A randomized controlled trial to improve cognitive functioning in older adults: the Iowa Healthy and Active Minds Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000218
Article Type:	Protocol
Date Submitted by the Author:	14-Jun-2011
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Primary Subject Heading:	Geriatric medicine
Keywords:	GERIATRIC MEDICINE, Delirium & cognitive disorders < PSYCHIATRY, PUBLIC HEALTH, Clinical trials < THERAPEUTICS

A randomized controlled trial to improve cognitive functioning in older adults: the Iowa Healthy and Active Minds Study

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Words in Abstract = 291
Words in Text = 4,492
Figures = 5
References = 49

June 14, 2011

Running Head: An RCT of visual processing speed training: IHAMS

Abstract

Objectives: Gradual age-related cognitive deteriorations are common and are hypothesized to be partially attributable to declines in information processing speed. The Iowa Healthy and Active Minds Study (IHAMS) will evaluate the efficacy and effectiveness of a computerized visual processing speed training program (*Road Tour*, Posit Science Corporation, San Francisco, CA, USA).

Methods and Analysis: Using a 3:3:4:4 ratio within two age strata (50-64 vs. ≥ 65 years old), 681 men and women attending family care clinics were randomized to four treatment groups: 10 hours of on-site *Road Tour* training, 10 hours of on-site *Road Tour* training with 4 hours of booster training at 11 months post-randomization, 10 hours of on-site attention control using computerized crossword puzzles(*Boatload of Crosswords*, Boatload Puzzles, LLC, Yorktown Heights, New York, USA), and 10 hours of at-home *Road Tour* training using the participant's personal computer. The primary outcome, visual processing speed, was assessed at randomization and post-training (6-8 weeks post-randomization), and is being re-assessed at one-year post-randomization using the Useful Field of View test. Five secondary outcomes (Symbol Digit Modalities Test, Trail Making Tests A and B, Controlled Oral Word Association Test, Digit Vigilance Test, and the Stroop Color and Word Test) were assessed at randomization and will be re-assessed at one-year post-randomization. Seven hypotheses will be tested using intent-to-treat analyses involving multiple linear, logistic, Poisson, and negative binomial regression.

Ethics and Dissemination: Ethics approval was provided by the University of Iowa Institutional Review Board (IRB-03 protocol 200908789). All participants completed

signed informed consent prior to enrollment. *Road Tour* is commercially available from Posit Science Corporation, which provided it to IHAMS at no cost. All participants will receive a free copy of *Road Tour* for unlimited perpetual use at study completion.

Clinical Trial Registration Number: NCT01165463.

Article Summary

Article Focus:

- Given that age-related declines in cognitive functioning are part of the normal aging process, there is a pressing need for efficient and effective training interventions that improve cognitive functioning in older adults.
- This protocol paper outlines the design of a study that overcomes several important limitations of a prior, large, multi-site randomized controlled trial (RCT) that used memory, reasoning, and speed of processing interventions, but found that only the latter effectively translated to improved health outcomes.
- This RCT evaluates the efficacy and effectiveness of a second-generation computerized visual speed of processing intervention using three modes of delivery (on-site without booster training, on-site with booster training, and at-home use) vs. an attention control (on-site computerized crossword puzzles without boostertraining) in improving cognitive processing speed and health outcomes.

Key Messages:

- This is an RCT protocol.
- IHAMS is the first RCT to evaluate the efficacy and effectiveness of a commercially available computerized visual speed of processing intervention known as *Road Tour*.

- If this intervention is successful, the product vendor pledges to make the computerized intervention software available to governments for widespread distribution and use at a fraction of the current commercial cost.

Strengths and Limitations of This Study:

- Strengths: this study uses six well-established, objective neuropsychological assessments of cognitive processing speed, as well as three highly reliable and valid self-reported measures of health outcomes in a large sample of men and women 50 years old and older.
- Limitations: although the sample is large, it was drawn from just one large primary care center in which minorities are underrepresented, and the key assessments are only conducted at randomization, after initial training (6-8 weeks post-randomization), and at one-year post-randomization, thereby reducing the opportunity to demonstrate the long-term effects of the intervention.

Introduction

Some degree of gradual, age-related cognitive decline is recognized as universal and as a normal part of the aging process. This decline is evident across several domains including memory, orientation, attention, abstract thinking, and perception [1-4]. Age-related cognitive changes can best be viewed as one end of a continuum that includes preclinical disease, mild cognitive impairment, and dementia [5-8].

As the brain and the visual system age, many changes occur from the periphery through the central nervous system, contributing to deficits in visual perception and cognition [9-11]. Deficits are particularly notable in visual tasks requiring high levels of temporal precision (visual speed of processing) and attention (tracking multiple objects). These deficits are significant contributors to declines that emerge in visual cognition and visually-guided basic and instrumental activities of daily living (ADLs and IADLs) [12,13], and can be understood as the consequence of central nervous system changes involving brain plasticity. These brain-plasticity-driven changes are likely important contributors to the speed, memory, and cognitive deficits common in normal aging[14,15]. Brain plasticity, however, also creates an opportunity to strengthen cognitive abilities, and many studies have investigated the effects of interventions targeting specific abilities like memory, attention control, spatial orientation, inductive reasoning, figural relations, and artistic expression, or more globally by targeting multiple domains.

