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Cognitive Training Changes Hippocampal Function in Mild Cognitive Impairment: A Pilot Study

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Abstract

A randomized pilot experiment examined the neural substrates of response to cognitive training in participants with mild cognitive impairment (MCI). Participants performed exercises previously demonstrated to improve verbal memory and an active control group performed other computer activities. An auditory-verbal fMRI task was conducted before and after the two-month training program. Verbal memory scores improved significantly and left hippocampal activation increased significantly in the experimental group (gains in 5 of 6 participants) relative to the control group (reductions in all 6 participants). Results suggest that the hippocampus in MCI may retain sufficient neuroplasticity to benefit from cognitive training.

Keywords

MRI; dementia; cognition; MCI; mild cognitive impairment; fMRI; functional MRI; cognitive training; hippocampus; medial temporal lobe

INTRODUCTION

A fundamental goal in research on Alzheimer's disease (AD) is to intervene early in the progression from healthy aging to AD so that conversion to AD can be significantly slowed or prevented. Mild cognitive impairment (MCI) describes the transitional state in conversion from healthy aging to dementia in which there is cognitive (typically memory) dysfunction but not functional disability [3]. Early intervention may be important because brain changes leading to AD occur years before the diagnosis of AD [4, 5], by which time pathology is so

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DISCLOSURE STATEMENT

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severe that treatment is difficult. Epidemiologic studies suggest that enriching mental activity may moderate the trajectory of the disease because healthy older adults who participate in a variety of social and cognitive activities are less likely to develop MCI and less likely to progress to dementia [6–9]. Although some of these studies were prospective and longitudinal [e.g. 7, 8, 10], the strongest evidence supporting the claim that mental activity slows disease progression would be a randomized intervention study that alters both the key cognitive disability and the neural system affected early in AD. There have been several cognitive training programs for MCI participants [e.g. for a review see 11], but none has examined brain changes in a randomized intervention study.

Medial temporal lobe (MTL) regions, including the hippocampus, are most commonly affected in MCI and early AD [4, 12, 13]. These MTL regions are essential [14, 15] for consciously recollected memory [16, 17]. Demonstrating both memory improvements and changes in the functioning of the MTL would thus provide evidence that it is possible for interventions to alter the brain system most affected by MCI and AD.

The cognitive training program from Posit Science involved adaptive games aimed at enhancing the speed and accuracy of auditory verbal processing [18–20], and has been demonstrated to improve memory performance in healthy elderly and MCI participants [1, 2, 18, 21]. Although the mechanism by which perceptual training could enhance MTL function is unknown, any influence of training on explicit or declarative memory likely involves MTL function.

Here, we examined the influence of this cognitive training program on memory ability and brain function in MCI participants in a random assignment design with an active control group. For the neuroimaging study, twelve participants with MCI (6 experimental, 6 active control) were recruited from a larger clinical trial of MCI [21], and fMRI researchers were blind to the assigned treatment conditions. An incidental repetition (versus novelty) fMRI paradigm was used because such a paradigm reveals impaired MTL function in AD [22], and is easy for memory-impaired participants to perform. AD participants exhibit reduced MTL differences between novel and repeated items [22], which indicates that MTL injury in AD reduces the typically greater MTL response for novel than repeated items during encoding. We used an auditory-verbal repetition paradigm to relate to the auditory-verbal nature of the training program. Because we were examining memory for verbal material, we expected any difference to be left-lateralized [23–25]; verbal memory has been associated with left hippocampal volume both in healthy aging and in mild AD [26, 27].

METHODS

Participants and procedure

Twelve participants provided informed consent as approved by institutional review boards at UCSF and Stanford University (neuropsychological data in Table 1). Diagnosis of MCI has been described previously [28] and was made by the Memory and Aging Center at UCSF according to recommendations of an international consensus committee [29]. Participants had to show evidence of cognitive decline based on patient and informant report. In addition, they had to be nondemented by DSM IV criteria and show no to minimal impairment in complex daily activities. Participants on acetylcholinesterase inhibitors were eligible, but only if they had been on a steady dose for at least two months. The two groups did not differ significantly on age or mental status (MMSE). The control group had significantly more years of education, but all participants had completed at least a college education.

