Title: Strategic Training to Optimize Neurocognitive Functions in Older Adults

Date: 2/20/2019

Protocol Synopsis

Brief Summary

We will conduct a parallel-arm, double-blind individually randomized control trial (RCT) in 30 healthy older adults, where attentional control demands in working memory training will be systematically increased using engaging game-based simulations. There are three parallel arms. The first two arms use experimenter-designed simulation games, where participants will be trained on either predictable low attentional control (Arm 1: Low-C) or unpredictable high attentional control (Arm 2: High-C) working memory games. The third arm uses a commercially-available strategy video game requiring highest level of attentional control (Arm 3: High-C+), by adding multi-tasking to the unpredictable attentional shifts in working memory. In all three training arms, neural and cognitive changes in both near and far tasks will be examined immediately after the 8-week long intervention. Long-term cognitive changes will also be assessed at 6 months after completion of training. The far and near cognitive domains that will be examined in this RCT are episodic memory (the primary cognitive outcome, and a marker of early stages of AD) and executive control (the secondary cognitive outcome). We expect that the high attentional control training arms will greatly improve both primary and secondary cognitive outcomes in older adults not only immediately after the training, but also at the +6-month period. We also expect cognitive frailty to interact with the extent to which attentional control is trained.

Additionally, a single-session, baseline functional neuroimaging data-set will be collected in a control group of 18 younger adults. These younger adults will not undergo any training. High attentional control training arms (High-C and High-C+) are also expected to heighten compensatory brain activation in older adults after intervention, for both episodic memory (primary outcome) and executive control (secondary outcome) in-scanner tasks, paralleling the baseline activity of younger brains. These high attentional control training arms are also expected to positively impact brain structures that progressively decline with aging. The data from younger adults, our functional control group, will provide critical information about the brain regions activated in young, healthy brains during episodic memory (far transfer) and executive functions (near transfer). It will also help us determine whether older adults' brain activity following training resembles that of younger brains.

The primary objectives of this double-blind RCT are to evaluate the efficacy of high attentional control training on episodic memory (primary cognitive outcome) in an older adult population, by evaluating a) immediate training-related

changes in performance and neural activation during episodic memory tasks, and b) long-term changes at a +6-month retention period in performance during episodic memory tasks. The secondary objective of this RCT is to evaluate the efficacy of high attentional control training on executive functions (secondary cognitive outcome) in an older adult population by evaluating neuro-cognitive changes in executive functions immediately after the training, and cognitive gains at +6-month retention period.

In order to achieve these objectives, cognitive measures of both primary and secondary outcomes will be collected in healthy older adults at before training (baseline), immediately after 8 weeks of training (immediate post-training), and 6 months after training completion. MRI scanning, including fMRI tasks of episodic memory (primary outcome) and executive functions (secondary outcome), will be conducted at baseline and at immediate post-training for older adults, and only once in younger adults.

Study timeline for Year 1

The first quarter of year 1 (that is, 0-3 months after the notice of the award) will include a study preparation phase, where we will finalize the study protocol, acquire and set-up the testing computers, tablets and licensed neurocognitive tests, advertise to recruit young and old participants, hire required personnel, and test the final versions of the games and the neurocognitive computerized tasks on the newly acquired computers and set up data safety protocols. In addition, data collection on 25 younger adults (the functional control group) and 26 older adults (10 Low-C; 10 High-C; 6 High-C+) will be completed within during this first year. This will provide us with some pilot data by the end of year 1 to establish that the clinical trial can be successfully conducted, and identify age-related differences in brain functions during the near and far transfer tasks by comparing baseline fMRI data of older adults to that of younger adults. Recruitment and enrollment of older adults for the clinical trial will begin in the third quarter of year 1 (that is, 6 months after notice of the award), after the clinical trial has been registered with clinicaltrials.gov.