A new generation of these intervention studies is quite promising. Especially encouraging are recent studies that provide [14, p. 1]:

> "…structured experience in situations demanding executive coordination of skills—such as complex video games, task-switching paradigms, and divided attention tasks…"

The advantage of these studies is that they "train strategic control over cognition that does transfer to different environments" [14, p. 1]. Several such studies focus on improving visual processing speed [16-19].

Salthousehas hypothesized that declines in processing speed adversely affect cognition in two ways—the limited time and simultaneity mechanisms [20]. Limited time refers to the restriction in the amount of time available to successfully accomplish a task when certain cognitive processes are completed too slowly. Simultaneity operates when slowed information processing promotes the loss of early cognitive processing products through decay or displacement before they are needed for later operations. Extensive evidence supports the speed of processing theory of age-related cognitive decline [19-23]. Associations between various subjective and objective health status measures and cognitive functioning are also related to processing speed to a greater degree than to other higher order cognitive processes, suggesting an important link between speed of processing and health outcomes [24]. Moreover, Salthouse has shown that processing speed peaks at about age 23, plateaus until age 28, and then declinesin a linear fashion throughout the remainder of the life course [25].

One of the most impressive interventions focused on improving visual processing speed was developed by Ball and Roenker[19,20,26]. It improves the efficiency and accuracy of visual information processing and the ability to perform complex visual attention tasks. Specifically, users are trained to improve the speed and accuracy with

which they identify and locate visual information using a divided attention format. Over time, the difficulty and complexity of each task is systematically increased as users attain specified performance criteria. Manipulations to increase difficulty include decreasing visual stimuli duration, adding visual or auditory distracters, increasing similarity between target and distracter stimuli, and presenting visual targets over a broader spatial expanse. The basic tasks, however, are always the same—central discrimination and peripheral target location.

Ball and Roenker's [19,20,26] program was extensively evaluated in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial [27]. ACTIVE hypothesized that each of three intervention arms (memory, reasoning, and visual processing speed training) would have a direct effect on targeted, trained outcomes (proximal outcomes), and nonspecific effects on its non-targeted, untrained outcomes (via social contact or cognitive engagement mechanisms). The reasoning and memory interventions were expected to affect only everyday problem solving and ADLs and IADLs, whereas the speed of processing intervention was hypothesized to have more diverse effects, including ADL and IADL functioning, everyday speed, and driving habits. All three interventions were expected to affect the secondary outcomes, including health-related quality of life (HRQoL), depressive symptoms, and locus of control. Although all ACTIVE treatments were effective at improving their targeted abilities, visual speed of processing led to the largest gains [28,29]. Moreover, the greatest relative improvementswere clearly associated with visual speed of processing training as well, which produced effect sizes more than double those associated with the two other interventions at every time point.

The effects of ACTIVE'svisual speed of processing intervention (vs. the no-contact control group) on the secondary, or health outcomes have been shown as well. These included: (1) a $244 per person-year (3%) reduction (p = .012) in predicted medical expenses at one-year [30]; (2) a 38% reduction in the risk of global decline in HRQoL at two-years (p = .004), and a 25.6% reduction in the risk of global decline in HRQoL (p< .038) at five-years [331,32]; (3) a 30% reduction in the risk of worsening depressive symptoms at both one-year (p = .012) and five-years (p = .023) [33]; (4) a 38% reduction in the risk of the onset of suspected clinical depression at one-year (p< .01) [34]; (5) improvements in self-rated health at two-, three-, and five-years equivalent to at least half of the difference between "excellent" and "very good" responses (p values < .05), which is known to be associated with a 0.8% absolute reduction in the five-year mortality rate, and a 10% relative mortality reduction[35]; and, (6) a 64% greater likelihood (p< .05) of improvements in internal locus of control at five-years [36]. No adverse effects of speed of processing training in ACTIVE have been identified.

As important as it was, however, ACTIVE had five serious limitations. First,ACTIVE used a no contact rather than an attention control group, making it impossible to rule out placebo effects. Second, ACTIVE's approach to booster training was compliance-conditioned,making it impossible to separate adherence effects from dosing levels. Third, ACTIVE relied on only one speed of processing assessment test (the Useful Field of View, or UFOV; [37]), which was sufficiently thematically comparable to the speed of processing intervention itself that the results could merely reflect "training to the test." Fourth, ACTIVE used an early version of the speed of processing training that required supervised assistance, and is thus not practical for

widespread implementation. Finally, ACTIVE only included participants ≥ 65, and thus cannot be used to address the important issue of whether earlier age-related declines [25] can be avoided or ameliorated.

