Compensatory training to support everyday function and adherence to brain healthy lifestyle changes in those at risk for Alzheimer's disease

Significance and Background. The older adult population is rapidly growing as are the number of individuals harboring the early substrates of Alzheimer's disease (AD). Developing approaches to preventing or delaying AD-associated symptoms is imperative to address this emerging public health crisis. In the absence of medical treatments, behavioral interventions provide effective and cost-efficient alternatives. The maintenance of functional independence is a particularly important priority for older adults and is associated with quality of life[1] and economic burden[2]. **Maintaining daily function and delaying disability are important intervention targets**; however, very few interventions have *explicitly* targeted functional capacities. Researchers at UC Davis showed functional limitations in everyday life begin very early in the disease course (i.e., 'pre-MCI' period) when there are often subjective cognitive/functional concerns on the part of the older adult but no cognitive impairment on objective testing[3]. Mounting evidence suggests subjective concerns represent a significant risk of incident MCI (Caselli et al) for developing clinical AD and many of these individuals harbor other indicators of early disease (e.g., amyloid[4-6] and brain atrophy[7]). Further, it has been shown that very subtle self-reported concerns about functional difficulties increase one's risk for subsequent loss of independence/disability[8]. The period in which subtle functional and cognitive concerns are present but performance on cognitive testing remains grossly normal offers a critical window of opportunity to intervene to build resilience by developing compensation strategies to use in everyday life and to increase other behaviors that will support better function and reduce risk of decline and dementia. In the proposed project we target this 'at-risk' subjective concerns (SC) group.

Scientific premise and rationale for the proposed intervention:

Compensatory training. The Executive and Memory Support System (EMS)

Changes in memory and executive function are some of the earliest signs of evolving Mild Cognitive Impairment[12] and are strong determinants of everyday functioning[13, 14]. With our Executive and Memory Support compensatory system (EMS), we aim to support both areas of cognitive function. In individuals with significant memory impairment due to Mild Cognitive Impairment or traumatic brain injury (TBI) for example, interventions that focused on teaching compensatory strategies (e.g., adapting to rather than ameliorating the memory deficit) have been more successful in having a positive impact on daily function[9]. One aspect of the EMS system is the Memory Support System, comprised of a standardized calendar and journaling system[10, 11]. The MSS is one of five components of the Mayo Clinic HABIT Health Action to Benefit Independence and Thinking ® program, a clinical treatment program for patients with MCI and a partner offered across the Mayo Clinic enterprise. Results from our randomized controlled trial of the MSS demonstrated improved **memory-based functional abilities** in the treatment group compared controls (Cohen's d = 1.0 immediately after the intervention and d = .88 at 8-week post intervention). The curriculum for the MSS also involves training in keeping and prioritizing a 'to do' list as well as breaking a larger task into a smaller tasks for organization and planning—aspects of executive functioning. A number of other compensatory cognitive rehabilitation interventions have also impacted everyday executive functions, most commonly among individuals with traumatic brain injury (TBI) or attention deficit hyperactive disorder (ADHD). For example, training in goal setting, execution and monitoring has been shown to increase participation in everyday activities among individuals with TBI[15]. Compensatory interventions to treat adult ADHD have also focused on restructuring and organizing one's physical environment and work space to maximize functioning[16, 17]. Comparatively few intervention studies have evaluated the provision of executively-based compensatory training to older adults. One exception is Goal Management Training (GMT;[18]) which teaches identification and achievement of specific goals to older adults. Drawing from this literature, the team at UC-Davis developed a curriculum of compensatory training that comprehensively includes aspects of the above programs including the development of short and long terms goals, use of a daily 'to do' lists to accomplish goals and other daily activities, as well as organizational strategies applied to the environment (Denny et al.). In the present study this curriculum will be combined with the MSS curriculum. We will evaluate the acceptability, adherence and efficacy of this comprehensive training in compensation strategies to support everyday memory and everyday executive functions – the Executive and Memory Support (EMS) System.