Study Design

Overview. This parallel arm, individually randomized control trial (RCT) will recruit 34 older adults from Dallas and neighboring counties. We aim to retain at least 30 participants on whom immediate post-training gains in both *near* and *far* abilities can be observed. This RCT shall be registered at ClinicalTrials.gov. There will be a Clinical Coordination Team (co-directed by Dr. Fishwick and the Project Manager) that will implement the intervention and check in with the participants on a weekly basis regarding their training progress. A blinded data collection team, directed by a post-doctoral fellow, will collect both behavioral and neuroimaging assessments before and after training. There will also be

a Data Coordination Team (co-directed by Dr. Basak and a post-doctoral fellow) that will be responsible for scoring and preprocessing the data. All data will be deposited in a HIPAA compliant server at the PI's laboratory. The team leaders will meet twice a month and each team will meet weekly to oversee any issues with subject recruitment, logistics and data collection. We will also recruit a total of 20 younger adults (YA, 18-30 years of age) for neuroimaging, who will be the functional controls for the older adults in the RCT.

This is a Phase 1 trial with multiple interventions in older adults, where the goal is to compare high attentional control trainings (High-C and High-C+) to low attentional control training (Low-C) and evaluate training-related changes in neurocognitive functions of both near (secondary outcome) and far transfer (primary outcome) tasks.

Experimental Design. There are three intervention arms for older adults (*OA*) in this RCT trial, where attentional control demands in working memory training will be systematically increased using engaging game-based simulations. Arm 1: Low Attentional Control Group (Low-C). Low attentional control training using an n-back simulation game (*Birdwatch*), requiring predictable shifts of cued-attention. Arm 2: High Attentional Control Group (High-C). High attentional control training using the Birdwatch simulation game, requiring unpredictable shifts of cued-attention. Arm 3: Highest Attentional Control Group (High-C+). This arm uses a commercial strategy video game for training (*Sushi Chef*), rather than the experimenter-developed simulation games proposed in the other two arms. Additionally, a *comparison group of younger adults (YA)* will undergo pre-screening, mock scan, and MRI scan sessions (but no training). All older participants will undergo 3 behavioral assessment sessions, each lasting a maximum of 3.5 hours, in the PI's lab. These assessments will be conducted at baseline, immediately post-training and 6 months after completion of training. All older adults will also undergo 2 neuroimaging assessments, one at baseline, and another at immediate post-training. There will no more than 5-day difference between the MRI scan and the respective behavioral assessment at either baseline or at immediate post-training.

The training period will last for 19 h over 8 weeks, and will include both in-lab and at-home training on a device provided to the participant. All training will be administered individually to the participant, not in a group. Fig. 5 and Fig. 6 show the computerized games used in the three training arms.

Screening and Randomization. In this individually randomized trial, all interested participants will first be prescreened and will undergo a Mock Scan session to determine their eligibility to participate in the study. Participants will be consented to screening for eligibility. In order to exclude participants with memory-related disorders, primarily MCI and AD, participants will be required to have both a Mini-mental Status Examination (MMSE) score of 26 or greater, and a

Montreal Cognitive Assessment (MoCA) score of 24 or greater. A composite of these two standardized scores will comprise an index of *cognitive frailty*. The cutoff scores are conservative and should screen out most cases of MCI, although we acknowledge that some early stage MCI individuals could still be included. Additionally, brain scans will be screened by a neuroradiologist if a pathology is suspected.

If after the pre-screening and the Mock Scan sessions, a volunteer meets the inclusion and exclusion criteria, he or she will be randomized into one of the three training arms. This assignment will be based on a random computerized allocation plan, where the average cognitive frailty, age, education and gender distribution will be maintained to be equivalent across the three arms. By randomly assigning participants in the training arms and by assessing outcomes by blinded experimenters, we will avoid selection bias and outcome assessment bias. The power analyses for sample size justification, therefore, is for this individual randomized trial, where Type 1 and type II errors are defined, expected meaning difference between the experimental groups and Low-C are specified, and attrition is estimated at follow ups. The participant will need to be randomized to a training arm prior to any baseline assessments.

Minimizing Attrition and Enhancing Adherence. Attrition at follow ups will be minimized because in addition to the weekly in-lab training, there will be weekly at-home training where the participants can conduct the training from the comfort of their home during their preferred time on the device (Windows tablet) provided to them. Compliance for at-home sessions will be measured by the device's time stamp, which will be recorded every time the participant logs into the training program. Participants will also be provided with a diary to keep a log of their training schedule to enhance compliance. Moreover, participants will be encouraged to call researchers of the unblinded, training group with any questions about the game. The weekly in-lab testing will ensure that any difficulties participants may encounter during at-home training is resolved.

