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Brain Training and Meditation's Effects on Memory in Subjects with Vascular Cognitive Impairment

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BRAIN TRAINING AND MEDITATION'S EFFECTS ON MEMORY IN SUBJECTS WITH VASCULAR COGNITIVE IMPAIRMENT

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Table of Contents

Abstract

Vascular Dementia (VaD) is an important public health concern, which causes significant morbidity and mortality amongst populations around the world. With the increases in average age of individuals and prevalence of cardiovascular risk factors, the incidence of vascular cognitive impairment (VCI) and VaD are on the rise. Most of this increase will come from cerebral small vessel disease (CSVD) as treatment for large vessel disease improves. Yet, very few interventions are recommended for CSVD beyond control of risk factors.

In this thesis, we propose a non-pharmacological intervention, which we believe may address executive dysfunction in VCI due to CSVD. CSVD impairs functional frontal-subcortical connectivity and results in cognitive and functional impairments. Given the plasticity in these circuits, despite old age, cognitive training may be a good candidate for improving cognition in CSVD. However, previous studies have suffered from heterogeneity of pathologies in VCI by including both large and small vessel disease. Furthermore, they have often not considered the effects of anxiety and depression, which we aim to exclude from the study. Finally, these studies do not use validated composite scores as a primary endpoint and currently do not use any biomarkers to follow the progress of subjects. In this study, we aim to partially address these shortcomings and offer a more rigorous approach to cognitive training.

Chapter 1 – Introduction

1.1 Background: Vascular Dementia

1.2 Vascular Dementia: Large vessel vs. small vessel disease

Vascular dementia (VaD) is a widely recognized public health concern which imposes significant clinical, social, and financial burdens on society. Vascular dementia is the second most common form of dementia after Alzheimer's Disease (AD). Its prevalence in the United States is reported to be 8-10%,[1] but this is likely to be an underestimation given that most cases of mixed vascular and Alzheimer's pathology are reported as AD.[2] Currently, research into VaD is in its infancy with definitive diagnostic criteria and biomarkers still in development. Research into VaD is a critical and urgent area of medical research since VaD is shown to lower median life expectancy, create greater health care expenditures, and have higher rates of comorbidity when compared to AD.[1]

VaD is the result of vascular brain injury from large vessel strokes or cerebral small vessel disease (CSVD). There are important distinctions between these two categories as they are distinct diseases and require different approaches: Large vessel disease is caused by lesions in the setting of a large vessel becoming occluded. All large vessels and their tributaries may suffer from strokes including branches of the carotids, anterior, middle, and posterior cerebral arteries. Occlusion may occur due to cardioembolic, arterioembolic, or atherosclerotic etiologies. Large vessel strokes can affect cognition proportionate to the extent of damage they cause to the brain. In contrast, "strategic infarcts" can cause severe cognitive deficits by anatomically limited lesions when they affect highly connected areas of the brain networks. These include the anterior and median thalamus, medial temporal lobes, basal ganglia, angular gyrus, and the fornices.[3] Treatment strategies for strokes are well established. In the acute setting, thrombolysis and endovascular interventions may be considered, to reverse vessel occlusion. In the immediate post-stroke period, stroke rehabilitation aims to mitigate functional impairments in speech, vision, strength, coordination, or balance.[4]

Multidisciplinary interventions are commonly implemented, and include exercise, cognitive training, and learning compensatory strategies.[4] There is evidence that constraint-induced movement therapy, mental practice, mirror therapy, and high doses of repetitive exercises are effective in regaining motor function.[5]

Cerebral small vessel disease is patho-physiologically distinct from large vessel disease. CSVD was originally thought to be an accumulation of small strokes,[6] however this paradigm has been abandoned as large vessel disease treatments proved to be ineffective in CSVD.[7] We have learned that CSVD is a heterogenous disease that can damage the cerebral vasculature by different pathological processes. Different pathologies may be at play in CSVD. These pathologies are sorted into six broad categories based on their etiology in the Pantoni classification system which includes arteriosclerosis, cerebral amyloid angiopathy, hereditary angiopathies, inflammatory angiopathy, venous collagenosis and others.[8]

In this project, we will confine our interest to CSVD caused by arteriosclerosis, cerebral angiopathy, and micro embolism. These represent the increasingly common "white matter disease" seen in memory clinics. Stroke rehabilitation is well characterized and established. The role of non-pharmacological intervention in CSVD is less well established and may represent a major new way in which CSVD is managed.

Several lesions related to CSVD appear to contribute to the pathophysiology of cognitive disorders. One category is that of lacunar infarcts. Lacunar infarcts are small, non-cortical infarcts, of about 0.3 mm to 15 mm in size, that result from a small, single penetrating branch from a large cerebral artery becoming occluded.[9] These occluded branches tend to be acutely angled and stem from the Circle of Willis, causing lacunar infarcts to have a predilection for the basal ganglia, subcortical white matter, and the pons.[10] Lacunar infarcts are reported to account for 15% to 26% of ischemic strokes.[11] These lacunar infarcts preferentially affect the cortico-subcortical circuitry passing though the basal ganglia and the thalamus.

Other pathologies include cerebral amyloid angiopathy, which is caused by the deposition of amyloid in small vessels. For most part, this causes occlusion of small vessels especially in the partieto-occipital white matter.[12] It also increases the risk of microhemorrhages seen preferentially in the posterior fossa.[12] Enlarged perivascular spaces are another marker of vascular disease. Finally white matter hyperintensities represent various vascular related pathologies.[8]

1.3 Current therapeutic approaches to CSVD

Presently there are no interventions for cognitive impairment caused by CSVD which are strongly rooted in evidence. Short of a disease modifying strategy, approach to the cognitive effects of CSVD probably fall into the following categories:

- Secondary prevention measures addressing vascular pathology:
    - Pharmacological: For example, there is good evidence that strict blood pressure control may slow the progression of CSVD and its cognitive consequences.[13] The evidence for other vascular risk factors is less strong.
    - Exercise and diet: Aerobic-based exercise in the acute period improved memory moderately, but long-term exercise, defined as 14 months, did not.[14] Aerobic intervention however has been associated with stimulating the release of factors that promote dynamic network connectivity and neuro-vasculature protection, like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor (IGF-1).[15]
- Interventions to improve cognition:
    - Pharmacological: there is evidence that cholinesterase inhibitors have a modest effect on cognition in CSVD.[16,17]
    - Non-pharmacological: Cognitive training was shown in one study to improve cognitive function up to five years post-training in the elderly with healthy cognitive functions.[18] A Cochrane review found it to have only small beneficial effects in people with mild-to-moderate AD and VaD for cognitive rehabilitation and not cognitive training, but the quality of the studies were graded as low-to-moderate.[19] In the Cochrane review on Attention Process Training, small benefits were found in performing activities of daily living.[20] Studies also found a relative association between attentional processes and behavioral outcomes.[21]
- Treatment of neuropsychiatric comorbidities: Improvements in depression and anxiety will prevent against cognitive decline because psychiatric diseases can increase one's risk for dementia.[22,23]

1.4 The Science Underlying our Proposed Experiment

1.5 Network disruption in CSVD

CSVD affects white matter preferentially, and as such, can be seen in terms of changing connectivity in the brain. CSVD has a predilection for interruption of frontal-subcortical circuitry.[24] Frontal-subcortical impairment is characterized by prominent deficits in executive functioning, mentation speed, memory retrieval, attention[25], as well as gait apraxia[26], bladder dysfunction, pseudobulbar affect, apathy[27], and depression[28]. [24]

Classically the frontal-subcortical circuitry are divided into five sub-circuits, three of which seem particularly vulnerable to CSVD: the dorsolateral prefrontal circuit, anterior cingulate circuit, and the orbitofrontal circuit. [29] These circuits send afferent projections to the thalamic nuclei, basal ganglia, or amygdalate nuclei, and send efferent projections to the inferotemporal, posterior parietal, or pre-striate cortices.[29] Collectively, disruptions to these circuits have persistently presented with deficits in executive functions, apathy, and impulsivity.[29]

More specifically, disruptions to these individual circuitries, or functional networks, will present with specific-behavioral deficits. Dorsolateral prefrontal dysconnectivity is associated with poor behavioral responses because it can no longer organize the information that is integrated into task-related actions.[29] Anterior cingulate dysconnectivity is associated with poor motivational behavior.[29] Orbitofrontal circuit dysconnectivity is associated with emotional dysregulation because it integrates limbic and emotional information into behavioral responses.[29]

Given that CSVD causes disruption of brain's neural networks, one approach to improving task-specific performance may be adaptive changes, both functional and structural, to the network. Brain's ability to change itself adaptively in response to experience is called neuroplasticity.

1.6 Neuroplasticity

The definition of neuroplasticity is varied and evolving. Neuroplasticity refers to adaptive changes in brain connectivity and structures in response to experience. The oldest conception of plasticity belongs to Donald Hebb who discovered that concurrent activation of both pre- and post-synaptic neurons causes strengthening of synaptic connection. This is sometimes expressed as "neurons that fire together, they wire together."[30] More broadly, neuroplasticity may involve changes in synaptic strength or neuronal excitability. These can occur due to changes in the probability of neurotransmitter release and/or changes in receptor density.[31] In the short term, plasticity is protein synthesis independent.[31] In the long term, there are transcriptional changes which can target individual dendritic spines.[31] Dendritic spines are highly dynamic: they are created and either grow, shrink or disappear.[31] Dendritic spine turnover increases during adolescence, stimulation and exercise.[31] Often-used dendritic spines consolidate, while rarely used connections are pruned.[31] These, along with mechanisms that change synaptic strength and neuronal excitability, represent important mechanisms by which the brain learns and compensates for damage. Experience-induced neuroplasticity may be useful in 'rewiring" damaged networks.[31]

The properties of experience-induced neuroplasticity were summarized by Kleim and Jones.[32] Here we paraphrase and summarize their list as follows:

- General premise:[32]
    - Synaptic density and neuronal excitability decrease with disuse of brain function and increase with use.
    - Changes that occur within used and unused networks are specific for brain function.
- Dosing: plasticity occurs for skillful tasks performed at: [32]
    - High repetition
    - High intensity
    - Sufficient duration of time
- Optimization: Plasticity is most effective: [32]
    - In particular windows of time, including brain damage
    - For high salience tasks

    - In younger subjects

- Interaction with other domains:[32]

    - Transference: the property that training for one brain function will improve similar brain functions using similar anatomical structures.
    - Interference: that improvement in one brain function may be detrimental to the performance of another function.

One particular form of plastic changes in neuronal excitability relates to the connections in layer III of the prefrontal cortex.[33] Arnsten and others have worked extensively on this phenomenon, which they have termed *Dynamic Network Plasticity*.[33] The basic premise is that high levels of norepinephrine cause reduced neuronal excitability, and in essence, will cause reduction in functional connectivity.[33,34] This is significant for our purposes because fluctuations in anxiety from day-to-day may confound any measurement of connectivity in subjects. We will now turn our attention to the techniques which we hope to employ in this experiment.

1.7 Intervention 1: Dual N-Back

Dual N-Back is one of the most studied types of adaptive brain training. It is a game in which participants are presented with two series of stimuli, and the task is to decide whether the current stimulus matches with the one presented n-items back. The goal is to increase task-difficulty level, which is adjusted to one's performance. In the Dual N-Back model, the ability to manipulate two tasks simultaneously is possible because of working memory and the coordinated interactions between the prefrontal cortex (PFC) and the basal ganglia (BG).[35]

Increase in task-difficulty is an important feature of Dual N-Back because of its associations with greater learning and structural change. Cognitive loading involves modulation and recruitment of additional networks when completing complex tasks or when other networks have become compromised.[36-39] Cortical areas recruited by Dual N-Back include the lateral premotor cortex; dorsal cingulate and medial premotor cortexes; dorsolateral and ventrolateral prefrontal cortexes; frontal poles; medial and lateral posterior parietal cortexes and parietal lobe; and, the anterior corpus collosum.[40]

Involvement of frontoparietal, striatal, and thalamic regions support the possibility of cognitive transfer gains to other cognitive domains.[41] This is supported by improvements in attention[42,43], reasoning, and the ability to solve novel problems ("fluid intelligence") after playing Dual N-Back.[44] Executive functioning is believed to be dependent on working memory, attention, and episodic memory retrieval,[45] which are cognitive domains that have been strengthened by Dual N-Back.[42,44,46] Executive functioning is also likely to improve more directly since Dual N-Back strengthens the frontoparietal network.[47]

Adaptive cognitive trainings have shown only modest improvements in cognition of the elderly with mild cognitive impairment (MCI) and dementia.[19] The small effect size may be due to one of the following:

1) Incorrect experimental design: problems with placebo-task, dosing, patient selection, or outcome measurements.
2) Short-comings of the modality used.
3) A lack of efficacy for adaptive cognitive training in general.

1.8 Intervention 2: Mindfulness meditation

In a "state of mindfulness," a person becomes purposefully and nonjudgmentally aware of the present moment by learning acceptance and how to be actively present.[48] Mindfulness is rooted in Buddhist philosophy and has various implementations in medical literature. Mindfulness meditation practice focuses attention on one's own breathing while increasing awareness of the streams of information of both internal and external stimuli.[48]

The purpose of mindfulness training is the deactivation of the default mode network.[49,50] The default mode network consists of the hippocampus and its connections to the posterior cingulate cortex and precuneus posteriorly, and its connections to the anterior cingulate cortex and mesial frontal lobes anteriorly.[50] It is thought to consist of self-generated thoughts including un-cued memories and day-dreaming.[50] Default mode network can be thought of as "internal attention" compared to the dorsal attention network[51] engaged in the Dual N-Back task.[50] A loss of anticorrelation between these two networks can cause problems with attention.[50] Most commonly

practiced forms of meditation seem to reduce default mode network activity leading to improved attentional function.[50]

1.9 Combining the two interventions

Combining the two interventions, one which activates the dorsal attention network and the other which deactivates the counter-correlated network, may create a synergistic effect which may be more efficacious than the other two methods on their own.

1.10 Designing the experiment:

1.11 Our experiment

We hypothesize that subjects with mild vascular cognitive impairment (mild-VCI) who receive combined Dual N-Back and Mindfulness Meditation Practice (MMP) will have improved executive functioning capacities compared to those treated with placebo.

Primary outcome is executive functioning capacity, and it is defined as mean change in executive functioning scores from baseline to one-year post-treatment initiation, as measured through Alzheimer's Disease Neuroimaging Initiative (ADNI)- Executive Function (ADNI-EF) test. The mean changes will be reported as a Z score.

Secondary aims include the following:

1) Show increased connectivity in the high-performance network as defined by connectome predictor modeling (CPM) methodology.
2) Explore improvements in other neuropsychological parameters.

1.12 An imaging biomarker: A network approach to CSVD

A network is a representation of a number of interconnected objects with nodes representing the objects and the edges representing the connections.[52,53] The degree of connectivity may be represented by connection strength.[52,53] We can simplify the relationship between the different cortical and subcortical structures connected by white matter tracts we discussed in the last section in terms of a network. [52,53] We can then explore the relationship between individual connection strength and the ability to perform a particular task.[52,53] This network may then be

simplified by keeping only those edges that have a high positive or negative correlation with the performance of the particular task in question.[52,53] These can respectively be called high-performance network and low-performance network.[52,53] Strengthening of low-performance network could potentially diminish behavioral performance, despite stability in high-performance networks. It is theoretically possible by manipulating the strength of connections in the network to change performance.[52,53]

1.13 Definitions or Terminology

1) VCI is the spectrum of the cognitive disorder that ranges from mild cognitive impairment (MCI) to dementia.[2]

2) MCI-CSVD: Mild cognitive impairment due to cerebral small vessel disease.

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Chapter 2 - Review of the Literature

2.1 Background

Cerebral small vessel disease is an understudied population. The medical community still has more to learn about its pathophysiology, and its diagnostic criteria is still being refined. We know that CSVD disrupts the frontal-subcortical circuitry[1] and can present with deficits in executive functioning, mentation speed, memory retrieval, and attention[2], along with other impairments, but we do not currently know how to best treat this disease.

2.2 Objectives

In this literature review, we will be assessing the clinical efficacy of Mindfulness Meditation and Dual N-Back versus an active-placebo control group on delaying executive functioning decline in people with MCI-CSVD. We will also review Donepezil and other nonpharmacological interventions that are being studied on trying to improve cognitive functioning in MCI disease.

2.3 Methods: Criteria for considering studies for this review

2.4 Search Methods and Selection Criteria

We searched ClinicalTrials.gov and Cochrane databases up until July 1, 2018, to identify relevant, peer-reviewed, primary articles of clinical RCT's and systematic reviews of non-pharmacological interventions in the treatment of VCI; treatments in CSVD population was too narrow of a search.

In ClinicalTrials.gov, the terms "Vascular Cognitive Impairment," "Cognitive dysfunction," "Cognitive decline," and "Vessel" were used. We searched for completed, clinical trials with published results and found only four studies. The interventions used were NA-1[3], a peptide that is designed to reduce ischemic brain damage in post-stroke patients, vitamin B[4], calf-blood called Actovegin,[5] and blood pressure control by prescribing lisinopril, candesartan, or

hydrochlorothiazide.[6] No non-pharmacological interventions populated, so studies from this search were not used.

In Cochrane database, we used the MeSH Terms "Cognitive Dysfunction (vascular cognitive impairment)," "Dementia," and "Vascular (subcortical dementia)." We included all randomized trials of non-pharmacological interventions that are relevant to current practice guidelines in MCI treatment.[7] The interventions outcomes had to include cognition or anxiety/stress. All trials selected must have had published results.

2.5 Types of Participants

Participants were either cognitively healthy or elderly with MCI or dementia due to AD or VAD. Studies that included healthy participants were to study the intervention's effects on synaptic plasticity.

2.6 Types of Interventions

Cognitive Training. We included studies that used Dual N-Back or other similar forms of adaptive cognitive training. Interventions could be delivered individually or in groups. The studies included come from Cochrane: "Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer's or vascular type: a review"[8] and from "Benefits of Cognitive Treatments Administered to Patients Affected by Mild Cognitive Impairment/Mild Neurocognitive Disorder."[9]

*Mindful Meditation Practice. W*e included trials that used MBSR or its modified versions.

Donepezil. We included all randomized, double-blinded trials that compared donepezil with placebo. Participants enrolled had VCI, which had to be confirmed by either NINCDS-ADRDA or DSM-IV criteria.

2.10 Types of Outcome Measures

We assessed the following outcomes when applicable. Please refer to the appendix section for more information on the studies that are included in this review.

1) Interventions effects on executive functioning scores
2) Interventions effects on stress
3) Interventions effects on brain activity assessed by imaging
4) Interventions effects on other neurocognitive or behavioral domains
5) Connectome Predictor Modeling

2.11 Results

2.12 Description of studies: Cognitive training, MMP, and Donepezil

Only one study was identified that compared MMP, cognitive training, and Donepezil's effects on cognition in the elderly with mild-to-severe AD (Quintana-Hernández DJ).[10] The two-year, double-blinded RCT was an equivalency and non-inferiority study that compared MMP-Donepezil to Cognitive Stimulation Training (CST)-Donepezil and Donepezil-only in delaying cognitive decline in AD. The study enrolled 168 patients with mild-to-severe AD that was confirmed by the NINCDS-ARDA criteria. The inclusion criteria limited the trial to patients who were older than 65 years-old, scored between 3-5 points on the GDS, and never had been prescribed Donepezil before. The study controlled for education, age, APOE biomarker, HTN, diabetes, dyslipidemia, psychiatric diseases, antidepressants, and anxiolytics. Some of the exclusion criteria included dementia or behavioral disorders like agitation.

Risk of bias: The effects of the intervention appear to be true since there were no baseline differences across groups in cognition, sociodemographic factors, or clinical variables. The study blinded participants by making them unaware of the other non-pharmacological interventions. Outcomes may be affected by informational biases, as MMP was the only single-blinded procedure because class sessions were conducted by the main researcher.

Effects of intervention: The MMP-Donepezil group had significantly higher CAMCOG and MSSE scores in comparison to the Donepezil-only group and was equivalent in scores to the

CST-Donepezil group (Repeated-measures, $p<0.05$).[10] CAMCOG and MMSE measure spatial memory, language, memory, perception, attention, and praxia.[10]

2.13 Description of studies: Combined MMP and Dual N-Back

Only one study was identified that studied MMP and Dual N-Backs' effects on attention and worrisome behavior (Course-Choi).[11] The weeklong, non-clinical RCT enrolled 86 healthy adults with worrisome traits and randomized 15 participants to MMP-Dual N-Back, 15 participants to the sham-control group (non-adaptive 1-back task), 15 participants to MMP, and 15 participants to Dual N-Back. The inclusion criteria limited the trial to participants who were older than 17 years-old and scored higher than 44 on the Pennsylvania State Worry Questionnaire (PSWQ). The study controlled for baseline differences in PSWQ scores, age, and gender.

Risk of bias: The effects of the intervention appear to be true because the study was single-blinded, participants were randomized, and intention-to-treat analyses were run. The observed outcomes

are more likely true because the study controlled for baseline differences in worrisome and attention scores and sociodemographic variables, but it did not control for baseline differences in prior experiences with MMP or Dual N-Back. The study found a near significant correlation between trait worry scores and Dual N-Back performance: Individual differences in performance could have affected results at a group level, preventing the between group's analysis from detecting significance. Also, the study was short and training times are associated with greater cognitive gains.[12] However, worry score outcomes may be over-estimated because they were measured by STAI (self-reports). In addition, practice-effects in the active-control group could have confounded results.

Effects of intervention: Combined MMP and Dual N-Back suggest long-term positive benefits in improving anxiety traits in young healthy adults ($t(14) = 5.35$, $p < 0.001$).[11]

2.14 Description of studies: Adaptive Cognitive Training

Studies conducted by Willis[13], S. Salminen, T. (2016)[14] Zhang, Y.[15] and Salminen (2016)[16] were included in this review. Willis, Salminen, and Salminen, T. (2016) conducted single-blinded RCT's, while Zhang's randomization and blinding methods were not disclosed.

