Study Protocol and Statistical Analysis Plan

Impact of Challenging Engagement on Cognition in Older Adults (engAGE)

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PROJECT SUMMARY:
IMPACT OF CHALLENGING ENGAGEMENT ON COGNITION IN OLDER ADULTS

Purpose.

Understanding what behaviors will support cognition into late adulthood has become a major public health issue as the baby boomer generation enters old age. At present, there are no effective drugs for Alzheimer's Disease (AD), and clinical drug trials continue to fail. However, the Alzheimer's Association estimated in 2015 that delaying the onset of symptoms by 5 years would reduce the rate of incidence by 50 percent. Hence, it has become increasingly urgent to investigate other avenues that might delay the onset of symptoms. It is widely believed that maintaining an active lifestyle is important for maintaining cognitive health with age. Current methods of measuring whether engagement is protective of cognition in late adulthood are largely based on observational studies. These types of studies, however, limit the isolation of cause-effect relationships and the identification of what aspect of engagement is driving the enhancement of cognition.

Scientific evidence that engagement is protective of cognition in late adulthood is largely based on observational studies. The use of observational studies, however, limits both the ability to isolate cause-effect relationships and to determine what aspect of engagement is driving the enhancement of cognition. In a previous study (the Active Interventions for the Aging Mind or AIM study – approved by UTSW IRB #072010-144), we developed an experimental design that allows us to infer causality that sustained engagement in mentally challenging activities enhances or maintains cognition in older adults. In Phase I of the original AIM study (conducted from 2008 to 2012), participants were placed in one of six conditions in which novice subjects learned to quilt, learned to use digital photography, learned a combination of the two, engaged in social activities, engaged in workbooks at home, or experienced no intervention. During their time in the intervention, participants spent five hours each week in structured courses with professional instructors engaging in their activity and an additional ten hours working on their skill with others and without instruction. Subjects who completed the behavioral testing and who, through screening, volunteered and were eligible to participate completed MRI imaging both pre- and post-intervention in which they completed two fMRI tasks. This AIM study found both the photography and quilting groups displayed significant benefits in their ability to remember personal events and episodic memory when compared to the social and placebo group, the photography group experienced the most significant benefit to cognition, especially regarding memory functioning (Park et al., 2014). The photography and quilting engagement groups also experienced increased neural modulation (Park et al., 2014), which is correlated with more efficient use of neural resources – and less compensatory neural scaffolds – in older adults (McDonough et al., 2015).

We propose a study that would allow us to evaluate the effectiveness of engagement on cognitive function and determine whether mental effort is a contributing factor to changes in cognitive function. We plan to enroll 90 participants in the Impact of Challenging Engagement study and assign them to one of three groups: high-demand photography, moderate-demand photography, and active placebo. These initial groups will allow us to collect data and address the feasibility for converting the project into a full trial. Participants will engage in their different engagement conditions for 15 hours per week, based on successful results from the initial AIM study. In the Impact of Challenging Engagement study, we expect to expand on the results of the AIM study to determine if high-demand activities result in any observable brain changes when compared to moderate demand or placebo activities. Behavioral and neural measures of cognitive change will be assessed, providing considerable insight into mechanisms of change. Subjects will be characterized thoroughly in terms of behavioral tests of cognitive function, and a subset of subjects who meet neuroimaging criteria will undergo an fMRI procedure.

Background.

In the present study, we consider that cognitive engagement may lead to improved cognitive and neural function. In support of this hypothesis, Kempermann, Kuhn, and Gage (1998) demonstrated that old rats maintained in complex visual and play environments showed birth of new neurons in the hippocampus. Kobayashi, Ohashi, and Ando (2002) reported improved learning ability in rats exposed to an enriched environment, even in old age, and concluded, "These results show that aged animals still have appreciable plasticity in cognitive function and suggest that environmental stimulation could benefit aging humans as well." Kempermann, Gast, and Gage (2002) reported a similar effect and demonstrated that short-term exposure of rats to an enriched environment, even in old age, led to five-fold increase in hippocampal neurogenesis, as well as a decrease in age-related atrophy in the dentate gyrus. The authors make a direct link of their findings to human behavior and ask, "Could this plastic response be relevant for explaining the beneficial effects of leading an 'active life' on brain function?" There is strong evidence that intellectually challenging environments and physical activity impact favorably upon human cognition during late adulthood. For example, Schooler et al. (1999) reported that engagement in "substantively complex" work, which would require the development of new schemas and change of existing ones across the lifespan, predicted better intellectual functioning in old age than engagement in less challenging work, even after education and other related factors were controlled. Other evidence in support of the productive engagement hypothesis comes from the Maastricht Longitudinal Study. At the beginning of the study, none of the participants enrolled (aged 50 to 80) showed cognitive impairment, but three years later, 4% of those with low cognitively demanding jobs showed some cognitive

impairment, whereas only 1.5% of those with mentally demanding jobs were impaired (Bosma et al., 2003). Overall, we found 13 studies in the literature that assessed the impact of jobs that varied in demands on cognitive function. Of these 13 studies, all but one showed a positive impact on cognition, with more demanding work resulting in better cognitive function.

Next, we examined studies that assessed the impact of engaging in cognitively demanding activities such as reading, playing bridge, or doing crosswords puzzles. We found a total of 13 such studies. Of these, nine showed positive effects, either in terms of improved cognitive function measured in the laboratory or a delay in the onset of dementia. We note here that many of these activities are relatively low in their cognitive demands, such as playing games or even listening to the radio or watching television, and would qualify as forms of receptive engagement. Then, we isolated studies that involved the impact on cognitive function of engagement in a combination of both leisure and cognitive activities. Of these studies, all but one demonstrated an enhancement effect, suggesting that breadth of experiences may be important in supporting cognitive function. Finally, we found five studies that examined the impact of exclusively social engagement on cognition or incidence of dementia, and all of these showed a positive impact of social engagement on cognition. Our examination of the literature makes it clear that there is experimental evidence in animals that engaging environments result in enhanced neural structure and function in old age, while correlation studies of humans overwhelmingly indicate that productive engagement (and sometimes even receptive engagement) across the lifespan is related to higher cognitive function and resilience in the face of mild levels of brain disease.