Modifiable healthy-brain behaviors. Cognitive impairment/dementia and loss of functional independence are multifactorial and require multimodal interventions. There is growing recognition a variety of risk factors encompass modifiable behaviors and lifestyles. A challenge to any program that encourages the adoption of

healthy lifestyle changes is getting people to actually make the changes and sustain them. A unique aspect of the present intervention is that we employ the use of the various compensatory strategies that are aimed at supporting everyday functioning (the EMS) to also help participants implement the sustained adoption of modifiable lifestyle behaviors to enhance brain health.

There is an impressive body of literature demonstrating the impact of physical exercise on cognition and brain health[19-21]. In recent reviews, physical inactivity has been identified as the number one modifiable risk factor for prevention of Alzheimer's disease[22]. A recent meta-analysis of 36 exercise interventions for cognitive function in adults over 50 showed that physical exercise improved cognitive function, and this effect was seen with aerobic exercise, resistance training, multicomponent activity, and tai chi. The benefit was seen both in those without objective cognitive impairment as well as those with Mild Cognitive Impairment (Northey et al). Similarly, there is a large body of observational, epidemiological data linking engagement in cognitively stimulating activities to better cognitive function in old age[23, 24,25]. As a result, there is a growing literature aimed at translating such findings into interventions that promote increased participation in a variety of cognitively stimulating activities. For example, Smith et al. showed that adaptive computerized cognitive training improves attention and memory as well as self-report of daily functioning. Stress and poor mental health can also impact cognition and brain health. Notably, previous work has shown associations between chronically elevated stress and structural brain changes,[26] due to prolonged activation of complex hormonal systems (e.g., HPA axis[26]). It is likely that reducing stress and improving mental health can also promote brain health. The present intervention focuses on meditation practice, which has been shown to reduce stress and improve mental health[27].

In sum, the goals of the proposed intervention are two-fold: 1) bolster the consistent and effective use of compensation strategies that support everyday memory and executive functioning and 2) utilize these strategies to promote adopting, enhancing, and maintaining engagement in activities that have been shown to promote brain and overall health, well-being and daily function. Portions of this intervention have been utilized in patients with MCI at Mayo Clinic but the full combination program utilizing interventions developed at UC Davis has not been evaluated for feasibility, acceptability, or effect size estimates in a Mayo Clinic older adult at-risk population. This small pilot trial will aim to address these parameters. Development of this intervention incorporates well-established theories of behavioral change and approaches to enhance self-efficacy (e.g., providing the scientific basis for lifestyle changes; identifying and overcoming barriers to change; the use of social facilitation through modeling, reinforcement, and mutual support). It employs a Person-Centered approach that is more effective than highly standardized interventions at facilitating behavior change and maximizing adherence and long-term maintenance[28]. Finally, because evidence suggests involvement of significant others facilitates implementation and maintenance of new behaviors[29], participants are strongly encouraged to bring a significant other to the last three sessions, which provide review and further practice of all course materials.

The proposed intervention will pilot test a novel compensatory training program that intervenes to benefit both everyday memory and executive function in individuals at risk for cognitive decline. It is innovative in: 1) directly targeting the support of *functional capacities*; 2) utilizing compensatory training to also bolster engagement in other healthy lifestyle activities that support brain health and better function, and 3) targeting an at-risk population who is motivated and capable of learning new behaviors to forestall decline.

Preliminary Results.

The MSS is effective in improving everyday memory. The Memory Support System (MSS) was initially developed for patients with amnestic Mild Cognitive Impairment (MCI), where the hallmark of the syndrome is memory impairment. The system was developed based on cognitive rehabilitation literature demonstrating the success of compensatory memory techniques in patients with memory impairment due to other issues (brain injury, stroke). To date, it has been shown that (1) MCI patients can learn to use the MSS to compensate for memory loss[11], (2) they learn to use the MSS better if they receive individual training sessions on the system than if they are just told to use a calendar[10], (3) those who receive the **MSS plus training show improvement in memory based activities of daily living** (d=1.0) and memory self-efficacy (d=.47) and their care partners show improved mood (d=.90) and less caregiver burden (d=.90) 6 months post intervention compared to those who receive the MSS but no training[10]. Similar trends but with expected smaller effect sizes (memory ADL d = .39; self-efficacy d = .37; caregiver depression d = .35, caregiver burden d = .32) were seen when using a more active control comparing those who receive the MSS with training to those who received the MSS without

training as well as cognitive exercise training[10]. The MSS is also part of the larger HABIT Healthy Action to Benefit Independence & Thinking ® program offered across the Mayo Clinics and those in the HABIT program who master the MSS show sustained improvement in functional status at one year follow-up[36].