Willis[13] conducted a large-scale trial that examined cognitive trainings effects in healthy, elderly participants. The studies outcomes were improvements in functional performance and cognition five-years, post-cognitive training. The study enrolled 2802 participants aged 65 years or older. The inclusion criteria limited the trial to participants who had mild functional impairments (<2 ADL disabilities), MMSE scores >23, and were unlikely to have dementia. The study controlled for sex, education, age, health status, and MMSE and Short-Form-36-Physical Function scores.[13]

Salminen (2016)[14]'s RCT examined Dual N-Back's effects on executive functioning gains in the elderly. The study enrolled 47 healthy, elderly participants aged 55 years or older. The inclusion criteria limited the trial to participants who had MMSE scores $\geq$28, Mehrfachwahl-Wortschatz-Intelligenz test scores >110, and participants who did not have visual or auditory impairments. The study controlled for cognitive differences at baseline, years of education, age, gender, and hand dominance.

Zhang, Y.[15] conducted an investigational trial that first assessed if there are functional connectivity differences between controlled, Type-II Diabetics (T2DM) and euglycemics, and if single-back could modify working memory (WM)'s functional systems. The study enrolled 20 cognitively healthy, T2DM and enrolled 19 matched euglycemic patients. The inclusion criteria limited the study to T2DM without complications, MMSE scores >27, and participants had to screen negative for metabolic syndromes, cerebrovascular events, and history of substance use. The study controlled for clinical variables (HbA1c, lipid panel, and HTN), cognitive status (MMSE scores), initial performance on Dual N-Back, symptoms of anxiety and depression

(Self-Rating Anxiety Scale and Self-Rating Depressive Scale), Short-term memory performance (AVLT Test scores), age, gender, and education.

Salminen, T. (2016)[16]'s RCT assessed Dual N-Back's effects on white matter integrity in healthy participants. The study enrolled 56 participants and randomized 20 participants to Dual N-Back, 18 participants to single-back active control group, and 18 participants to the control group-no contact. The study did not discuss its inclusion criteria in detail, but it did reference enrolling people with normal vision and hearing and right-hand dominance. The study controlled for age, sex, and baseline performance scores.

Risk of bias: The effects of the interventions appear to be reliable because the studies included were randomized, single-blinded, and ran intention-to-treat analyses, except for the investigational study. There were also no baseline differences across groups in age, gender, education, clinical variables, cognitive variables, and adherence to protocol.

Willis reported a 67% retention rate by the end of the five-year study, but the missing data did not significantly affect result outcomes, as supported by the multiple-imputation calculation on missing data.[13] Due to the large sample size, Willis's study should have determined if a smaller sample size could have detected significant results.[13]

Salminen (2016) found significant improvements in executive functioning scores in the elderly Dual N-Back group. To show that Dual N-Back caused this effect, he ran a MANOVA, which was found to be significant (Group x Session x Age, $F(10, 67) = 3.38$, $p < .005$, $\eta 2\ p = .34$).[14]

Zhang, Y. supported significant findings by running statistical analyses. He confirmed that the increase in brain activity was occurring in WM systems by running a voxel-wise one-sample *t*-test across the spatial components of the WM networks ($p<0.05$).[15] The inclusion of the component analysis also strengthened the study's findings because it can reveal hidden factors that underlie sets of random variables, measurements, and signals.[15] The study may have selection bias because it did not discuss blinding.

Salminen, T. (2016) used only quality images in his study, but outcomes may have been affected by not controlling for baseline differences in white matter integrity between groups.[16]

***Effects of the interventions**:* Willis's study found that Memory (effect size, 0.23 [99% CI, 0.11-0.35), speed-processing (0.76 [99% CI, 0.62-0.90), and reasoning training (effect size, 0.26 [99% CI, 0.17-0.35]) may be able to improve and maintain higher scores within those cognitive domains 3-5 years post-training in elderly individuals.[13]

Salminen (2016)'s study found that Dual N-Back can significantly improve executive functioning post-test scores in the elderly who are cognitively healthy. Scores may be comparable to that of a young adults' who has not received training (M = 1.64 and M = 2.34, respectively), [t (43) = −7.24, p < .001, Cohen's d = 2.14).[14]

Zhang, Y.'s study found that in the setting of WM functional dysconnectivity, single-back might be capable of recruiting other brain regions to complete working memory tasks. This is supported by the significant correlation that was observed between improved AVLT scores and increased levels of activity found in the left ventral lateral prefrontal cortex ($t = 3.432$, $P = 0.001$, effect size [ES] = 0.793), the inferior parietal lobule ($t = 2.901$, $P = 0.006$, ES = 0.936), and the right fronto-parietal network ($t = 3.115$, $P = 0.004$, ES = 1.002), despite them being significantly lower during the 1-back task ($P < 0.05$, Alphasim corrected).[15] These findings may be applicable to people with CSVD because both study populations share right-frontoparietal network dysconnectivity. The right-frontoparietal network is associated with execution control, attention and working memory. The study's findings support previous trials that support U-shape compensatory mechanisms, which have been reported in AD participants.[17]

Salminen, T. (2016)'s study found that Dual N-Back can significantly increase white mater integrity in the superior and inferior longitudinal fasciculi (SLF), the inferior fronto-occipital fasciculus, the forceps minor (FM), and the corticospinal tract in healthy, young adult participants ($p<0.05$).[16] The SLF is associated with informational processes between frontal and

parietal regions; and, the FM is associated with supporting communication between frontal areas. We cannot discern if the increase in FA values is due to an increased amount of myelination or axon density in the bundle fibers. The lack of significance between increased FA values and improved Dual N-Back performance may be due to the short duration of the study. Anatomical changes, like performance gains, could be dependent on amount of training sessions.

2.15 Description of studies: Mindfulness Meditation

Three studies on MMP were identified that examined its effects on anxiety levels, synaptic plasticity, and/or cognition. The studies included were by Hölzel, B.[18] Wetherell, J,[19] and Newberg.[20]

Hölzel conducted a double-blinded, RCT that assessed whether MMP can alleviate anxiety symptoms and induce neuroplastic changes in young adults with anxiety disorders. The study enrolled 29 participants, and the DSM-IV was used by clinicians to confirm the diagnosis. The study randomized 15 participants into MBSR and 14 participants into the control group-stress management education class. The inclusion criteria limited the study to right-handed dominance, little experience with mediation (<10 sessions in one's life-time), participants who could undergo f-MR imaging, and participants who were either not taking SSRI's or have been on a stable dose for at least two months. The study controlled for age, gender, education level, comorbid anxiety diseases, and SSRI's.

Wetherell conducted a single-blinded, RCT that assessed whether MMP can alleviate anxiety and improve mild neurocognitive dysfunction in the elderly. The study enrolled 103 older adults with anxiety or depressive disorders and subjective cognitive impairment. Depression and anxiety disorders were confirmed by clinicians using the DSM-IV. The study randomized 56 participants into the control group-health education class and 47 participants into MBSR. The inclusion criteria limited the study to people who have clinically diagnosable anxiety or depression disorders (assessed by the DSM-IV and Patient-Reported Outcomes

Measurement Information System PROMIS test scores), subjective cognitive dysfunction, scores less than 10 on the Short-Blessed test, deny psychotic or substance use disorders, and participants who were either not taking anxiolytics or have been on a stable dose for greater than one month. The study controlled for age, clinical variables, gender, education, medications that can affect mood and cognition, cognitive differences at baseline (assessed by the PROMIS scale, Wechsler Test of Adult Reading, Digit Span subtest, Grooved Pegboard Test, Memory composite test, and Cognitive control composite test), prior experiences with mindfulness or yoga practice, and regular use of corticoid steroids.

Newberg conducted a single-blinded, RCT that assessed whether Kirtan Kriya can improve cognitive scores and increase cerebral blood flow (CBF). The study enrolled 14 participants with MCI, which was confirmed by NINCDS-ADRD.[20] The study randomized 7 participants into Kirtan Kriya and 7 participants into the control group-music group. The inclusion criteria limited the study to participants who were older than age 60, scored >16 on the MMSE, and had no prior experiences with meditation or yoga. The study controlled for age, cognitive outcome measures, and prior experience with meditation or yoga. However, the study did not control for anxiety or other psychiatric diseases or baseline differences in CBF.

Risk of bias: The effects of the interventions appear to be reliable because the studies sampled participants randomly, were blinded, randomized participants to either MBSRB or a control group, and ran intention-to-treat analyses. There were no significant differences across groups in age, gender, education level, comorbid anxiety diseases, SSRI's, or adherence to protocol. SSRI's typically take about six weeks to reach a steady-state, so both studies controlled for this well by excluding participants who have been on an SSRI less than one month.

Hölzel's study ensured that the differences observed in BOLD signals between groups where not due to baseline differences in brain activity by running a post-hoc analysis ($p>0.05$).[18] When the study enrolled healthy participants for comparison data, the inclusion criteria controlled for confounding variables by excluding people with any anxiety or other psychological traits and

if they had been recently on any medications that would alter cerebral blood flow. BAI outcomes may be overestimated due to self-reporting biases, and the novelty of MRI imaging could have confounded outcomes as well. Over-estimation of BAI scores appears less likely since Perceived Stress Scale scores were not significantly correlated to changes in BOLD signal.[18] To avoid over-estimations, changes in stress could have been quantified by measuring am serum cortisol levels.

Wetherell's study had a low percentage of missing data, approximately 1%.[19] The study showed that the missing data did not significantly affect outcomes by running the Missing Value Analysis add-on module ($\chi 2 = 15.7$, $P = .61$).[19] The findings may not be applicable to elderly with cognitive impairment since the diagnosis of MCI was subjective. Outcomes on anxiety scores could be over-estimates since they were measured by self-reported results, but this is unlikely because significant changes in cortisol levels were observed.

Newberg ran a False Discovery Rate - multiple comparisons to verify that the significant changes in cerebral blood flow in the intervention group were accurate. Also, there were no significant differences between groups in adherence to protocol: both groups adhered about 75% to protocol.[20] Outcomes may be affected however because the study did not control for baseline differences in CBF or control for psychiatric diseases.

Effects of intervention: The results of both studies are applicable to people with anxiety because diagnoses were confirmed by the DSM-IV.

Hölzel's study found that MMP significantly lowers BAI scores, increases BOLD activity in the right pars opercularis, left pars triangularis, and right rostral middle frontal cortex, and increases the right amygdala's functional connectivity with the left rostral middle frontal cortex ($\rho = -.648$, $p < .001$), the right rostral middle frontal cortex ($\rho = -.487$, $p = .018$), and the right superior frontal cortex ($\rho = -.424$, $p = .044$) (ANOVA group-by-time interaction and Spearman's ρ (0.05).[18] Therefore, MMP can modify functional connectivity. MMP's ability to increase activity in the VLPFC activity could be significant because higher activity has been observed in

the VLPFC during Cognitive Behavioral Therapy and on SSRI's, which are standards of care in anxiety treatment.[21] These results are applicable to cognitively, healthy adults.

Wetherell's study found that MMP significantly improves memory functioning and alleviates anxiety in the elderly with GAD and subjective cognitive impairment ($p<0.05$).[19] The study showed that a meaningful relationship exists between cognition and anxiety by finding a significant correlation between improvements in anxiety and memory scores (($\chi 21 = 4.5$, $P = .03$), along with a significant decrease in cortisol levels in the MMP group (paired $t = 3.8$, $P = .0015$).[19] The study did not find significant improvements on executive functioning scores (DSST). To bolster its findings, the study also should have run a regression analysis between anxiety scores and cortisol levels and between cognitive scores and cortisol levels. Measuring cortisol levels is a more accurate way to measure stress, and we can further study its effects on increasing amygdala activity and suppressing Brain-derived neurotrophic factor (BDNF), a factor that modulates neuronal survival and regulates synaptic plasticity.[22]

Newberg's study found that Kirtan Kriya caused significant changes in CBF and improvements on the following test measures: Right prefrontal cortex - Trails B task ($R = -0.61$, $p = 0.02$), left thalamus - Trails B task ($R = -0.62$, $p = 0.02$) and, left thalamus - Digit Span Test ($R = 0.56$, $p = 0.02$).[20] Listening to a neutral-stimuli served as a good control because no significant changes in outcomes were observed on neuropsychological tests, cerebral blood flow, and correlations between test scores and blood flow. More importantly, the active-control group did not affect observed outcomes in the intervention group.

2.16 Description of studies: Donepezil

Studies conducted by Chen, X[23]., Wilkinson, D. [24], and Black, S.[25] were included in this review. The studies were double-blinded, RCT's that compared Donepezil to a placebo group. Wilkinson and Black enrolled participants with probable MCI-due to VCI, with diagnoses confirmed by NINDS-AIREN criteria. Chen enrolled participants with probable MCI-due to AD,

which was assessed by using neuropsychological tests. A score of 1SD below age-adjusted normative values on at least one memory and learning test was defined as probable-MCI. There are varieties of different tests that can assesses this, but Chen used the Hopkins Verbal Learning Test–Revised, Mattis Dementia Rating Scale: Memory subscale, Wechsler Memory Scale–III: Logical Memory, and Brief Visuospatial Memory Test–Revised tests.

Chen's study examined if Donepezil could enhance cerebral blood flow in MCI-AD participants while performing a verbal memory task and HVLT test. The study enrolled 11 participants and randomized six participants to the Donepezil group and five participants into the placebo group. The inclusion criteria limited the study to participants with subjective and objective measures of MCI and global cognition scores within normal limits (MMSE average score was 29). The study screened for vascular diseases and functional deficits to exclude people with cognitive impairments due to probable VCI or dementia from enrolling. The study controlled for age, baseline cognitive test scores, education, and gender.

Wilkinson and Black conducted similarly designed studies that assessed whether Donepezil could improve cognitive scores over a twenty-four-week trial. Wilkinson enrolled 616 participants and randomized 193 participants to the placebo group, 208 participants to Donepezil 5mg/daily group, and 215 participants to Donepezil 10mg/daily group. The inclusion criteria limited the study to participants who met at least one of the NINDS-AIREN criteria, scored between 11-25 points on the MMSE, and screened negative for unstable medical conditions and psychiatric disorders. The study controlled for demographic characteristics, clinical variables, neuropsychological tests, past cognitive enhancing drug-use, and primary outcomes at baseline. Black enrolled 603 participants and randomized 199 participants to the placebo group, 198 participants to Donepezil 5 mg/daily group, and 206 participants to the Donepezil 10 mg/daily group. Black used the same inclusion criteria and controlled for the same variables as Wilkinson. Both studies also measured the same outcomes, which were mean changes between groups on ADAS-COG, CIBIC, Alzheimer's Disease Functional Assessment and Change Scale (ADFACS),

and Clinical Dementia Rating-Sum of the Boxes (CDR-SB) tests. Wilkinson included MMSE test scores, while Black did not. Neither trials used tests that directly measured executive functioning.

***Risk of bias**:* The effects of the interventions appear to be reliable because the studies sampled participants randomly, were blinded, and randomized participants to either Donepezil or a control group, and ran intention-to-treat analyses. There were no significant differences across groups in age, gender, education, CT scan images, cardiovascular risk factors, and neuropsychological tests.

Chen supported his observations that Donepezil significantly decreased cerebral blood flow decline during the verbal memory task by running an analysis to detect for cerebral flow differences at baseline ($p<0.05$). Selection biases may affect outcomes because MMSE scores of 26 or 27 are typical cut-off scores with similar educational and socioeconomic backgrounds to avoid missing true cases.[26] However, participants did need to score 1 SD below normative scores in at least 1 cognitive domain.

Wilkinson and Black's results are applicable to elderly with VCI because the study confirmed the diagnosis with the NINDS-AIREN criteria. The study's sample included (33%) of participants with identified subcortical strokes, so the studies' results may be applicable to CSVD as well. Executive functioning deficits are common though in VCI and Donepezil's effects on this measure are unknown because it was not directly assessed.

Effects of intervention: Chen's study found that Donepezil caused less cerebral blood flow decline in the left temporal by 1.51 ml/min/100g and in the left frontal tissue by 1.69 ml/min/100g in comparison to the control group ($p<0.05$).[23] There were no significant differences between group scores on these tasks. Therefore, Elderly who have been diagnosed with MCI-due to AD for six months or less may experience less cerebral decline while performing some memory tasks and it may improve memory performance scores. People who do not take Donepezil may maintain memory performance scores for at least six months into their disease.

Wilkinson's study found that elderly persons, who have been diagnosed with mild VCI for 24 weeks or less, might experience small improvements on global cognitive functioning assessments on 5 or 10mg of Donepezil in comparison to people who do not take the drug.

Black observed similar smaller effect sizes. At 24 weeks, Black's study found significant improvements in baseline ADAS-cog scores and ADFACS Scores in the Donepezil 5 mg/d group (ADAS-cog effect size = −1.90, p = 0.001; ADFACS effect size = −1.31, p = 0.02) and Donepezil 10 mg/d group (ADAS-cog effect size= −2.33, p<0.001; ADFACS effect size = −1.31, p=0.02).[25] Significant improvements in baseline CIBIC-Plus scores were only observed in the donepezil 5 mg/d group (p=0.014), while significant improvements in baseline CDR-SB scores were only observed in the donepezil 10 mg/d group (p=0.007).[25] Both studies showed that Donepezil was well tolerated by observing no significant differences between groups in adverse side effects and withdrawal rates (p>0.05).[24,25]

2.17 Description of studies: Multidomain Intervention Study: Physical Exercise

Ngandu's multi-domain intervention was included into this review because it was a double-blinded RCT that enrolled healthy-to-MCI elderly who had similar clinical traits that are found in CSVD, like HTN and diabetes. MCI was determined by Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery test scores, which assessed memory and recall.

The study assessed if diet, exercise, cognitive training, and metabolic control could synergistically slow cognitive decline. Cognitive decline was measured by mean change in baseline NTB (z score) scores over two-years. Secondary outcomes measured changes in executive functioning, memory, and speed processing scores, and the intervention's effects on improving risk of cognitive decline were assessed.

The RCT enrolled 1,190 elderly participants and randomized 591 participants to the multidomain intervention group and 599 participants to the control group to receive health

education. The inclusion criteria limited the study to participants who were between the ages 60–77 years old, scored a 6 or higher on CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score, and scored 1SD below normative scores on either the MMSE (<26 points), word-recall list task (<75%), or word-list memory task (19 points).[27] The study did not exclude cognitive impairment possibly due to CSVD. The study controlled for age, education, MMSE scores, vascular and lifestyle risk factors, and cognitive differences at baseline (NTB total score, executive functioning, processing speed, and memory).[27]

Risk of bias: The effects of the intervention appear to be reliable because participants were randomly sampled, blinded, and randomized. There were no significant differences across groups in age, education, vascular and lifestyle risk factors, and cognitive scores at baseline. The drop-out rate was minimum, with only 4% from the multidomain group and 7% from the control group.[27] Missing data was handled by performing modified intention-to-treat analyses. Missing results did not affect significance, as determined by the re-calculation with intention-to-treat analysis.[27] Outcomes may have been affected by information biases since adherence to protocol was only self-reported, and practice effects may have confounded outcomes.

Effects of intervention*:* The study observed a 25% risk of cognitive decline in NTB z-scores over two years in the control group. The multidomain approach also improved speed processing and executive functioning scores (p=0.039) in the intervention group.[27] The study did not compare the different interventions to determine if one was significantly better than another was. There is a debate as to whether physical exercise versus cerebral blood flow helps promote cognitive improvement. One review observed moderate gains in memory in elderly participants without MCI after acute exercise, but the benefits were lost after 14 months.[28] The observed gains may be due to physical exercise stimulating the release of BDNF, nerve growth factor (NGF), and insulin-like growth factor (IGF-1).[29] MMP is another intervention that has been associated to increase BDNF release.[22]

2.18 Review on Instruments of Measurement

2.19 Description of studies: Alzheimer's Disease Neuroimaging Initiative-Executive Functioning (ADNI-EF) test

The ADNI-EF test is a composite of seven, executive functioning tests. These tests include Category fluency: Animals and Vegetables, Digit Span Backwards, WAIS-R Digit Symbol Substitution (DSST), Clock Drawing, and Trails B–Trails A.[30] These seven tests were included into the Vascular Cognitive Impairment Harmonization Standards by the National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN).[31] These standards were created to help identify VCI patients for future studies. In the VCI Harmonization standards, Clock Drawing and Trails-B are considered supplementary test.[31]

The composite ADNI-EF has only been studied in one trial that began in 2003 and was supported by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), and private and non-private pharmaceutical companies.[30] The ADNI-EF study was created to determine if MRI and PET imaging, biological markers, and neuropsychological assessments could detect the progression of MCI to AD. The three-year study examined this by trying to determine if a significant correlation existed between ADNI-EF z-scores and cortical changes on MRI, amyloid $\beta_{1\text{-}42}$, total tau, and phosphorylated $\text{tau}_{181\text{-}P,}$ levels in CSF, and MCI-AD conversion rates.[30] The study sampled participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and recruited 229 participants with normal cognition (Age 76.0 ± 5.0, N= 229), 397 participants with MCI (n= 390, 74.9 ± 7.5), and 193 participants with AD (n=181, Age= 75.7 ± 7.4).[30] The inclusion criteria limited the study to either elderly with healthy cognition, MCI-due to AD, or AD. The study controlled for age, education, sex, and the presence of one or more APOE ε4 alleles.[30]

Risk of bias: The ADNI-EF model appears to be reliable because significance could have been observed with a 40% smaller sample size and individual test performances do not

affect outcomes.[30] The study found statistical significance on its three validation markers, even with a reliability curve ranging from 0.85 to 0.75 ($p<0.05$).[30] MR-imaging was one if its validation markers and ADNI-EF z-scores were significantly correlated to frontal lobe cortical thickness ($p<0.05$).[30] The model may have failed to reach higher reliability because the tests were administered to a study population that is distinctively known to have impairments in declarative episodic memory.[32] The study did not compare the seven tests to determine if one was significantly better than another, and there is no guarantee that these tests truly measure frontal lobe executive performance. The significant correlation found between ADNI-EF z-scores and frontal lobe cortical thickness helps disprove this. In addition, normal distribution calculations are more reliable than skewed calculations, which must be calculated on some neuropsychological tests.

***Effects of intervention**:* ADNI-EF z-scores were significantly correlated with MCI-AD conversion rates, MRI images from selected brain regions, and levels of amyloid $\beta_{1\text{-}42}$, total tau, and phosphorylated tau_{181P} in CSF levels.[30] Though VCI participants were not enrolled in the study, the ADNI-EF composite test may be a useful measurement to assess an intervention's effect on improving executive dysfunction.