Current Study

We designed the Iowa Healthy and Active Minds Study (IHAMS) to overcome ACTIVE's five limitations. IHAMS is a four-group RCT (NCT01165463). The first group received a standard dose (10 hours) of computerized visual processing speed training in our laboratory. The second group also received a standard dose of computerized visual processing speed training in our laboratory, but they were invited back to the laboratory for 4 hours of subsequent booster training regardless of their adherence to their training. The third group (attention control) received a standard dose of training using computerized crossword puzzles in our laboratory. The final group took the computerized visual processing speed training software home to use it on their personal computer (PC) for at least a standard dose. The primary outcome is visual processing speed, which was assessed at randomization and after the completion of training (at 6-8 weeks post-randomization), and will be assessed again at one-year post-randomization. Five secondary cognitive processing speed outcomes were assessed at randomization and will be assessed again at one-year thereafter.

We specified seven *a priori* hypotheses(**Hn**) that we expect to be supported by separate analyses in each age-stratum. The first addresses changes in the primary outcome between randomization and post-testing. Because no standard booster training occurred by this time, and because supplemental training beyond 10 hours should in the at-home group should have been minimal, we hypothesize (**H1**) that participants randomized to *Road Tour* training (Groups 1, 2, and 4) should have

significantly and similarly greater improvements in visual processing speed immediately after training than the attention control group (Group 3).

The six remaining hypotheses address expectations about changes in all six of the primary and secondary outcomes between randomization and one-year post-randomization. **H2**replicates ACTIVE (i.e., on-site delivery) and hypothesizes that the basic and booster effects of visual speed of processing (Group 2) will be significantly greater than those observed for the attention control group (Group 3). To separate the basic effect(Group 1) from the basic plus booster effect(Group 2), wefurther hypothesize (**H3**) that Group 1 will also improve significantly more than Group 3 (attention control), but that (**H4**) Group 2 will improve significantly more than Group 1. **H5**examines the effect of the at-home delivery of the visual speed of processing training (Group 4) vs. the effect of the attention control training (Group 3); herewe expect significantly greater improvement for Group 4 than Group 3. **H6** and **H7** evaluate the different modes of implementing the visual speed of processing intervention. We hypothesize (**H6**)that given the potential for individual dosing and maintenance in Group 4 (at-home training) it will have significantly greater improvement than Group 1 (on-site training without boosters). **H7**evaluates the potential for individual dosing and maintenance vs. standard booster training; here we hypothesize that the improvements for Group 4 (unlimited at-home dosing) will exceed those for Group 2 (in which standard and booster training doses are fixed).

Methods and Analysis

Figure 1 shows the IHAMS study design and participant recruitment results. IHAMS is a four-arm parallel RCT using a 3:3:4:4 allocation ratio and block randomization separately within two age-strata (50-64 and 65-87 years old). Participants were randomized to one of the following groups: (1) 10 hours (over the first 5-6 weeks) of on-site training using *Road Tour*(Group 1), (2) 10 hours of on-site training using *Road Tour* plus 4 hours of booster training at 11 months post-randomization (Group 2), (3) 10 hours of on-site attention control using computerized crossword puzzles (Group 3), or (4) at-home training using *Road Tour* for 10 hours or more (Group 4). When enrollment closed in late November 2010, 681 participants had been randomized with 154 in Group 1, 148 in Group 2,188 in Group 3,and 191 in Group 4. Post-training assessments occurred at 6-8 weeks post-randomization, and complete data were obtained for 616 participants (90.5%). One-year post-randomization assessments are scheduled to be completed by late November 2011. IHAMS was sized to provide ≥ 80% power to detect an effect size of 0.25 for **H2** at one-year post-randomization with alpha = 0.05.

Study Sample and Recruitment. The sampling frame included all patients attending either the general internal or family medicine clinics of the University of Iowa's Family Care Center (FCC). The electronic medical record(*Epic*, Verona, Wisconsin, USA) was used toinitially select potentially eligible participants who met the inclusion criteria: (1) age ≥ 50 years old, (2) regularly receiving primary care from the FCC (≥2 visits in the past year), and (3) the absence of cognitive impairment indicated by ICD9-CM codes for Alzheimer's disease (331.0), Pick's disease (331.1), arteriosclerotic

dementia (290.4 to 290.43), other senile or pre-senile dementia (290.0 to 290.9), dementia due to alcohol (291.1 to 291.2) or drugs (292.82 to 292.83), amnestic syndrome (294.0), or dementia due to other organic conditions (294.1). A total of 5,743 potentially eligible patients were identified.

Weekly random (without replacement) replicates of 100-250 of the 5,743 potentially eligible patients received a letter describing the study that was co-signed by the FCC medical directors (CG and SW) and the principal investigator (FDW). These patients were asked to telephone the project office to indicate whether they were or were not interested in participating. A fortnight later, we initially telephoned non-responders to determine their interest, but because this approach had a very low rate of return, it was abandoned.

Telephone Screening for Eligibility. We attempted to screen all 5,743 potentially eligible patients. Despite ≥ 3 telephone calls each, we were unable to reach 1,627. Upon achieving telephone contact with the remainder, 2,079 declined to participate. We then conducted brief screening interviews among interested patients. These screening interviews identified potential participants who met any of the exclusion criteria that could not be ascertained using *Epic*: (1) significant cognitive impairment evidenced by≥3 errors on a 10-item mental status exam[38], (2) self-reported uncorrected visual acuity problems that would interfere with using a PC, (3) not having a PC with a CD-ROM in the home, (4) not having internet access, and (5) having previously used a cognitive training program. This led to the exclusion of 1,356 potential participants.