Sample Size Justification for the older adults in the RCT. We estimated the power (using G*power3.1[100]) to detect the differences between the Training Arm (3) x Assessment (2) interaction on the primary cognitive outcome. *The current study is the first phase of a larger randomized controlled trial. We calculate our power for the full trial, but our requested sample size for this study is 51*. We will recruit 177 older adults with the aim to retain a total sample size of 144 older adults at immediate post-training with the expected attrition of 18%. We report two expected effect sizes of Cohen's *f* for our calculations. One, *f*=.35, the minimum effect size obtained across our 3 pilot studies. Another, *f*=.16, based on a meta-analysis on computer-based cognitive training in older adults. The proposed total sample size of 144 older adults will provide us with >93% power to detect the Training Arm (3: Low-C, High-C, High-C+) x Assessment

(A vs. B) interaction at *f*=.16 and >98% power to detect the interaction at *f*=.35 on the primary cognitive outcome at *p*<.05. It will also provide > 90% power to detect a meaningful between-group difference (*f*=.35) at immediate post-testing, after controlling for baseline cognition, at *p*<.05. At +6mo retention period (Assessment C), we expect to retain a total of 117 older adults, after the expected ~20% attrition between Assessments B and C. This will provide us with >87% power to detect the Training Arm (3: Low-C, High-C, High-C+) x Assessment (2: A vs. C) interaction at *p*<.05 at *f*=.16. We will conduct 2 ANOVAs, one for primary and one for secondary. Our proposed sample size will provide us with sufficient power (>87%) to detect the Training Arm (3) x Assessment (2) interaction at a corrected *p* value of .025 (=.05/2 for 2 cognitive outcomes of interest).

Data Analysis Plan

All data will be initially tested for normality, outliers, and errors. We will then compute summary statistics and derive across-group statistical comparisons to identify any demographic variables, such as age, gender, education, or cognitive frailty, group differences after the randomization process. If group differences are detected for a variable, all analyses will include that variable as a covariate. We will also present primary and secondary outcome measures using descriptive statistics, summarize categorical variables using frequencies and proportions, and report descriptive statistics as medians and interquartile ranges.

Analyses of Primary and Secondary Cognitive Outcomes. Outcomes will be tested according to the intention-to-treat principle with analysis of variance, evaluating both the changes from baseline to the completion of training (immediate treatment effects) and the changes from baseline to +6mo after training (retention effects). All analyses will be conducted on the baseline-normed Blom transformed scores for each measure, an approach used in prior intervention research on older adults. Composite cognitive scores (for each cognitive outcome) will be formed by averaging these scores. Therefore, we shall conduct all statistical analyses on one composite cognitive score representing the primary outcome (episodic memory) and one composite score representing the secondary outcome. There will be, for both outcomes, three composite scores- one for each Assessment (A, B and C). Specific Aim 1 focuses on the increases in cognition between the three training arms at both immediate post-testing and +6mo period. Change scores for each composite score for each individual will first be plotted to evaluate the treatment-related cognitive benefits. We will then examine the composite scores for the primary outcome using repeated measures ANOVA, with Training Arms (3: Low-C, High-C, High-C+) as a between-subject factor and Assessment (2) as a within-subject factor, for both immediate post-training gains (Assessments A and B) and for long-term retention of these gains (Assessments A and C). Of main

interest is the interaction between the Training Arms and Assessments. To evaluate the extent of immediate post-test cognitive gains across the three training arms, we will conduct pairwise contrasts between High-C and High-C+. Similar analysis will be conducted for the secondary outcome. The two ANOVAs will be adjusted to $p<.025$ (=.05/2) to adjust for multiple comparisons.

Additional analyses will investigate how *cognitive frailty,* as measured by MOCA and MMSE, interacts with training difficulty (High-C vs. High-C+) and extent of transfer, because cognitively fit older adults show faster learning rates for complex skills and working memory. We predict that older adults with greater cognitively frailty will exhibit less cognitive plasticity and therefore will benefit most from moderate attentional control training (High-C), whereas older adults with higher cognitive functioning will find the most challenging training dose (High-C+) to be most beneficial and exhibit greatest cognitive plasticity.