2.20 Description of studies: Connectome-based predictive modeling (CPM)

CPM is a relatively new technique that receives inputs of connectivity and behavioral performance data and outputs high and low functional performance networks that are correlated to high and low behavioral scores.[33] The significant correlation between functional connectivity and behavioral performance enables the model to predict behavioral outcomes in that individual subject. The CPM networks can then be trained on new data sets and make accurate behavioral predictions in new cohorts. CSVD's white matter damage leads to dysconnectivity, affecting many functions and brain regions. CPM is well suited to measure

these dysconnectivity's and can provide a gestalt measure of executive functioning abilities and executive dysfunctions in CSVD.

CPM's methods are still being refined as we learn more about brain networks and improve computational methods to create more accurate predictor models. The NIH is funding the Human Connectome Project and has provided open source sharing to allow researchers assess to templates and protocols to conduct experiments in order to add meaningful data to the brain mapping project.[34] A part of the human connectome project is to identify and learn how functional networks produce certain behaviors. Behavioral templates that are currently offered by the NIH are rest, emotion, gambling, language, motor, relational, social, and working memory.[34,35] Executive functioning is not a behavioral task offered. The ADNI-EF can be completed under MR-imaging and provide meaningful data about functional connectivity in executive functioning. We will not discuss the CPM protocol because templates are provided by the NIH[34], Nature has published in detail how to perform the CPM computations in MATLAB[33], and an architype of CPM was developed here at Yale in the study of functional connectivity in attention and Attention Deficit and Hyperactivity Disorder (ADHD).[36]

Risk of bias: CPM'S outcomes may be affected by the statistical test chosen to calculate the connectivity matrix edges. The *Nature* protocol states that edge calculations can be made with either Pearson's correlation, Spearman's correlation, or robust regressions.[33] The ADNI-EF computed its model with robust regressions and calculated a reliability between 0.85 to 0.75.[30] The ADHD study computed its edges with "Spearman-Brown-corrected split-half correlation" and calculated a reliability of 0.975, which is considered excellent.[36] Either regression model would still overestimate or underestimate performances, and therefore, CPM provides good relative data. The amount of imaging data from participants may also affect outcomes: the ADHD study enrolled 25 individuals, and the ADNI-EF study's data comes from 800 participants. The imaging modality of choice is 3T or 7T magnetic resonance imaging and a variety of accepted imaging software is available.[34]

2.21 Description of studies: Diffusion tensor (DTI) and dynamic susceptibility contrast (DSC)

The MRI images that will be used in CPM will come from DTI - DSC sequence protocols. In accordance with *Standards for Reporting Vascular Changes on Neuroimaging (STRIVE)*[37] and *Fisher criteria,*[38] lacunar infarcts can be visualized on T1-, T2-FLAIR, and T2-weighted sequences on MRI. Functional connectivity is assessed with brain-blood-oxygenation-level-dependent (BOLD) f-MRI.

Only one studied was identified that visualized leukoaraiosis with 3T BOLD and DTI MR-imaging (Sam, K.).[39] The study tried to assess whether impaired cerebrovascular reactivity (CVR) is significantly correlated with white mater tissue integrity and evaluated this by using diffusion and perfusion MR-imaging. The participants were conveniently sampled and 75 patients with moderate to severe leukoaraiosis were enrolled into the study. The inclusion criteria limited the study to participants who had cortical infarcts or white mater lesions less than two centimeters, a Fazekas score greater than two, older than fifty-years of age, hemodynamic instability less than 70%, and no subcortical infarcts within three months of enrollment.

Participants whose BOLD images had motion artifacts were excluded from the study. The study controlled for poor imaging quality, such as imaging spatial confounds. [39]

Risk of bias: The study's outcomes may be compromised because imaging could not discern if there were other factors besides ischemia that were causing WMH. The study did control for head motion artifact and imaging spatial confounds.[39] Selection bias of convenience sampling may also affect outcomes.

Effects of intervention: The study observed that T2-weighted images are less likely to detect subtle changes in the conversion of normal white mater to WMH.

2.22 Description of studies: Neuropsychological and behavioral tests

Please refer to the appendix for more information on the neuropsychological and behavioral tests that are used in this study.

2.23 Effects of interventions on primary and secondary outcomes

Non-pharmacological effect sizes on primary and secondary outcomes that are used in this study were found in a systematic review on cognitive training. The systematic review was called "Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer's or vascular type: a review." Cognitive training was observed to have a large effect of 7.47 (-14.19, 29.14) on DSST scores in a sample of 153 participants;[8] a large effect of 14.53 (-9.35, 38.41) on Trail-B Test scores in a sample of 77 participants;[8] and, a large effect of 25.26 (-76.70, 26.19) on Trail-A Test scores in a sample of 76 participants.[8] On secondary outcomes, cognitive training had a poor effect size of -0.94 (-3.67, 1.79) on BOLD activity in a sample of 35 participants;[8] and, a poor effect size of 0.03 (-0.34, 0.41) on anxiety scores in a sample of 114 participants.[8] Observing similar effect sizes from cognitive training are unknown because these measures were not obtained in CSVD participants.

2.24 Conclusion

2.25 Summary of main results

The aim of this review was to evaluate the current evidence regarding the efficacy of adaptive cognitive training and MMP on improving executive functioning for people with MCI-CSVD. We included nine studies of adaptive cognitive training and MMP into this literature analysis, along with two studies on Donepezil and one multi-domain study. These interventions' effects on executive functioning could not be analyzed because of the variability in outcome measures across the studies. The high-quality studies included in this review support cognitive

training and MMP to have the potential to generate small-to-medium effects on executive functioning.

2.26 Applicability of evidence

Cognitive training and MMP have not yet been studied in MCI-CSVD, so the interventions' effects may or may not be reproduced in this study population. Ngandu[27] and Zhang's[15] studies support cognitive training to promote some cognitive improvements in the elderly with cardiovascular risk factors that would predispose them to lacunar infarcts.[40] The systematic review on cognitive training in participants with AD or VaD supported small improvements on some executive functioning tests.[8]

This review may have missed significant effects because of the limited number of relevant RCT's available, the varying terminology that references this study population and the interventions studied, and because of the included studies methodological limitations. Limitations in study design include duration of intervention, active versus no-contact groups, and the use of neuropsychological tests to assess functional performance. Jaeggi found that the number of treatment doses is directly correlated to behavioral performance gains.[12] The standard number of doses to reproduce effects remains unknown, as it would be individualized for participants. The superiority of active-control groups over no-contact groups remains unknown. Participants have received cognitive gains from single-back, so this may serve as a poor control group, whereas listening to a neutral stimulus may act as a better placebo. Neuropsychological tests can confound results by Hawthorne and practice effects. The studies included in this review prevented against Hawthorne affects by administering many versions of the same test. Many studies administer multiple tests because one neuropsychological test does not accurately assess functional performance. A better way to measure functional performance is to calculate the correlation between neuropsychological test scores and micro-structural or functional changes on imaging, assessed by DTI- DSC and BOLD.

2.27 Disagreements with other studies

The current "Grade A" recommendation in the treatment of MCI is to discuss with patients the options of cholinesterase inhibitors.[7] The evidence does not support the administration of Donepezil to be a Grade A practice. The studies failed to assess the interventions effects on the disease's most common deficit, executive functioning. Instead, both studies administered tests that are commonly used in AD studies. Furthermore, when Donepezil was studied in the elderly with MCI-due to AD, the placebo group maintained their memory performance scores over the six-month period and no significant differences were observed between the two groups.

2.28 Implications for research

The high-quality studies offered in this review support combined MMP and adaptive cognitive training (Dual N-Back)'s beneficial effects on cognition. However, this cannot be confirmed until a well-designed, single-blinded RCT is conducted in this population. Furthermore, the use of CPM and imaging will allow us to measure these interventions' effectiveness on functional and executive functioning performance. The literature review supports the need for this current study to be conducted.

2.29 Key Terms

VaD: vascular dementia; Subcortical ischemic vascular dementia; Lacunar infarction; Vascular factor; Cerebrovascular disease; MCI: mild cognitive impairment; AD: Alzheimer's disease; Carotid stenosis; Dementia; Anxiety; Stress; Agitation; Depression; CIND: Center for Imaging of Neurodegenerative Diseases; NPI: Neuropsychiatric Inventory; Cognitive intervention; Cognitive training; Mindfulness-based stress reduction; Mind–body interventions; Mental stimulation; fMRI: functional magnetic resonance imaging; CDSR: Cochrane Database of Systematic Reviews; RCT: randomized controlled trial; Treatment

MeSH terms: Cognitive Dysfunction/diagnosis*, Dementia, Vascular/classification, Dementia, Vascular/diagnosis*, Dementia, Vascular/etiology, Cognitive Dysfunction; MeSH terms: Brain/diagnostic imaging*, Cognition/physiology, Diffusion Tensor Imaging/methods, Machine Learning, Memory, Neural Pathways/diagnostic imaging, Neuronal Plasticity/physiology*, White Matter/physiology*, Short-Term/physiology*; MeSH terms: Anxiety/therapy*, Mind-Body Therapies*, Mindfulness*, Stress, Psychological/therapy*

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Chapter 3 - Study Methods

3.1 Study Design

The present study will be implemented as a two-arm superiority, single-blinded randomized control trial (RCT) that will randomize and allocate participants with MCI-CSVD into either the control group who will engage in placebo (solitaire and music listening) per day or into the experimental group to receive mindfulness meditation and Dual N-Back to assess its efficacy in slowing the progression of executive dysfunction.

3.2 Synopsis

- Ninety-seven people will be recruited and consented after screening for eligibility. We will be screening for vascular cognitive impairment due to small vessel disease phenotype rather than large vessel disease.

- Subjects with anxiety, depression and alternative diagnoses will be ruled out.

- They will be randomized to a low intensity (placebo group) and high intensity intervention group.

- The low intensity group includes playing solitaire for half an hour and listening to music for another 30 minutes – daily.

- The high intensity intervention group consists of playing Dual N-Back for 30 minutes and meditating for 30 minutes – daily. There are group sessions three times per week which are required for the first two weeks of enrollment but voluntary from then on.

- Each subject will be in the study for 12 weeks after which a voluntary subset may decide to continue the routine for future studies and measurements.

- Imaging and neuropsychological testing is performed at baseline and at the end of the 12 weeks.

- Primary endpoint is changes in Alzheimer's Disease Neuroimaging Initiative (*ADNI*)- Executive Function (ADNI-EF) composite measure. Secondary endpoints include changes in neuropsychological scores and changes in connectivity, especially in the sub-graph of the connectome that correlates with executive function.

3.3 Recruitment

Our sample size for this study is 74 participants. However, we will enroll 97 participants because we expect a 30% drop-out rate based off other MCI studies that involved physical exercise in the ederly.[1] Sample size was calculated with *G*Power 3.1.9.2* software and a priori

power analysis computed that 74 participants would be needed to determine a significant difference between two groups, with the study set at a 5% significance level, powered at 80%, and effect size F of 0.25. Please refer to the appendix to view sample calculation.

The source population is elderly people with VCI due to CSVD without mood disorders. Our sources of referral will include Yale Memory Clinic, Yale Stroke Center, Adler Geriatrics Centre, and Yale Program on Aging. We will ask physicians to participate and to help provide referrals. For those physicians who agree to participate, we can help them identify appropriate referrals to our study by asking Epic's Joint Data Analytics Team to cross reference VCI, white matter disease, lacunar infarct, vascular dementia and CSVD with participating physicians. We will post an advertisement of our study on the *Help Us Discover Now* site. The advertisement will ask for elderly people with MCI due to cardiovascular risk factors, like stroke or DM, to participate in a study that is trying to slow the progression of cognitive decline. Identified individuals will present to *Church Street Research Unit* for eligibility screening.

3.4 Study population

We will be enrolling both men and women equally into our study, and we expect to enroll ethnicities that are more prevalent in the state of CT, which are Caucasians, African-Americans, and Hispanics. Participants must be English-speaking.

3.5 Inclusion Criteria

1) Participants need to be between the ages 50 to 89 years-old with MCI due to vascular pathology according to VASCOG criteria.[2]
2) The cognitive deficit should be subcortical, more than cortical, suggesting small rather than large vessel disease pathology.
3) Study partner should confirm cognitive decline.
4) Relative novice to cognitive training and meditation.
5) Possession of a smart phone or computer to run the Dual N-Back program on.

3.6 Exclusion Criteria

1) Drug or alcohol substance misuse

2) Use of medications that affect cognition within 30 days of the study

3) Exclude patients with depression and anxiety

4) Major neuropsychiatric conditions such as Parkinson's disease, Huntington's disease, multiple sclerosis, tumor, epilepsy, or psychiatric diseases like schizophrenia

5) Consumption of greater than five alcoholic drinks per week within the last 30 days

6) Participants' whose past medical history is pertinent for Chronic Obstructive Pulmonary Disease, active infection, cancer, autoimmune diseases, or serious systemic illnesses, such as hepatic, renal, or heart failure

7) Participants with visual, auditory, or other physical impairments that would interfere with completing the study's procedures and interventions:

    a) Participants who are physically unable to partake in the interventions mindful meditation and Dual N-Back
    b) Participants who have relative or absolute contraindications for undergoing magnetic resonance imaging (MRI), which includes claustrophobia and metal pieces implanted inside the body

8) Education less than 9 years

3.7 Screening Procedure

1) The subject should meet the criteria for VCI, according to the VASCOG criteria.[2] These include:

    a) Subjectively: Participants should state that they now require greater effort to complete multiple tasks and feel fatigued and/or struggle with word finding and memory retrieval, and/or bladder control. Presence of vascular risk factors will also support a diagnosis of VCI.

    b) Objectively:

        i) Physical Exam: Participants must present with at least one of the following clinical features suggestive of CSVD: gait apraxia, urinary urgency, affective dysregulation that includes apathy, or pseudobulbar affect.[3]
        ii) Imaging at Magnetic Resonance Research Center (MRRC): Participants' MRI imaging must be positive for lacunar-strategic infarcts. Lacunar infarcts will be identified in accordance with the *Standards for Reporting Vascular Changes on Neuroimaging (STRIVE)*[4] and Fisher criteria.[5] Lacunar infarcts will be visually inspected on T1-, T2-FLAIR, and T2-weighted images (WI) on MRI scans.[5] To be classified as a lacunar infarct, the lesion must be approximately 3-15 mm in diameter and accepted locations are angular gyrus, thalamus, basal forebrain, basal ganglia, anterior cingulate, genu of

corpus callosum, fornix, lentiform nucleus, internal capsule, centrum semiovale, and brainstem.[6,4] Lacunar infarcts will be identified as round or ovoid-shaped rims of increased signal relative to white matter on T2WI and T2-FLAIR images or decreased attenuation on T1WI.[5] Accepted lesion severity will be a Fazekas score of ≥2.[7] Images must be absent for cortical and watershed infarcts, hemorrhages, hydrocephalus, and white matter lesions caused by non-vascular causes.[3] Participants' must have a Scheltens atrophy score of zero in the hippocampus and entorhinal cortex.[1]

2) A MOCA score of less than 23 and more than 19 will be used to recruit participants.[8] They should lose at least one point on Letter fluency (F, A and S)[9] or vigilance A[10].

3) Participants' surrogates must confirm his or her MCI by completing the Informant Questionnaire for Cognitive Decline in the Elderly.[3] With a threshold score of 65, the test has a sensitivity of 66.1% and specificity of 59.8%.[11]

4) Participants must screen negative for depression: Participants must score less than 16 on the Centre for Epidemiologic Studies-Depression Scale (CES-D).[12] The test has a specificity of 90%, sensitivity of 86%, and a positive predictive value of 80 with a cut-off score of 16.[12]

5) Participants must screen negative for anxiety, which will be measured by the Beck Anxiety Inventory (BAI) test. A score less than nine will be accepted because it indicates "mild anxiety."[13] BAI is a strong, valid, and reliable test in psychiatric populations, but it may not always be able to discriminate between somatic factors and true anxiety.[13] However, the BAI is superior to the STAI in discriminating between somatic anxiety and trait anxiety and separating patients with a current anxiety disorder from patients without the disorder.[14]

Please refer to the appendix to view baseline characteristics of participants.

3.8 Baseline and follow-up testing

Baseline testing will include tests not performed during the screening. Both baseline and screening tests will be repeated during the follow-up. The tests will be scored and normed according to age and education of the subjects.[15] The tests include Category fluency (Animal, Fruit, Vegetable)[16], Digit span[16], Digit symbol (DSST)[3,16,17], Trails A and Trails B[16], Boston Naming Test (BNT)[3,18], Neuropsychiatric Inventory (NPI)[3,19], Letter fluency (F, A and S)[9], Rey Auditory Verbal Learning Test[20] (RAVLT), Logical memory[21], and Functional Activities Questionnaire (FAQ).[22] Please see the appendix section for more information on these tests. The BNT, RAVLT, Logical memory, and Vigilance A test instruction and scoring manuals are not included because they will need to be purchased.

3.9 Randomization and Blinding

Once patients have passed screening, they will be assigned to placebo or intervention arms by a pseudorandom number generator. The investigators will be blinded to the intervention and placebo arms. The subjects will be told that we are comparing two different types of non-pharmacological interventions.

3.10 Interventions

3.11 Control Group: Low-Intensity Intervention

Participants who are randomized and allocated to the low-intensity intervention are offered tuition for playing solitaire and listening to selected music for a total of one-hour per day. Participants will be expected to play 30 minutes of solitaire followed by 30 minutes of listening to relaxation music for 12 weeks. These activities will be placed on a server onto which they will need to log onto to have their compliance recorded. They will be paid 5 dollars per session completed. For those with less than 80% compliance on a weekly basis, one warning will be given, followed by dys-enrollment from the study if low compliance continues.

3.12 High-Intensity Intervention

Participants enrolled in the combined mindfulness meditation (MM) and Dual N-Back will come to clinic 3 times a week to play 30 minutes of Dual N-Back, followed by 30 minutes of meditation. Participants will be expected to follow this same protocol on days that they are not at clinic. These activities will be placed on a server onto which they will need to log onto to have their compliance recorded. For those with less than 80% compliance on a weekly basis, one warning will be given, followed by dys-enrollment from the study if low compliance continues. Groups session will be mandatory during the first two weeks of the study, but after that, the subjects may do the exercises at home if they wish.

3.13 Cognitive Training

Participants will play the computerized adaptive training program, Dual N-Back, on their devices. The Dual N-Back is adaptive as to ensure adequate intensity of training in these individuals. The objective is to increase the length of time, or number of n-trials, one can correctly recall information from. Participants will be presented every three-seconds with two series of stimuli, single letters and images.[23] Participants will need to determine if the presented number and image location match what was presented to him or her two trials ago. Participants will respond by pressing or not pressing a designated letter on a keyboard.

The game changes in level of task-difficulty based on performance. As performance improves, the number of trials participants must recall stimuli from will increase. If performance worsens, the number of trials will either decrease or stay at two. At the beginning of the study, all participants will start with having to remember stimuli from two trials ago, but the training adapts to participants' own cognitive abilities and is personalized across participants. Participants' results will be automatically uploaded into a computer to be analyzed later by an outcome assessor. We will keep track of n-trials for each participant.

For participants to be included into data analysis, they must complete 80% of the total Dual N-Back sessions. Adherence is measured by attendance and total number of uploaded results. We will record the number of trails completed and task-difficulty level for each participant.

3.14 Mindfulness Meditation

Participants will need to practice MM every day for thirty-minutes either at clinic or at home. Group sessions will be offered three times per week. On days participants are not at clinic, they will need to log onto a server at the beginning and end of each MM session to clock in and out of the activity.

Class sessions will include breath-awareness, body-scan, and gentle Hatha yoga. Breath awareness exercises will ask participants to be cognizant of their breathing and to expand their awareness onto other body sensations, thoughts, and emotions.[24] Participants will then be asked to nonjudgmentally accept those sensations and return their mental focus onto their breath.[24] Body scans will ask participants to scan their body's from head-to-toe to explore for different types of sensations, such as pressure or tightness, and then to intentionally release that focus before shifting onto the next body part.[24] Hatha yoga exercises will require participants to gently stretch and slowly move through different poses while focusing on present experiences.[24]

For participants to be included into the data analysis, they must complete 80% of the total sessions. Adherence is measured by attendance and total number of logged in sessions on the server.

3.15 Imaging Protocol

We will measure alterations in white matter microstructure by using Diffusion Tensor Imaging (DTI), so called structural connectivity, and we will measure functional connectivity by using c-fMRI. The c-fMRI images will be obtained while positive-tasks are being performed by participants in the scanner. The positive task will be a succession of the Category Fluency—Animals, Category Fluency- Vegetables, WAIS-R Digit Symbol, Digit Span Backwards, Trails A, and Trail B tests. For each participant, connectivity matrices will be made during each of these subtasks and averaged over the entire scan periods. Yale MRRC already standardizes the nodes and regions of interest, and we will use these in our study. The aggregate subject connectivity matrices are then used to look at correlations between connection strengths and test scores. This can also be referred to as an edge and only significant edges will be kept ($p<0.01$). This analysis can be run for both high-performance and low-performance. We will then examine if the sum of the connection strengths in the high-performance network can predict ADNI-EF parameters. We will also examine the sum off the connection strengths in the low-performance network to

determine if it improves our model's prediction power. We will repeat these steps for each of the tests that composite the ADNI-EF. The same analysis will be performed using DTI, however it is difficult to think of a mechanism whereby structural connectivity changes in a short period in response to training. Please see the appendix section.

We will then see if changes in ADNI-EF, after cognitive training, are reflected in connection strength in the high-performance network. If so, this would provide one of the most convincing evidence for neuroplastic changes in response to cognitive training in the experimental literature.

3.16 Study Variables and Measures

The composite ADNI-EF scores will be calculated for each intervention group in the same manner it was computed in the study, "A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment."[16] Once composite ADNI-EF scores are computed, we will then calculate a z score for each intervention group by using the below equation. The Z score will be standardized to the baseline mean and SD, with higher scores suggesting better performance.

Z= raw score – mean of the sample / standard deviation (SD) of the sample.

We will use these standard scores to compute our own prediction interval calculations. Interval calculations will be computed by using the following standardized, mathematical equation.

