognition, quality of life and neuropsychiatric state in mild to moderated AD dementia. According to the current and prior research, CST appears to induce short-term global cognitive improvement in earlier stages of AD dementia by triggering the complementary neuroplasticity mechanism. Importantly, given our small-scale sample, our study provided imaging-based proof on the ameliorating effect of CST on cognition (Behfar et al., 2023).

Although further research with larger samples, other age groups, and at multiple centers are necessary, our results increase the evidence that non-pharmacological therapeutic approaches may be beneficial in mild to moderate AD dementia (Behfar et al., 2023).

The field of CST is evolving rapidly, driven by advancements in neuroscience, technology, and our understanding of cognitive processes. There are some potential directions and trends that might shape the future of CST. While these trends are plausible, the putative advancements in CST are likely to involve a combination of new

and emerging technologies, such as virtual reality and artificial intelligence, to enhance its effectiveness and reach.

- **Virtual reality**: Virtual reality technology can be used to create realistic and engaging environments for people with dementia to participate in cognitive exercises. This could help to improve engagement and motivation during CST sessions.

- **Artificial intelligence**: Artificial intelligence can be used to personalize and adapt CST sessions to the individual needs and abilities of the person with dementia. This could help to optimize the effectiveness of CST and make it more accessible to a wider range of people with dementia.

- **Telehealth**: Telehealth technologies such as video conferencing can allow for CST sessions to be delivered remotely, which could increase accessibility and reduce barriers to participation.

- **Combination with other therapies:** CST may be combined with other therapies, such as physical or occupational therapy and/or non-invasive brain stimulation, to improve overall cognitive and functional outcomes.

- **Research**: There is increasing interest in researching the effectiveness of CST in different stages of dementia and other cognitive disorders, as well as its long-term effects, to better understand its potential benefits.

It's important to note the actual future of CST will depend on a complex interplay of scientific discoveries, technological advancements, regulatory frameworks, and societal priorities. Ongoing research and collaboration between scientists, clinicians, technologists, and policymakers will shape our understanding, the benefits and limitations of CST.

7. Summary

This research endeavor aimed at understanding the mechanisms behind the effectiveness of Cognitive Stimulation Therapy (CST) in addressing cognitive

challenges in Alzheimer's disease (AD) patients. The study, conducted at the Neurology Department of Cologne University Hospital, involved mild to moderate AD patients undergoing CST. Utilizing MRI, our goal was to uncover neural transformations underlying cognitive benefits observed in CST participants, thus advancing understanding of CST's therapeutic potential.

Brain plasticity refers to the brain's ability to adapt and reorganize itself in response to experiences and injuries. This process allows for the formation of new neural connections, supporting the development of new skills and improving cognitive function. CST is designed to enhance brain plasticity and promote compensatory mechanisms in individuals with cognitive decline. Building on knowledge of neuroplasticity's role in CST and its manifestation as compensatory effects in brain imaging, our study established a framework to detect resting-state compensatory effects in healthy aging and Mild Cognitive Impairment (MCI). Using graph theory analysis of resting-state functional MRI data and volumetric analyses of structural MRI, we identified compensatory regions in the brain associated with cognitive performance. Our analysis revealed increased connectivity in certain brain regions despite atrophy, suggesting a compensatory mechanism to counter cognitive decline.

These findings align with existing models of compensation in aging and neurodegeneration. Specifically, we identified regions such as the prefrontal cortex and parietal lobe showing successful compensation in MCI patients, with similarity to patterns observed in task-based compensational effect, suggesting that these regions may serve as targets for non-invasive stimulation techniques to enhance neuronal performance.

With evidence of brain plasticity-driven compensation in healthy aging and MCI, our study then focused on CST's capacity to mitigate cognitive decline in mild to moderate AD, using an eight-week CST program on patients with mild to moderate AD compared to a control group with no intervention. We evaluated changes in cognition, quality of life (QoL), and brain connectivity immediately after the intervention period and at a three-month follow-up. CST was found to significantly improve cognitive function, QoL, and neuropsychiatric measures in the intervention group compared to the control group.

Furthermore, our study examined the role of cognitive reserve in predicting response to CST, finding a significant correlation between improvement in cognition and years of education as a proxy measure for cognitive reserve. However, baseline total brain

volume did not correlate with CST outcomes, suggesting that CST efficacy is not dependent on brain reserve in patients with mild to moderate AD.

Analysis of brain connectivity using functional MRI revealed enhanced connectivity between the hippocampus and memory-related regions, suggesting neuroplastic changes induced by CST. Additionally, increased connectivity in the parietal lobes is observed, consistent with compensatory mechanisms in healthy aging and prodromal AD.

Our results are suggestive of CST-induced neuronal activity, promoting compensatory neuroplasticity, particularly in regions associated with memory and self-representation. Autobiographical recall and narrative tasks incorporated into the CST program may contribute to memory enhancement and restoration of self-continuity.