Analyses of Primary and Secondary Neuroimaging Outcomes. There are two main fMRI tasks of interest- one for primary cognitive outcome (episodic memory), called *subsequent memory*; another for secondary cognitive outcome (executive control), called *task-switching*. An additional fMRI task, *working memory updating*, a near transfer task for all arms, will also be evaluated. For each task, we will derive a summary BOLD measure that best characterizes neural activity for the task after correcting for multiple comparisons. Those summary values will be entered into an ANOVA, where the Training Arm (3: Low-C, High-C, High-C+) x Assessment (pre-test vs. post-test) interaction will be evaluated, followed by post-hoc analyses of these interaction effects. We will also calculate group differences in the contrasts of interest at the post-test scans. The critical contrasts of interest for the subsequent memory is Remembered vs. Forgotten items, and for task-switching is Dual vs. Single task. The resulting ROI clusters, after correcting for multiple comparisons, will be used to extract percent signal change for all individuals at both pre-test and post-test. Specific Aim 2 evaluates whether the post-training changes in fronto-parietal activations are largest in the High-C and High-C+, compared to the Low-C, training arms. The percent signal change data will be submitted to a Training Arm x Assessment ANOVA, which will be followed by planned-comparisons between the groups to evaluate the specific aim 2. These interaction effects will be conducted for all task difficulty conditions in the fMRI tasks, because post-intervention activation patterns are hypothesized to be different for simpler conditions (e.g., 0-back; Single task; water present) compared to the more difficult conditions (e.g., 3- back, Dual task; water absent) of the fMRI tasks. We will also calculate task-specific activations for difficult vs. simpler condition contrasts (e.g., 3-back>0-back; Dual>Single; water absent>water present) in younger adults (YA), after correcting for multiple comparisons. The resulting ROI

clusters from YA will be used to extract percent signal change for all older individuals (OA) at both assessments. A univariate ANOVA with 3 groups (post-test Low-C, post-test High-C+, and YA) will be conducted to evaluate whether the post-test activations in High-C+ older adults in these task-related regions are closest to that of YA. We predict that for the primary (subsequent memory) and secondary (task-switching) outcomes, High-C and High-C+ older adults at post-training will have increased task-related neural activations mimicking that of younger adults, and reduced non-compensatory over-activations compared to baseline.

For the network analyses, we will utilize seed-to-voxel based connectivity from the major nodes within two cognitive networks, Fronto-Parietal (FP) and Cingulo-Opercular (CO), at both pre- and post-testing sessions. Changes in post-training functional connectivity in these two networks will be evaluated at all task difficulty conditions for memory updating (0-back, 3-back), task switching (single task, dual task), and subsequent memory task (water present, water absent). The interaction effects will help evaluate whether the connectivity of attentional networks change most for the higher attentional control training groups. We will also conduct separate pair-wise comparisons between High-C and High-C+ for both primary (*Subsequent Memory*) and secondary (*Task Switching*) cognitive outcomes, corrected for multiple comparisons, to determine if High-C+ engenders most neural changes.

Other neuroimaging analyses. For structural data, gray matter volumes of fronto-parietal and subcortical regions from FreeSurfer parcellations as well as white matter integrity Fractional Anisotropy (FA) maps from pre-test, along with cognitive scores at pre-test, will first be subject to a Multiple Factor Analyses using the ExPosition package for R to reduce the number of brain regions for future analyses. Significance of resulting components, via 1000-iteration permutation test, and component contributors, via 1000-iteration bootstrap test, will be assessed. The volumes and FAs of *only* the significant components, as well as specific ROIs that have been linked to game learning or cognitive control (e.g., right cingulum/hippocampus FA, genu FA, striatal volume), will then be entered into a Training Arm (3: Low-C, High-C, High-C+) x Assessment (pre-test vs. post-test) ANOVA to evaluate training-related structural changes in both gray matter volume and white matter integrity. We will also calculate correlations between changes in brain function, changes in brain structure and cognitive gains in primary and secondary outcomes for all training arms. We expect greater coupling of changes in brain and changes in cognition in the high attentional control training arms (High-C and High-C+) compared to the Low-C training arm.

Outcome Measures

Name:

1. Episodic Memory: Cognitive
2. Episodic Memory: fMRI
3. Executive Functions: Cognitive
4. Executive Functions: fMRI
5. Reasoning
6. Working Memory Capacity
7. Psychosocial Well-being
8. Diffusion Tensor Imaging

Primary Outcome: Episodic Memory: Cognitive; Episodic Memory: fMRI

Secondary Outcome: Executive Functions: Cognitive; Executive Functions: fMRI

Other: Reasoning, Working Memory Capacity, Psychosocial Well-being, Diffusion Tensor Imaging

Time Frame. All behavioral and cognitive measures (episodic memory, Executive functions, reasoning, working memory and psycho-social well-being) will be collected at the following three time points: Baseline (Assessment A), Immediate Post-training (Assessment B), and Retention (Assessment C).