The Impact of Challenging Engagement project is a bridge from the animal to the human data, as it provides a mechanism to create different types of engagement environments and to determine experimentally if such engagement enhances cognitive function.

Concise Summary of Project.

In the proposed research, we will enroll a total of 90 subjects over 16 weeks. Just as in the original AIM study (approved by UTSW IRB #072010-144), subjects will be randomly assigned to participate in one of 3 conditions with 30 subjects per group. Two of the groups involve active intellectual engagement. In these groups, novice subjects will engage in high-demand or moderate-demand photography in five hours of structured courses with professional instructors for each of the 16 weeks. Subjects will also be required to put in an additional investment of 10 hours each working on a project to which they can apply their learned skills. Subjects are expected to be working on their projects for a total of 210 hours of engagement over the 16 weeks. We will measure pre/post change in multiple measures of cognitive and neural function, affect, and activity over the 16 weeks, and contrast change with one control group. The control group, the Placebo Control, will engage alone at home in tasks that are relatively low in intellectual engagement such as listening to music and radio or completing work-books that rely primarily on activation of knowledge. Preliminary data collected at the University of Illinois has indicated that volunteers willingly engage in a similar program.

Study Procedures.

This study takes place over 16 weeks and is broken down into pre-testing (weeks 1-2), intervention (weeks 3-16), and post-testing (weeks 15-16).

Participant Recruitment

90 subjects will be recruited to participate in this study that lasts 16 weeks. Subjects will participate in one of 3 conditions with 30 subjects per group. Two of the groups involve active intellectual engagement. In these groups, novice subjects will engage in high-demand or moderate-demand photography in five hours of structured courses with professional instructors for each of the intervention weeks. The third group consists of an active placebo group that will engage in cognitively demanding activities at home (like completing crosswords and listening to music).

Pre-Intervention Testing (Weeks 1-2)

Cognitive Battery: Participants will complete consent forms, vision screening, and cognitive tasks including assessment for episodic memory, executive function, inductive reasoning, working memory, verbal fluency, speed of processing, and crystallized intelligence. The cognitive session will last around 3 hours in total. Details of the cognitive battery participants will complete during this period can be found in Appendix A.

Take-Home Questionnaires: Self-reported questionnaires are completed by the participants on their own by logging into our website. Login information will be e-mailed to participants immediately following the pre-test cognitive battery. Participants may log in and out to complete the questionnaires at their own pace, but if they choose to complete all questionnaires in one sitting, it will take approximately 160 minutes in total. See Appendix A for the list and description of the questionnaires.

Neuroimaging: Participants who meet the MRI screening requirements will be given the option of completing the MRI battery. MRI scanning will last approximately 75 minutes and include both structural and functional scans. Details of the MRI scans can be found in Appendix A.

Intervention (Weeks 3-16)
Subjects will be pseudo-randomly assigned to intervention groups (based on gender and education criteria and the needs of the study) and then will participate for at most 14 weeks in the manipulation to which they were assigned. All will be told that there are numerous studies in the literature suggesting that the condition to which they were assigned is a form of engagement that has been shown to improve cognition. This is true, as many correlational studies have shown that engagement in tasks as passive as watching television is related to better cognition. All subjects will be required to agree to participate in any of the three conditions so that no condition will be biased. They will be novices at the use of the digital camera and will have had only minimal experience with computers, , or digital photography. Subjects who use traditional cameras will be permitted to enroll.

Productive Engagement Groups. (High-Demand and Moderate-Demand Photography) Sixty total participants will be assigned to one of the productive engagement groups (with thirty participants in each group): high-demand photography, and moderate-demand photography. Before the intervention begins, subjects will be provided equipment appropriate to their intervention for them to loan throughout the 12- to 14-week intervention. Participants in either of the photography groups will be supplied digital cameras. These 30 participants in each group may be separated further into smaller sections based on instructor availability in order to take advantage of smaller class sizes.

Each group will meet for 2.5 hours twice a week (5 hours per week total) at the research site. During this time, subjects will be stepped through a detailed curriculum by professional instructors, and those who learn techniques quickly will be pushed along so that maximum new learning occurs for each subject. Additionally, all subjects will be required to spend an additional 10 hours working on a special project at the research site without any formal instruction. This project is meant to provide participants with an opportunity to apply their skills to a task as they are learning. The high-demand photography group will learn similar skills as the moderate-demand photography group, but will learn them at a significantly quicker pace and, therefore, will learn more skills by the end of the intervention than the moderate-demand group.

Based on our experience, we find that the final week of the interventions can be very busy and that some subjects experience somewhat lower affect in the last week due to their regrets that the class is ending. To ease this problem, we offer all subjects the opportunity to continue to work for at least two more weeks after the formal 12-week class is over, and subjects are paid sufficiently well to allow them to purchase a camera, should they desire to continue their work. Additionally, many subjects make plans for continued social relationships among group members.

At-Home Engagement Group (Placebo Control). Thirty subjects will be assigned to this group. Each participant will be given a personal DVD player, if they do not have one already, to borrow while they are enrolled in the study. Each week, subjects will come to the lab to maintain contact with the researchers and receive a new set of materials to work on that week. Subjects will be supplied with a range of stimulating activities to complete each week at home.

Subjects will have five hours of required activities each week and will select an additional 10 hours of activities of their choice from a provided list. For the five required hours, subjects will (1) watch 1 hour of humorous programming, (2) watch 1 hour of educational programming, (3) read 1 hour of an educational magazine, (4) listen to 1 hour of classical or world music, and (5) complete 1 hour of puzzle games that rely on activation of existing knowledge (such as crossword puzzles or handheld games). Subjects will then select the additional ten hours of activities which include (1) 2 hours of watching humorous programming of their choice, (2) 2 hours of watching educational programming and reading educational material, (3) 2 hours of listening to music CDs, (4) 2 hours of completing paper and pencil or handheld games, and (5) 2 hours of watching classical programming of their choice including Oscar-winning movies and movie classics. All participants will answer simple questions about the amount of time they spent on each task, how well they liked each task, and how it made them feel, including questions about whether it made them feel more alert.

Subject Diaries. Subjects from all three groups will keep detailed diaries of their behaviors over weeks 3 through 14, describing not only how much time they spend on the project activities, but also the time spent on outside activities. The instructors/group leaders will also complete weekly assessments of subjects' level of engagement and activity level.