Training in everyday executive abilities. The compensatory training aimed at supporting everyday executive abilities was initially piloted by researchers at University of California-Davis with 30 older adults with subjective cognitive complaints in an open, single-group design study in 2015 to test initial acceptability and program satisfaction. They found that self-reported compensation significantly increased from pre- to post-intervention ($p<.001$; effect size using Cohen's $d = 1.0$)[37]. Increased compensation was maintained at 3 month follow-up, suggesting durability of findings. Importantly, previous work has shown that more frequent compensation is associated with a better level of everyday functioning[38]. During this early pilot study engagement in cognitively stimulating activities increased from pre to post-intervention ($p <.004$; Cohen's $d = .56$) as did the engagement in stress management activities (primarily meditation)[37]. Exit interviews also showed a high degree of satisfaction and perceived benefit. Based on feedback, several modifications were made: increasing class length from 1.5 to 2 hours; lengthening the program to 10 weeks; a focus on meditation in the stress management; incorporation of more in-class exercises; and development of written handouts for every session. In a subsequent larger, wait-list controlled randomized trial of the 10 week program (2 hour classes, once per week) the weekly groups were well attended (the majority attended 9/10 classes). Satisfaction ratings were uniformly high (average score of 4.4/5).Participation proved to be effective in increasing use of compensation strategies in the intervention group relative to the wait-list control in the areas of: Shopping (diff=0.5, 95% CI: 0.2-0.8, p=0.005); Managing Finances (diff=0.6, 95% CI: 0.2-1.1, p=0.01), and Managing Medications (diff=0.4, 95% CI: 0.01-0.8, p=0.04). Importantly, the intervention group showed **enhancements in everyday abilities related to executive functioning** compared to the waitlist (p=.03). There was a significant increase in the total number of cognitively stimulating activities the intervention group engaged in compared to controls (diff=2.4, 95% CI:0.3-4.5, p=0.02). Changes in exercise or emotional well-being across the groups did not reach significance. We believe use of a more systematic calendar and to do system (the MSS) in the proposed study will increase adherence to these lifestyle changes.

Study Design and Methods

Study Design. This study will have a mixed, within and between subject design where 40 participants will receive the MSS materials as well as recommendations for executive functioning improvements and lifestyle changes. Subjects will then be randomized to (1) implement these behaviors on their own (n=20) or (2) attend the 10-week intervention that provides support for implementation of the behaviors (n=20). Between-group comparisons (active treatment vs recommendation only controls) will be made for time points immediately before and after the 10-week treatment interval to assess immediate treatment effects and at 3 and 6 months to assess for durability. We will also examine within-person comparisons among those receiving treatment from pre to post.

Recruitment: 40 participants will be recruited. Dr. Locke will partner with multiple colleagues to recruit individuals with subjective cognitive complaints but who are felt by that provider to have only normal aging related cognitive changes. This includes but is not limited to:

- Dr. Shah, as liaison to the geriatricians in primary care areas at Mayo Clinic Arizona
- Dr. Stonnington, as a liaison to the neuropsychiatrists in Psychiatry.
- Dr. Caselli, as liaison to the behavioral neurologists in Neurology at Mayo Clinic Arizona and clinical core director of the Arizona Alzheimer's Consortium, which may have eligible participants in the clinical core.

Participants. Participation will include cognitively normal older adults with subjective concerns (SC) but with normal cognitive and functional status for age. Participants referred for consideration for study participation will complete a formal study eligibility visit to establish the following eligibility inclusion and exclusion criteria

Inclusion Criteria:

1) Age 50 or older
2) A positive complaint or concern in response to two questions ('Do you feel like your memory or other aspects of thinking are becoming worse?' and 'Does this worry you?')