Neuroimaging measures, including DTI and the fMRI tasks of episodic memory and executive functions will be collected at only two time points: Baseline (Assessment A) and Immediate Post-training (Assessment B).

Episodic memory (Cognitive) will be characterized by a single score that will be obtained by averaging standardized scores of 4 episodic memory tasks, including a task of everyday memory. These tasks are *Picture Sequence Memory task* (from NIH toolbox), *Buschke's Selective Reminding Test, Story Recall* (from expanded MMSE) and *Rivermead Behavioral Memory Test* (a test of everyday memory).

Episodic memory (fMRI) will be characterized by BOLD activations in an event related *subsequent memory* fMRI task. Scanning will take place during encoding of 96 color photographs of outdoor scenes (4 s duration) interspersed with baseline trials of a fixation cross (of 4-16 s). During encoding, the participant will determine if water is present in the scene with a keypress. Twenty minutes after the scan, the participant will undergo a recognition judgement task along with confidence ratings of their responses, assessing their subsequent memory of scenes presented in the scanner. In this episodic memory task, the following contrasts will be assessed for each subject for both "water present"

(easy condition) and “water absent” (hard condition) scenes: Forgotten>Remembered items and Remembered>Forgotten items.

Executive Functions (Cognitive) will be characterized by a single score will be obtained by averaging the standardized scores of 6 tasks of executive functions, with 2 tasks for each subcomponent of executive function, namely, task-switching, inhibition and updating. The tasks are *Stroop* (Eprime) and *Dimensional Change Card Sort* (NIH Toolbox) for task switching; *Flanker* (NIH Toolbox) and *Cued-discrimination* for inhibitory control; *Visual n-back* and *Verbal n-back* for memory updating.

This will be characterized by BOLD activations in two fMRI tasks. 1) A hybrid event-related task-switching paradigm with 2 single and 2 dual task blocks (TR=2 s). In one single block, the participant will decide if the digit presented is odd or even; in other, s/he will decide if the digit presented <5 or >5. Digit 5 won’t be used. In dual blocks, the two tasks will be randomly intermixed. Neural activity for the following three contrasts will be assessed for each subject: Single>Fix, Dual>Fix, and Dual>Single. 2) n-back memory updating task (TR=2 s, 2 runs of 4 task and 5 fixation blocks). During the task block, digits will be presented in the center of the screen. In 0-back blocks, s/he will just make a perceptual decision about the digit color. In 3-back blocks, s/he will compare the identity of the current digit with the digit presented 3-positions before. Neural activity for the following contrasts will be assessed for each subject: 3-back>Fix, 0-back>Fix and 3-back>0-back.