Mid-Intervention Cognitive Behavioral Battery: (Weeks 8-9)
Mid-way through the intervention period, participants will be asked to complete the cognitive battery again (found in full in Appendix A). This will help with statistical analysis, specifically growth curve analysis.

Post-Intervention Test (Weeks 15-16)
In the final two-weeks, participants will repeat their cognitive testing and take-home questionnaires. In addition, if they had an MRI session at pre-test, subjects will be asked to repeat the neuroimaging portion of the study as well.

Subject Compensation

All subjects will be compensated $75 each time they complete the behavioral testing (pre-testing, mid-testing, and post-testing) for a cognitive testing total of $225. Subjects will receive $50 compensation for completing the take-home questionnaire at pre-test and an additional $50 for completing the take-home questionnaires at post-test ($100 total). Subjects who are eligible and complete an MRI session will also be compensated $100 for each MRI scan session completed (pre-test and post-test) for an MRI scanning total of $200. Subjects will be compensated an additional $75 if they complete all 3 months of the study. If subjects complete all possible sessions in the study, they will be compensated $600.

Criteria for the Inclusion of Participants.

- Participants must be adults between 60 and 90 years old.
- At least 35% of participants will be men, and at least 15% will be minorities.
- 10th grade education or higher is required
- Fluent in English
- ADAS-COG score of zero (a perfect score).
- A score of 18 or higher on the Barthel Index of Daily Functioning.
- Right-handed for MRI scanning.

Criteria for the Exclusion of Participants.

- MMSE score lower than 27*
- TICS score lower than 27
- Depression based on CESD screening (a score of 27 or greater)
- Major psychiatric or neurological disorder
- Chemotherapy presently or in past year
- Coronary bypass presently or in past year
- History of major substance abuse
- History of central nervous system disease or brain injury
- Corrected vision poorer than 20/40 on Snellen Eye Chart after correction
- Recreational drug use in past six months
- Conditions which would contra-indicate MRI: Prior surgeries and/or implant of pacemakers, pacemaker wires, artificial heart valve, brain aneurysm surgery, middle ear implant, non-removable hearing aid or jewelry, braces or extensive dental work, cataract surgery or lens implant, implanted mechanical or electrical device, artificial limb or joint; foreign metallic objects in the body such as bullets, BB's, shrapnel, or metalwork fragments; pregnancy, vertigo, claustraphobia, left handedness, BMI > 35, uncontrollable shaking, or inability to lie still for one hour.
- More than minimal experience with photography during the last 12 years
- Work at a structured job/volunteer more than 10 hours per week
- Computer experience that involves more than internet surfing and email

- Use of electronic devices to shop, pay bills, bank, and perform other higher-order functions
- Extensive experience with digital photography or post processing photo programs

These exclusion criteria omit individuals who do not possess sufficient skills or health to contribute useful data to the study. Individuals must meet some (relatively low) cognitive criterion to be able to complete the cognitive tasks. Individuals who are in extremely poor health (either physical or psychiatric) will not have sufficient resources to participate in the sustained nature of this resource. The exclusion criteria regarding past experience in digital photography, or sustained computer work are required so that participants are novices on the to-be-trained skills and the effects of sustained intellectual engagement can be assessed.

*There is evidence in the literature that an MMSE score of 18 or greater provides participants with sufficient capacity for informed consent (Gregory et al., 2007). In an abundance of caution, we will exclude anyone from the study who does not have an MMSE over 26, eight points higher than that recommended in Gregory et al. (2007), in order to ensure that all participants are capable of giving consent. The MMSE will be used for screening criteria for all participants, given before the cognitive and psychosocial testing begin, in order to ensure participants are able to consent to the study.

Sources of Research Material.

Information collected in the study from subjects and responses provided by subjects will be used for research. No materials will be used from medical records or other medical data. All data is obtained exclusively for research purposes. All data will be stored on a password protected, HIPAA-secure server in the PI's lab at the Center for Vital Longevity. All

data files, both behavioral and neuroimaging, will be coded by numbers, with no linkage to subject identity except via a password-protected file that is not directly linked to the data files.

Recruitment of Subjects.

Subjects will be recruited through radio ads and flyers distributed throughout the community. The advertisements will direct potential participants to sign up either through our website (utdengage.com) or via phone.

For website signup: Participants will complete an initial screening form. Research staff will follow up with all participants within 48 hours/2 business days – for those who are not eligible based on the screening, an email will be sent to participants informing them as such. For those participants who may be eligible based on the initial screening, they will receive a phone call from a member of research staff with a second brief screening questionnaire for eligibility (the Telephone Interview for Cognitive Status (TICS)), as well as provided with upcoming dates for informational meetings. They will also be invited to fill out the enrollment form online or via email.

For phone signup: Participants will call in and receive the initial screening form over the phone. For those who are deemed ineligible based on this screening, participants will be informed immediately. For those who may be eligible, research staff will inform participants that they will receive a second phonecall within 48 hours/2 business days for a potential second screening. At this second screening, participants will be administered the TICS screening, and be given information about upcoming informational meetings. They will also be invited to fill out the enrollment form, either online or via email. Interested individuals will attend the informational meetings and learn about the logistics of the study, the time commitment, randomization of group assignment, compensation and criteria for potential participants, as well the minimal risks associated with each condition. These meetings are meant to educate a potential pool of participants who, after the meeting, may be screened and eligible to be enrolled in the study. The sustained nature of the commitment to the project will be explained to subjects. Those volunteers who meet the inclusion/exclusion criteria and are interested in participation after learning more will be provided with a detailed consent form by trained laboratory personnel. Written consent will be obtained. Additionally, individuals who participate in the behavioral portion of this study will also be screened for the MRI portion of the study. If subjects meet the MRI criteria, they may be invited to participate in an fMRI session, in addition to the behavioral component for which they have already qualified.

Potential Risks.

Behavioral Testing. There is minimal risk associated with the cognitive/psychosocial tests, but subjects may feel emotionally distressed if they perceive their performance is not satisfactory.

Intervention. Subjects in the interventions will experience risks that are no more than a person is faced with on a daily basis, and subjects are monitored at all times. There is also the risk of lower affect and disappointment as the engagement manipulation ends.