Informed Consent and Baseline Interviews. After successfully completing the screening telephone interview, eligible patients were scheduled for a two-hour

appointment in our laboratory where the purpose and design of the study were explained, and written informed consent was obtained. The informed consent process took about 15 minutes. After providing informed consent, the 681 enrollees were administered their baseline (randomization) interviews by trained research assistants using computer-assisted interviewing protocols. The baseline interviews took about 1.5 hours, and included the neuropsychological assessments, health outcomes, and covariates described below. Immediately after their baseline interview, participants were randomized to one of the four study groups.

Randomization Procedure. The study biostatistician (MPJ) determined the order of assignments using a computer-generated list of random numbers anda 3:3:4:4 ratio based on *a priori* power calculations. Block randomization was used to maintain balance on two age-strata (50-64 and ≥ 65). Block sizes of 4, 8, and 12wererandomly varied. The assignment for each participant's ID number was recorded on a participant letter and then sealed in an opaque envelope with only the ID number visible. Two age-strata specific boxes containing the assignment envelopes were stored in a locked cabinet in the Project Coordinator's office. The Project Coordinator (MMD) had the responsibility of unsealing the envelope (from the appropriate age-stratum box) and revealing each participant's group assignment.

Cognitive Processing Speed Outcomes. The six IHAMS neuropsychological assessments are: (1) the UFOV PC mouse version [19]; (2) the Symbol Digit Modalities Test (SDMT) [39]; (3) the Trail Making A and B Tests (TMT) [40]; (4) the Controlled Oral Word Association Test (COWAT) [41]; (5) the Digit Vigilance Test (DVT) [42]; and, (6) the Stroop Color and Word Test (Stroop) [43]. The UFOV is the primary outcome and

was administered at randomization and post-training (6-8 weeks post-baseline), and will be re-administered at one-year post-randomization. The UFOV includes three subtests—stimulus identification, divided attention, and selective attention—each scored from 17-500 milliseconds (ms) reflecting the shortest exposure time at which the participant could correctly perform each subtest 75% of the time, with a composite ms outcome score ranging from 51-1500 ms.

The SDMT, TMT, COWAT, DVT, and Stroop tests are secondary outcome measures and were all administered at randomization, and will be re-administered at one-year post-randomization. SDMT captures divided attention and processing speed, and is based on how many of 110 possible digit-symbol pairs were scored as correct pairs by the participant in 90 seconds. TMT assesses visual scanning ability, processing speed, and set-shifting/executive functioning, and is coded as the number of seconds needed to correctly complete connecting the number and number-letter sets. COWAT assesses verbal fluency based on the number of unique words beginning with the letter C (or F or L) generated by the participant during 60 seconds, with a composite score of the number of correct words used across the three letter trials. DVT assesses sustained attention and psychomotor speed, is performed by crossing out randomly placed 6's in 59 rows of numbers, and is scored as the error and time totals. The Stroop assesses processing speed and executive functioning, and is scored as the correct number of words, colors, and color-words identified in 45 seconds on each subtest.

Health Outcomes.Three health outcome measures—HRQoL, depressive symptoms, and sense of control—are included. Each has established reliability

andvalidity, and yet is relatively brief. The 36-item SF-36[44] is used to measure HRQoL. Scores on each of its 8 subscales are transformed to range from 0 (worst health) to 100 (best health).Depressive symptoms are measured using the 12-item Center for Epidemiologic Studies Depression scale (CESD-12)[45]. CESD-12 scores range from 0 (no symptoms acknowledged) to 36 (all 12 symptoms acknowledged to occur most or all of the time), with scores ≥ 9 being the screening threshold for suspected clinical depression [34].Sense of control is measured using Mirowsky and Ross' eight-item 2x2 Index [46]. The sense of control score is the sum of the item responses, and ranges from maximally denying (-16) to maximally claiming control (+16).

Covariates. To adjust for potential heterogeneity across the treatment groups, several covariates were obtained at randomization. These included various sociodemographic characteristics, multiple indicators of socioeconomic status, medical history, ADLs and IADLs, perceived stress, self-efficacy, and attitudes towards and the use of computers in everyday life, among others.

The *Road Tour* Training Program.In November 2007, Posit Science Corporation (San Francisco, California, USA) acquired the rights to Ball and Roenker'soriginal visual speed of processing training program [19,20,26]. While Posit Science retained all of the original tasks, it modified the delivery platform to be user-friendly and self-administered, improving the ease of dissemination and implementation. The addition of certain game elements also improves user engagement and enhances compliance. The resulting second-generation computerized speed of processing training program is known as *Road Tour*, and is commercially available (http://www.positscience.com/our-products).