P (Lower end-point of the mean population – z-score*SD) - mean population / SD < Z score < (Upper-end point of the mean population – z-score*SD) – mean population / SD = probability

3.17 Statistical Analysis

3.18 Primary Outcome

To determine a significant difference between groups (group × time interaction) at the end of the study, we will run an ANOVA Repeated Measures, Between Factors. Significance will be set to $p < 0.05$. Analysis will follow per protocol. The independent variables are the interventions, Low - intensity versus High - intensity interventions, and the dependent variable is ADNI-EF z-score. The confounding variables that will be controlled for are for BAI scores, age and sex.[16]

3.19 Secondary Outcomes

Modifications in cerebral blood flow and structural connectivity. To assess whether both groups experienced significant changes in cerebral perfusion and structural connectivity over 12 weeks, we will run a Two-Way Mixed-Model ANOVA (within-subjects' factor: time; between subjects' factor: treatment). Significance will be set to $p < 0.05$. If significance is found, we will run a post hoc test.

Effects on cognitive domains. To test the interventions' effect on different cognitive areas, we will calculate mean change in scores from baseline to twelve weeks post-treatment initiation within-groups. To determine significance between groups, we will run a repeated measures ANOVA.

3.20 Missing Data

Continuation in the study requires more than 80 % compliance with the interventions. As with problems with missing data on neuropsychological testing, if the constituents of ADNI-EF are missing from the data, the subject will be excluded from the analysis. Proc MI will be used to determine the distribution of missing values.[1]

3.21 Ethical Parameters

3.22 Subject Protection and Confidentiality

The study design will be carried out in accordance with the guidelines set by *Yale's Human Investigation Committee* (HIC) and *Institutional Review Board* (IRB) by adhering to their regulations written in Procedures 100 PR1.[25] Our study will also follow the guidelines written in *Policy 340: Participation of Individuals with Impaired Consent Capacity*.[26] Participants must have capacity to enroll into the study and also designate a study partner for collateral information. Participants will need to sign the consent forms during the visit for eligibility screening. Lastly, our protocol will include adequate provisions for monitoring collected data and ensuring privacy and confidentiality so that our study is HIPPA compliant. Consent forms and study protocol will be submitted to the Yale New Haven Research Unit Committee so that we may receive documented approval and begin our study.

Experimental studies may involve potential and unforeseeable risks that include physical harm or loss of confidentially. To mitigate potential harm, we have created a list of potential risks and corresponding action plans to address them should they occur. This list will be provided to participants in the consent form. Please refer to the consent forms in the addendum. Below, we included our minimal risk data safety monitoring plan.

3.23 Minimal Risk Data and Safety Monitoring Plan

The Principal Investigator (PI) will be responsible for monitoring and protecting the data under the laws of HIPPA, assuring that those involved in the study are adhering to the study protocol that is provided to the IRB, and conducting, at minimum, monthly safety reviews. During these review processes, the PI will assess whether the study's protocol should continue unchanged, require amendments, or close to enrollment. Changes in protocol will only be made in the interests to protect participants' safety. Before these changes are made, we will inform both participants

and the IRB. The PI and the IRB will have the authority to stop or suspend the study or require modifications.

Subjects' overall risk for adverse events in this study are low, as exemplified by the potential risks and associated action plans provided in the participants' consent forms. Interventions and methods will only be carried out by certified professionals who have completed the training module, "Ethics on Human Research." Medical tests and imaging will be conducted by licensed staff members from the hospital; diagnoses will be made by certified neurologists; outcome data will be collected and analyzed by experienced research assistants; meditation will be taught by a certified instructor; neuropsychological tests will be evaluated by a psychiatrist or neurologist.; and, the principal investigator, Dr. Salardini, is an appropriately trained medical professional who has been trained in neuropsychiatry, neurology, and internal medicine.

In terms of risks unrelated to health, there is low-risk associated with collection and attainment of subjects' protected health information. We will be requesting for a signed consent waiver during the recruitment process because this research could not be conducted without access to and use of the protected health information. However, we ensure that the collected protected health information will not involve increased risk to patient's privacy; adequate plans will prevent against the improper use and disclosure of identifying information; and, the identifying information will be shredded and destroyed at the earliest opportunity, unless such retention is required by law in the interests of patient safety. Lawful authorities will include members overseeing the research, such as the IRB.

To protect confidentiality, methods to protect data will include the use of password protected programs, encrypted software, use of secured servers, along with storing papers in locked-filing cabinets. We will also separate personal identifying information and results, and results will be published as group data to avoid using identifying information. Our study will adhere to these provisions to avoid the potential harm that could occur should confidentiality be unlawfully breached about one's psychiatric and substance use history, serious illness, or the

harmful consequences that can occur in the setting of a stolen identity. In the event of illegal disclosure, the event will be documented in the "accounting for disclosures log," and then forwarded to the Deputy HIPAA Privacy Officer. Participants will be subsequently made aware of the disclosure.

Additional safety measures will be included in this study because elderly with MCI impairments are a vulnerable population. Security measurements will require participants to identify a study partner who will be willing to provide additional help with participant participation and accompany participants to each drop-off session and to all procedures. Participants must have capacity to enroll in this study, which will be assessed by a medical provider. We will submit a protocol application to the IRB, along with our signatures attesting to the protection of health information, and the required HIPPA Authorization forms that participants must sign to participate in the study.

3.24 Monetary compensation

Subjects will receive $5 per session and can receive a total compensation of $420 upon completing the 84 sessions. They will receive a further $100 for completing both baseline and follow-up testing, which includes MRIs and neuropsychological testing. These are nominal fees and not coercive, they merely introduce a form of token economy to increase compliance.

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Chapter 4 – Conclusion

4.1 Rationale

4.2 Choice of condition to treat

a) As we discussed in detail within the introduction, the brain has different kinds and degrees of neuroplasticity depending on the localization and age of subjects. The best examples of neuroplasticity which appear to be present lifelong, or at least into old age, seem to pertain to the frontal-subcortical circuitry which connect the frontal lobes with the basal ganglia, and through the basal ganglia's connections to the thalamus, to the rest of the brain. The executive and cognitive control role of the frontal-subcortical circuitry means that dysfunction in these areas have a disproportionate effect on overall cognitive functioning.
b) Additionally, we argued that evidence shows that the frontal-subcortical circuitry is particularly vulnerable to the effect of CSVD.
c) It follows from a and b that a mechanism that might engage neuroplasticity may have the opportunity to treat some of the executive dysfunction seen in CSVD.

4.3 The choice of intervention

a) We also reviewed how Dual N-Back has some of the best track records suggesting effects on neuroplasticity of the brain. Some of our choices regarding this modality included:

    a. Using a single modality to reach enough intensity and repetition to cause plastic changes, as well as avoiding interference.
    b. We use a relatively high dose of intervention, which is at the limits of compliance from our clinical experience for the same purpose.
    c. The period of intervention is 12 weeks after which there is enough repetitions in the task for it to become habitual.

b) We reviewed the effects of mindfulness meditation and how it suppresses the counter-correlated networks. There is a possibility that this may augment the effects of Dual N-Back.

4.4 Hypotheses

1) Our primary hypothesis is that the high-intensive intervention in the form of Dual N-Back training and mindfulness meditation will have a differential effect on executive functioning in subjects with CSVD.

2) Exploratory hypothesis 1: We hypothesize that improved executive function will positively affect other cognitive domains.

3) Exploratory hypothesis 2: Changes in executive function may be correlated with changes in the connectivity in the cortico-subcortical circuitry.

4.5 Specific Aims:

1) To demonstrate less negative change in ADNI-EF score during follow-up compared to baseline, in the high-intensive intervention group compared to non-intensive intervention group.

    a) Subjects in the high-intensive intervention group will receive instructions to play Dual N-Back daily (30-minutes) and to meditate (30-minutes) for 12 weeks, during which they have an option of performing this task in supervised groups three times per week.
    b) Subjects in the non-intensive arm will also receive instructions to play solitaire daily (30-minutes) and to listen to calming music (30-minutes) for 12 weeks.
    c) Nominal cash reward is given to increase compliance. A compliance of more than 80% is required.
    d) We will form the ADNI-EF composite score at baseline and after follow-up for comparison.

2) To demonstrate that non-executive cognitive domains may be improved by a strengthened executive functioning network:

    a) We will perform neuropsychological testing and look at other domains namely visuospatial, language and memory to see if there are improvements.
    b) In our analysis, we will gauge what proportion is directly related to executive function improvements.

3) To demonstrate changes in connectivity in response to cognitive training, we will correlate c-fMRI with ADNI-EF

    a) C-fMRI task positive imaging are constituents of ADNI-EF performance.
    b) A composite weighted high-performance network is formed as per CPM protocol.
    c) Show that there is increased strength of connectivity in the high-performance network.
    d) Show that changes in f-MRI correlate with changes in ADNI-EF scores.

4.6 Expected outcomes

1) We expect the ADNI-EF in the intensive intervention to change in the positive direction in the period of the study. The non-intensive group may show minor changes. The expectation of positive change comes from the relatively short period of the study, during which deterioration due to natural history is likely to be minimal.

2) We expect increases in the connectivity measures in the high-performance network.

4.7 Pitfalls

1) Non-pharmacological interventions are only incompletely standardized.

2) We have not previously determined the maximum tolerated dose of intervention. However, from the literature and our clinical experience, it is somewhere between 1 and 2 hours.

3) We have not performed a dose-response study. Given that interference is not a major issue in this single-task training, at worst, the highest tolerated dose may be partially redundant but is unlikely to have a negative effect. With unlimited funds and time, both 2 and 3 would have been proposed.

4) The diagnostic criteria for CSVD are as not optimal and can often include other subcortical cognitive impairments in the cohort.

5) CPM is a new and hitherto unproven technology.

6) We make high demands on our subjects and compliance may become an issue.

4.8 Innovation

1) To our knowledge, our study will be the first to investigate in a cohort of MCI-CSVD the impact of combined meditation and Dual N-Back on executive functioning, provide biomarkers which may correspond to this change, and thus offer insight into executive function's relationship to connectivity.

2) We use a rigorously validated but underused measure, the ADNI-EF, which was developed by looking at the ADNI database. The composite score allows us to use one endpoint as to minimize multiple comparisons and makes the experiment more rigorous.

3) We use a highly innovative imaging biomarker, and if useful, it will open new possibilities for clinical trials in this area.

4.9 Clinical and/or Public Health Significance

CSVD form of vascular cognitive impairment represents one of the major causes of morbidity in our ever-aging population. Presently there are no interventions which have been proven to improve cognition in this population. Demonstration of benefits, however small given the number of people afflicted by this condition, will be greatly beneficial to public health.

Additionally, the technique we are auditioning in this study include ADNI-EF and CPM have wider applications in other studies of cognitive training and rehabilitation and may lend greater rigors to future experiments.

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Appendix I

Sample Calculation

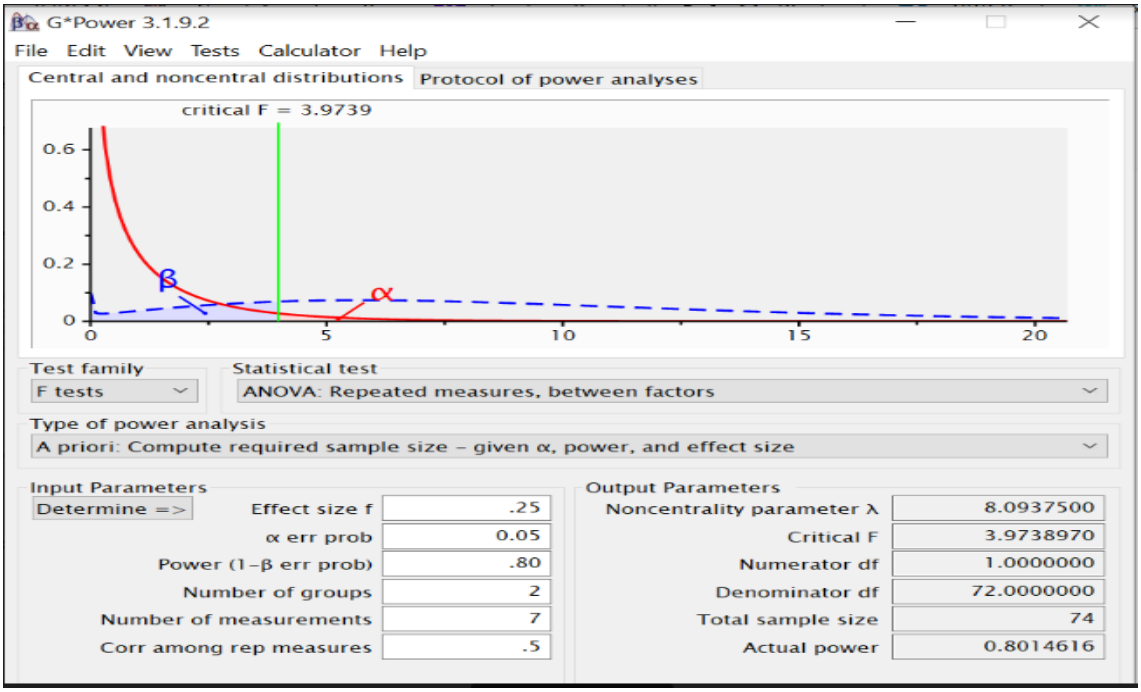


Figure 1. Sample size calculation. *G*Power 3.1.9.2* software was used to calculate our sample size. We ran ANOVA Repeated measures, between factors. A priori power analysis computed that 74 participants would be needed to determine a significant difference between two groups with the study set at a 5% significance level, powered at 80%, and effect size-f set to 0.25. The ADNI-EF test has not yet been studied in our sample population so we choose a medium effect size, Cohen f 0.25.[1] Please see the above figure to view the input parameters we set. The output parameters were given to us by *G*Power*.

Appendix II

Table 1. Baseline characteristics of subjects who were randomized to the study.

	Combined MMP and Dual N-Back (n=37)	**Control Group (n=37)**	**P-Value**	**X^2**
Demographics Variables				
Female (%)				
Male (%)				
Age (years) (mean± SD)				
Education (years) (mean± SD)				
Clinical Variables				
Time Diagnosed with MCI Before Start of Study (weeks) (Mean ± SD)				
Risk Factors for Developing Subcortical Dementia				
HTN (%)				
Type I DM (%)				
Type II DM (%)				
Average Hemoglobin A1C (Mean ± SD)				
Obesity (%)				
Hyperlipidemia (%)				
Physically Inactive (%)				
Smoking (Packs-per- Year) (Mean ± SD)				
Drinks Per Week (Mean ± SD)				
APOE ε4 Alleles: Average Present (Mean ± SD)				
Number of VaD Biomarkers Present: (Mean ± SD)				
Severity of VCI				
Number of Clinical Symptoms Suggestive of CSVD (Mean ± SD)				
Number of Cognitive Domains Impaired (Mean ± SD)				
Neuropsychological and Behavioral Tests				
MOCA (Mean ± SD)				
Letter fluency (F, A and S) (Mean ± SD)				
Vigilance A (Mean ± SD)				
Informant Questionnaire for Cognitive Decline in the Elderly (Mean ± SD)				
Neuropsychiatric Symptom: Centre for Epidemiologic Studies-Depression Scale (CES-D) (Mean +/- SD)				
Beck Anxiety Inventory (Mean +/- SD)				
Proof of Vascular Disease				

Brain Parenchymal Fraction Volume (Mean +/- SD)				
Lacuna Volume (Mean +/- SD)				
White Mater Hyperintensities, Average Fazekas Score (Mean +/- SD)				
Other Factors				
Number of Medications Prescribed Within the Past Month that Affect Cognition (Mean +/- SD)				
Number of Medications Prescribed Within the Past Month that Affect Mood (Mean +/- SD)				

The Shapiro-Wilk test will be used to confirm that the random sample is normally distributed for each of the outcome variables studied. Student t-test will be used to confirm that mean variables are not significantly different between groups. Chi-square test will be used to confirm that dichotomous variables are not significantly different between groups. Wilcoxon rank-sum will be used to confirm that ordinal variables are not significantly different between groups. Factors that affect the primary outcome, ADNI-EF, will be controlled for by multiple linear regression analysis, which include age, education, gender, and any *APOE*-ε4 alleles.

Appendix III

Table 2. Neuropsychological and behavioral tests used in this study.

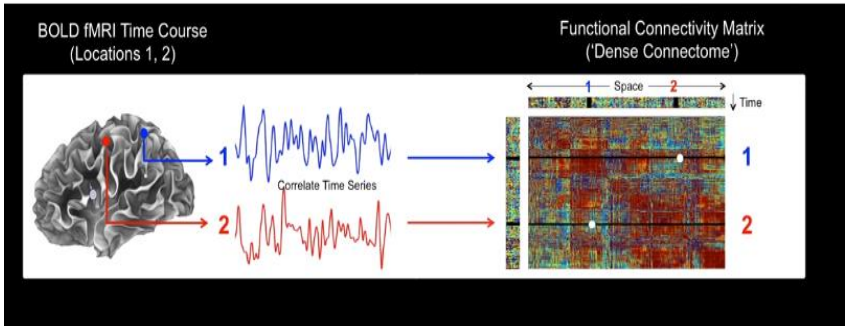
Study / Test	No. of Healthy Participants	Age and +/- Years of Education of Healthy Participants (years)	Normative Scores of Healthy Participants and/or Test Score Cut-off Values	Test Validity
Nasreddine, Z: [2] MOCA	N= 90	Age = 72.84±7.03; Education = 13.33±3.40	Cut-off score = 23.7±4.1	To detect MCI: Sensitivity = 90%, Specificity = 87%, Test-retest reliability= correlation coefficient=0.92, P<.001, Internal consistency Cronbach alpha = 0.83
Letter fluency (F, A and S) [3,4]	N= 134[3]	Age = 53.63 (19.65) [3]; Education = 13.94 (2.01) [3]	Mean score = 40.48 [3]	Interrater reliabilities (Pearson correlation coefficients): r(42) = .95, and switching, r(42) = .96.[4]
Vigilance A[5]	N = 50	Age = 79.9 ± 7.8	Cut off-score > 27, significantly impaired vigilant (or sustained) attention	Sensitivity = 75.0 (65.7–82.8); Specificity = 73.1 (72.4–90.1); Positive Predictive Value = 85.3 (76.5–91.7); Negative Predictive Value = 71.0 (60.6–79.9)
Informant Questionnaire for Cognitive Decline in the Elderly[6]	Mild dementia = 107	Age = 70.10 ± 9.22, Education = 6.21 ± 1.70	Discrimination between mild-moderate dementia: cut-off score of 65	AUC of 0.666 (95% confidence interval (CI), 0.601–0.732), sensitivity = 66.1%, specificity = 59.8%
Centre for Epidemiologic Studies-Depression Scale (CES-D) [7]	N =80 post-stroke patients	Age > 65	Cut-off score of 16	Specificity = 90%, sensitivity = 86%, and a positive predictive value = 80
Beck Anxiety Inventory[8,9]	N = 71 Adults with Anxiety disorders	Age = 34 y/o, Mean duration of anxiety symptoms = 11.8 years	Mild anxiety < 9 points	Internal consistency Cronbach's alpha = 0.90 to 0.94, retest reliability ranges between 0.62 - 0.93
Category fluency: Animals + Vegetables[10]	N = 229	Age = 76.0±5.0; Education = 16.0±2.9	Average Score = 34.6±8.1	p-value[c] = <.001
Digit span[10]	N = 229	Age =76.0±5.0; Education = 16.0±2.9	Average Score = 7.4±2.2	p-value[c] = <.001

Digit symbol[10]	N = 229	Age = 76.0±5.0; Education = 16.0±2.9	Average Score = 45.7±10.2	p-value[c] = <.001
Trails A[10]	N = 229	Age = 76.0±5.0; Education = 16.0±2.9	Average Score = 36.4±13.2	p-value[c] = <.001
Trails B[10]	N = 229	Age = 76.0±5.0; Education = 16.0±2.9	Average Score = 89.2±44.3	p-value[c] = <.001
Boston Naming Test[11]	Healthy Participants (N)= 307	Age = 77.2 (4.47); Education = 13.5 (3.46)	Average score = 12.0 (SD+/-2.46)	Relatively reliable when readjusted for age and education[12]
Neuropsychiatric Inventory[13]	N = 40, MMSE scores mean of 28.4 (healthy elderly)	Age >65	Mean depression score = 0.25, mean disinhibition score = 0.13, mean irritability score = 0.05	Test-retest scores = 0.79 for frequency (p = 0.0001) and 0.86 for severity (p = 0.0001)
Rey Auditory Verbal Learning Test[14]	N= 27 male veterans with dementia	Age = 67.37 (7.64) Education = 10.48 (3.28)	Dementia group = 25.36	P< 0.01, when age and education are adjusted (F (2,113) = 15.56, Pc .001)
Logical memory[15]	MCI participants (n) = 5883 Healthy participants (n) = 10,741		From the ADNI 2: LM-II education-based cutoffs: 16 years of education: normal ≥9; early MCI = 9–11; AD ≤8 8–15 years of education: normal ≥5; early MCI = 5–9; AD ≤4 0–7 years of education: normal ≥3; early MCI = 3–6; AD ≤2	AUC area under the receiver operating characteristic curve Early MCI in ADNI 16+ years of education: 0.72 8-15 years of education: 0.70
Functional Activities Questionnaire[16]	N = 1108 MCI participants	Age = 75.8 (8.9) Education = 15.0 (3.2)	Differentiating AD from MCI, cut-off point of 5/6	ROC analysis = area under the curve of 0.903, sensitivity = 80.3%, specificity = 87.0%, classification accuracy = 84.7%

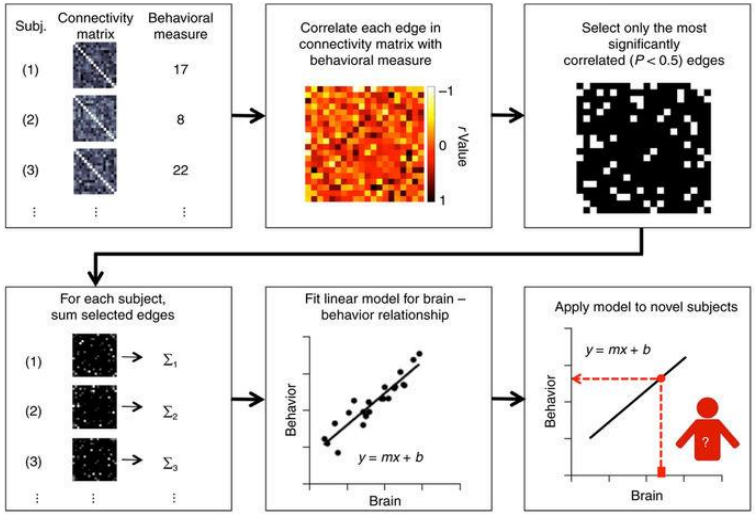
We reported normative values from cognitively healthy, elderly participants because a memory deficit is usually defined as 1 to 1.5 SD below the normative value when matched in age and education level.[17]