MRI. MRI scanning involves the use of magnetic and radio frequency energy. Therefore, participants with the following metal permanently attached to or with their bodies will not be allowed to participate in the MRI session: permanent eyeliner or eyebrows; heart pacemaker, heart valve replacement, or aortic clips; metal fragments in the eyes, skin, or elsewhere in the body; brain clips or pieces of metal used in aneurysm surgery or intercranial bypass; venous umbrella; pieces of metal in the body resulting from work as a sheet-metal worker or welder; clips placed in an internal organ; prosthetic devices, such as middle ear, eye, joint, or penile implants; joint replacement; hearing aid that cannot be removed; neurostimulator; insulin pump; intrauterine device (IUD); shunts or stents; metal mesh or coil implants; metal plate, pin, screws, or wires, or any other metal implants. The technologist and investigators will screen the participants for such contraindicators.

Because of the strong magnetic field associated with the scanner, it is rare, but possible, that a metallic object could fly through the air toward the scanner and hit the subject. To reduce this risk, everyone in the vicinity of the magnet will remove all metal from their clothing or pockets.

There are no known risks or adverse effects resulting directly from exposure to magnetic fields and radio frequency energy used in this study. Some people experience nervousness from confinement in a tight space (claustrophobia). Also, the MR scanner produces tapping sounds during operation, which may reach very loud levels. To minimize any discomfort from this noise, the patient will be provided with disposable earplugs and headphones that suppress external noise levels but do not eliminate voice communication with the scanner operator. If the participant is unable to tolerate being in the scanner, we will stop the scan immediately.

Other risks of MRI, but that rarely occur: 1) Neurostimulation. In some cases, it is possible that the subject might experience neurostimulation effects, such as muscle twitches and tingling sensations, due to the rapid switching of

magnetic field gradients used in these examinations. There are no known risks associated with these effects; 2) Quench Hazard. The MR scanner uses liquid nitrogen and liquid helium. It is possible that the liquid nitrogen and helium will boil off rapidly and fill the magnet room with extremely cold dense gaseous nitrogen and helium, which can be dangerous if breathed for more than a few moments. The scanner operator will obviously detect this and immediately provide assistance to anyone inside the magnet room.

Although there is no evidence of any risk to pregnant women, we will exclude women who are pregnant or suspect they may be pregnant. Pregnancy is an exclusion.

We anticipate that the results of these studies will help in the overall understanding of cognitive function and may lead to improved treatment modalities for patients with cognitive deficits. The potential benefits anticipated in improved treatment and management of patients with memory disorders are expected to far outweigh the minimal risks associated with these studies. MRI examinations are generally considered non-invasive and the risks involved in this study are no more than the MRI scans routinely employed in clinical practice. Therefore, the risks of this study are minimal.

Special Precautions. The risks associated with specific study procedures will be thoroughly explained to participants. Written informed consent will be required before each session. To minimize the risk of anxiety during MR scans, participants will be in the scanner for a maximum of 90 minutes per session. We will make it clear to participants that they can stop the study and exit the scanner at any time. Participants will be checked multiple times for metal or other devices that could pose a danger in the MR environment. Also, participants will be given hearing protection during scanning. Reassurance will be provided as needed and they will be reminded that their continued participation in the study is completely voluntary.

Subject Safety and Data Monitoring.

To ensure study integrity and to reduce any risk to participants, study personnel will closely monitor: (1) the participant's study experience, (2) the actual versus target accrual rates, (3) participant attrition (e.g. withdrawals, dropouts), (4) patterns of adverse events and unanticipated events, (5) patterns of protocol deviations and violations, (6) study stopping points, and (7) changes in risks and benefits. Potential risks and discomforts will be prevented and/or minimized to the greatest extent possible using procedures such as the appropriate training of personnel, monitoring of personnel, withdrawal of subject upon evidence of difficulty or adverse event, and referral of participants for treatment, counseling, or other necessary follow-up in accordance to the guidelines mentioned above. The study records will be treated as private as the extent permitted by law. Reassurance will be provided as needed, and participants will be reminded that their continued participation in the study is completely voluntary.

Procedures to Maintain Confidentiality.

All data will be stored on a HIPAA-protected server. Only researchers associated with this study will have access to any personally identifying information, that is, contact information for each participant and MRI eligibility. This information will not be stored with the participant data. Each participant will be assigned a research code. The research code will be included with the contact information and the participant's data. The researcher will destroy the personal identifiers upon completion of data collection for the study.

The cognitive and neuroimaging data are stored at the Center for Vital Longevity at 1600 Viceroy Dr., Dallas, TX. The Center for Vital Longevity has security personnel who work 24 hours, Monday to Sunday. The site is secured by keyed entry doors only accessible by employees of the Center. Paper data are stored in a locked room at the Center for Vital Longevity that is only accessible by study personnel. Electronic data are stored in a central server located at the Center for Vital Longevity. The data are accessed by a password-protected, secure database. Study personnel has personalized password access to this database maintained by central IT personnel. All information obtained that can be identified with an individual subject will remain confidential and will be disclosed only with a subject's permission. All data collected will be coded with an experiment and subject-specific code to maintain confidentiality. Only the members of the research team will be able to access to this coding information. In addition, accessibility to the research data will be restricted to the investigators and staff members involved in this project. Paper records of experiments and copies of executed consent forms will be locked in the cabinets in the PI's laboratories.

Potential Benefits.

Subjects receive a direct benefit from participating in this study if they are in any of the engagement conditions, as they will receive instruction in a complex task that has the potential to be a form of lifetime engagement and much pleasure at no cost. Subjects also have the explicit opportunity to increase their social network.

Risk/Benefit Assessment.

The benefits of the participation far exceed the risks. The subjects have the potential to personally improve their quality of life from participation. Moreover, the gains to determining that meaningful work and play in late adulthood is a critical way to maintain one's cognitive health will affect social and public policy as well as retirement decisions. This work has the potential to make a high impact contribution to affecting the goals and activities individuals pursue in late adulthood.

Appendix A.

Descriptions of Research Plan Tasks

Descriptions of all aforementioned (I) behavioral and (II) take-home questionnaires, as well as (III) MRI components are described in detail below.