Road Tour's appearance is shown in Figure 2. After clicking on the start button to initiate training, Figure 2b is shown. Here, both the license plate area and the eight circular locations in the near orbit surrounding it are empty. The empty license plate is then replaced, as in Figure 2c, with the target vehicle, either a car or a truck. Similarly, the eight empty circular locations surrounding the license plate are then replaced with seven distracter stimuli (rabbit crossing signs) or the target sign (Route 66). The stimuli (car vs. truck, and rabbit crossing vs. Route 66 sign) are presented for a specified time and are then replaced by Figure 2d. The amount of time that Figure 2c remains on the screen before being replaced by Figure 2d is measured in ms. In Figure 2e, both target vehicles (the car and truck) are presented in the center of the screen. The user first clicks on the correct target vehicle (car or truck), and then on the circular location where the correct peripheral target (Route 66 sign) appeared (Figure 2f). The goal is to improve cognitive processing speed by progressively reducing the ms of exposure that Figure 2c remains on the screen with subsequent correct identification of both the stimuli (car or truck) and target (Route 66) sign.

The training program is tailored to the participant's performance such that it maintains a 75% success rate before advancing to a shorter exposure time. The gaming aspect involves the user deciding where to place a car in the ring of cars when a trial (identification of the vehicle and Route 66 sign) is correct (Figure 2f). When car placement produces a sequence of three cars of the same color, these cars disappear, and the user's car moves around the ring. This gaming element increases the user's engagement in the exercise. Each lap around the ring gets the user's car closer to the next destination. In the initial (early) trials of the exercise, there are only seven

distracters within the near orbit around the license plate. As the user progresses, three changes occur to increase task difficulty: (a) the target visual field expands (Figures 3a-c) by progressing outward from the license plate to add medium and distal orbits; (b) these are accompanied by an increasing number of distracters to populate all three orbits (up to 47; Figures 4a-b); and, (c) the vehicle pairs morph through 9 different stages or pairs to become more similar and thus more difficult to differentiate (Figure 5).

*Road Tour*captures the participant's experiencetwo ways, both of which are routinely sent in the background to Posit Science and our research laboratory over the internet using secure file encryption protocols. One assessment is the amount of time spent playing *Road Tour*. The targeted standard training dose was 10 hours. Usecan alsobe assessed by the percentage of completion of all 81 of the available exercise sets. In addition to monitoring use, *Road Tour* also administers an assessment of visual processing speed at random intervals. This assessment is the number ofms that Figure 2c must remain exposed to the participant to achieve the specified correct identification (success) rate. It is estimated as the log mean of two randomly interleaved ZEST (zippy estimation by sequential testing; [47]) adaptive Bayesian algorithms [48] which employ a cumulative Gaussian curve starting at 6.75% (chance correct rate) and ending at 95% (100% minus 5% lapse rate) with the threshold set at 50%.

Group 1. Immediately after completing their informed consent and baseline interviews, participants randomly assigned to Group 1 (on-site *Road Tour* training without boosters) were scheduled for their first two-hour session in our laboratory, which includes two identical training rooms configured with 5 private PC workstation areas. The *Road Tour* training software is on the PCs in one training room, and the

computerized crossword puzzle software is on the PCs in the other. At their first session, Group 1 participants were assigned their study specific ID number, and after receiving about 5-10 minutes of scripted instruction on how to use *Road Tour*, were asked to use the training program for the remainder of that session. Participants were then scheduled for their next two-hour training session, which usually occurred the following week. A total of five, weekly two-hour training sessions were scheduled for the standard training dose. After completing 10 hours of training, or by 6-8 weeks post-randomization, whichever came first, Group 1 participants were invited back to the laboratory for their post-training assessments using the UFOV test.

Group 2. Participants randomly assigned to Group 2 (on-site *Road Tour* training with boosters) were treated the same as those in Group 1 with one exception. Unlike Group 1 participants, Group 2 participants were invited back to our laboratory for two 2-hour booster training sessions at 11 months post-randomization. Group 2 participants also completed additional UFOV testing both before and after their booster training.

Group 3. Participants randomized to Group 3 (on-site computerized crossword puzzle training; attention control) were treated the same as participants randomized to Group 1, with one exception. Instead of using *Road Tour*, Group 3 participants were taken to our second training room and instructed how to use the computerized crossword puzzle program (*Boatload of Crosswords*, Boatload Puzzles, LLC, Yorktown Heights, New York, USA).

Group 4. Participants randomly assigned to Group 4 (at-home *Road Tour* training) were scheduled for their first session in our laboratory immediately after completing their informed consent and baseline interviews. They, however, were taken

to a third room in which they were assigned their study specific ID number, and were then shown (step-by-step) how to load the software on a PC. After this, they received about 5-10 minutes of scripted instruction on how to use *Road Tour*, and then practiced using it for about 10-15 minutes. Group 4 participants were then sent home with the CD containing the *Road Tour* software to load on their home PCs, as well as a detailed set of step-by-step instructions containing all of the screen-shots that they would encounter in doing so. They were also given the phone number and email information for contacting the Project Coordinator (MMD) to answer any questions they might have about loading the software onto their home PCs. Group 4 participants were asked to use *Road Tour* at home for 10 hours or more during the next 5-6 weeks. At 6-8 weeks post-randomization, Group 4 participants were invited back to the laboratory for their post-training assessments using the UFOV test. At that time, they were reminded that they could continue using *Road Tour* as often as they liked.