Appendix IV

Connectome Predictor Model



(A)



(B)

Figure 2. ***The steps into making an Executive Function Network Linear Model***.
A) BOLD signal will be measured from each participant as they complete the ADNI-EF test and will be computed into a program as a functional connectivity matrix. Image was taken from "Relating Brain Circuits to Behavior: David Van Essen at TEDxCaltech."[18]
B) BOLD average signal time will be calculated in each voxel, or node. The strength of connection between nodes represents the matrix. We will input each subject's connectivity matrix and ADNI-EF scores into our executive functioning connectivity predictor model. With the aggregated data, we can then compute a robust regression to show the association between ADNI-EF z-scores and the connectivity matrix ($p<0.01$). By applying significance testing, edge strengths in the positive tail will be summed together to produce the predictive positive network strength, and the edge strengths in the negative tail will be summed together to produce the predictive negative network strength. Positive and negative network strengths can predict ADNI-EF z-scores by applying the "leave-one-out cross validation method."[19] The linear network strengths that significantly correlate ($p<0.01$) functional connectivity to ADNI-EF z-scores can then be used to predict ADNI-EF z-scores in new subjects. Image was taken from "Using connectome-based predictive modeling to predict individual behavior from brain connectivity."[20]

Appendix V

ADNI-EF Calculation

	Categorization									
Original EF Score	0	1	2	3	4	5	6	7	8	9
Category Fluency—Animals	0–5	6–7	8–9	10–12	13–16	17–20	21–23	24	25–27	28–60
Category Fluency—Vegetables	0–3	4–5	6	7–8	9–11	12–14	15–17	18	19–20	21–31
WAIS-R Digit Symbol	0–9	10–15	16–19	20–29	30–38	39–46	47–53	54–56	57–61	62–87
Digit Span Backwards	1–2	3	4	5	6	7	8	9	10	11–12
Trails A	118–150	94–117	73–93	53–72	40–52	32–39	27–31	24–26	21–23	5–20
Trails B	261–300	226–260	196–225	137–195	96–136	73–95	60–72	54–59	49–53	10–48

Figure 3. ***How to calculate composite ADNI-EF scores for each intervention group.***
The first step is to calculate "Original EF Scores" for each participant. To calculate "Original EF Score," each of the six tests will need to be graded per its instructed protocol. Each test's final score is assigned a numerical categorical value, which is listed above on the first line. Original EF score will be calculated by adding the categorical values from the six tests and then dividing by six. After we determine each participant's "Original EF score," we will then calculate composite ADNI-EF score for the two intervention groups. For each intervention, we will add the "Original EF" scores and then divide by total number of participants in that intervention group. The above figure came from the study "A composite score for executive functioning, validated in Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment."[10]

Appendix VI

Table 3. Summary on review of the literature

Study	Age and Cognitive Status	Conditions Compared	Duration	Variables Controlled For	Measures of Outcome	*Main Findings*
B Quintana-Hernández DJ[21]	65-86, Mild-severe dementia	MMP-Donepezil (n=42); Cognitive- Donepezil (n=38); PMR- Donepezil (n=45); Donepezil-Only (n=43).	288 sessions total, each session 90minutes	Education, age, APOE biomarker, HTN, diabetes, dyslipidemia, psychiatric diseases, antidepressants, and anxiolytics.	Primary outcome: delay cognitive decline as measured by MMSE and CAMCOG scores, significance determined by Repeated-measures ANOVA ($p< 0.05$) and Cohen's d CAMCOG measures spatial memory, language, memory, perception, attention, and praxia	*MMP-Donepezil was the only intervention whose Cohen effect sized on MMSE (Cohen D= 1.45) and CAMCOG (Cohen D= 1.73) scores remained steady throughout the two-year study in the mild-moderate dementia group. These scores declined significantly at 18 months in the Cognitive Stimulation-Donepezil group and at 6 months in the Donepezil-only and PMR-Donepezil groups. These interventions had no significant effects in moderate-severe dementia.*
Course-Choi [22]	Control: M = 27; N-back: M = 28; MMP: M = 31; Combined: M = 29 Healthy adults	MMP-Dual N-Back (n=15); sham-control group non-adaptive 1-back task (n=15); MMP (n=15); Dual N-Back group(n=15) MMP: Free Mindfulness Project Audio Sham-group: Non-adaptive 1-back task	Total of 5 hours across 7 days; post-follow up seven day after the study completed Dual N-Back: 24 practice trials and 160 experimental trials MMP: 23-minute audio clip Sham-group: 24 practice trials and 160 experimental trials	Baseline differences in anxiety scores, age, and gender	Outcomes: Attention (measured by anti-saccade task); performance (mean difference in Dual N-Back performance between groups over 7 days); and, worrisome behavior (measured by STAI trait worry scores) Significance determined by mixed ANOVA's (Group x Time) ($p<0.05$)	*Participants in combined group experienced significant most improvements in Dual N-Back performance ($t(14) = 4.98$, $p < 0.001$ ($p<0.05$) and decreases in STAI trait worry scores ($t(14) = 5.35$, $p < 0.001$); and, this was the only intervention group were a significant correlation was observed between attention and STAI trait worry scores ($r = -0.36$, $N = 30$, $p = 0.05$) and an almost significant correlation between trait worry scores and improved performance ($p=0.07$)*
Willis, S. [23]	Memory: M= 74 y/o; Speed: M= 73 y/o; Reasoning: M= 74 y/o;	Speed-processing (n = 702): visual search and divided attention; Memory Training (n = 703): teaching mnemonic strategies; Reasoning	Majority of participants: 10 sessions, approximately 75 minutes long at beginning of study	Sex, education, age, MMSE score, health status, and Short-Form-36-Physical Function score.	Outcomes: Memory (measured by Hopkins Verbal Learning Test, Rey Auditory-Verbal Learning Test, and the Rivermead Behavioral Paragraph Recall test); Reasoning (measured by letter	*Memory (effect size, 0.23 [99% CI, 0.11-0.35), speed-processing (0.76 [99% CI, 0.62-0.90), and reasoning training (effect size, 0.26 [99% CI, 0.17-0.35]) significantly improved participants test scores*

	Control: M= 74 y/o MMSE >23	training (n = 699): remembering and finding patterns over trials; and, Control Group- no contact (n = 698)	Sub-group of participants: 10 sessions in addition to four, 75 minutes sessions at 11 and 35 months Outcomes were collected yearly for five years		series, letter sets, and word series); Speed of processing (measured by 3 field of view subscales); and, Functional outcomes: IADL difficulty (measured by the Minimum Data Set–Home Care). Modified intention-to-treat protocol, significance calculated by repeated-measures, mixed-effects model, and Bonferroni ($p<0.01$)	*within that cognitive domain. The effect sizes remained over five years compared to the control group-no contact.*
Salminen, T. [24]	Dual N-Back: M= 65.0 y/o; Control: M= 65.0 y/o MMSE $\geq$28 Dual N-Back young adults: M= 24; Control-Group young adults: M=24	Control group- no contact (n= 21); Dual N-Back (n= 26) Exploratory analyses: Dual N-Back young adults (n=20) Control-Group young adults (n=18)	14 sessions, 50 minutes in duration	Cognitive differences (assessed by MMSE >28 and Mehrfachwahl-Wortschatz-Intelligenz test>110), years of education, years in occupation, age, and gender	Outcomes: Executive functioning (defined by reaction times and error rates in attentional blink, task-switching, and WM updating tasks) Intention-to-treat protocol, three-way mixed-ANOVA (Between-subject factors: Group; Within-subject factors: Session (pretest vs. posttest)) and Cohen's d ($p < .01$)	*Dual N-Back significantly improved the three executive functioning task scores in comparison to the control group ($p<0.01$).* *The game's plasticity was assessed by comparing post-test performance scores in the elderly who received Dual N-Back with the younger adult's pre-test scores who received Dual N-Back: no significant difference between the two groups was found ($p>0.05$), despite significant differences between their pre-test scores ($M = 1.64$ and $M = 2.34$, respectively), [$t(43) = -7.24$, $p < .001$, Cohen's $d = 2.14$).*
Zhang, Y. [25]	MMSE >27	T2DM (n=20); Control group (n=19); f-MRI data obtained during resting state and digital 1-back WM task	One-day: 1 instructional trial, 11 practice trials, and 12 test trials	Clinical variables (HbA1c, lipid panel, and HTN), cognitive status (MMSE), performance with Dual N-Back, symptoms of anxiety and depression (Self-Rating Anxiety Scale and Self-Rating Depressive Scale), Short-term memory performance, age, gender, and education.	Outcomes: Differences in working memory systems' activity levels, as measured by β-estimates, between groups during the 1-back task and AVLT test. Significance was determined by two-sample t-tests and Cohen's d. Differences in functional connectivity in working memory systems between groups were compared, as assessed by voxel-wise one-sample t-test and Cohen's d ($p< 0.05$)	*Significantly lower BOLD signals during the 1-back task was observed in T2DM patients' in the bilateral lingual gyri, the left ventral lateral prefrontal cortex, the inferior parietal lobule, and in the right fronto-parietal network's connection with the lingual gyri ($P < 0.05$, AlphaSim correction). However, these areas became significantly more activated when completing the short memory tasks in comparison to euglycemic patients. The fronto-parietal network's increase in amplitude of activity was significantly correlated with improved AVLT short-term memory scores ($p<0.05$).*

Salminen, T. [26]	Dual N-Back: M= 24 y/o; Active control group/ single-back: M= 24; Control-No contact: M= 25	Dual N-Back (n=20); Active control group/ single-back (n=18); and, Control-No contact (n=18)	16 sessions, thirty-minutes in duration: in each session, Dual N-Back and single n-Back participants received 20 practice trials and 12 test trials	Age and sex	Outcomes: Changes in white matter density, as measured by fractional anisotropy and mean diffusivity; correlation between changes in white matter and Dual N-Back performance Intention-to-treat protocol, group × time effects ($p<0.05$)	*Significantly higher mean changes in fractional anisotropy values were observed in the Dual N-Back group when compared to both single-Back group and passive control group ($p<0.05$). Significant increases in FA were observed in the superior and inferior longitudinal fasciculi, the inferior fronto-occipital fasciculus, the forceps minor, and the corticospinal tract. The increases in FA were not significantly correlated with mean improved changed in Dual N-Back scores ($p > .57$). The study also did not find significant differences in mean diffusivity values.*
Hölzel, B. [27]	MBSR: M= 39; Control: M = 36; Healthy: M= 36, demographically matched individuals	MBSR (N=15); Control group-stress management education (n=14)	MBSR (N=15): Once a week, 2-hour sessions for eight-weeks; weekly homework assignments that take about 1000 minutes to complete; and, one eight-hour retreat day Control group-stress management education (n=14): Once a week, 2-hour class session; weekly homework assignments that take about 1000 minutes to complete; and, one eight-hour retreat day	Age, gender, education level, comorbid anxiety diseases, SSRI's, hand-dominance	Outcomes: Reduced anxiety (measured by decreases in pre-post Beck Anxiety Inventory and Perceived Stress Scale scores); mean change in BOLD signal; correlation between anxiety scores and areas in the brain that underwent significant changes in activity levels; and, differences in brain activity between GAD participants and healthy participants. Intention-to-treat protocol, ANOVA group-by-time interaction ($p<0.05$)	*MMP significantly reduced BAI and PSS scores in comparison to the control group (ANOVA: group x time, $p<0.05$). MMP caused significant mean increases in BOLD signal in the right pars opercularis, left pars triangularis, and right rostral middle frontal cortex in comparison to the control group. These activated areas were significantly correlated with mean changes in BAI scores, but not PSS scores. The BAI scores were also significantly correlated to the right amygdala strengthening its functional connectivity with the left rostral middle frontal cortex ($\rho = -.648$, $p < .001$), the right rostral middle frontal cortex ($\rho = -.487$, $p = .018$), and the right superior frontal cortex ($\rho = -.424$, $p = .044$) (ANOVA group-by-time interaction and Spearman's ρ (0.05).* *Differences in brain activity between GAD participants and healthy participants was assessed by comparing combined GAD imaging data to newly enrolled healthy participants'. Healthy participants were matched in*

						demographic variables. At baseline, GAD participants' right amygdala activity was significantly higher when viewing neutral faces in comparison to healthy participants' (p = 0.0001). The right amygdala, the right caudal middle frontal (p = 0.009) and the right lateral orbitofrontal cortex areas (p = 0.0054) underwent significantly lower pre-post BOLD signals in comparison to healthy participants'. These changes were not significantly correlated to BAI index scores.
Wetherell, J. [28]	MMP: M= 70 y.o; Control: M= 73 y.o Subjective cognitive impairment	MMP (n= 47): Baseline characteristics: WTAR score = 37.7 (8.5); Memory composite score = -0.07 (0.68); Verbal fluency = -0.205 (0.899); Stroop = 0.077 (0.954); Digit Span = 10.1 (2.7); Grooved = 105.1 (38.8); Peak cortisol (ng/mL) = 5.2 (2.5); PROMIS Anxiety = 20.8 (5.8); PSWQ = 28.4 (6.6) Control Group (n= 56): Baseline characteristics: WTAR score= 40.6 (8.2); Memory composite score = -0.23 (0.85); Verbal fluency = -0.0900 (1.0); Stroop= 0.088 (1.149); Digit Span = 10.0 (2.8); Grooved = 105.0 (27.6); Peak cortisol (ng/mL) = 4.9 (2.4); PROMIS Anxiety = 19.9 (7.1); PSWQ = 27.7 (8.2)	MMP (n= 47): 8 weekly sessions, 90 minutes in duration. Received homework assignments Control Group (n= 56): Health classes = 8 weekly sessions, 90 minutes in duration. Received homework assignments	Age, clinical variables, gender, education, medications that can affect mood and cognition, cognitive differences at baseline (assessed by the PROMIS scale, Wechsler Test of Adult Reading, Digit Span subtest, Grooved Pegboard Test, Memory composite test, and Cognitive control composite test), prior experiences with mindfulness or yoga practice or yoga, and regular use of corticoid steroids.	Primary outcomes: 1) Mean change over time on memory and cognitive control composite scores between groups. Memory composite scores were measured by Immediate List, Immediate story, Delayed list, and Delayed Story. Cognitive control composite scores were measured by Verbal fluency, and Stroop: Color-Word. 2) Mean change over time between-groups on the Digit Span and Grooved Pegboard. Primary outcomes were analyzed by covariance models that controlled for baseline score, condition, and WTAR scores ($p<0.05$). Secondary Outcomes: 1) Mean change over time on anxiety and depression scores, which were assessed by PSWQ, PROMIS Depression, and PROMIS Anxiety. These outcomes were analyzed by mixed effect models ($p<0.05$). 2) Mean change in peak cortisol levels between groups, assessed by paired t-test ($p<0.05$) Intention-to-treat analysis	*MMP caused significant improvements in memory composite scores ($p<0.046$, effect size = 0.28), PSWQ scores ($p<0.042$, Effect size=-0.48), and PROMIS Anxiety scores ($p<0.061$, effect size = -0.42). A significant correlation was found between improvements in memory composite scores and changes in anxiety and depression scores ($\chi 21 =4.5$, $P = .03$). Significant decreases in cortisol levels were observed in the MMP group (paired $t = 3.8$, $P = .0015$).* *No significant differences were observed in Digit Span scores between groups ($p<0.99$, effect size=-0.09)*
Newberg, A.[29]	MMP- Kirtan Kriya: M = 64 ± 8 years old,	MMP- Kirtan Kriya (N=7): Baseline characteristics: Category Fluency-Animals = 21.1 ± 7.9; Trails A = 30.5	8 week-long study MMP-Kirtan Kriya (n=7): 12 minutes of Kirtan Kriya	Age, cognitive outcome measures, MMSE scores <16, and prior experience with meditation or yoga	Outcomes: Mean changes in test scores within-groups on Category Fluency task, Wechsler Adult Intelligence Scale, Digit Symbol	*Kirtan Kriya: Significant findings between changes in CBF and test score improvements were observed on the following measures: right*

	MMSE = 28.1 ± 0.7 Placebo-Music group: M = 65.0 ± 9., MMSE = 29.0 ± 1.0 MCI diagnosed by NINCDS-ADRD	± 12.2; Trails B= 105.5 ± 52; Digit Symbol = 63.7 ± 25.3; Logical Memory Delayed = 10.6 ± 5.2; and, POMS = 52.2 ± 12.9 Placebo-Music Group (n=7): Baseline Characteristics: Category Fluency-Animals = 21.5 ± 5.0; Trails A = 37.0 ± 11.7; Trails B= 132.5 ± 58; Digit Symbol = 67.6 ± 21; Logical Memory Delayed = 12.3 ± 6.5; and, POMS = 47.5 ± 17.2	daily; Placebo-Music (n=7): 12 minutes of listening to a neutral stimulus daily		Substitution Test, Logical Memory task, Trails A, and Trails B (paired t-test, $p < 0.05$); correlation between imaging and neuropsychological test scores (Pearson's correlation, $p<0.05$); and, mean changes in cerebral blood flow within groups in regions of interest (paired t-test, $p < 0.05$). Regions of interest included the inferior frontal, superior frontal, superior parietal, DLPFC sensorimotor, posterior cingulate, orbitofrontal, anterior cingulate, superior frontal thalamus, superior parietal, medial frontal, and amygdala precuneus.	*prefrontal cortex - Trails B task ($R = -0.61$, $p = 0.02$); left thalamus - Trails B task ($R = -0.62$, $p = 0.02$); and, left thalamus - Digit Span Test ($R = 0.56$, $p = 0.03$) No significant findings (changes in CBF or neuropsychological test scores or correlations) were observed in the music group*
Chen, X. [30]	Donepezil: M= 75 y/o, MMSE = 29.8 Placebo: M = 67 y/o, MMSE= 29.6	Donepezil (n=6); Placebo (n=5)	Six months Donepezil (n=6): titrated to 10 mg daily over six weeks and then continued 10 mg daily dose for six months Placebo (n=5)	Age, baseline cognitive test scores, education, and gender.	Outcomes: Mean changes in cerebral blood flow during verbal memory task and HVLT test, as assessed by GE Signa 1.5T MR scanner (independent-sample t tests without correction, $p<0.05$)	*Donepezil did not cause significant changes in cerebral blood flow during the HVLT test in comparison to the place group ($p>0.05$). Performance on the HVLT remained stable in the placebo group but increased in the Donepezil group. However, donepezil did cause a significantly less decline in cerebral blood flow during the verbal memory task in comparison to the placebo group. In the Donepezil group, participants had a -1.32-mean decline in the left temporal tissue and a -1.44-mean decline in the left frontal tissue in comparison to the placebo group's -3.13 mean decline in the left frontal tissue and -2.83 mean decline in the left temporal tissue ($p<0.05$)*
Wilkinson, D. [31]	Placebo: M = 74 y/o; Donepezil 5mg: M= 75 y/o, Donepezil 10mg: M= 76 y/o,	Placebo (n=193): Baseline characteristics in scores: Hachinski score= 9.6 ± 0.2; ADAS-cog= 18.8 ± 0.7; MMSE= 22.2 ± 0.3; CDR-SB= 5.6 ± 0.2; ADFACS= 15.1 ± 0.7 Donepezil 5mg (n=208): Baseline characteristics in scores: Hachinski score =	Donepezil 5mg (n=208): 5 mg nightly for 24 weeks Donepezil 10 mg (215): 5 mg nightly for 4 weeks followed by 10 mg/nightly until week 24 Placebo group= 193	Demographic characteristics, clinical variables, medications, and neuropsychological tests (Hachinski score, ADAS-cog, MMSE, CDR-SB, and ADFACS)	Primary Outcomes: Mean change from baseline scores on the ADAS-cog and CIBIC-plus tests. Secondary Outcomes: Mean changes from baseline on MMSE, CDR-SB, and ADFACS tests Intent-to-treat (ITT) analysis between groups ($p<0.05$); study completion rate was 79.7%	*Significant mean changes in improvement from baseline ADAS-cog scores were observed in the Donepezil 5mg group (-2.65 ± 0.48 at week) and Donepezil 10mg group (-2.19 ± 0.44) but not the placebo group (-0.10 ± 0.39) at the end of the study ($p<0.001$). Significant mean changes in improvement from baseline MMSE scores were also observed in both*