I. Behavioral Component of Study.

Screening Tests:

Prior to being tested on the cognitive battery, participants will be screened with the tools listed below

Mini Mental State Exam (MMSE)
Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98.

- 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment.
- Commonly used in medicine and allied health to screen for dementia.

ADAS-COG
Skinner, J., Carvalho, J. O., Potter, G. G., Thames, A., Zelinski, E., Crane, P. K., & Gibbons, L. E. (2012). The Alzheimer’s Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. *Brain Imaging and Behavior*, *6*(4), 10.1007/s11682–012–9166–3. http://doi.org/10.1007/s11682-012-9166-3

- The ADAS-Cog was developed as an outcome measure for dementia interventions; its primary purpose was to be an index of global cognition in response to antidementia therapies.
- The ADAS-Cog assesses multiple cognitive domains including memory, language, praxis, and orientation

Barthel Index of Daily Functioning
Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:61-65.
Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. Int Disabil Stud. 1988;10(2):61-63.

- Assess participants ability to perform basic everyday functions such as grooming, mobility, and feeding.
- 0 -20 score, with lower numbers indicating more disability.

Center for Epidemiologic Studies Depression Scale (CESD)
Radloff, L. S. (1977). The CES-D Scale. A self-report depression scale for research in the general population. Applied Psychological Measurement, 1(3), 385-401.

- Participants are asked how they felt or behaved during the past week.
- This questionnaire has 20 questions.
- Scores range from 0 to 60, with higher scores indicating more symptoms of depression.

Cognitive Tests:

The cognitive tests participants may complete are broken down by behavioral constructs below.

Episodic Memory
The construct of episodic memory measures the participant's ability to encode and retrieve verbal information tied to a specific context. The tests used to measure episodic memory are listed below.

Hopkins Verbal Learning Test
Brandt, J. "The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms." The Clinical Neuropsychologist 5.2 (1991): 125-142.

- Immediate: Participants memorize a semantically categorized list of 12 words that are read aloud by the experimenter at a rate of one word every 1.5 seconds. Immediately following the presentation, participants are asked to recall as many words from the list as they can.
  Delayed: After 20 minutes, participants are again asked to recall as many words as possible from the list.

Logical Memory
Wechsler D. WMS-R: Wechsler Memory Scale–Revised. San Antonio, TX: Psychological Corporation; 1987.

- Two short stories are orally presented. The participant is asked to recall each story from memory immediately after hearing it. The delayed condition assesses long-term narrative memory with free recall. The examinee is asked to recall both stories after about 30 min.
- The number of correct items and the number of correct themes recalled are used as the final scores.

Woodcock-Johnson Memory for names
Johnson, R.W. (1989). Woodcock-Johnson tests of achievement. DLM Teaching Resources

- Immediate recognition: "This auditory-visual paired-associate task is a subtest from Woodcock–Johnson Psychoeducational Battery, Revised (Woodcock and Johnson, 1989). During acquisition, the participant is asked to learn associations between an imaginary space creature and the creature's name. At test, the participant is shown a target creature and an array of nine additional creatures, and is asked to point to the target creature that the experimenter names. During this acquisition phase, corrections are given to incorrect responses. The level of difficulty increases progressively as the participants are required to remember the names of more space creatures" (Rodrigue & Raz, 2004).
- Delayed recognition: After a 20-minute delay, participants are given a surprise recognition test in which they must point to all the space creatures named by the experimenter.

NIH Auditory Verbal Learning Test
Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinsky CJ. NIH Toolbox for Assessment of Neurological and Behavioral Function. *Neurology.* 2013; 80:S1-S92.

- A word-list learning task in which 15 unrelated words are presented orally (via audio recording) over three consecutive learning trials1. After each presentation, the participant is asked to recall as many of the words as he/she can.

Verbal Recognition Memory
CantabEclipse (2007) http://www.cambridgecognition.com/academic/cantabsuite/tests

- Immediate: Participants memorize 12 words they read aloud from the computer screen one at a time. Immediately following the presentation of the word list, participants are asked to recall as many words as possible. Immediately following recall, participants complete a recognition test in which they make "old"/"new" judgments about a list of words, comprised of the 12 target words and 12 distracters.

Processing Speed
The construct measures the rapidity with which individuals make perceptual comparisons and is a fundamental building block of many cognitive processes. The tests used to measure processing speed are listed below.

WAIS Digit Symbol
Wechsler, D., 1997. WAIS-III administration and scoring manual The Psychological Corporation, San Antonio, TX.

- Participants are shown nine geometric symbols that are each assigned to a digit from 1 to 9. They are then presented with randomized digits and asked to draw the corresponding symbol below each digit as quickly as possible for 90 seconds.

WAIS Symbol Search
Wechsler, D., 1997. WAIS-III administration and scoring manual The Psychological Corporation, San Antonio, TX.

- The task requires the participant to determine whether target symbols (simple line drawings) appear in line of various simple symbols within 120 seconds.

WAIS Cancellation
Wechsler, D., 1997. WAIS-III administration and scoring manual The Psychological Corporation, San Antonio, TX.

- Participants scan a random sequence of shapes and crosses out target shapes within 45 seconds.

NIH Toolbox Pattern Comparison Processing Speed
Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinsky CJ. NIH Toolbox for Assessment of Neurological and Behavioral Function. *Neurology.* 2013; 80:S1-S92.

- This test measures speed of processing by asking participants to discern whether two side-by-side pictures are the same or not.
- Participants' raw score is the number of items correct in a 90-second period.
- The items are designed to be simple to most purely measure processing speed.

- The test overall takes approximately 3 minutes to administer.

Digit Comparison

Hedden, T., Park, D. C., Nisbett, R., Ji, LJ, Jing, Q., & Jiao, S. (2002). Cultural variation in verbal versus spatial neuropsychological function across the life span. Neuropsychology, 16, 65-73." Adapted from Letter Comparison Task of *Salthouse T. A., Babcock R. L. (1991). Decomposing adult age differences in working memory. Developmental Psychology, 27, 763-776.*

- Participants have 45 seconds to decide whether two strings of numbers, either 3, 6, or 9 digits in length, are the same or different.

Working Memory

The construct of working memory measures the ability of the participant to process, store, and update information in the service of complex cognitive skills. The tests used to measure working memory are listed below.