Finally, we discussed the potential of Maintenance Cognitive Stimulation Therapy (MCST) as a longer-term intervention to maintain cognitive gains and prevent further decline in individuals with dementia. Overall, our findings highlight the effectiveness of CST in improving cognition, QoL, and brain connectivity in patients with mild to moderate AD, and provide further evidence for the broad recommendation of CST as a cost-effective non-pharmacological treatment approach for AD and emphasizes the need for its widespread accessibility in various settings, while underscoring the importance of further research to refine intervention strategies and understand underlying mechanisms.

8. Zusammenfassung

Ziel dieses Forschungsvorhabens war es, die Mechanismen zu verstehen, die hinter der Wirksamkeit der kognitiven Stimulationstherapie (CST) bei der Bewältigung kognitiver Herausforderungen bei Alzheimer-Patienten stehen. An der Studie, die an der Neurologischen Klinik der Uniklinik Köln durchgeführt wurde, nahmen leichte bis mittelschwere Alzheimer-Patienten teil, die sich einer CST unterzogen. Unser Ziel war es, mit Hilfe der MRT die neuronalen Veränderungen aufzudecken, die den bei den CST-Teilnehmern beobachteten kognitiven Vorteilen zugrunde liegen, und so das Verständnis für das therapeutische Potenzial der CST zu verbessern.

Unter Plastizität des Gehirns versteht man die Fähigkeit des Gehirns, sich als Reaktion auf Erfahrungen und Verletzungen anzupassen und neu zu organisieren. Dieser Prozess ermöglicht die Bildung neuer neuronaler Verbindungen, die die Entwicklung neuer Fähigkeiten unterstützen und die kognitiven Funktionen verbessern. Die CST wurde entwickelt, um die Plastizität des Gehirns zu verbessern und die

Kompensationsmechanismen bei Menschen mit kognitivem Abbau zu fördern. Aufbauend auf dem Wissen über die Rolle der Neuroplastizität bei der CST und ihrer Manifestation als kompensatorische Effekte in der Bildgebung des Gehirns wurde in unserer Studie ein Rahmen geschaffen, um kompensatorische Effekte im Ruhezustand bei gesundem Altern und leichter kognitiver Beeinträchtigung (MCI) zu erkennen. Mithilfe der graphentheoretischen Analyse funktioneller MRT-Daten im Ruhezustand und volumetrischer Analysen der strukturellen MRT identifizierten wir kompensatorische Regionen im Gehirn, die mit der kognitiven Leistung in Verbindung stehen. Unsere Analyse ergab, dass die Konnektivität in bestimmten Hirnregionen trotz Atrophie zunimmt, was auf einen kompensatorischen Mechanismus zum Ausgleich des kognitiven Verfalls hindeutet.

Diese Ergebnisse stimmen mit bestehenden Modellen der Kompensation bei Alterung und Neurodegeneration überein. Insbesondere haben wir Regionen wie den präfrontalen Kortex und den Parietallappen identifiziert, die bei MCI-Patienten eine erfolgreiche Kompensation zeigen, mit Ähnlichkeit zu Mustern, die bei aufgabenbasierten Kompensationseffekten beobachtet wurden, was darauf hindeutet, dass diese Regionen als Ziele für nicht-invasive Stimulationstechniken zur Verbesserung der neuronalen Leistung dienen könnten.

Angesichts der Belege für die Kompensation durch Hirnplastizität bei gesundem Altern und MCI konzentrierte sich unsere Studie auf die Fähigkeit der CST, den kognitiven Abbau bei leichter bis mittelschwerer Alzheimer-Krankheit abzuschwächen, indem wir ein achtwöchiges CST-Programm bei Patienten mit leichter bis mittelschwerer Alzheimer-Krankheit im Vergleich zu einer Kontrollgruppe ohne Intervention durchführten. Wir untersuchten die Veränderungen der kognitiven Fähigkeiten, der Lebensqualität und der Konnektivität des Gehirns unmittelbar nach der Intervention und nach einer dreimonatigen Nachuntersuchung. Es zeigte sich, dass die CST die kognitiven Funktionen, die Lebensqualität und die neuropsychiatrischen Messwerte in der Interventionsgruppe im Vergleich zur Kontrollgruppe deutlich verbesserte.

Darüber hinaus untersuchte unsere Studie die Rolle der kognitiven Reserve bei der Vorhersage der Reaktion auf die CST und fand eine signifikante Korrelation zwischen der Verbesserung der kognitiven Fähigkeiten und den Jahren der Ausbildung als Ersatzmaß für die kognitive Reserve. Das Gesamthirnvolumen zu Beginn der Studie korrelierte jedoch nicht mit den Ergebnissen der CST, was darauf hindeutet, dass die

Wirksamkeit der CST bei Patienten mit leichter bis mittelschwerer Alzheimer-Krankheit nicht von der Hirnreserve abhängt.

Die Analyse der Konnektivität des Gehirns mittels funktioneller MRT ergab eine verbesserte Konnektivität zwischen dem Hippocampus und gedächtnisrelevanten Regionen, was auf neuroplastische Veränderungen durch CST hindeutet. Außerdem wurde eine erhöhte Konnektivität in den Parietallappen beobachtet, was mit kompensatorischen Mechanismen bei gesundem Altern und Alzheimer-Prodromen übereinstimmt.