	MCI-VCI confirmed by NINDS-AIREN	9.4 ± 0.2; ADAS-cog= 20.8 ± 0.7; MMSE= 21.8 ± 0.3; CDR-SB= 6.0 ± 0.2; ADFACS= 15.7 ± 0.7 Donepezil 10mg (n=215): Baseline characteristics in scores: Hachinski score= 9.5 ± 0.2; ADAS-cog= 20.6 ± 0.7; MMSE= 21.5 ± 0.3; CDR-SB= 6.1 ± 0.2; ADFACS= 16.1 ± 0.7	Reductions in doses was not permitted Outcomes collected at weeks 12, 18, and 24			*Donepezil groups at the end of the study but not in the placebo group (p<0.01). Significant mean changes in improvement from baseline CDR-SB scores was only observed in the Donepezil 10mg at the end of the study. No significant improvements in ADFACS scores were observed in the three groups at the end of the study (p>0.05). Donepezil appears to be safe in participants because there were no significant differences in adverse events between the three groups. Most common adverse events included nausea, abnormal dreams, insomnia, leg cramps, and rhinitis.*
Ngandu, T [32]	Multidomain: M= 70 y/o; MMSE= 26; Control group: M= 69; MMSE=26	Multidomain group (n= 591): Baseline scores: NTB Total score= –0·03 (0·55); Executive functioning= –0·03 (0·66); Processing speed = –0·02 (0·78); and, Memory = –0·03 (0·68) Control group (n=599): Baseline scores: NTB Total score= 0·03 (0·59); Executive functioning= 0·03 (0·69); Processing speed = 0·05 (0·84); and, Memory = 0·03 (0·66).	Multidomain group: Diet (based on Finnish Nutrition Recommendations-10 dietary eating sessions); Physical exercise (based on Dose Responses to Exercise Training study protocol: 1-3 times per week muscle strength training and 2-5 times per week aerobic exercise); Computer-based training: 72 sessions (three times per week, 10-15 minutes per session). This was conducted again 6 months later into the study. Training included executive processes, working memory, episodic memory, and mental speed. Management of	Age, education, MMSE scores, vascular and lifestyle risk factors, and cognitive differences (NTB total score, executive functioning, processing speed, and memory).	Primary Outcomes: mean change and estimated mean change in NTB scores at 24 months between groups (group × time interaction, P<0.05) Secondary outcomes: mean change and estimated mean change in executive functioning scores, processing speed scores, and memory scores between groups at 24 months (between group differences, p<0.05). Executive functioning was measured by: digit span, concept shifting test (condition C), trail making test (shifting score B – A), and shortened Stroop tests. Processing speed was measured by: letter digit substitution test, concept shifting test (condition A), and Stroop test (condition 2). Modified intention-to-treat to account for missing data (p<0.05)	*The multidomain group's estimated mean change in NTB total z-score at 2 years was 0.20 (SE 0.01, SD 0.51), and it was 0.16 (0.01, 0.51) in the control group. The mean difference in NTB total scores per year between groups was 0.022 (95%CI 0.002–0.042, p=0.030). Multidomain approach significantly affected executive functioning scores (p=0.039) and processing speed scores (p=0.029). The control group's risk for decline in NTB total score (odds ratio 1.31, 95% CI 1.01–1.71), executive functioning, and processing speed were significant in comparison to the multidomain group (p<0.05).*

			metabolic and vascular risk factors (based on their national evidence-based guidelines). Control group: health advice classes given at start of study and months 6, 12, and 24 Outcomes collected at baseline, and at 6, 12, and 24 months			
Gibbons, L.[10]	Healthy: M= 76 y/o; MCI: M= 75 y/o; AD: M= 75 y/o	Healthy (n= 229): Baseline characteristics: Education = 16 years; APOE allele = 27%; ADNI-EF score = 0.70±0.67; Category Fluency Combined = 34.6±8.1; WAIS-R Digit Symbol = 45.7±10.2; Digit Span Backwards = 7.4±2.2; Trails A = 36.4±13; Trails B = 89.2±44.3; Clock Drawing = 4.7±0.6; and, white matter hyperintensities (cm^3) = 0.68±2.34. MCI (n= 390): Baseline characteristics: Education = 16 years; APOE allele = 54%; ADNI-EF = −0.03±0.77; Category Fluency Combined = 26.7±7.3; WAIS-R Digit Symbol = 36.9±11.2; Digit Span Backwards = 6.2±2.0; Trails A = 44.3±21.7; Trails B = 131.0±73.5; Clock Drawing = 4.7±0.6; and, white matter hyperintensities (cm^3) = 0.60±1.09 AD (n= 181)	Outcomes collected at baseline and at months 6, 12, 18, 24, and 36	Age, education, sex, and the presence of one or more APOE ε4 alleles	Outcomes: Validate the utility of ADNI-EF z-scores, defined as: 1) find a significant correlation between ADNI-EF scores and detecting MCI-AD conversion; 2) find a significant correlation between baseline ADNI-EF z-scores and MRI images from selected brain regions: Regression models, controlling for age, education, sex, one or more APOE alleles, and intracranial volume, were used to predict EF z-scores. White matter hyperintensities were transformed to log scale. Robust standard errors were used ($p<0.05$). 3) determine ADNI-EF scores ability to detect change over time Criteria for inclusion into data analysis: all outcome measures obtained from at least one visit	*Results of Interest: ADNI-EF z scores were significantly correlated to MRI changes in the Caudal Middle Frontal (2.29); Rostral Middle Frontal (3.52); Superior Middle Frontal (2.88); Lateral Orbito-frontal (3.8); Medial Orbito-Frontal = 2.34; and, Pars-Triangularis (2.61); and, significantly correlated with changes in white matter hyper-intensities (WMI) (−2.09) ($p<0.05$). WAIS-R Digit Symbol had the strongest correlation with WMH (−2.31); Clock Drawing had the strongest correlation with thickness in the caudal middle frontal regions (3.14); and, the Trails had a strong correlation with the rostral (3.73) and superior middle frontal (3.14) regions and with the pars-triangularis (3.03) ($p<0.05$)*

Sam [33]	Age range: 50–91 years old	75 participants, participants enrolled were confirmed to have moderate to severe leukoaraiosis with no cortical infarcts or white mater lesions > 2cm and Fazekas score > 2	Outcomes collected at one session	Imaging spatial confounds	Outcome: cerebrovascular reactivity (CVR)'s correlation with white mater tissue integrity Repeated-measures one-way analysis of variance (ANOVA) with dependent variable defined as MRI parameters and independent variable defined as regions of interest. Mauchly test and corrections were made with Greenhouse-Geisser. Significance set to per-comparison p value <0.05/3comparisons= 0.0167. Bonferroni-corrected.	*Negative CVR is significantly correlated with decreased FA, CBF, and cerebral blood volume*

Appendix VII

Imaging Protocol

We will measure alterations in white matter microstructure by using DTI-DSC imaging, and we will measure cerebral blood flow by using BOLD f-MRI. BOLD imaging data will generate a map of long-distance connections between one area of grey matter to another and will provide information on functional connectivity. DTI- DSC images will provide information on structural connectivity. Informatics platforms are provided through the Human Connectome Project, a project funded by the NIH. We will use 3T GE MRI scanners with an 8-channel phased head coil to image participants.[34] Prior to imaging, participants will be injected with a single dose of imaging contrast, 0.1 mmol/kg of gadolinium, and will be asked to abstain from ingesting caffeinated products eight hours before imaging. [34] We will follow the same imaging protocol from a study that used DTI- DSC imaging, which is called "Cerebrovascular reactivity and white matter integrity." We will use the following eight image sequences from that study.[34] Total imaging time is about one-hour long for each participant.[18]

1) *T1-weighted 3D spoiled gradient echo sequence*: Slice thickness: 1.5 mm; no interslice gap; matrix size: 256 × 256; field of view: 22 × 22 cm; flip angle: 8/20°; echo time (TE): 2.3/3 ms; and, repetition time (TR): 7.8/9.5 ms

2) *BOLD fMRI using a T2*-weighted echoplanar imaging gradient echo sequence:* Slice thickness: 3.0/5.0 mm; field of view: 24 × 24 cm; matrix size: 64 × 64; flip angle: 85/90°; TE 30 ms; and, TR 2,000 ms

3) *FLAIR images:* Slice thickness: 3 mm; slices per volume: 36–52; no interslice gap; matrix size: 256 × 224/240 × 240; field of view: 22 × 22 cm; flip angle: 90°; TE 125/165 ms; TR 9,000/9,145 ms; and inversion time 2,200/2,800 ms

4) *Diffusion tensor imaging with echoplanar imaging spin-echo sequence*: Slice thickness: 3 mm; matrix size: 76 × 62/128 × 128; field of view: 22 × 22 cm; b = 1,000 s/mm^2; diffusion-encoding

gradients: 23; non-diffusion-weighted B0 image: 2; TE 55/80 ms; and, TR 9,150/14,500 ms

5) *Proton density/T2-weighted images using fast spin echo-XL sequence*: Slice thickness: 3 mm; matrix size: 128 × 128/256 × 209; field of view: 22 × 22 cm; flip angle: 90°; TE: 11.1/90 to 11/102 ms; TR: 2,500/7,200 ms

6) *Multiecho T2 mapping using a fast spin echo-XL sequence*: Slice thickness: 3 mm; no interslice gap; matrix size: 256 × 192; field of view: 230 × 184/22 × 22 cm; TE: 13, 26, 39, 52, 65, 78, 91, 104, 117, 130, 143, 156 ms; and, TR: 5,000/6,000 ms

7) *DSC perfusion scan using gradient-multiphase echo echoplanar imaging sequence:* Slice thickness: 5 mm; matrix size: 128 × 128; field of view: 27 × 27 cm; flip angle: 90°; TE: 31.5 ms; TR: 1,725 ms; and, 50 slices per location

Image Reconstruction.

Each subject's MRI data will be uploaded to image processing software for pre-processing and data analysis. Images will be pre-processed for quality control, which will be assessed by the same standards as in the ADNI-EF[35] and Connectome Predictor Modeling studies.[19] Image quality will be evaluated quantitatively by boundary shift integral, voxel-based morphometry, tensor-based morphometry, atlas-based mapped volumetric, a measure of gray-white matter contrast to noise, and size of head motion movements.[35] Images also will be evaluated qualitatively by having a radiologist assess for the presence of artifacts, blurring/ghosting, flow artifact, intensity and homogeneity, and gray-white CSF contrast.[35] Only images with mild to no-artifacts will be used. Other images that will not be included in data analysis are: images from subjects with missing ADNI-EF scores, one or more missing nodal data, and head artifacts greater than 0.06 mm.[19]

DTI- DSC Images-Structural Connectivity. To quantify cerebral white matter dysfunction, T2 image sequences will be used. T2 images will be measured with multi-echo fast spin-echo sequence.[34] T2 images will be pre-processed with a product called "FMRIB's Diffusion Toolbox (FDT)" to improve quality image.[34]

To calculate fractional anisotropy and mean diffusivity, diffusion-weighted images will be

imported into *FSL software* for pre-processing and measurement calculations.[34] Cerebral blood flow maps will come from the time-signal attenuation data obtained from the preprocessed weighted images. The area of perfusion that will be assessed is from the middle cerebral artery.[34]

BOLD-Functional-Connectivity. Each subject's MR-images will be pre-processed and analyzed in *AFNI* and *FSL* softwares.[36] Pre-processing will include slice timing correction, motion correction through a general linear model, correcting signal-to-noise ratio, and controlling for anatomical variability across subjects with the "Gaussian smoothing filter" set at 6 mm.[36] The imaging software will enable us to smooth out the cortex's convoluted surfaces and view portions of the brain in left and right hemisphere surfaces and volume slices to view subcortical structures.[18] The representation of the brain's shape will remain preserved.[18] We will use left and right hemisphere surface maps combined with volume slices to visualize and analyze functional MRI.[18] BOLD data will be analyzed within our regions of interest in these right and left hemisphere surfaces and in subcortical, cerebellar, and cortical ribbon f-MRI views.[18]

Combining Participant's Images. We will aggregate participants' BOLD and T2-weighted images by pre-processing them in SPM8 software and FSL.[36] To help align subject data, myelin map data will be used because they have landmarks that help align cortical areas between subjects.[18] Myelin maps of activity will be generated by dividing the intensity value of T1-Weighted images from the intensity value of T2-Weighted images.[18] Red myelin indicates a heavily, active myelinated region.[18] The myelin map will then be compared to functional connectivity maps to determine if these maps colocalize.[18]

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Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not at all	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring **-** Sum each column. Then sum the column totals to achieve a grand score. Write that score here _____.

Interpretation

A grand sum between **0 – 21** indicates very low anxiety. That is usually a good thing. However, it is possible that you might be unrealistic in either your assessment which would be denial or that you have learned to "mask" the symptoms commonly associated with anxiety. Too little "anxiety" could indicate that you are detached from yourself, others, or your environment.

A grand sum between **22 – 35** indicates moderate anxiety. Your body is trying to tell you something. Look for patterns as to when and why you experience the symptoms described above. For example, if it occurs prior to public speaking and your job requires a lot of presentations, you may want to find ways to calm yourself before speaking or let others do some of the presentations. You may have some conflict issues that need to be resolved. Clearly, it is not "panic" time but you may want to find ways to manage the stress you feel.

A grand sum that **exceeds 36** is a potential cause for concern. Again, look for patterns or times when you tend to feel the symptoms you have circled. Persistent and high anxiety is not a sign of personal weakness or failure. It is, however, something that needs to be proactively treated or there could be significant impacts to you mentally and physically. You may want to consult a counselor if the feelings persist.

CATEGORY FLUENCY TEST

Adopted from Sager MD, MA. *Screening for Dementia in Community-based Memory Clinics.*

Instructions

The instructor will say the following:

"I'm going to give you a category and ask you to name all the different examples that you can think of from that category in one minute. For instance, if I said flowers, you might say rose, daisy, etc. Do you understand?"

"Now go ahead and tell me all the different **ANIMALS** you can think of."

Procedure:

1) Time for 60 seconds and tape record all responses.
2) If the person stops before 60 seconds, say "Any more animals?"
3) If the person says nothing for 15 seconds, say "A dog is an animal. Can you tell me more animals?"
4) Repeat the above instructions for the category vegetable.

Notes

1. Write down everything that the subject says, including comments
2. Note down the corresponding times at which the participant provides an answer
3. If participants ask questions during the test, instructors may provide brief answers
4. If subjects stop before the minute is over, encourage them to continue with the task. If subjects continue to refuse, say "There are a few seconds left, so we'll just let the time run on."

Sager MD, MA; Hermann PhD, BP; LaRue PhD, A; Woodard PhD, JL, Screening for Dementia in Community-based Memory Clinics. Wisconsin Medical Journal 2006.105(7)25-29

SCORING Category Fluency

Animal Naming

1. _____ 12. _____
2. _____ 13. _____
3. _____ 14. _____
4. _____ 15. _____
5. _____ 16. _____
6. _____ 17. _____
7. _____ 18. _____
8. _____ 19. _____
9. _____ 20. _____
10. _____ 21. _____
11. _____ 22. _____

Scoring: Count the total number of animals but do not include repetitions or non-animal words.
Total score: _____

Vegetable Naming

1. _____ 12. _____
2. _____ 13. _____
3. _____ 14. _____
4. _____ 15. _____
5. _____ 16. _____
6. _____ 17. _____
7. _____ 18. _____
8. _____ 19. _____
9. _____ 20. _____
10. _____ 21. _____
11. _____ 22. _____

Scoring: Count the total number of vegetables but do not include repetitions or non-vegetable words.
Total score: _____

Note: A score less than 14 is abnormal.

Directions for Scoring Animal and Vegetable Naming Tasks
Individual credit can be given for general category terms, like dog and terriers. However, only 1 point can be given when people name the same animal or vegetable at different developmental stages, such as sheep and lamb.

Sager MD, MA; Hermann PhD, BP; LaRue PhD, A; Woodard PhD, JL, Screening for Dementia in Community-based Memory Clinics. Wisconsin Medical Journal 2006.105(7)25-29

Center for Epidemiologic Studies Depression Scale (CES-D)©, NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get "going."	☐	☐	☐	☐

SCORING: Zero points for answers in the first column, 1 point for answers in the second column, 2 points for answers in the third column, and 3 points for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with higher scores indicating the presence of more symptomatology.

DIGIT SYMBOL SUBSTITUTION TEST

1. Background and rationale

The Digit Symbol Substitution Test (DSST) may be a more sensitive measure of dementia than the MMSE. The DSST requires response speed, sustained attention, visual spatial skills and set shifting. It is part of the Wechsler Adult Intelligence Scale, one of the most widely used measures of intelligence. It has been associated with subsequent mortality, independent of comorbidity in the CHS cohort.[1]

The DSST requires that the participant fill in a series of symbols correctly coded within 90 seconds. In this test, the higher the score, the better the person's performance.

2. Equipment and supplies

- No. 2 pencils with eraser
- Stop watch
- DSST task sheet
- Scoring template for DSST

3. Safety issues and exclusions

None

4. Participant and exam room preparation

The DSST should be administered in a quiet place with minimal distractions at a desk or table the participant can use to write on. Unless it is policy at the clinic for examiners to never knock or open a closed examination room door, we strongly encourage that a special sign be posted indicating that the DSST is being administered and to please not interrupt the test. If any temporary condition that may detract the participant from their optimal performance cannot be removed, the participant should be moved to another location; if this is not possible, reschedule the exam.

Ask the participant if they are comfortable. Reassure them that this is a routine test of concentration that will be done several times during the course of the study.

5. Detailed measurement procedures

5.1 General issues/description

This is a standard neuropsychologic test. The participant completes the task of recording the symbols that correspond to a series of digits. The task is timed. This is a pencil and paper task. The participant practices on a sample, copying the correct symbol given for each number. The participant then is timed on the actual task. The score is the number correct in 90 seconds.

- It is imperative to review the instructions very deliberately and to speak **slowly**, and for those participants who are hard of hearing, **speak low, not loudly**.

- Be certain that participants understand the instructions before proceeding with the test.

- Be certain that participants who wear reading glasses are wearing them.

- Read the standardized script **exactly** as it is written.

- Do not offer encouraging words or in any way distract the participant, unless they actually stop and need to be encouraged to continue.

5.2. Preparation for test: Determine if participant wears glasses for reading.

Script: "Do you usually wear glasses to read?"

If the answer is yes, ask the participant to put on their glasses.

Script: "Please put on your glasses."

5.3 Instructions

1) Place the task sheet before the participant and point to the task.

   Script: "Look at these boxes across the top of the page. On the top of each box is a number from one through nine. On the bottom part of each box, there is a symbol. Each symbol is paired with a number."

   Point to the four rows of boxes.

   Script: "Down here are boxes with numbers on the top, but the bottom part is blank. What I want you to do is to put the correct symbol in each box like this."

   Fill in the first three sample boxes.

   Script: "Now I want you to fill in all boxes up to this line."

   Point to the line separating the samples from the test proper.

2) Let the participant attempt the sample.
   - If the participant has difficulty completing the ten sample items or does not understand the task, help them complete the sample items.
   - If the participant still has difficulty or does not understand the task, discontinue the task, and indicate on the form that the participant was unable to complete the sample.
   - Give participants with physical limitations (e.g., arthritis or visual limitations) an opportunity to complete the sample.

- If a visually or physically impaired participant cannot complete the sample, check "unable to test" on the form or do not record scores.

3) After the demonstration and practice is complete, point to the first box following the sample items and say:

Script: "When I tell you to begin, start here and fill in the boxes in these four rows. Do them in order and don't skip any. Please try to work as quickly as possible. Let's begin."

4) If the participant stops filling in the boxes before the 90 seconds have passed, give them standard encouragement.

Script: "Can you go further?"

5) If the participant begins to erase filled boxes, tell the participant not to waste time erasing.

6) Stop the participant after 90 seconds. (Note: do not tell them what the time limit is)

Script: "That's good. That completes this set of tasks."

5.4 Scoring

1) Indicate whether or not the participant completed the sample.

- If they were not able to complete the sample (not due to a physical limitation, such as poor vision), check off "unable to complete sample," record "00" for "number completed," and mark "00" for "number incorrect."

- If they refused to complete the sample, check off "refused" and do not attempt to score the test.

- If they are unable to complete the sample due to a physical limitation, such as poor vision, do not attempt to score the test.

2) If they completed the sample, check "sample completed" and go on to the timed test.

3) When it is known that a participant is dyslexic and will therefore draw some types of symbols backward, those symbols which are drawn exactly backward are scored as being correct.

4) Single blank spaces between two completed items are not considered incorrectly coded symbols.

5) Two or more blanks which occur consecutively signal the end of the task. Symbols coded after two or more blanks are not included in totals recorded.

6) Enter the number completed.

7) Enter the number of symbols incorrectly coded.

8) One blank space does not count as completed or as incorrect.

9) Additional Scoring Notes

- An "A" is not acceptable for the carat "^" sign (symbol for number 7).
- A "U" with a tail is acceptable for the "U" symbol (symbol for number 5).
- A flat-bottomed "U" is also acceptable for the round-bottomed "U" (symbol for number 5).

6. Alert values/follow-up/reporting

When testing is completed, thank the participant without offering specific feedback on their performance.

7. Quality assurance

7.1 Training requirements

The examiner requires no special qualifications or prior experience for performing this assessment. Training should include:

- Read and study manual
- Attend training session on techniques (or observe administration by experienced examiner)
- Practice on volunteers
- Discuss problems and questions with local expert or QC officer

7.2 Certification requirements

- Complete training requirements
- Conducts exam on two participants while being observed by QC officer
- Correctly scores sample forms

7.3 Quality assurance checklist

- ☐ Exam performed in quiet, private area without interruptions
- ☐ Participant asked if they wear reading glasses
- ☐ Explanation of test:
  - ☐ Instructions are given clearly, concisely and slowly
  - ☐ Participant was asked if they understand testing procedure
- ☐ Test demonstration and practice:
  - ☐ Script read exactly as written (no omission, deletions or substitutions) - Subtle changes allowed only if instructions need to be repeated.

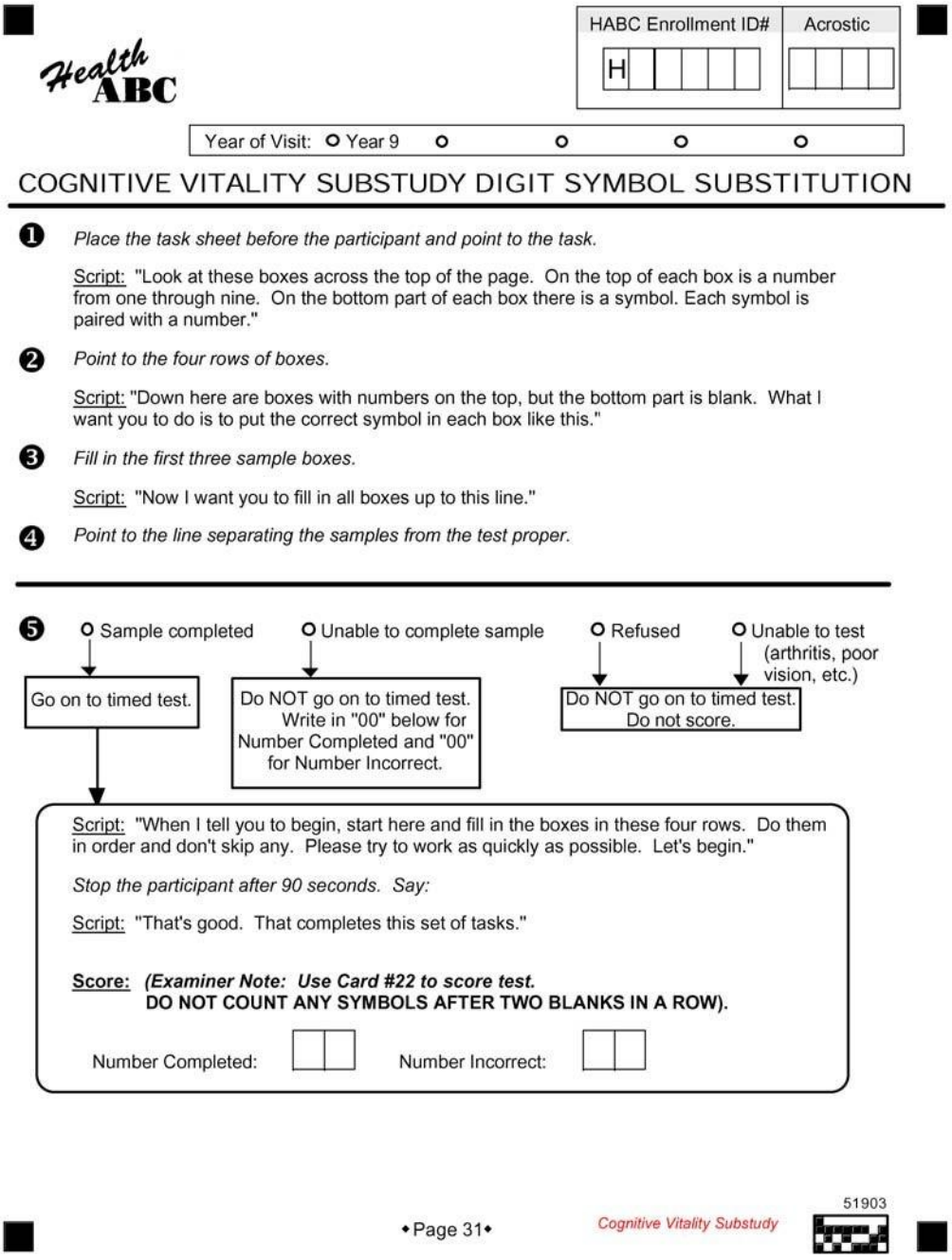
- Demonstrated in first 3 sample boxes
- Participant completes 10 sample items - proper aid is given if participant has difficult completing items.
- Proper coding of answers for difficulty in completing or visual impairment

- Test administration:
  - Script read exactly as written
  - Participant instructed to begin and asked to stop after 90 seconds
  - Scores are coded properly (# completed, # incorrect); symbols not counted after two blanks.
- Reviews form for completeness
- Correctly completes form

8. Reference

1. Fried LP, Kronmal RA, Newman AB, et al: Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. JAMA 1998 Feb 25;279(8): 585-592.