WMS Symbol Span

- The subject is briefly shown a series of abstract symbols on a page and then asked to select the symbols from an array of symbols, in the same order they were previously presented.

NIH Toolbox List Sorting Task

Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinsky CJ. NIH Toolbox for Assessment of Neurological and Behavioral Function. *Neurology.* 2013; 80:S1-S92.

- This test requires immediate recall and sequencing of different visually and orally presented stimuli.
- Pictures of different foods and animals are displayed with accompanying audio recording and written text (e.g., “elephant”), and the participant is asked to say the items back in size order from smallest to largest, first within a single dimension (either animals or foods, called 1-List) and then on 2 dimensions (foods, then animals, called 2-List).
- The score is equal to the number of items recalled and sequenced correctly, and the test takes approximately 7 minutes to administer.

Spatial Working Memory

CantabEclipse (2007) http://www.cambridgecognition.com/academic/cantabsuite/tests

- The objective of the task is to collect blue tokens that are hidden in an array of 3 to 8 boxes. Participants search through the boxes on the screen by touching each one so that it ‘opens up’ to reveal what is inside. The participant’s task is to remember where they find the tokens because once a token has been found in a box, that box will never contain another token for that set. Two kinds of errors can be made: if a participant returns to a box where they previously found a token during the same search trial (between search error) or if a participant returns to a box already open and shown to be empty earlier in the same search sequence (within search error).

Reasoning

The construct of reasoning measures the participant's ability to recognize novel patterns and then utilize them appropriately to solve similar problems. The tests used to measure reasoning are listed below.

WAIS Figure Weights

Wechsler, D., 1997. WAIS-III administration and scoring manual The Psychological Corporation, San Antonio, TX.

- The participant is presented with a picture of a pair of scales in which there are missing weights, and they have to choose the correct weights to keep the scales in balance.

WAIS Visual Puzzles

Wechsler, D., 1997. WAIS-III administration and scoring manual The Psychological Corporation, San Antonio, TX.

- The individual is shown a pattern and has to choose three possible parts to make up that pattern.

Raven’s Progressive Matrices

Raven, J., Raven, J. C., & Court, J. H. (1998a). Manual for Raven’s Progressive Matrices and Vocabulary Scales. Section 1: General Overview. San Antonio, TX: Harcourt Assessment.

- Participants are presented with visual patterns that have one piece missing and must determine which pattern out of 6 or 8 options is required to complete that visual pattern. Problems are divided into four sets of six items arranged by increasing difficulty.
- Participants are given 15 minutes to complete 24 problems.

Stockings of Cambridge
CantabEclipse (2007) http://www.cambridgecognition.com/academic/cantabsuite/tests

- Stockings of Cambridge is a computerized version of Tower of London (Shallice 1982) in which participants are shown a split screen with two displays each containing three colored balls. The balls are arranged in such a way that they look like they are stacked in stockings hanging from a beam. Participants must move the balls in the bottom arrangement one at a time in order to match the top arrangement in as few moves as possible.

Crystallized Knowledge
The construct of crystallized intelligence provides estimation about the participant's world knowledge or vocabulary-based knowledge. The tests used to measure crystallized knowledge are listed below.

WAIS Similarity
Wechsler D. Wechsler adult intelligence scale-Fourth Edition (WAIS-IV). San Antonio: NCS Pearson; 2008.

- The participant is presented with two words and asked how they are alike, for example, they may be asked how a peach and an apple are alike.

WAIS Vocabulary
Wechsler D. Wechsler adult intelligence scale-Fourth Edition (WAIS-IV). San Antonio: NCS Pearson; 2008.

- The individual is presented with words and is asked to define them.

WAIS Information
Wechsler D. Wechsler adult intelligence scale-Fourth Edition (WAIS-IV). San Antonio: NCS Pearson; 2008.

- The participant is given a series of general knowledge questions, such as: How far is it from London to Paris?

NIH Toolbox Picture Vocabulary
Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinsky CJ. NIH Toolbox for Assessment of Neurological and Behavioral Function. *Neurology.* 2013; 80:S1-S92. doi: 10.1212/WNL.0b013e3182872e90.

- This measure of receptive vocabulary is administered in a computerized adaptive format.
- The respondent is presented with an audio recording of a word and four photographic images on the computer screen and is asked to select the picture that most closely matches the meaning of the word.

Graded Naming Task
CantabEclipse (2007) http://www.cambridgecognition.com/academic/cantabsuite/tests

- Thirty line drawings are presented on a computer screen, one at a time, with increasing difficulty. Participants must identify the exact name of each drawing (e.g., kangaroo, bellows).
- This task is not timed.

II. Take-Home Questionnaires

The take-home questionnaires participants will complete are listed below in alphabetical order.

Activities Questionnaire
Hultsch, D.F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999). Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? Psychology and Aging, 14(2), 245-263.

- Participants are asked how often they had participated in the activities that follow within the last six months. Participants select the response from: a). Never; b). Less than once every 6 months; c). Once every 6 months; d). 2 or 3 times every 6 months; e). Once a month; f). 2 or 3 once a month; g). Once a week; h). 2 or 3 times a week, i). Daily.

AIRC Survey
No Official Citation

- A 2-page survey developed to determine if it is safe for participants to undergo an MRI Scan at the Advanced Imaging Research Center with UTSW.

Basic Information (Including Education)
Self-developed

- Participants are asked for basic demographic information.
- This questionnaire has 39 questions concerning:
- Live Alone/Housing Status
- Marital Status
- Education
- Date of Birth
- Gender
- Occupation
- Native Language/Bilingualism
- Birth Country

Busyness and Routines
Martin, M. & Park, D. C. (2003). The Martin and Park Environmental Demands (MPED) Questionnaire: Psychometric properties of a brief instrument to measure self-reported environmental demands. Aging Clinical and Experimental Research, 15(1), 77-82.

- Participants are asked for their views about their daily busyness and routines.
- The original published questionnaire had 11 questions: 7 items for busyness and 4 items for routines. The DLBS questionnaire includes two additional questions relating to forgetfulness.

Fitness Survey
Revised version based on Youth Risk Behavior Surveillance System (YRBSS) 1999.

- Participants are asked about their daily fitness activities.
- This questionnaire has 9 questions.