3) Normal cognitive performance on the Montreal Cognitive Assessment (adjusted for age and education)
4) Self-reported independent function in daily life as measure by the Lawson IADL scale (IADL=8)
5) English speaking
6) Approval letter from a physician (due to the exercise component)

We recognize older adults with SC are heterogeneous and have been variably defined, however, our definition conforms to the international Subjective Cognitive Decline Initiative Working Group[39] and is consistent with other large scale studies[40, 41].

Exclusion Criteria:

1) Known neurological disorder with potential cognitive symptoms (a diagnosis of Parkinson's disease, epilepsy, a history of moderate to severe TBI, etc.)
2) Uncontrolled moderate or severe depression (e.g., CES-D > 21).

Description of the Intervention. The intervention is administered over 10 weeks in 2-hour weekly sessions provided in a group format. Weekly sessions feature a new technique or behavior, but the last three weeks are review to allow time for skill building and practice (see Appendix A-Manual). Each class follows a similar format - a brief review of class material and homework; new class material (including group discussion and in class activity); and discussion of homework for the coming week. Components of the program:

Everyday compensatory/support training – the Executive and Memory Support (EMS) System – includes three training components:

1.) *Calendar System (based largely on the original 'Memory Support System' (MSS)[10, 11])*:
The calendar system includes a: (1) two-page per day calendar/note-taking system for the current month and (2) a monthly view annual calendar for the year-at-a-glance. It is small enough to fit in a breast pocket or purse. The two-page per day section has three sections: 1) a daily calendar where events/appointments are recorded on one page, and the other page contains 2) a daily "to do" list, and 3) a journaling section (see Appendix B). As part of the expanded EMS System, the journaling section will be where short- and long-term goals are maintained and updated (see Goal Planning below) which will also be incorporated into the 'to do' task list. Training follows well-established learning theory and rehabilitation methods that incorporate an initial training/acquisition phase (in-class training session), followed by an application and adaption phase through practice and feedback. A key component is to make a *habit* of: a) reviewing the calendar routinely (i.e., designated times daily) and b) entering *all* re-occurring and non-reoccurring activities. Class discussions focus on barriers and resistances. Homework includes entering specified activities into MSS.

2) Goal Planning: While the original MSS calendar system included a section for a 'to do' list, it did not incorporate formalized curriculum on goal planning and management. This second compensatory/support component encompasses training in identifying short- and long-term goals, planning and prioritizing steps to accomplish goals, breaking goals into manageable, sequential steps, writing them down in the MSS journal section and transferring steps to their daily 'to do' section of the MSS. Individualized goal-setting serves to motivate participants and enhances a sense of purpose is important to well-being. It increases productivity and provides a "behavioral contract." Class discussion/homework subdivides goals and uses the daily 'to do' list.

3) *Organization Systems for the Environment.* This final compensatory/support component focuses on structuring and organizing the environment to maximize effectively and efficiently accomplish of daily tasks. One's physical environment and life space is parsed into 'functional zones' associated with specific daily activities (e.g., home office, kitchen, gym bag). Discussion includes the benefits of well-organized zones (e.g., find things easily so saves time), identifying one's own functional zones, and developing a plan for better organization of selected zones by participants. Homework focuses on reorganizing personal functional zones.

Training in healthy lifestyle engagement: A novel aspect of this intervention is the use of compensation strategies in adopting brain-healthy lifestyles. For example, participants set goals related to these activities (incorporated into Goal Planning) and utilize the MSS 'to do' list or schedule activities at a specific time, and use organizational strategies to help support and sustain these activities .

1) *Physical exercise*: Psychoeducation is provided about the impact of regular aerobic exercise on cognitive/brain health and participants are taught how to monitor heart rate. Rather than prescribing a strictly standardized exercise regime, participants develop an individualized physical activity plan. A list of specific options of physical activities is provided and discussed. Group classes involve discussion of barriers to exercise and solutions for overcoming those barriers. For homework, participants engage in physical activities at least 150 minutes per week. Physical activities are scheduled into one's calendar or included in the 'to do' list in order to assist with pre-planning and committing to an exercise routine.