10. Data collection form



Health ABC

HABC Enrollment ID# H | Acrostic

Year of Visit: O Year 9 O O O O

COGNITIVE VITALITY SUBSTUDY DIGIT SYMBOL SUBSTITUTION

❶ *Place the task sheet before the participant and point to the task.*

Script: "Look at these boxes across the top of the page. On the top of each box is a number from one through nine. On the bottom part of each box there is a symbol. Each symbol is paired with a number."

❷ *Point to the four rows of boxes.*

Script: "Down here are boxes with numbers on the top, but the bottom part is blank. What I want you to do is to put the correct symbol in each box like this."

❸ *Fill in the first three sample boxes.*

Script: "Now I want you to fill in all boxes up to this line."

❹ *Point to the line separating the samples from the test proper.*

❺ O Sample completed → Go on to timed test.

O Unable to complete sample → Do NOT go on to timed test. Write in "00" below for Number Completed and "00" for Number Incorrect.

O Refused / O Unable to test (arthritis, poor vision, etc.) → Do NOT go on to timed test. Do not score.

Script: "When I tell you to begin, start here and fill in the boxes in these four rows. Do them in order and don't skip any. Please try to work as quickly as possible. Let's begin."

Stop the participant after 90 seconds. Say:

Script: "That's good. That completes this set of tasks."

Score: ***(Examiner Note: Use Card #22 to score test.***
DO NOT COUNT ANY SYMBOLS AFTER TWO BLANKS IN A ROW).

Number Completed: ☐☐ Number Incorrect: ☐☐

◆Page 31◆ *Cognitive Vitality Substudy* 51903

DIGIT	1	2	3	4	5	6	7	8	9
SYMBOL	—	⊥	⊐	L	∪	0	∧	X	=

SCORE

SAMPLES									
2	1	3	7	2	4	8	1	5	4

2	1	3	2	1	4	2	3	5	2	3	1	4	6	3

1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3

6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7

9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

Cognitive Vitality Substudy

Draft

THE DIGIT MEMORY TEST
Adopted from Martin Turner

Digits forwards

Start Item A

Finish Failure on both trials of a pair**.**

Directions "Listen carefully as I say some numbers. When I finish, you say them."

Delivery Digits should be given at the rate of one per second. Administer both trials of each item. Recite digits in an even monotone without any variation in pitch of voice.

Scoring The individual's score is the total number of items correctly repeated forwards.

WORKED EXAMPLE

Item	First Trial	√ or X	Second Trial	√ or X
A	43	√	16	√
B	792	√	847	√
C	5941	X	7253	√
D	93872	X	75396	X

In this example, the total correct is 5.

Digits Backwards

Directions Instructor will say, "Repeat these numbers after me, but this time, I want you to say the digits backwards." Give two practice trials of two digits first – any two numbers. If the subject gets them wrong, correct her or him**.** If the subject repeats the digits *forwards,* give a reminder that they should be reversed.

Score Same as for digits forwards.

Final score Sum total correct for backwards and forwards. Consult Standard Score table, which is listed below. This can also be expressed as a percentile equivalent, please refer to Percentile Equivalent table which is also listed below.

Comparison Most people can remember two more digits forwards than they can backwards. If the gap is larger than three, or smaller than one, this may be worthy of note.

DIGITS FORWARDS

Item	First trial	√ or X	Second trial	√ or X	Total
A	43		16		
B	792		847		
C	5941		7253		
D	93872		75396		
E	152649		216748		
F	3745261		4925316		
G	82973546		69174253		
H	246937185		371625948		
				Forwards score:	

DIGITS BACKWARDS

Item	Trial one	√ or X	Trial two	√ or X	Total
A	83		29		
B	475		615		
C	2619		3852		
D	28736		59413		
E	624719		276391		
F	4183627		1586937		
G	52624197		94617385		
				Backwards score:	

FINAL SCORE:

Total forwards and backwards:	
Standard score:	
Percentile equivalent:	

Martin Turner
Jacky Ridsdale
revised 6th October 2004

Table 1. Estimated standard scores for digit memory performances from six years-old to adulthood (Adopted from Martin Turner).

Age	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Adult**
Raw score 4	74	57	60	56	54	55	50	48	52	52	51	50
5	79	63	65	61	59	59	55	53	56	56	55	54
6	85	69	70	66	64	64	59	57	60	60	59	57
7	90	75	75	71	69	68	64	61	64	64	63	61
8	96	81	80	76	74	73	68	66	68	68	66	64
9	101	87	85	81	79	77	73	70	72	72	70	68
10	106	93	90	86	85	82	77	74	76	75	74	71
11	112	99	95	91	90	86	81	78	80	79	78	75
12	117	105	100	96	95	91	86	83	84	83	82	79
13	123	111	105	101	100	95	90	87	88	87	86	82
14	128	117	110	106	105	100	95	91	92	91	89	86
15	134	123	115	111	110	105	99	96	96	95	93	89
16	139	129	120	116	115	109	104	100	100	98	97	93
17	144	135	125	121	121	114	108	104	104	102	101	96
18	150	141	130	126	126	118	112	109	108	106	105	100
19	155	147	135	131	131	123	117	113	112	110	108	104
20	161	153	140	136	136	127	121	117	116	114	112	107
21			145	141	141	132	126	122	120	118	116	111
22			150	146	146	136	130	126	124	121	120	114
23			155	151	152	141	134	130	128	125	124	118
24			159	156	157	145	139	134	132	129	127	121
25						150	143	139	136	133	131	125
26						154	148	143	140	137	135	129
27						159	152	147	144	141	139	132
28						163	157	152	148	144	143	136
29								156	152	148	147	139
30								160	156	152	150	143
31									160	156	154	146
32									164	160	158	150
33												154
34												157
35												161
36												164

Table 2. Standard scores expressed as a percentile equivalent. (Adopted from Martin Turner).

Standard score	Percentile equivalent	Standard score	Percentile equivalent	Standard score	Percentile equivalent	Standard score	Percentile equivalent
54	0.1	77	6	100	50	123	94
55	0.1	78	7	101	53	124	95
56	0.2	79	8	102	55	125	95
57	0.2	80	9	103	58	126	96
58	0.3	81	10	104	61	127	96
59	0.3	82	12	105	63	128	97
60	0.4	83	13	106	66	129	97
61	0.5	84	14	107	68	130	98
62	0.6	85	16	108	70	131	98
63	0.7	86	18	109	73	132	98
64	0.8	87	19	110	75	133	99
65	1	88	21	111	77	134	99
66	1	89	23	112	79	135	99
67	1	90	25	113	81	136	99.2
68	2	91	27	114	82	137	99.3
69	2	92	30	115	84	138	99.4
70	2	93	32	116	86	139	99.5
71	3	94	34	117	87	140	99.6
72	3	95	37	118	88	141	99.7
73	4	96	39	119	90	142	99.7
74	4	97	42	120	91	143	99.8
75	5	98	45	121	92	144	99.8
76	5	99	47	122	93	145	99.9

try this: dementia series
Best Practices in Nursing Care to Older Adults with dementia
From The Hartford Institute for Geriatric Nursing, New York University, College of Nursing, and the Alzheimer's Association
alzheimer's association

Issue Number D13, Revised 2016

Editor-in-Chief: Sherry A. Greenberg, PhD, RN, GNP-BC
New York University Rory Meyers College of Nursing

Use of the Functional Activities Questionnaire in Older Adults with Dementia

By: Ann M. Mayo, DNSc, RN, FAAN
Hahn School of Nursing & Health Science, University of San Diego

WHY: Dementia is a neurodegenerative disease where functional ability in individuals with dementia (IWD) declines over time. The majority of care costs in IWD are directly attributed to functional disability (Hurd, 2013). Compromised functional ability is unsafe for IWD, anxiety provoking for families and costly to health care organizations. Valid and reliable clinical information about functional ability can be used to individualize care and design safe and supportive environments thereby promoting the highest level of independence for individuals with dementia. Therefore, an effective and efficient method for measuring functional ability is important.

BEST TOOL: The Functional Activities Questionnaire (FAQ) measures instrumental activities of daily living (IADLs), such as preparing balanced meals and managing personal finances. Since functional changes are noted earlier in the dementia process with IADLs that require a higher cognitive ability compared to basic activities of daily living (ADLs) (Hall, 2011; Peres et al., 2008), this tool is useful to monitor these functional changes over time. The FAQ may be used to differentiate those with mild cognitive impairment and mild Alzheimer's disease. To further exemplify the importance and utilization of the FAQ, thousands of research participants across the United States are administered the FAQ annually as part of the National Alzheimer's Coordinating Center (NACC) longitudinal research study taking place in 29 National Institute on Aging-funded Alzheimer's Disease Centers (Weintraub et al., 2009).

TARGET POPULATION: Older adults with normal cognition, mild cognitive impairment, as well as mild, moderate, and advanced dementia (Weintraub et al., 2009). The FAQ is appropriate for clinical settings, such as acute and primary care, rehabilitation, assisted living, and home settings, as well as for research.

VALIDITY AND RELIABILITY: In IWD the FAQ is a consistently accurate instrument with good sensitivity (85%) to identify an individual's functional impairment. The FAQ demonstrates high reliability (exceeding 0.90). Tests of validity have been performed on the FAQ establishing it as an instrument for the bedside and research because it can discriminate among different functional levels of individuals, predict neurological exam ratings and mental status scores such as

the Folstein Mini-Mental Status Examination (MMSE) and demonstrate sensitivity to change (Assis, 2014; Malek-Ahmadi, 2015; Pfeffer, 1982).

STRENGTHS AND LIMITATIONS: The FAQ is efficient to administer to older adults giving consistent results across different professionals and settings including primary care settings, as well as with different forms of dementia (Mayo, 2013; Tabert et al., 2002). As with other instruments that measure functional activities using indirect approaches, there may be over or under estimation of abilities because of the lack of direct observations.

FOLLOW-UP: Continued monitoring of IADLs in IWD is important to ensure environmental adaptations keeping these individuals safe. The measurement of IADLs is also important for advancing science. Therefore, the FAQ is an important measure for clinicians and researchers.

MORE ON THE TOPIC:

Best practice information on care of older adults: http://consultgeri.org/.

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Weintraub, S., Salmon, D., Mercaldo, N., Ferris, S., Graff-Radford, N.R., Chui, H., & et al. (2009). The Alzheimer's Disease Centers' Uniform Data Set (UDS): The neuropsychologic test battery. Alzheimer's Disease and Associated Disorders, 23(2), 91-101.

Functional Activities Questionnaire

Administration

Ask informant to rate patient's ability using the following scoring system:

- Dependent = 3
- Requires assistance = 2
- Has difficulty but completes task independently = 1
- Normal = 0
- Never did [the activity] but now can = 0
- Never did and would now have difficulty = 1

1.	Writing checks, paying bills, balancing checkbook	
2.	Assembling tax records, business affairs, or papers	
3.	Shopping alone for clothes, household necessities, or groceries	
4.	Playing a game of skill, working on a hobby	
5.	Heating water, making a cup of coffee, turning off stove after use	
6.	Preparing a balanced meal	
7.	Keeping track of current events	
8.	Paying attention to, understanding, discussing TV, book, magazine	
9.	Remembering appointments, family occasions, holidays, medications	
10.	Traveling out of neighborhood, driving, arranging to take buses	
	TOTAL SCORE:	

Evaluation

Sum scores (range 0-30). Cut-off point of 9 (dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment.

Pfeffer, R.I., Kurosaki, T.T., Harrah, C.H. Jr., Chance, J.M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. Journal of Gerontology, 37(3), 323-329. Reprinted with permission of Oxford University Press.

Tip Sheet 5 – The IQCODE (Short Form)

What is the IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a tool used to assess cognitive impairment in older people.

The tool requires an informant to rate cognitive change over time on a 5 point likert scale.

The IQCODE was developed by Jorm and Jacomb in 1989 and consisted of 26 questions; in 1994 a 16 item short version of the IQCODE was developed by Professor Anthony Jorm.

Information in this tip sheet will focus on the short version on this tool as it is quicker to administer, and therefore more practical to use during an ACAS assessment; it has also been recommended by the 2010 Expert Clinical Reference Group (ECRG) (Sansoni et al., 2010) at a national level.

The IQCODE should be used to supplement the other patient administered tools (e.g. the SMMSE; to increase sensitivity and specificity (Flicker et al, 1997; Flicker, 2010), or used in situations where the patient is unable to complete the assessment.

Benefits of the IQCODE: The IQCODE takes approximately 10-15 minutes to administer and is filled out by an informant. It can be used for people with lower levels of education and for those who are illiterate.

Cut-off score: The cut-off scores are based on the total score divided by the number of questions (average item score range 1-5). Higher scores indicate greater impairment. A score below 3.00 indicates improvement, 3.00 indicates no change, 3.01 – 3.50 indicates slight decline; 3.51- 4.00 indicates moderate decline; and 4.01 – 5.00 indicate severe decline.

Translated Tools

Translated versions of the IQCODE (both short and long forms) can be found at the website listed below (please note that the tools on this site may not have been validated):

http://ageing.anu.edu.au/Iqcode/

In addition to these tools the following versions of the tool are also available:

Chinese: Fuh et al (1995) and Lim et al (2003) 26-item version with the cut-off score of 3.4 (tools can be requested from the authors).

Further Resources and References

The web page listed below provides copies of the tool in short and long form in various languages (including English) and information on how to score the tool:
http://ageing.anu.edu.au/Iqcode/

The Assessment of Older People with dementia and depression of Culturally and Linguistically Diverse Backgrounds: A review of current practice and the development of guidelines for Victorian Aged Care Assessment Services (funded by the Victorian Department of Health; undertaken by the National Ageing Research Institute, 2011)

References

- **Tool Reference:** Jorm, A. F. (1994). A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): Development and cross-validation. *Psychological Medicine, 24*, 145-153.

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Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)©

Instructor will say the following:
"Now, we want you to remember what your friend or relative was like 10 years-ago and to compare it with what he/she is like now today. 10 years-ago was in (write down the year). Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same, or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance *with 10 years ago*. For example, if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered 'Hasn't changed much'. Please indicate the changes you have observed by circling the appropriate answer."

Compared with 10 years ago, how is this person at:

	1	2	3	4	5
1. Recognizing the faces of family and friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
2. Remembering the names of family and friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
3. Remembering things about family and friends e.g. occupations, birthdays, addresses	Much improved	A bit improved	Not much change	A bit worse	Much worse
4. Remembering things that have happened recently	Much improved	A bit improved	Not much change	A bit worse	Much worse
5. Recalling conversations a few days later	Much improved	A bit improved	Not much change	A bit worse	Much worse
6. Forgetting what he/she wanted to say in the middle of a conversation	Much improved	A bit improved	Not much change	A bit worse	Much worse
7. Remembering his/her address and telephone number	Much improved	A bit improved	Not much change	A bit worse	Much worse
8. Remembering what day and month it is	Much improved	A bit improved	Not much change	A bit worse	Much worse
9. Remembering where things are usually kept	Much improved	A bit improved	Not much change	A bit worse	Much worse
10. Remembering where to find things which have been put in a different place from usual	Much improved	A bit improved	Not much change	A bit worse	Much worse

11. Adjusting to any change in his/her day-to-day routine	Much improved	A bit improved	Not much change	A bit worse	Much worse
12. Knowing how to work familiar machines around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
13. Learning to use a new gadget or machine around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
14. Learning new things in general	Much improved	A bit improved	Not much change	A bit worse	Much worse
15. Remembering things that happened to him/her when he/she was young	Much improved	A bit improved	Not much change	A bit worse	Much worse
16. Remembering things he/she learned when he/she was young	Much improved	A bit improved	Not much change	A bit worse	Much worse
17. Understanding the meaning of unusual words	Much improved	A bit improved	Not much change	A bit worse	Much worse
18. Understanding magazine or newspaper articles	Much improved	A bit improved	Not much change	A bit worse	Much worse
19. Following a story in a book or on TV	Much improved	A bit improved	Not much change	A bit worse	Much worse
20. Composing a letter to friends or for business purposes	Much improved	A bit improved	Not much change	A bit worse	Much worse
21. Knowing about important historical events of the past	Much improved	A bit improved	Not much change	A bit worse	Much worse
22. Making decisions on everyday matters	Much improved	A bit improved	Not much change	A bit worse	Much worse
23. Handling money for shopping	Much improved	A bit improved	Not much change	A bit worse	Much worse
24. Handling financial matters, e.g. the pension, dealing with the bank	Much improved	A bit improved	Not much change	A bit worse	Much worse

25. Handling other everyday arithmetic problems, e.g. knowing how much food to buy, knowing how long between visits from family or friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
26. Using his/her intelligence to understand what's going on and to reason things through	Much improved	A bit improved	Not much change	A bit worse	Much worse

LETTER FLUENCY TEST

Instructions

Instructor will say the following:
"I'm going to give you a letter of the alphabet and ask you to name as many different words as you can think of that start with that letter. I don't want you to include names of people or places. You'll have one minute to think of as many different words as you can. Try not to give the same words with different endings, like for example, run, runner and running."

"Now go ahead and tell me all the different words that you can think of that start with the letter **F**."

Repeat the above instructions for the letters **A** and **S**.

SCORING LETTER FLUENCY

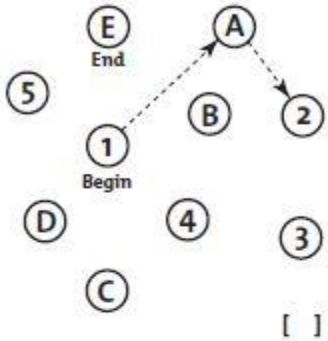
1) Scoring Tip: Consult a dictionary to see if the word given is a noun. As a rule of thumb, if the word has a separate entry to a similar word, as for pill and pillbox, it is scored as a correct response.
2) Sum the total number of correct responses.
3) Note the corresponding times the answers are provided
4) Compute reaction times by calculating the mean time interval between the first word retrieved and subsequent words retrieved.

Patterson J. (2011) F-A-S Test. In: Kreutzer J.S., DeLuca J., Caplan B. (eds) Encyclopedia of Clinical Neuropsychology. Springer, New York, NY

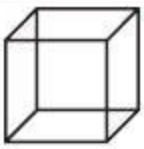
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube



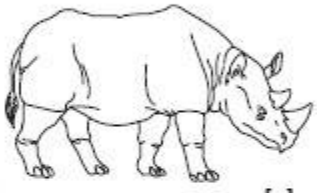
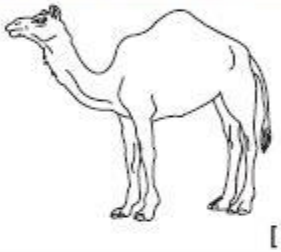
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING

[ ] [ ] [ ] __/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) __/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

npiTEST

The Neuropsychiatric Inventory Questionnaire:

Background and Administration

By Jeffrey L. Cummings, MD

The Neuropsychiatric Inventory–Questionnaire: Background and Administration

The Neuropsychiatric Inventory–Questionnaire (NPI-Q) was developed and cross-validated with the standard NPI to provide a brief assessment of neuropsychiatric symptomatology in routine clinical practice settings (Kaufer et al, J Neuropsychiatry Clin Neurosci 2000, 12:233-239). The NPI-Q is adapted from the NPI (Cummings et al, Neurology 1994; 44:2308-2314), a validated informant-based interview that assesses neuropsychiatric symptoms over the previous month. The original NPI included 10 neuropsychiatric domains; two others, Nighttime Behavioral Disturbances and Appetite/Eating Changes, have subsequently been added. Another recent modification of the original NPI is the addition of a Caregiver Distress Scale for evaluating the psychological impact of neuropsychiatric symptoms reported to be present (Kaufer et al, JAGS, 1998;46:210-215). The NPI-Q includes both of these additions.

The NPI-Q is designed to be a self-administered questionnaire completed by informants about patients for whom they care. Each of the 12 NPI-Q domains contains a survey question that reflects cardinal symptoms of that domain. Initial responses to each domain question are "Yes" (present) or "No" (absent). If the response to the domain question is "No", the informant goes to the next question. If "Yes", the informant then rates both the Severity of the symptoms present within the last month on a 3-point scale and the associated impact of the symptom manifestations on them (i.e. Caregiver Distress) using a 5-point scale. The NPI-Q provides symptom Severity and Distress ratings for each symptom reported, and total Severity and Distress scores reflecting the sum of individual domain scores.