Participants were randomly assigned to experimental or control groups. The randomization sequence was blinded from research personnel who enrolled participants or who administered cognitive tests. Participants were told that the purpose of the study was to compare the effects of two computer-based cognitive training programs.

Cognitive training was performed in participants' homes on study-provided computers. Participants were contacted weekly to make sure they were progressing through the training and to solve problems if necessary related to computer difficulties and issues of compliance. The experimental group completed a computer-based, cognitive training program developed by Posit Science Corporation (San Francisco, CA). The program involved 7 exercises designed to improve processing speed and accuracy in auditory processing: (1) determine whether 2 sounds were sweeping upward or downward; (2) identify a target syllable when it interrupted a repeated, similar sounding syllable; (3) distinguish between 2 similar sounds (e.g., "bo" and "do"); (4) match sounds on a spatial grid; (5) distinguish between 2 similar sounding words (e.g., "rake" and "lake"); (6) follow a series of instructions that increased in complexity; and (7) identify the picture that corresponded to the sentence. Each exercise employed adaptive tracking methods to continuously adjust task difficulty based on performance. Participants used the program for 100 minutes per day, 5 days per week until either achievement of asymptotic performance levels over a several day period or completion of 80% of the training material in a given exercise. Progress was monitored automatically through weekly electronic data upload. The control group performed 3 types of computer-based activities to control for the time intensity of the intervention and to keep participants "blind" as to their group assignment. Specifically, participants were given weekly "assignments" that involved listening to audio books, reading online newspapers, and playing a visuospatially oriented computer game (Myst) for 30 minutes each, for a total of 90 minutes per day, 5 days per week. Progress was monitored through self-report. Training lasted an average of two months across participants. In the beginning of the training, there was a slight difference between the groups in the way time on the task was structured before the regular-length sessions (100 minutes) began. Training for the experimental group lasted 100 minutes per session for 24 sessions; the length gradually increased (20 minutes on the first day, 40 the second, 60, 80, then 100 on day five) for a total of 2200 minutes of training. In order to equate training time in the control group and adjust for the graded onset in the experimental group, training for the control group was 90 minutes per day for 24 sessions; the training session length was fixed for a total of 2160 minutes of training.

MEASURES

Neuropsychological evaluation

The RBANS [Repeatable Battery for the Assessment of Neuropsychological Status, 30] was administered to evaluate whether training enhanced memory ability. There were two parallel forms of this measure and because the person conducting the assessments was blind to the group status of participants, Form A was used at time 1 and Form B was used at time 2. Because patients with MCI typically have poor memory, we used the immediate subtests rather than delayed memory subtests to avoid floor effects. Immediate memory scores for list learning (sum of word list learning trials) and story recall were averaged for each session (hereafter referred to as the RBANS memory score). Participants were impaired on memory tests, but the control group scored higher than the experimental group on some measures (Table 1). There were no group differences in the delay between pre- and post-testing ($M = 72$ days, $SD = 26$, $p = 0.13$) or the delay between the end of training and post-testing ($M = 10$ days, $SD = 7$, $p = 0.44$).

Functional neuroimaging evaluation

Participants underwent fMRI sessions before and within 2 ½ weeks after finishing training. Each session began with practice outside the MRI in which the participants performed several trials in which they were exposed to the repeated stimuli. Data were collected on a 3 Tesla GE Signa scanner using a spiral [31] acquisition sequence (TR 3000 ms, TE = 30 ms; flip angle = 70, FOV = 24 cm; 64 × 64 matrix; 3.75 mm in-plane resolution, 22 contiguous, axial, 5 mm slices, number of excitations = 1). In order to achieve improved data collection within the MTL, a spiral in/out sequence was used [32]. Clustered acquisition was applied such that the scanner remained silent when the words were presented, over the first 1500 ms of the TR, and the images were collected during the second 1500 ms in each of two 7 minute 21 second runs (data from the first 9 seconds were not collected to allow the MR signal to stabilize) (Fig. 1).