2) *Cognitive stimulation*: Psychoeducation is provided on the benefits of cognitive stimulation. Emphasis is placed on engaging in activities that require novelty, challenge, speed, and sustained processing. Participants will start with a one month subscription to BrainHQ an adaptive computerized cognitive training program utilized in prior research in cognitive aging. In addition, a list of cognitive activity options is provided and participants identify an individualized set of activities to engage in each week. Group classes involved discussion of barriers to exercise and solutions for overcoming those barriers. As homework, participants engage in stimulating activities at least 150 minutes per week. Cognitive activities are also scheduled into one's calendar or included in their regular to do list in order to assist with planning and committing to regular engagement in mentally stimulating activities.
3) *Stress management*: Information is provided on the contribution of depression, anxiety, and other forms of emotional distress to reduced brain health, as well as education on the physiological stress response. Stress management focuses primarily on the use of various meditative and mindfulness practices, in particular sitting mediation, mindful movement, and the body scan which have been previously found particularly feasible to implement. As homework, participants will engage in meditative practices or mindfulness exercises at least 4x/wk for at least 15 minutes at a time. Meditation or mindfulness exercises are also scheduled into one's calendar or 'to do' list to facilitate planning and committing to regular engagement in this activity.

Outcome measurements.
Aim 1. Program **acceptability** metrics:
a) Enrollment: Percentage of eligible participants invited to participate who consent and enroll in the intervention will be tracked. We will also track reasons for declining to participate via a structured decline script utilized in our prior trials (Locke et al enrollment paper).
b) Satisfaction Survey: Likert scale ratings of each program component (not helpful to extremely helpful).

Aim 2. Program **adherence** Metrics:
a) Class attendance: Total number of classes attended.
b) Program completion: The percent of participants completing the majority (>50%) of classes.
c) Homework completion: A quantitative Adherence Assessment rating (see Appendix C) was developed for this study based on previously described methods[10, 11]. It measures specific, operationalized target behaviors associated with each training module (e.g., verification of specific calendar and 'to do' entries, development of goals that are transferred to 'to do' list; implementation of functional zones, participation in physical, cognitive and meditative activities (including how many times/week activity was completed and length of time in minutes)). The Adherence Assessment will be collected from the participant by a research assistant at each session. Data will coded as rate (%) of homework completed each week from which a summative score across the different program components will be calculated.

Aim 3. Program **efficacy** Metrics:
Both primary and secondary outcomes will be collected prior to the 10-week intervention, immediately after its completion, and at 3 and 6 months post intervention. Other data collected will include demographics (sex, age, education, race/ethnicity). Potential sex differences will be examined.

Primary outcomes:
Compensation metric: The Everyday Compensation Questionnaire (EComp;[38]) will be collected both from participants and an informant when available. It measures various types of compensation strategies used when completing specific activities of daily living that are taught as part of the EMS System (e.g., keeping a calendar on one's person at all times, using a calendar to track appointments, keeping home office organized, preparing ahead for an event, using an organized system for medications). The EComp has good reliability (e.g., Cronbach's alpha = .91) and it is related to objective measures of cognition and higher compensation is related to better everyday function.
Cognitive activity ratings: The Lifestyle Activities Questionnaire (LAQ, Carlson) will be completed by participants. The LAQ is a 23-item questionnaire measuring frequency of participation in cognitively stimulating activity (e.g., reading, playing games of skill, visiting museums. In addition, number of minutes the participant continues use of BrainHQ will be tracked after this module and post-intervention will be tracked via the BrainHQ portal.
Physical activity ratings: A 41-item Physical Activity (PA) Questionnaire will be completed by participants to capture self-reported lifestyle PA[42, 43]. Participants list frequency and duration spent weekly in each activity.