Most informants will be able to complete the NPI-Q in 5 minutes or less. It is recommended that responses to the NPI-Q be reviewed for completeness by a clinician and for clarifying uncertainties after each administration. The first time an informant completes the NPIQ, it may be useful to verbally review the instructions. In some instances, it may be necessary to conduct the NPI-Q in part or entirely as an interview.

For inquiries regarding the NPI-Q, contact:

Jeffrey L. Cummings, MD
Mary S. Easton Center for Alzheimer's Disease Research
10911 Weyburn Ave; #200
Los Angeles, CA 90095
jcummings@mednet.ucla.edu

The NPI-Q can be found at:
www.NPItest.net

Please answer the following questions based on changes that have occurred since the patient first began to experience memory problems.

Circle "Yes" only if the symptom(s) has been present in the last month. Otherwise, circle "No". For each item marked "Yes":

a) Rate the SEVERITY of the symptom (how it affects the patient):

1 = Mild (noticeable, but not a significant change)
2 = Moderate (significant, but not a dramatic change)
3 = Severe (very marked or prominent, a dramatic change)

b) Rate the DISTRESS you experience due to that symptom (how it affects you):

0 = Not distressing at all
1 = Minimal (slightly distressing, not a problem to cope with)
2 = Mild (not very distressing, generally easy to cope with)
3 = Moderate (fairly distressing, not always easy to cope with)
4 = Severe (very distressing, difficult to cope with)
5 = Extreme or Very Severe (extremely distressing, unable to cope with)

Please answer each question carefully. Ask for assistance if you have any questions.

Delusions Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Hallucinations Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear or see things that are not present?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Agitation/Aggression Is the patient resistive to help from others at times, or hard to handle?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Depression/Dysphoria Does the patient seem sad or say that he /she is depressed?

Yes No SEVERITY: 1 2 3 DISTRESS: 0 1 2 3 4 5

Anxiety Does the patient become upset when separated from you? Does he/she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?

Yes No **SEVERITY: 1 2 3** **DISTRESS: 0 1 2 3 4 5**

Elation/Euphoria Does the patient appear to feel too good or act excessively happy?

Yes No **SEVERITY: 1 2 3** **DISTRESS: 0 1 2 3 4 5**

Apathy/Indifference Does the patient seem less interested in his/her usual activities or in the activities and plans of others?

Yes No **SEVERITY: 1 2 3** **DISTRESS: 0 1 2 3 4 5**

Disinhibition Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people's feelings?

Yes No **SEVERITY: 1 2 3** **DISTRESS: 0 1 2 3 4 5**

Irritability/Lability Is the patient impatient and cranky? Does he/she have difficulty coping with delays or waiting for planned activities?

Yes No **SEVERITY: 1 2 3** **DISTRESS: 0 1 2 3 4 5**

Motor Disturbance Does the patient engage in repetitive activities such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?

Yes No **SEVERITY: 1 2 3** **DISTRESS: 0 1 2 3 4 5**

Nighttime Behaviors Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?

Yes No **SEVERITY: 1 2 3** **DISTRESS: 0 1 2 3 4 5**

Appetite/Eating Has the patient lost or gained weight or had a change in the type of food he/she likes?

Yes No **SEVERITY: 1 2 3** **DISTRESS: 0 1 2 3 4 5**

NPI-Q SUMMARY

	No	Severity	Caregiver Distress
Delusions	0	1 2 3	0 1 2 3 4 5
Hallucinations	0	1 2 3	0 1 2 3 4 5
Agitation/Aggression	0	1 2 3	0 1 2 3 4 5
Dysphoria/Depression	0	1 2 3	0 1 2 3 4 5
Anxiety	0	1 2 3	0 1 2 3 4 5
Euphoria/Elation	0	1 2 3	0 1 2 3 4 5
Apathy/Indifference	0	1 2 3	0 1 2 3 4 5
Disinhibition	0	1 2 3	0 1 2 3 4 5
Irritability/Lability	0	1 2 3	0 1 2 3 4 5
Aberrant Motor	0	1 2 3	0 1 2 3 4 5
Nighttime Behavior	0	1 2 3	0 1 2 3 4 5
Appetite/Eating	0	1 2 3	0 1 2 3 4 5
TOTAL			

Trail Making Test (TMT) / Trails "A" & "B"

This test of cognitive function has two parts: Trails "A" and "Trails B." Trials A requires the individual to connect a sequence of 25 numbers in order. Trails "B" requires the individual to alternately connect a sequence of 25 numbers and letters (e.g. 1-A-2-B-3-C, etc.).

	Trail Making Test (TMT) / Trails "A" & "B"
Link to Tool	http://www.sagelink.ca/uploads/tools/TrailMakingTestAB.pdf
Time to Administer	2 – 5 minutes
Type	Standardized Screening Tool
Setting	Primary care.
Administration	**Trail Making Part A:** 1. Provide the person with the sample Trails A first. Once completed correctly, then move on to the actual Trails A. 2. Instruct the individual to "Please draw a line connecting the numbers 1, 2, 3, 4 etc. in order until you reach the end. Try to draw the lines as fast as you can." 3. If the person makes a mistake on the sample Trails A, point it out to them and explain the error. Repeat the sample Trails A until they have completed it correctly or it becomes evident that they are unable to do the task. 4. Once the sample trails A has been completed correctly, give them the real Trails A. Repeat the instructions as given in step two. 5. Start timing the test as soon as the instruction is given to begin the test. **Trail Making Part B:** 1. Provide the individual with the sample Trails B. Once they have completed it correctly, then move on to the actual Trails B. 2. Instruct the individual that this second part of the test is slightly more difficult as it requires them to alternate between numbers and letters. Instructor will say, "On this page are some numbers and letters. Begin at 1 and draw a line from 1 to A, A to 2, 2 to B, and so forth until you reach the end. Remember first you have a number, then a letter, then a number, and so on. Draw the lines as fast as you can." 3. If the person makes a mistake on the sample Trails B, point out the error and explain why it is incorrect. Repeat this procedure until the task is performed correctly or it becomes apparent that they cannot complete the task. 4. After the person has completed the sample Trails B, provide them with the actual Trails B. Repeat the instruction given in step 2. Timing begins as soon as the person is told to begin. 5. Be alert for mistakes. If the person makes a mistake, point it out to them immediately, return the person to the last correct circle, and continue the test from that point. Continue timing and record the number of errors made until task is completed.

<table>
<tr><td>Interpretation</td><td>1. Part A and B are scored separately. The score for each part is the number of seconds required to complete the task.
2. More than 1 error or a score below the 10th percentile in time (seconds) raises concerns. Scores are compared against the 50th percentile.
3. Generally, time over 3 minutes or more than 1 error is a failure.

Norms for Trails A and B by age (in seconds) and education
<table><tr><th>Age</th><th>Percentiles</th><th>Trails A* (education – no change)</th><th>Trails B ≤Grade 12</th><th>>Grade 12*</th></tr><tr><td>65-69</td><td>50</td><td>37 seconds</td><td>86</td><td>68</td></tr><tr><td></td><td>10</td><td>53</td><td>137</td><td>77</td></tr><tr><td>70-74</td><td>50</td><td>38</td><td>101</td><td>84</td></tr><tr><td></td><td>10</td><td>61</td><td>172</td><td>112</td></tr><tr><td>75-79</td><td>50</td><td>46</td><td>120</td><td>81</td></tr><tr><td></td><td>10</td><td>70</td><td>189</td><td>178</td></tr><tr><td>80-84</td><td>50</td><td>52</td><td>140</td><td>128</td></tr><tr><td></td><td>10</td><td>93</td><td>158</td><td>223</td></tr></table></td></tr>
<tr><td>Reference</td><td>Corrigan J.D., Hinkeldey M.S. (1987). Relationships between parts A and B of the Trail Making Test. JClin Psychol., 43(4), 402–409.
Gaudino E.A., Geisler M.W., Squires N.K. (1995). Construct validity in the Trail Making Test: what makes Part B harder? J Clin Exp Neuropsychol., 17(4), 529-535.
Lezak M.D., Howieson D.B., Loring D.W. (2004). Neuropsychological Assessment. 4th ed. New York: Oxford University Press; 2004.
Reitan R.M. (1958). Validity of the Trail Making test as an indicator of organic brain damage. Percept Mot Skills, 8, 271-276.</td></tr>
</table>

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL: Hospital Research Unit

Study Title: *Brain Training and Meditation's Effects on Memory in Seniors with Vascular Cognitive Impairment*
Principal Investigator: *Dr. Salardini*
Funding Source: None

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at two safe, non-pharmacological interventions effects on slowing cognitive decline in Vascular Cognitive Impairment.

You have been asked to participate because we are seeking participants between the ages of 60- 89 who have mild cognitive impairment (MCI) due to cerebral small vascular disease (CSVD), and we would like to provide you an intervention that may slow the progression of certain cognitive declines that are common in this disease, like problem-solving capabilities. The study will be conducted at *Yale New Haven Hospital Research Unit.*

In order to decide whether or not you wish to be a part of this research study, we want you to carefully review its risks and benefits to make an informed decision. This consent form includes the study's purpose, its procedures and associated risks, possible benefits, and possible alternative treatments. If you still wish to participate in the study after reviewing this document, we ask that you sign this form.

Description of Procedures

If you agree to join this study, you will be asked to play a computer game and to engage in a relaxing activity. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. The site may post a summary of our results, but no participants will be able to be identified on this site.

Intervention- I

Participants enrolled in the combined mindfulness meditation (MM) and Dual N-Back will come to clinic 3 times a week to play 30 minutes of Dual N-Back, followed by 30 minutes of meditation.

Intervention- II

Participants who are randomized and allocated to the low-intensity intervention are offered tuition for playing solitaire and listening to selected music for a total of one-hour per day. Participants will be expected to play 30 minutes of solitaire followed by 30 minutes of listening to relaxation music for 12 weeks.

Participants will be expected to follow this same protocol on days that they are not at clinic. These activities will be placed on a server onto which they will need to log onto to have their compliance recorded. For those with less than 80% compliance on a weekly basis, one warning will be given, followed by dys-enrollment from the study if low compliance continues. Groups session will be mandatory during the first two weeks of the study, but after that, the subjects may do the exercises at home if they wish.

Risks and Inconveniences

Experimental studies may involve potential and unforeseeable risks that include physical harm or loss of confidentially. To mitigate potential harm, we have created a list of potential risks and corresponding action plans to address them should they occur.

Risks of Magnetic Resonance Imaging (MRI)

Magnetic resonance (MR) imaging is a technique that uses magnetism and radio waves to take pictures and measure chemicals of different parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we will carefully observe those guidelines.

MRI is usually a harmless procedure; however, risks can occur. On rare occasions, some people may feel uncomfortable or anxious due to claustrophobia or may develop dizziness, an upset stomach, a metallic taste, tingling sensations, or muscle twitches. These sensations usually go away quickly, but please inform the research staff if you have them.

People with metal objects both inside or physically on their bodies are at greatest risk for harm because the MRI's strong magnets will harm you. To minimize these risks, the exclusion criteria includes people with pacemakers, metal pieces inside their body, aneurysm clips, large colored tattoos, or any other contraindications for MRI, and people who are claustrophobic. To lower the risk of harm from metal objects, each participant will be scanned by a metal detector every time before entering the MRI room. No metal objects will be present in the MRI rooms and doors will remained closed during sessions to prevent metal objects from the outside entering the room. During the MRI study, participants will be provided earplugs and closely monitored.

Should a participant become anxious or experience any adverse event, the MRI study will be discontinued and rescheduled for a later time, if it is not contraindicated.

We want participants to be aware of the risks and harms associated with MRI's, so we request that participants read and answer the questions on the MRI Safety Questionnaire. Participants will be required to sign and hand-in the completed Questionnaire.

MRI results are for research purposes only. Only in the event of a concerning finding, will the image be reviewed by a certified, practicing radiologist at our facility to provide a diagnostic evaluation of the image. Based on the radiologist's impression, the PI will inform the subject of the finding and recommend that the participant seek his or her primary care provider for further medical advice. We, the investigators, the Magnetic Resonance Research Center, and Yale University are not responsible for further treatment.

Risks of Intravenous Catheter Placement and Gadolinium Contrast

Having an intravenous (IV) line placed is benign procedure. Though, standard risks include mild pain, infection, bruising, or clot formation. To minimize these risks, registered nurses will be performing these tasks and using proper technique. A total of 200 mL of blood will be collected during the entire study. Should an adverse event occur, participants will receive appropriate medical arrangements from a licensed health care health provider.

Gadolinium is an FDA approved contrast that is used in MRI imaging. This contrast is safe in participants with good kidney function, and very rarely do people experience an adverse reaction.

Gadolinium risks are greatest in people with kidney dysfunction because it could potentially cause a life-threatening disease Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). To avoid this risk, participants who have a glomerular filtration rate (eGFR) of <30 mL/min/1.73 m2, receive dialysis, or have acute kidney injury will not be included in this study. Detailed information on the contrast agent Gadolinium can be provided to you at your request.

Risks of Discontinuation of Pharmaceuticals

The inclusion criteria requests that participants not be on anti-anxiolytics or medications that alter cognition six weeks prior to the start of the study. These medications include tranquilizers, anti- anxiolytics, hypnotics, ionotropic, cholinomimetic agents, cholinesterase inhibitors, or NMDA antagonists. These medications would confound outcome measurements in our study. Participants who have relative contraindications in discontinuation of medications will not be included.

The risks of discontinuing these drugs are unknown. We cannot predict the risk of cognitive decline since there is no standard of care in mild-VCI treatment, only it is common practice to prescribe medications that are used in AD. Cholinesterase inhibitors are an off-label treatment because their benefits on cognitive outcomes or slowing disease progression is not supported by empirical evidence.[1]

In the advent that participants unexpectedly present with worsening cognitive impairments, he or she can choose to opt-out-of the study and receive donepezil or no treatment at all. Participants are able to withdraw from the study at any time, and his or her relationship with Yale Hospital will not be adversely affected.

Once the study is complete, the treatment with significantly better outcomes will be available to participants.

Risks of Worsening Cognitive Impairment Symptoms

Participants will be monitored for progressive cognitive decline that could potentially by exacerbated by our interventions or screening protocol. In the event that a participant experiences an abrupt decline from baseline, the participant will be evaluated by a neurologist at our clinic who is licensed to address changes in cognition and activities of daily living (ADL). These patients will be seen within 48-hours of onset of symptoms and appropriate medical arrangements will be made. We will track these participants until resolution. In the event that the decline is so severe that the participant's surrogate can no longer care for him or her, that participant will be admitted to the hospital and appropriate medical interventions will be provided, in addition to case management. We will track these participants until resolution. This risk is highly unlikely.

Risk of Fatigue

The intervention is one-hour in duration daily, which may cause participants to become fatigued. To avoid this, participants will be provided breaks as needed. Other ways we can mitigate fatigue is by splitting the sessions into smaller periods or provide longer rest breaks.

Risks of the Screening and Evaluation Process

The screening process requires us to ask personal psychiatric and medical history, which may make participants feel uncomfortable. To mitigate this risk, the screening process will only be conducted by trained and experienced research assistants who are able to conduct interviews in a sensitive manner.

Risks of Inconvenience

The study should be relatively convenient for participants. Participants will only have to engage in their assigned activity for a total of one hour each day. Coming to the research unit may be inconvenient but participants are only required to come to the clinic three times per week for the first two weeks and on days that outcome measurements are collected.

Benefits

The low risks associated with this study are outweighed by its potential benefits. The current treatment options in CSVD are poor, as it is common practice to prescribe off-label, AD medications.

The non-pharmacological interventions are harmless and some have shown to promote plasticity and functional network strengthening that may be able to improve functional and cognitive deficits. Participants will have the opportunity to help us learn more about these interventions neuroplastic effects by agreeing to undergo functional magnetic resonance imaging. The knowledge gained from our study could also lead to new treatment options in CSVD.

Economic Considerations

Participants will not be charged for any medical interventions that he or she receive in the study. Participants will need to own a computer device to play the computer game. Also, subjects will receive $5 per session and can receive a total compensation of $420 upon completing the 84 sessions. They will receive a further $100 for completing both baseline and follow-up testing, which includes MRIs and neuropsychological testing. According to the rules of the Internal Revenue Service (IRS), this payment may be considered taxable income.

Treatment Alternatives/Alternatives

The current guidelines from the American Academy of Neurology (AAN) in the treatment of mild cognitive impairment suggest that “Grade A” practice is to discuss with patients the option of cholinesterase inhibitors; however, clinicians must emphasize to patients that they are an off-label treatment because their benefits on cognitive outcomes or slowing disease progression is not supported by empirical evidence.1 “Grade B” practices are to not offer cholinesterase inhibitors or to add twice-weekly exercises into overall management.1 A “Grade C” practice is to recommended cognitive interventions because they may improve cognitive functioning.1 Guidelines also suggest that it is good practice to assess and treat comorbid, behavioral and neuropsychiatric symptoms because of their association with greater functional impairments2 and increased risk for disease progression.3,4 Other primary interventions that are

being studied are aerobic exercise and lifestyle modifications, such as diet, exercise, and reducing blood pressure.

In this study, participants will be asked to play a computer game and to engage in a relaxing activity. In the advent that participants unexpectedly present with worsening cognitive impairments, he or she can choose to opt-out-of the study and receive donepezil or no treatment at all. Once the study is complete, the treatment with significantly better outcomes will be available to participants.

Confidentiality

Members of the research team will be collecting protected health information, including medical information and some HIPAA identifiers, throughout this study for the sole purpose of research and medical charting. Upon participants signed consent, we will be able to access and collect information about your personal health history, which includes current and past medical history, medications, psychiatric and substance use history, family history, and diagnostic lab results. During the screening process, the HIPAA identifiers that will be obtained include names, telephone numbers, and medical record numbers. This information will remain confidential and protected, but adverse effects could potentially occur should confidentiality be unlawfully breached. In the event of illegal disclosure, the event will be documented in the "accounting for disclosures log" and then forwarded to the Deputy HIPAA Privacy Officer. Participants will be subsequently made aware of the disclosure.

To protect confidentiality, participants' information and outcome measures will be collected and handled only by trained personnel from the Hospital Research Unit and Magnetic Resonance Imaging Center. Data will be recorded into Excel spreadsheets on a protected server. Both excel documents and server will be password protected. Digital data will be stored onto password protected databases. All electronic devices will have encrypted software and be on a protected server. Papers with personal information will be stored in locked-filing cabinets. Only researchers involved in this study will have access to passwords and filing cabinets and will have successfully completed HIPPA training. We will access participant information only when necessary.

To help protect confidentiality, personal identifying information and results will be separated. Results will be published or presented in conferences as group data to avoid using identifying information. Unnecessary data will be shredded or permanently deleted at the earliest opportunity. Though, impactful data may be kept in a locked filing cabinet up to ten years but will only be accessible to authorized personnel. Any identifiable information that is obtained in

connection with this study will remain confidential. Information will not be disclosed to any other person or entity, unless with your permission or as required by law in the interests of patient safety. We are legally required to disclose abuse and certain reportable diseases. Lawful authorities include U.S. and State Law Officials and members overseeing the research, such as the Institutional Review Board. Representatives from the Yale Human Research Protection Program and the Yale Human Investigation Committee, a committee that reviews, approves, and monitors research on human subjects, may inspect study records during internal auditing procedures. These individuals are required to keep all information confidential.

Consent personnel includes I, Sarah Savoia, and PI, Dr. Salardini. Consent to screen for eligibility and participation in the study will be obtained at the Church Street Research Unit.

We request that participants with capacity and assigned caretaker sign the HIPPA Authorization form in order to participate in the study.

In Case of Injury

In the event that a participant is injured or experiences an abrupt decline from baseline, the participant will be evaluated by a neurologist at our clinic, and we will pay and provide for the appropriate medical arrangements. Injuries that are non-research related will not be financially covered by Yale-New Haven Hospital.

However, in the event that a concerning finding is observed on MRI, we, the investigators, the Magnetic Resonance Research Center, and Yale University will not be responsible for further treatment. The participant will be recommended to seek his or her primary care provider for further medical advice and treatment.

Voluntary Participation and Withdrawal

Participating in this study is voluntary, and participants are able to withdraw from the study at any time. Refusal to participate or withdrawal from the study will not adversely affect your relationship with Yale Hospital. We would still treat you with standard therapy or, at your request.

Withdrawing from the Study

To withdraw from the study, you can call a member of the research team at any time. The interventions will be discontinued and you will no longer be able to receive these interventions from us outside of the study. The monetary compensation will be forfeited as well. Participants will not be able to re-enroll into this study.

Participants may be withdrawn from the study in the event of disease progression, development of serious side effects, or less than 80% adherent to protocol.

In the event a participant is no longer a part of the study, we will immediately stop collecting outcome measurements and identifying information. Prior collected data may still be used in our study.

Participants will be unable to withdraw their data because we will be anonymizing it and separating results from personal identifying information.

You do not give up any of your legal rights by signing this form.

Questions

If you have any remaining questions about this study, please ask us before signing.

Authorization

I consent to voluntarily participate in this study after having read this document. I attest that I have full capacity and understand the study's general purposes, my involvement, and the possible hazards and inconveniences, as they were clearly explained to me. My signature also attests to having received a copy of this consent form.

Participant

Name of Participant: _____

Signature: _____

I assign, _____, to be my caretaker.

Caretaker

As the assigned caretaker, I voluntarily consent to let the above participant participate in this study after having read this document. I understand the study's general purposes, my involvement, and the possible hazards and inconveniences, as they were clearly explained to me. For the foreseeable future, I agree to accompany the above participant to all drop-off sessions and procedures.

Name of Designated Caretaker: _____

Signature: _____

Relationship: _____

Date: _____

For the Researcher

_____
Signature of Principal Investigator

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Dr. Salardini at (203) 785-4085.

If after you have signed this form and you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

References

1. Practice Guideline Update: Mild Cognitive Impairment. American Academy of Neurology. 2017. https://www.aan.com/Guidelines/Home/GetGuidelineContent/882.
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3. Peters ME, Rosenberg PB, Steinberg M, et al. Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: the Cache County Study. Am J Geriatr Psychiatry. 2013;21(11):1116-1124.
4. Ismail Z, Elbayoumi H, Fischer CE, et al. Prevalence of Depression in Patients With Mild Cognitive Impairment: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017;74(1):58-67.