Analysis. For the purposes of statistical modeling, we define three mutually exclusive 1-0 binary indicators ***G1***, ***G2***,and ***G4***to indicate whether the participant is in the on-site speed of processing intervention without boosters, the on-site speed of processing intervention with boosters, or the at-home speed of processing group. The on-site crossword puzzle (attention control; ***G3***) group participantwill have all threeof these indicators set to zero. Other covariates are contained in the vector ***X***. For continuous outcomes like visual processing speed we will use multiple linear regression models [49] that may be expressed in their simplest form as:

$$Y_{12} = \beta_0 + \beta_1 Y_b + \beta_2 G1 + \beta_3 G2 + \beta_4 G4 + \beta_5 X + \varepsilon$$

where Y_{12} is the dependent variable at the 12-month post-randomization assessment, β_o is the intercept, β_1 is the coefficient for Y_b (the baseline [randomization] value of the dependent variable), β_2 is the coefficient for *G1* (Group 1), β_3 is the coefficient for *G2* (Group 2), β_4 is the coefficient for *G4* (Group 4), β_5 is the vector of coefficients for *X* (the vector of covariates), and ε is the error term. The effect of β_1 represents a stability coefficient, the effects of β_2, β_3, and β_4 represent the effects of being randomized to the three *Road Tour* intervention groups (Groups 1, 2, and 4), respectively, on changes in the dependent variable compared to those observed for the attention controlgroup (Group 3), and the effects of β_5 represent the effects of the covariates on changes in the dependent variable. When the dependent variable is a count measure, we will use Poisson or negative binomial regression techniques, and for binary outcomes (such as the onset of suspected clinical depression [CESD-12 scores ≥ 9]),we will use logistic regression.

Ethics and Dissemination

IHAMS was viewed as a minimal risk trial by the University of Iowa IRB for three reasons. First, no adverse effects were reported from the earlier version that was used in ACTIVE. Second, *Boatload of Crosswords*, the computerized crossword puzzle program, is the most popular puzzle game commercially available. Third, our IRB protocol (200908789) established procedures to ensure that participation was voluntary, that participants could quit at any time they chose, that signed informed consent was obtained, that confidentiality was maintained, and that data security was rigorous. Participants received $25 for completing their randomization interviews, $5 for each UFOV test, and $50 for completing the one-year post-randomization interview.

We will disseminate the results from IHAMS via conference presentations and journal publications. Four subsequent journal articles will focus on (1) the post-training UFOV results, (2) the one-year post-randomization results on all six neuropsychological assessments, (3) the health outcome results at one-year post-randomization, and (4) effectiveness-derived dose-response curves. If the one-year post-randomization results demonstrate the efficacy and effectiveness of *Road Tour*, Posit Science will work with government agencies to make the program available for wide-scale implementation "at only a fraction of the current per-user cost."

End Matter

Acknowledgements: The authors acknowledge and applaud the 681 participants from the University of Iowa FCC general internal and family medicine clinics. Without their participation and support, this study would not have been possible. The authors also acknowledge the research assistants, work-study students, and other support staff involved in IHAMS.

Funding:This study was supported by US NIH grant RC1 AG-035546 to FDW.

Competing Interests: The *Road Tour* computerized visual speed of processingintervention used in IHAMS is commercially available from Posit Science Corporation (San Francisco, CA, USA).None of the members of the investigative team have any conflicts of interest or conflicts of commitment involving Posit Science. Specifically, no one on the investigative team will financially profit in any way from the use of *Road Tour* in IHAMS, or in any subsequent study using *Road Tour*.

Posit Science acquired ownership in October 2007 of the original speed of processing intervention that was used in the multi-site ACTIVE RCT on which FDW was an original co-investigator (at the ACTIVE Indiana University site). The ACTIVE speed of processing intervention had been developed earlier by Karlene Ball (ACTIVE site-PI at the University of Alabama-Birmingham, USA) andDan Roenker (at Western Kentucky University, USA). In collaboration with Professors Ball and Roenker, Posit Science subsequently developed the second-generation, value-added version of the visual speed of processing intervention known as *Road Tour* and used here in IHAMS. From December 2007 to March 2009, FDW had a limited, part-time consulting arrangement (15 days, total) with Posit Science to support additional analyses of the first five-years of

the ACTIVE follow-up data that had not been identified in the original ACTIVE protocols nor funded by the various US NIH grants supporting ACTIVE. This arrangement was approved in advance by the ACTIVE Executive Committee (which included the US NIH project officers), and was sanctioned by the Provost of the University of Iowa.

After terminating this limited, part-time consulting arrangement with Posit Science, FDW applied in April 2009 for, and was awarded in September 2009 the US NIH Challenge Grant known as IHAMS. Posit Science provided the 700 copies of *Road Tour* used in IHAMSat no cost whatsoever. Furthermore, in its letter of commitment to IHAMS and the US NIH, Posit Science stated should the results support the efficacy and effectiveness of *Road* Tour, they will"work with agencies at the federal government to make the program available for wide-scale implementation at only a fraction of the current per-user cost."

Ethics Approval: Ethics approval was provided by the University of Iowa Institutional Review Board (IRB-03; IRB protocol number 200908789), initially approved on September 12, 2009, and most recently re-approved on May 18, 2011.