Geriatric Depression Scale (Feelings Survey)
Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. Journal of Psychiatric Research, 17(1), 37-49.
Yesavage, J. A., & Sheikh, J. I. (1986). Geriatric Depression Scale (GDS) recent evidence and development of a shorter violence. Clinical Gerontologist, 5(1-2), 165-173.

- Participants are asked for their views about their moods.
- This questionnaire has 21 questions. Note that the original has 30 questions and our version is the first 21. But this is not the "official" short form which only has 15 questions, 2 of which are not included in our version.
- A higher score represents greater depressive symptoms.
- In the 30-item scale, a score of 11 to 20 represents mild depression and 21 to 30 represents moderate to severe depression.
- Because this is not the official 30 or 15 item scale, this cannot be used to classify depressed participants

Health Survey
No official citation.

- Participants are asked about their health.
- This questionnaire has 17 questions for female and 15 questions for male participants.

Lifetime Cognitive Activities
Wilson, R., Barnes, L., & Bennett, D. (2003). Assessment of lifetime participation in cognitively stimulating activities. Journal of Clinical and Experimental Neuropsychology, 25(5), 634-642.

- Participants are asked about the frequency with which they participated in cognitively stimulating activities in the past and present. Each set of questions refers to a time period in their life.

Metamemory in Adulthood (Memory Questionnaire)
Dixon, R. A., Hultsch, D. F., & Hertzog, C. (1987). The Metamemory in Adulthood (MIA) questionnaire. Psychopharmacology bulletin, 24(4), 671-688.

- Participants are asked to indicate how they use their memory and how they feel about it.

- This questionnaire has 108 questions.

Need for Cognition Survey (NFC)
Cacioppo, J. T., Petty, R. E., & Kao, C. F. (1984). The efficient assessment of need for cognition. Journal of Personality Assessment, 48(3), 306-307.

- Need for cognition is operationalized as "the tendency for an individual to engage in and enjoy thinking."
- Participants are asked to indicate for each statement whether or not it is characteristic of them.
- This questionnaire has 18 questions.

Psychological Well-being (SWQ; Perception)
Ryff, C. D. (1989). Happiness is everything, or is it? Explorations on the meaning of psychological well-being. Journal of Personality and Social Psychology, 57(6), 1069-1081.

- Participants are asked for their views about themselves.
- This questionnaire has 84 questions.

Satisfaction with Life Scale (Self-Reflection Survey)
Diener, E., Emmons, R. A., Larsen, R. J., & Griffin, S. (1985). The Satisfaction With Life Scale. Journal of Personality Assessment, 49(1), 71-75.

- Participants are asked for their views about their life.
- This questionnaire has 5 questions.

Scale of Positive and Negative Experience (SPANE; Emotional Experience Scale)
Diener, E., Wirtz, D., Tov, W., Kim-Prieto, C., Choi, DW, Oishi, S., & Biswas-Diener, R. (2009). New Well-being Measures: Short Scales to Assess Flourishing and Positive and Negative Feelings. Social Indicator Research, 97(2), 143-156.

- Participants are asked about what they have been doing and experiencing during the past four weeks.
- This questionnaire has 12 questions.
- Produces a score for positive feelings (6 items), a score for negative feelings (6 items), and the two can be combined to create a balance score.

Self-Concept Clarity (SCC) Survey
Campbell, J. D., Trapnell, P. D., Heine, S. J., Katz, I. M., Lavallee, L. F., & Lehman, D. R. (1996). Self-concept clarity: Measurement, personality correlates, and cultural boundaries. Journal of Personality and Social Psychology, 70(1), 141-156.

- Participants are asked for their views about phrases describing their behaviors. They are asked to describe themselves as they generally are now, not as they wish to be in the future.
- The original scale in Campbell et al (1996) had 12 questions.

SF-36v2
Ware, J. E., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2008). User's manual for the SF-36v2 Health Survey. Quality Metric.

- Participants completed 36 questions to measure functional health and well-being including domains of Physical Functioning, Role Limitations due to Physical Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems, Mental Health and Reported Health Transition.

SES
Adler, N. E., Epel, E. S., Castellazzo, G., & Ickovics, J. R. (2000). Relationship of subjective and objective social status with psychological and physiological functioning: Preliminary data in healthy, White women. Health psychology, 19(6), 586.

- Participants are asked for information about their socioeconomic status.
- This questionnaire has 16 questions.

SES-Childhood
Self-developed

- This questionnaire asks 5 questions about participants' SES as a child.

The HEAD Questionnaire
Self-developed

- This questionnaire asks participants to provide a detailed history of previous head injuries (specifically mild traumatic brain injury, also known as concussive head injury), as the DLBS does not currently have a measure of previous head injury that is administered to all participants.

III. MRI Neuroimaging Component of Study.

Functional Neuroimaging Component of Study. Prior to the scan, subjects will be familiarized with the tasks they will perform in the scanner and allowed to practice the tasks. Then they will be placed in the scanner and both structural and functional scans will be conducted. A summary of the tasks used are described below. Only those individuals who are deemed MRI-safe will be able to complete the MRI scan.

◊ *Word Encoding (8 minutes).* Subjects will encode concrete nouns in the scanner, at the rate of 3 seconds per word (2500ms presentation with a 500ms fixation). During this encoding phase, subjects will judge for each word whether it is a living or a nonliving entity and will indicate their choice with a button press. Half of the words used in the stimuli will be selected from the MRC Psycholinguistic Data Base (http://www.psy.uwa.edu.au.mrcdata-base/mrc.html), and the other half will be ambiguous words, like sponge, virus, or orange, that could be judged as living or nonliving. All words will be 4 to 8 letter nouns, with half nonliving things and half living. Each stimulus block will last 24 seconds and contain 8 stimulus trials. This task is one 8-minute run. After this task subjects will be asked outside of the scanner to rank the living or non-livingness of the words that they saw in the scanner so that we can create a normative sample of responses to these words.