Word stimuli consisted of abstract and concrete, auditorily presented nouns that were equalized for volume. Parallel but different word lists were used pre-and post-training, each list consisting of 96 words for the novel condition, and 2 words (one abstract and one concrete) in the repeated condition. The forms were equated for frequency, concreteness, and numbers of syllables [33]. Words were classified as abstract if their concreteness ratings were less than 400 and concrete if their concreteness ratings were greater than 500. Words that had more than one meaning but sounded identical (e.g. pair, pare, pear) were excluded even if both words resulted in the same response (e.g., son, sun). Because the neuroimaging researchers were blind to group assignment, the two lists were presented in a fixed order for pre- and post-testing. Because the study design involved the use of blocked trials, the ratio of abstract to concrete words was 1 : 4 so that for each block most nouns were concrete but there were enough “catch” (i.e., abstract word) trials that participants needed to attend and make decisions about each word.

Participants heard a series of auditorily presented words and performed a right index finger keypress to indicate whether or not each word was “touchable” (concrete). A blocked design was used with 3 conditions cycling 6 times in a pseudorandom order (novel, repeated, sensorimotor control). Trials lasted 3 seconds and there were 8 words in each 24-sec block. In novel blocks, 8 words were presented once only. In repeated blocks, there were 2 words, one abstract (2 times per block) and one concrete (presented 6 times per block) that were presented repeatedly in all repeated blocks. In the sensorimotor control periods, participants pressed the keypress in response to the auditorily presented command “press”. During the repeated and novel word conditions, the visual command “Touchable?” was displayed, and during the sensorimotor control condition the command “Press” was displayed (Fig. 1).

Functional MRI data were analyzed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK; SPM2) implemented in MATLAB (Version 6.5.1 Mathworks, Inc., Sherborn, MA). Functional images were motion corrected, normalized into a common stereotactic space (template from Montreal Neurological Institute) and spatially smoothed with a Gaussian filter (FWHM 6 mm). A model (a box-car reference function, corresponding to the time course of the novel, repeated, and control conditions convolved with an estimate of the hemodynamic response function) was fit to the fMRI time series data from each participant. Contrast images consisting of a weighted linear combination of parameter estimates at each voxel for the comparison of interest, the novelty effect (i.e., novel-repeated word judgments) were computed for each participant. Within-group and between-group random effects analyses were conducted on these contrast images. A mask of the left hippocampus was generated using the Wake Forest University pickatlas [<http://www.fmri.wfubmc.edu/cms/software#PickAtlas>, 34, 35]. This mask was applied to perform a small volume correction in the left hippocampus ($p < 0.05$, family wise error corrected). In order to explore whether any other region in the brain showed a significant

change due to treatment, we also performed a more liberal whole-brain analysis, $p < 0.001$, uncorrected, spatial threshold 5 voxels.

ANALYSES

The effect of training was examined in both the neuropsychological and fMRI data by submitting each to a mixed design ANOVA that tested for an interaction of time (pre- and post-training as a repeated measure) and group (experimental and control groups as a between subjects measure). Significant differences were interrogated with post-hoc t tests. We hypothesized that the experimental group would show a greater increase in RBANS immediate auditory verbal memory scores than the control group. This prediction was based on a prior finding of training-induced gains in healthy older people [1, 2], and a trend towards gains in MCI patients [21]. In the fMRI analysis, we hypothesized that the experimental group would demonstrate a greater increase in fMRI activation (novel > repeated conditions) than the control group. We also examined, via correlation analyses, whether there was any relation between changes in activation and either changes in RBANS scores.

RESULTS

Training progress in experimental participants

All participants in the experimental group made progress in the training program as measured by improved performance on training tasks from the beginning to the end of the program; improvements varied across participants from 43% to 100% of the stimulus content ($M = 78.8\%$, $SD = 26.2$).

Neuropsychological change

The experimental group (pre-training $M = 17.3$, $SD = 1.9$; post-training $M = 20.0$, $SD = 3.3$) showed a greater gain in performance than the control group (pre-training $M = 18.5$, $SD = 2.9$; post-training $M = 17.4$, $SD = 4.1$; $F(1,10) = 4.76$, $p = 0.054$) (no main effect of group or session). This trend toward an interaction reflected significantly greater gain in memory performance in the experimental group ($M = 2.67$, $SD = 3.16$) than in the control group, who declined ($M = -1.08$, $SD = 2.78$) in performance across sessions. Because there was reason to expect based on previous studies that the experimental group would have an advantage over the control group, a one-tailed test of change scores was performed ($t(10) = 2.61$, $p < .027$, Cohen's $d = 1.38$) (Fig. 2).