Contributors: FDW is the principal investigator on the study, wrote the original proposal, supervised the trial, conducted all of the analyses, and drafted the manuscript. MWV-W is co-principal investigator on the study, collaborated on the original proposal, co-supervised the trial, and reviewed the analyses reported here as well as the manuscript itself. MBH is a post-doctoral fellow working on the study, trained all of the interviewers, supervised the scoring of the neuropsychological tests, and reviewed the manuscript. MPJ is the study biostatistician, devised the randomization protocol, reviewed all of the analyses, and reviewed the manuscript. RM is a co-investigator on

the study, reviewed all of the ethics, consent, and IRB documents, and reviewed the manuscript. TML was a study Research Assistant who assisted with piloting the interview protocol, conducted randomization interviews, and reviewed the manuscript. KD is the study neuropsychologist, supervised selection of the neuropsychological tests, reviewed the psychometric analyses, and reviewed the manuscript. CG is the medical director of the FCC General Medicine Clinic, participated in subject recruitment, and reviewed the manuscript. SW is the medical director of the FCC Family Medicine Clinic, participated in subject recruitment, and reviewed the manuscript. MMD is the Project Coordinator.

Provenance and Peer Review: IHAMS was not a commissioned study. It was externally peer reviewed by a panel of Distinguished Editors (ZRG1 RPHB-E 58) convened by the US NIH to select approximately 200 Challenge Grant Applications (RC1s) submitted in response to the American Recovery and Reinvestment Act of 2009 (from a pool of about 23,000 submitted proposals).

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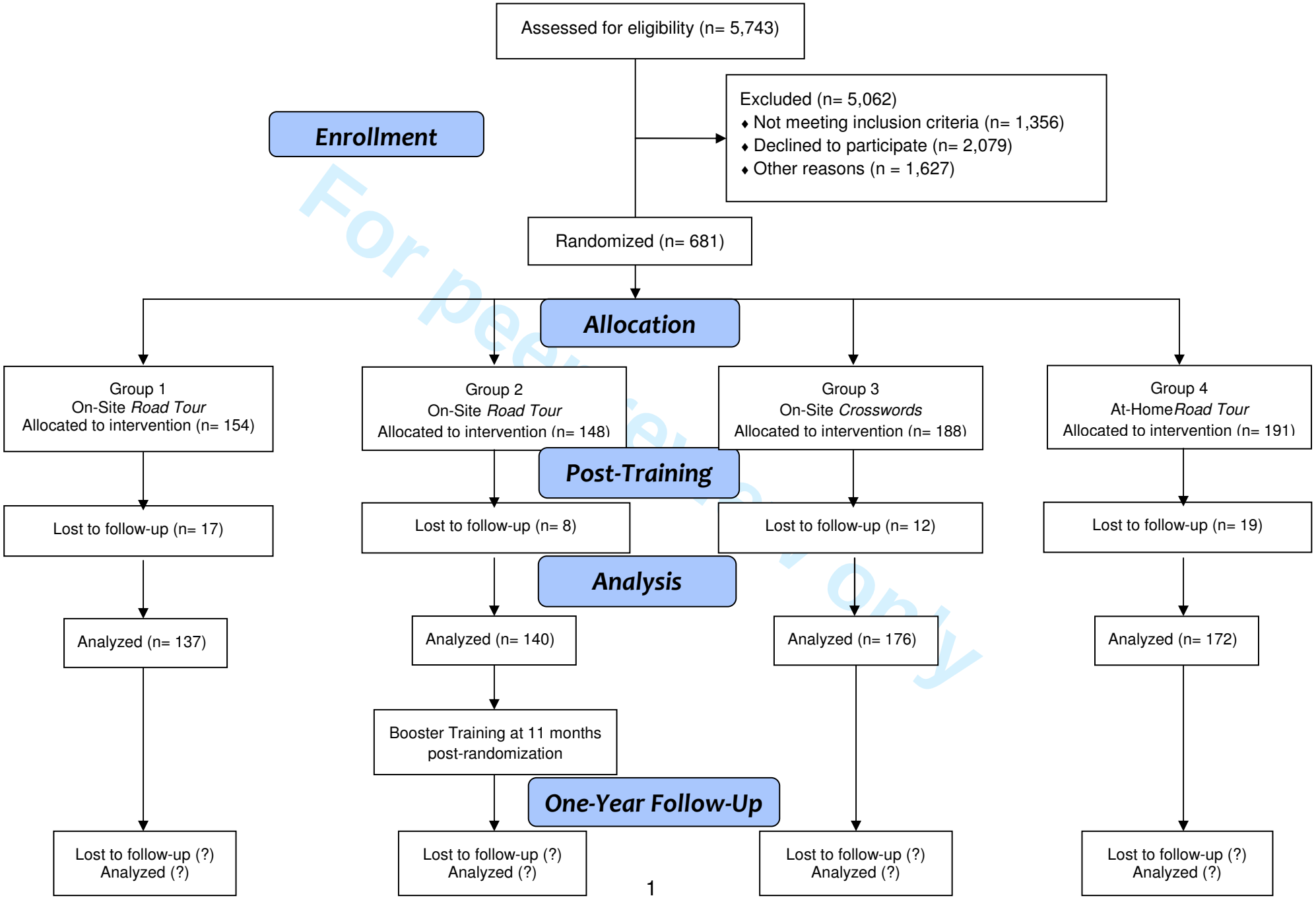
CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-10
	2b	Specific objectives or hypotheses	10-11
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	12
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	na
Participants	4a	Eligibility criteria for participants	12-13
	4b	Settings and locations where the data were collected	13-14, 18-20
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	17-20
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14-16
	6b	Any changes to trial outcomes after the trial commenced, with reasons	na
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	na
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	14
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	14
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	14
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	14
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	14