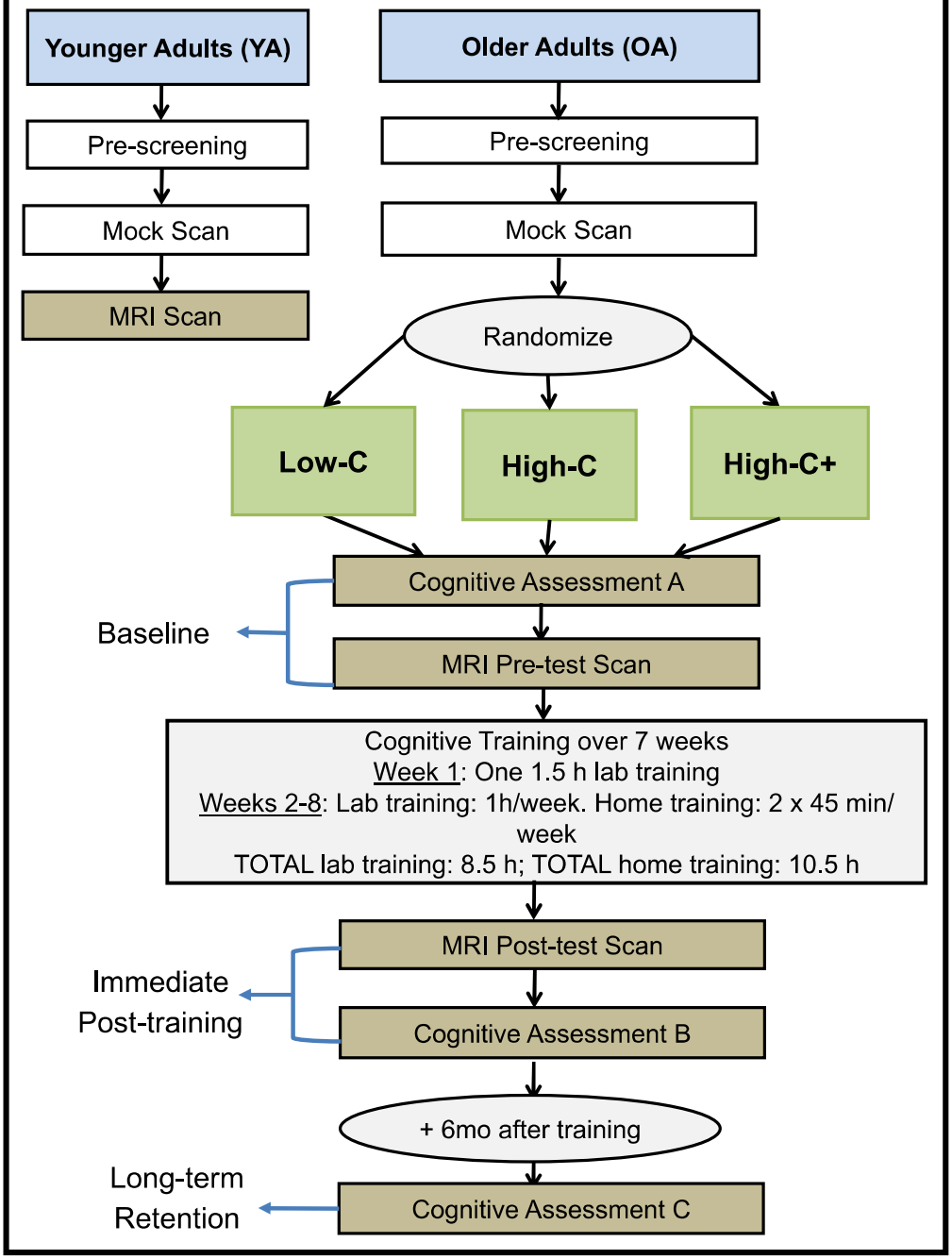
Reasoning will be characterized by a single score will be obtained by averaging the standardized scores of *Visual Puzzles* and *Matrix Reasoning* from WAIS-IV.

Working Memory Capacity will be characterized by a single score will be obtained by averaging the standardized scores of *List Sorting Working Memory Test* (NIH Toolbox) and *Operation Span* (Eprime).

Psychosocial well-being will be characterized by a single score will be obtained by averaging the standardized scores of *Geriatric Depression Scale*, MIDUS-*II, Cognitive Reserve Index,* and *Self-efficacy Scale*.

A 31-directions Diffusion Tensor Imaging (DTI; TR = 4001 ms, TE = 108 ms, FOV = 216 mm, voxel = 1.8 mm^3) or multi-band Diffusion Weighted Imaging (DWI), acquired in pairs of opposite phase encoding directions (RL and LR with 90 directions and a b-value of 2000 s/mm^2, and RL and LR with 91 directions and a b-value of 1000 s/mm^2) will be obtained. DTI will be characterized by fractional anisotropy (FA) and mean diffusivity (MD). Fractional anisotropy (FA) and mean diffusivity (MD) maps will be derived from tract-based spatial statistics, and regional values will be derived using the JHU atlas

Fig. 4. An Illustration of Data Collection Timeline



a

b

Fig. 5. (a) Trials from the Low-C Bird Watch game, where order of trees is predictable and the number of trees increase adaptively with the player's success. At the end of each game, feedback is provided. **(b)** A trial from the High-C Bird Watch game, where the order of the trees is unpredictable. Also, as shown, in some events when the trees change into fall color, the bird should be ignored for subsequent comparison.

Fig. 6. Screenshot of Sushi Chef simulation game showing day (i.e. level).