Brain function change

In the a priori region of interest in left hippocampus, there was a significant interaction between group, session, and activation in left anterior hippocampus (peak Talairach coordinates $-32, -13, -19$) (Fig. 2). This reflected a small but consistent gain in activation in this region in the experimental group (5/6 participants exhibiting post-treatment gains in activation) and a larger and consistent loss of activation in the control group (6/6 participants exhibiting post-treatment declines in activation). Exploratory whole-brain analysis revealed a significant interaction between group, session, and activation only in virtually the same location (peak Talairach coordinates $-30, -14, -21$). Pre-post changes in left hippocampal activation across all participants tended to correlate positively with pre-post changes in RBANS memory scores ($r = 0.49$, $p = 0.10$, Cohen's $d = 1.14$). Functional MRI pre-testing occurred an average of 4 days away from cognitive testing ($SD = 11$), and there were no differences between the groups in this delay ($p = 0.17$). Functional MRI post-testing occurred an average of 2 days away from the cognitive testing ($SD = 5$), and there was no difference between the groups in this delay ($p = 0.73$).

Behavioral effects in the MRI

Behavioral data from the scanner were lost on two participants from the experimental group during pretraining due to equipment error, and this left 4 experimental and 6 control subjects with complete behavioral data. Behavioral data were available from all 12 participants after training. There was no significant difference between the groups for either session with respect to accuracy (means in Table 1). An ANOVA of reaction times on the 10 participants with complete data comparing session (pre-, post-training), repetition (novel, repeated), and group (experimental, control) failed to detect any group differences, but responses were faster for repeated ($M = 746.8$, $SD = 90.3$) than novel words ($M = 1120.5$, $SD = 168.2$) (main effect of repetition ($F(1, 8) = 66.14$, $p < .001$), and there was an interaction between session and repetition ($F(1, 8) = 14.62$, $p < .005$). The interaction reflected a growth of the advantage for repeated relative to novel words from pre-training ($M = 301$ ms, $SD = 162$) to post-training ($M = 420$ ms, $SD = 133$). Importantly, there was neither a main effect nor an interaction with group, which means that any activation differences between groups cannot be accounted for by response-time or accuracy differences between groups.

DISCUSSION

In a random-assignment, active-placebo experiment with MCI participants, cognitive training positively affected memory ability and memory-related left hippocampal function. The small number of participants in the study warrants a conservative interpretation of the findings. In regards to MTL activation, the benefit for the experimental group appeared to reflect less of the continuing decline that was expected in MCI and was evident in the MCI control group. The hippocampal changes in function were, however, consistent at a single-patient level: There was virtually no overlap in pre-post activation changes between the experimental group (with 5/6 participants showing increased activation) and the control group (with all 6 participants showing decreased activation and with all decreases larger than the single decrease in the experimental group). Thus, these findings suggest that despite presumed injury to the hippocampus in MCI that typically leads to AD, the hippocampus in MCI retains sufficient neuroplasticity to benefit from cognitive remediation.

The behavioral and imaging findings are consistent with and extend previous work in older adults and participants at risk for dementia showing that mental activity is associated with brain plasticity. MTL chemistry was modified by prolonged cognitive training in a study of healthy older adults that demonstrated changes in hippocampus using MR spectroscopy [36]. A longitudinal study found that self-reported histories of higher life-span cognitive activity were associated with a reduced rate of hippocampal volume atrophy [37]. A small cohort of older adults (8 experimental, 9 control) with memory difficulty performed a variety of healthy lifestyle changes over the course of 2 weeks, including performing “brain teasers” and verbal mnemonic memory training [38]. Improved verbal fluency was associated with decreased dorsolateral pre-frontal metabolism, but there was no improvement in verbal memory.