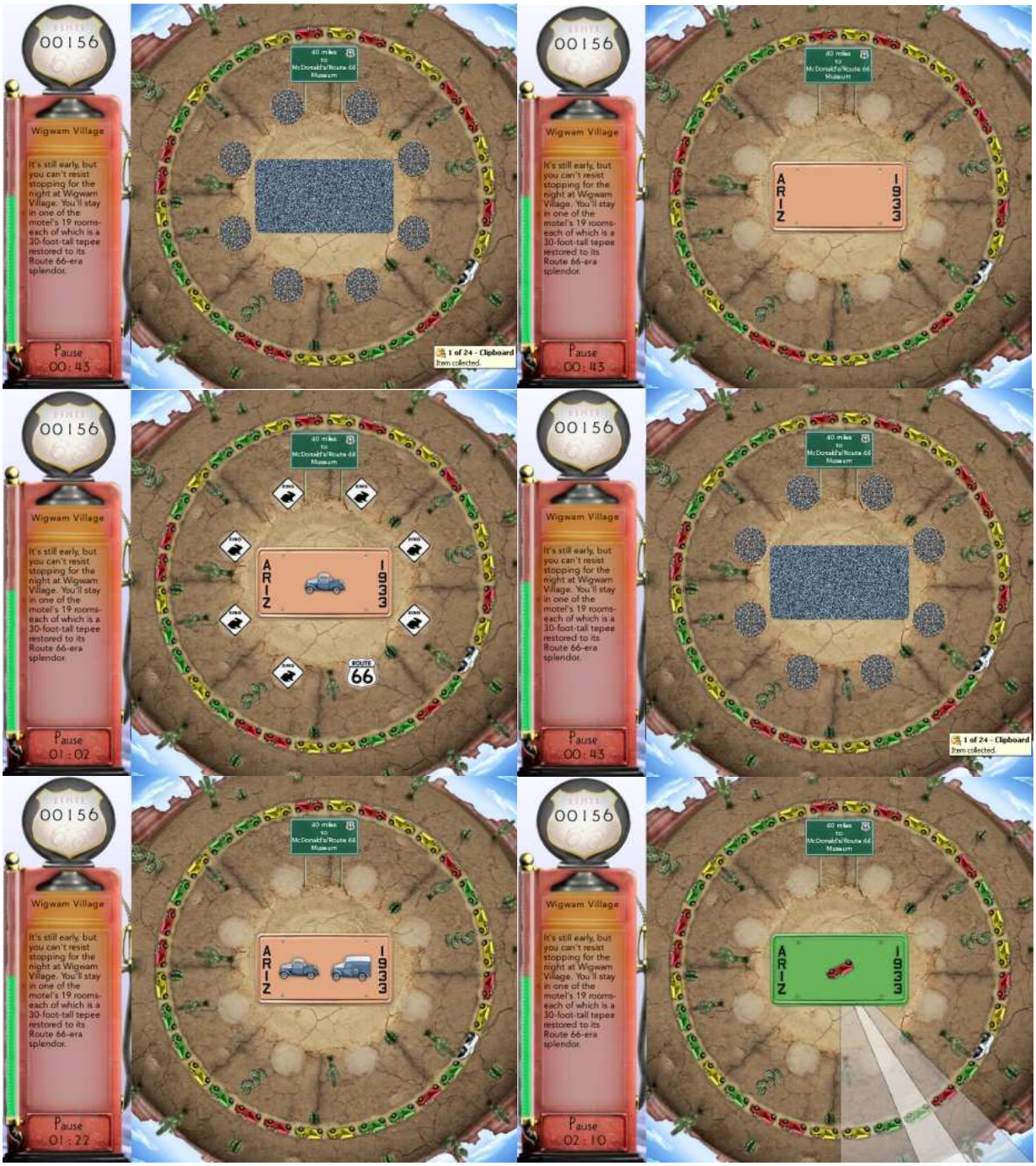
		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	18-20
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	20-21
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	20-21
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	33
	13b	For each group, losses and exclusions after randomisation, together with reasons	33
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	na
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	na
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	33
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	na
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	na
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	na
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	na
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	na
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	na
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	na
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	na
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	23

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Figure 1. IHAMS CONSORT Flow Diagram.



Figures 2a-f. The Initial *Road Tour* Sequence.



Figures 3a-c. Expansion of the Target Visual Field.

Figures 4a-b. Increasing the Number of Visual Distracters.

Figure 5.Vehicle Morphing.