Unsere Ergebnisse deuten auf eine CST-induzierte neuronale Aktivität hin, die eine kompensatorische Neuroplastizität fördert, insbesondere in Regionen, die mit dem Gedächtnis und der Selbstrepräsentation verbunden sind. Autobiografische Erinnerungs- und Erzählaufgaben, die in das CST-Programm integriert sind, könnten zur Verbesserung des Gedächtnisses und zur Wiederherstellung der Selbstkontinuität beitragen.

Schließlich erörterten wir das Potenzial der kognitiven Erhaltungstherapie (Maintenance Cognitive Stimulation Therapy, MCST) als längerfristige Intervention zur Aufrechterhaltung kognitiver Fortschritte und zur Verhinderung eines weiteren Rückgangs bei Menschen mit Demenz. Insgesamt unterstreichen unsere Ergebnisse die Wirksamkeit der CST bei der Verbesserung der Kognition, der Lebensqualität und der Konnektivität des Gehirns bei Patienten mit leichter bis mittelschwerer Alzheimer-Krankheit. Sie liefern weitere Belege für die breite Empfehlung der CST als kosteneffizienter nicht-pharmakologischer Behandlungsansatz bei Alzheimer-Krankheit und unterstreichen die Notwendigkeit ihrer breiten Zugänglichkeit in verschiedenen Settings.

9. Acknowledgment

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10. Abbreviations

AChEIs, acetylcholinesterase inhibitors

AD, Alzheimer’s disease

ADAS, Alzheimer’s Disease Assessment Scale

ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living

ADL, Activities of daily living

ADNI, Alzheimer’s Disease Neuroimaging Initiative

BOLD, blood oxygen level dependent

BPSD, behavioral and psychological symptoms of dementia

CERAD, Consortium to Establish a Registry for Alzheimer's Disease

CSF, cerebrospinal fluid

CRUNCH, compensatory-related utilization of neural circuits Hypothesis

CST, cognitive stimulation therapy

CVD, cerebrovascular dementia

DC, degree centrality

DMN, default mode network

DSM, Diagnostic and Statistical Manual of Mental Disorders

EPI, Echo planar imaging

EQ-5D-5L, European Quality of Life Five Dimension with Five Levels

FA, flip angle

FD, frame-wise displacement

FDA, Food and Drug Administration

FINGER, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

fMRI, functional magnetic resonance imaging

FMAP, Formative Method for Adapting Psychotherapy

FOV, field of view

FTD, Frontotemporal Dementia

FTLD, frontotemporal lobar degeneration

GM, grey matter

HAROLD, Hemispheric Asymmetry Reduction in Older Adults

HC, Healthy controls

IV, intravenous

MCI, mild cognitive impairment

MCST, Maintenance cognitive stimulation therapy

MNI, Montreal Neurological Institute

MMSE, Mini-Mental State Examination

MRI, magnetic resonance imaging

MYB, Maintain Your Brain

NMDA, N-methyl-D-Aspartate

NPI, Neuropsychiatric Inventory

PASA, Posterior-Anterior Shift with Aging

PET, positron emission tomography

QoL, quality of life

RAVLT, Rey Auditory Verbal Learning Test

RCI, reliable change index

RIMCAD-study, Retroactive Interference during Memory Consolidation in Aging and Dementia Study

RO, Reality Orientation

ROI, region of interest

RTC, randomized controlled trials

SCD, subjective cognitive decline

SPECT, single-photon emission tomography

SNR, signal-to-noise ratio

TE, echo time

TIV, Total intracranial volume

TMS, transcranial magnetic stimulation

TMT, Trail Making Test

TR, repetition time

VLMT, Verbal Learning and Memory Test

WHO, World Health Organization

WM, white matter

11.1. List of Figures

11.2. List of Tables

Table 10: Association between DC measures of cognition-correlated compensatory ROIs, total VLMT, and delta TMT scores in MCI patients. Correlation with significant p-values are highlighted in bold. All p-values are adjusted for multiple comparisons (Behfar et al., 2020).

Table 11: Association between DC measures of cognition-related compensatory ROIs, total VLMT, and delta TMT scores in senior HC. All p-values are adjusted for multiple comparisons (Behfar et al., 2020).

Table 12: Outcomes of neuropsychological assessments (Behfar et al., 2023).

Table 13: Outcomes of neuropsychological assessments (Behfar et al., 2023).

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Graph Theory Analysis Reveals Resting-State Compensatory Mechanisms in Healthy Aging and Prodromal Alzheimer's Disease. Behfar, Q*., Behfar, S.K., von Reutern, B., Richter, N., Dronse, J., Fassbender, R., Fink, G.R., Onur, O.A., 2020. Front. Aging Neurosci. 12, 1–13. https://doi.org/10.3389/fnagi.2020.576627*

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