Cognitive training in the present study appeared to enhance hippocampal function despite the fact that the training focused on auditory-verbal perception rather than memory per se. The finding that increased hippocampal activation was associated with better memory performance on neuropsychological testing is consistent with correlational evidence that increased hippocampal fMRI activation in MCI participants is compensatory [39]. Although it is expected that a gain, or reduced loss of, memory function in MCI would be associated with MTL plasticity, it is unknown as to why this training program was associated with MTL functional plasticity and not functional plasticity in auditory neocortex. Both frontal and hippocampal regions, as opposed to inferior parietal, superior temporal, and anterior cingulate regions, have exhibited upregulation in choline acetyltransferase activity in MCI

relative to healthy older adults, and thus both regions may be particularly amenable to intervention [40]. Also, although MTL functional plasticity was observed, that plasticity could reflect a functional benefit of primary, structural plasticity in other brain regions; however, in this study only MTL plasticity was robust enough to detect with fMRI.

A question of interest is what psychological and neural mechanisms translate training that focuses on auditory perception to gains in auditory memory and hippocampal function. One possibility is suggested by animal studies of neuroplasticity showing that degraded brain processing of perceptual inputs can degrade the quality of mental representations, and that perceptual training can improve the accuracy of higher order mental representations [18, 41]. Improved auditory representations of the words heard in the scanner may have enhanced experience-dependent plasticity. Several studies of aging have shown surprisingly strong correlations between basic sensory and memory declines (e.g. [42]). These could reflect a shared mechanism that is related to performance on both sensory and memory tests, such as attention. Alternatively, it may be that improved perceptual processing enhances memory performance in that modality. Some studies have found, for example, that cataract surgery improving vision also improves broader cognition [43]. We did not observe training-related alterations of activation in auditory temporal-lobe regions that could mediate perceptual training, but this may reflect the limited sample size.

There were several limitations to the current study beyond the small sample. The study was conducted prior to current MCI subtyping so it is uncertain how many participants would now be classified as amnesic-MCI. The baseline test scores suggest that the majority of the participants had significant memory dysfunction, with low standardized scores on delayed tests of memory, but average scores on visual construction, language, and attention indices (Table 1). Overall, this would be consistent with an amnesic-MCI subtype. The present study was not designed to examine the duration of benefits from cognitive training. In healthy adults, gains achieved via cognitive training were sustained over a 3-month no-contact period [1]. In the present study, imaging occurred days to weeks after training was completed, so benefits do not appear to end immediately after training. It seems likely, however, that benefits from a cognitive training program in the face of a degenerative brain disease would not last long without continued application (as would be the case with physical exercise or medications). We attempted to match exact time spent training between the groups, but the control group self-reported their training times (in contrast automatic data downloading for the experimental group) so that training times of the control group may be less accurate. Future studies should automatically track training times in all conditions.

Because of the relatively small group of participants, subtle individual differences may have an impact on our results and we address these differences here. One participant in the study had chronic, well controlled, temporal lobe epilepsy, but this participant's memory performance and activation pattern were typical for the treatment group and did not alter the overall outcomes. Also, the control group was slightly but significantly better educated than the experimental group. It is not possible to know the impact of this difference in education on the failure of the control group to benefit from training because so few studies of cognitive training in MCI have been conducted. A previous meta-analysis of 19 studies (30 training groups) comparing healthy older adults above and below 14 years of education (a median split) failed to find an effect of education on cognitive training outcome [44]. Education has also been found to be unrelated to disease progression in dementia, but is related to relatively higher cognitive functioning [45]. Thus, the available evidence suggests that the small but significant difference in education between the two groups is unlikely to account for the findings.

With the caveats noted above, however, the present findings report that cognitive training in a random-assignment, double-blinded, active-placebo design was associated with less loss of memory ability and growth of hippocampal activation in MCI. These findings ought to motivate larger studies to more definitively determine whether such cognitive training can slow memory loss and functional hippocampal degeneration and extend a higher quality of life in MCI.