Each of the 41 items has an assigned metabolic equivalent of task (MET;[44]). Moderate activities are classified as MET value _3.0 to <6.0, and vigorous activities are classified as MET _ 6.0. PA variables include the number of minute per week in light PA, moderate–vigorous PA, and total PA.
Mindfulness: The Mindful Attention Awareness Scale (MAAS;[45]) will be completed by participants. The MAAS is a 15 item measure of mindfulness where higher scores indicated more mindfulness.

Secondary outcomes
Everyday function: When an informant is available, the Everyday Cognition (ECog; [46]) will be used to measure functional abilities across six cognitively relevant domains: everyday memory, language, visuospatial abilities, planning, organization, and divided attention. A total and domain scores can be calculated. The ECog has been extensively validated and correlates highly with objective cognitive test scores, performance-based measures of function and biomarkers of disease. Test-retest reliability over an average of 29 days is good (r = 0.82).
Quality of Life: Quality of life will be measured using the Quality of Life AD (QOL-AD) scale (Logsdon).
Sense of Purpose: Assessed using Ryff's scale of Psychological well-being[50].
Depression: The participant will complete the Centers for Epidemiological Studies-Depression measure (CESD)[51].
Anxiety: The participant will complete the Anxiety Inventory Form (AIF), a 10-item rating scale modified from the State-Trait Anxiety Inventory by the Resources for Enhancing Alzheimer's Caregiver Health (REACH) project[52].
Cognition: Memory will be measured using the Hopkins list learning[47], executive function using the Trail Making[48], Stroop and COWA (CFL), and psychomotor speed using Symbol Digits[49].

Durability of primary outcomes.
Each of the measures from the primary and secondary outcomes above will be collected at baseline (pre-treatment), treatment end, and 3 and 6 month follow-up assessment to evaluate whether behavioral changes and treatment effects are sustained over time.

Measures	Consent & Eligibility Visit	Baseline Visit	Treatment visits	End of Treatment Visit	3 months	6 months
MoCA	x					
IADL	x					
CES-D	x	x		x	x	x
Decline script (if relevant)	x					
Satisfaction survey				x		
Number of classes				x		
Homework completion			x			
Ecomp		x		x	x	x
LAQ		x		x	x	x
PA		x		x	x	x
MASS		x		x	x	x
Ecog		x		x	x	x
QOL		x		x	x	x
Ryff's Well Being		x		x	x	x
AIF		x		x	x	x
HVLT		x		x	x	x
Trails		x		x	x	x
Stroop		x		x	x	x
Verbal fluency		x		x	x	x
Symbol Digit		x		x	x	x

Data Analysis Plan.

Aim 1. Assess the intervention acceptability. We will summarize the percent of invitees who chose to enroll in the class as well as reasons for decline. Descriptive summaries, including means, standard deviations, and quartiles will be obtained for the quantitative satisfaction ratings across participants in the program.
Aim 2. Assess intervention adherence. We will summarize the percent of classes attended, percent of participants who completed 50% and 80% of classes, the percent of weekly homework assignments completed.
Aim 3. Assess intervention efficacy. Primary outcomes include ratings of compensation use (EComp), physical activity(PA), cognitive activity (LAQ), and stress management (MAAS). Secondary outcomes include everyday function, Cognition, QoL, depression, anxiety, and purpose in life.

Data will be collected and stored using REDCap. After baseline data is collected, eligible subjects will be randomized into the intervention group or the control group using stratified random sampling to ensure balance of pertinent characteristics including age, gender, and baseline cognitive performance. We will numerically summarize various aspects of the cohort including demographics, program acceptance, attrition, program adherence, and outcomes using appropriate summary statistics (means, standard deviations, medians, interquartile range, frequencies, percentages, etc.) We will use repeated measures ANOVA models to assess improvement in the primary and secondary outcomes form pre- to post-treatment and extended follow-up periods in the intervention group as compared to the education control. Non-parametric alternatives may be used if statistical assumptions are not met. Estimates with p-values < 0.05 will be considered statistically significant. All analyses will be conducted using statistically programs such as R and/or SAS by a biostatistician.