◊ *Scene Encoding (18 minutes).* Subjects will encode a total of 96 color photographs of outdoor scenes interspersed with baseline trials consisting of a crosshair fixation. There will be three 6-minute runs. Pictures of outdoor scenes were selected from commercially available CDs of full-color photographs. As each picture is presented, participants will make a button press to indicate whether water is present in the scene (press “yes” if present, “no” if not). There will be 32 4-second picture trials in each of 3 runs interspersed with baseline trials ranging in length from 4 to 16 seconds, with additional 20-second baseline periods at the beginning and end of each run. Following the scanning, subjects will perform recognition judgment tasks assessing their memory for the scenes and words presented in the scanner.

◊ *Resting State Component (12 minutes*). Subject will see a fixation cross two times for six minutes each. We will ask them to relax and to keep their eyes open.

Structural Neuroimaging Component of Study. Because function is facilitated by the physical structure of the brain we will collect a variety of structural sequences, summarized below.

◊ *MPRAGE*. A high-resolution T1-weighted structural scan.

◊ *FLAIR*. (fluid-attenuated inversion recovery). A T2-weighted sequence specifically attuned to white matter lesions.

◊ *Diffusion Tensor Imaging* (DTI). This sequence measures the directionality of water diffusion, useful in assessing white matter integrity.

◊ *Measurement of Hippocampal Subfields.* We also will measure hippocampal subfields using a high resolution T2-weighted fast spin echo sequence will be used (TR = 8150 ms, TI = 50 ms, 0.4 x 0.4 mm in plane resolution, 2 mm slice thickness, 31 slices covering the anterior three quarters and in some cases the whole hippocampus.

Following the scanning, subjects will perform a task assessing their judgment of the ambiguousness of the words presented in the scanner.

Statistical Analysis Plan

Preliminary Analyses. In initial analyses, we will summarize categorical variables by proportions and continuous variables by means and quantiles. We will graph continuous variables and assess them for skewness, transforming if necessary (for example by logs or square roots) to render them more nearly normally distributed. We will explore relationships among variables by examining scatter plots and correlation matrices. We will conduct all analyses in R (version 3.3.2 or later) or SAS (version 9.4 or later).

Analysis of Primary Outcome Variables. The primary cognitive outcome endpoint will be a composite, scalar episodic memory score, as described in earlier research from the SYNAPSE project (5). This measure will exhibit substantial between-subject variability, in that subjects who give high scores at baseline are likely to give high scores at follow-up as well. To account for this, in primary analyses we will adjust for baseline levels by analysis of covariance — i.e., including baseline values together with treatment arm in a regression model for the post-treatment outcome. Alternatively (and equivalently), we can analyze the outcome variable in a mixed model, evaluating a treatment effect by estimating a time-by-treatment interaction. We will moreover conduct mixed-model analyses including the intermediate (6-week, mid-treatment) and long-term (1-year) values of the cognitive outcomes together with the end-of-treatment (12-week) outcome. As a secondary analysis to further elucidate the magnitude and timing of treatment effects, we will seek to create parsimonious models of this outcome as a function of time, treatment arm, stratification factors (center, age, sex, education) and potentially other factors measured at baseline. The primary brain outcome will be a vector measure of fMRI activation in four brain regions of interest, as described above and in previous work from SYNAPSE (7). This measure is also likely to exhibit substantial between-subject variability. We will again analyze the outcome variable in a mixed model, evaluating the treatment effect by estimating a time-by-treatment interaction, and conduct a secondary analysis where we model activation in the four regions as functions of time, treatment arm, stratification factors (center, age, sex, education) and potentially other factors measured at baseline.

Analyses of Secondary Outcomes.
Dose-response. We anticipate that there will be a dose-response relationship, with the control arms having the lowest values, high-engagement arms, the highest values, and moderate-engagement arms having values in between. We will construct mixed models to estimate the sizes of these effects, and to determine whether effects are linear or nonlinear in the degree of engagement.
Subgroup Analyses. We will conduct a number of analyses aimed at estimating treatment effects within strata of age (younger or older than age 72), gender (male or female), education (greater or less than 14 years), and center (Dallas or Hamburg). We expect each of these strata to comprise roughly half of the subjects, except that our sample will likely be 65% female, reflecting the sex imbalance in the elderly. We will replicate our main analyses in each of the stratum subgroups, and additionally test for interactions.
Incomplete data. A major concern in any follow-up study is that there will be substantial dropout, eroding trial power. As indicated above, we expect no more than 15% to 20% of subjects to fail to complete the followup evaluation schedule. This is not a large fraction of dropout, and we have provided for its effects on power in our sample-size calculations. A second concern is that dropouts may differ systematically from completers, potentially introducing bias into estimated treatment contrasts. Our primary approach to analysis is to use mixed models, which give correct results as long as the dropout mechanism is missing at random — i.e., the probability of dropout, given the potentially missing observation and all prior observed data, does not depend on the potentially missing observation. Moreover, as long as the dropout is roughly balanced between treatment arms, it is unlikely to have a substantial biasing effect on estimated treatment effects, even if the dropout mechanism is not missing at random. In any event, if dropout is excessive or is unbalanced between arms, or there is concern that it is not missing at random, we are prepared to conduct analyses for sensitivity to nonignorable (i.e., biasing) dropout using general methods that Dr. Heitjan has developed.

Latent Factor Modeling. As a further form of secondary analysis, we will analyze the cognitive outcome variables simultaneously using a latent-variable approach. With this method, one models the several cognitive variables at each measurement time as being statistically independent given an unobserved, subject-specific latent variable. One accommodates serial correlation within subjects by estimating correlation of the latent variable within subjects over time. The approach evaluates treatment and time effects by modeling the mean of the latent variable as a function of the predictors, and each subject's estimated latent trajectory serves as a summary of his outcome status. We will also apply such models to the four-variate fMRI primary outcome.

Neuroimaging Analyses. We will test for a Group x Time interaction on the primary measure of modulation capacity. For the large-scale brain network analyses, we will utilize measures of connectivity between major nodes within the networks as indicators to develop constructs for the executive fronto-parietal network, salience network, and default network at each interval of data collection. To measure increases in hippocampal volume, we will segment the left and right hippocampus into four regions of interest (subiculum, CA1 and CA2/CA3/CA4, dentate gyrus, and entorhinal cortex) for all individual high-resolution MRI images. This division into 4 regions of interest (ROI) will ensure sufficient reliability and reproducibility of the subfield distinctions. These ROIs will be entered into the same Group x Time ANOVA as in the fMRI analyses.