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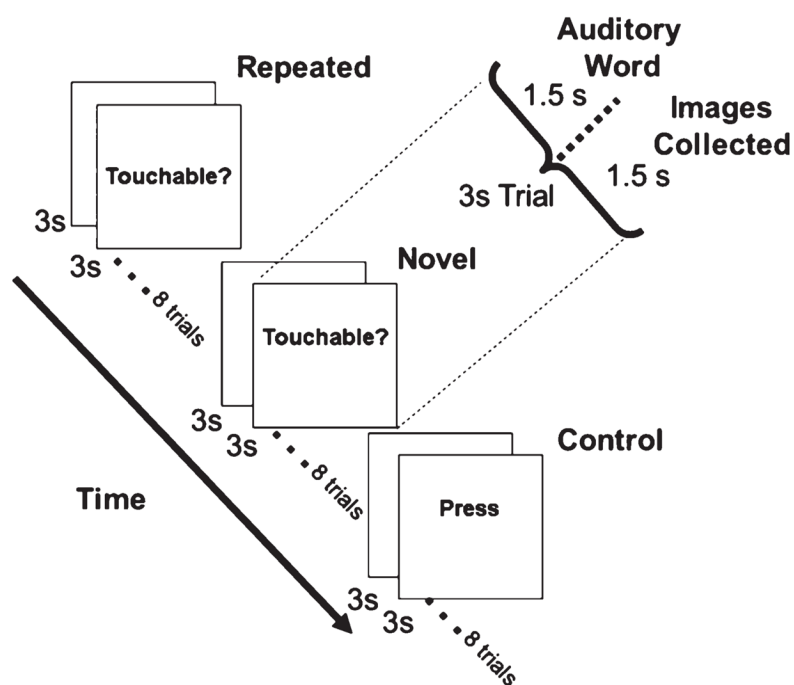
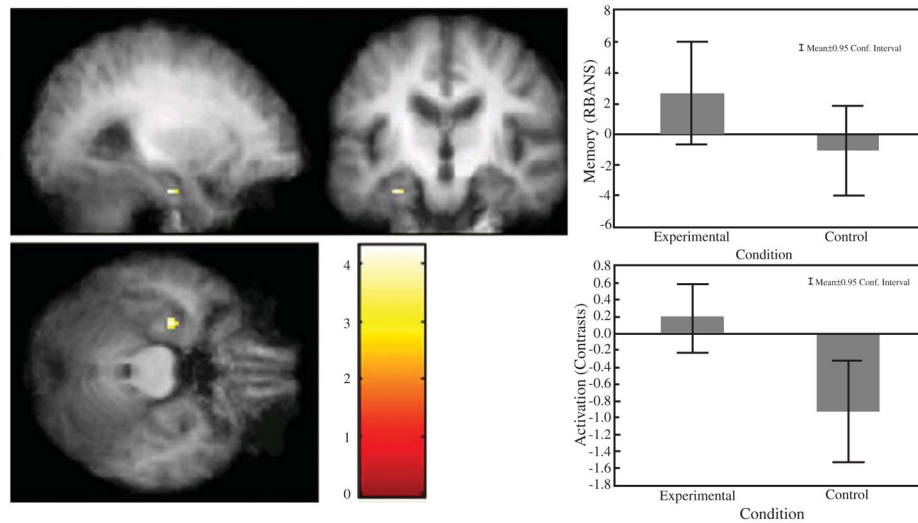


Fig. 1.

The design of the experiment was that words were presented during periods when the MRI was silent so that participants could hear them. The instructions were displayed visually and word stimuli were presented auditorily.

**Fig. 2.**

Brain and behavioral differences between experimental and control groups before versus after intervention. The left panel depicts the location in left hippocampus that showed a significant interaction between group and intervention, such that the experimental group showed increased activation and the control group showed decreased activation for novel relative to repeated words after intervention (shown in bottom right panel). Top right panel shows changes in memory performance before versus after intervention, with a gain in memory performance for the experimental group and a loss in memory performance for the control group. Bars in histograms depict 95% confidence intervals.

Table 1
Baseline demographic and neuropsychological data and fMRI accuracy and reaction times

	Experimental				Control			
	Mean Raw	SD	Mean SS	SD	Mean Raw	SD	Mean SS	SD
Age	70.67	(10.58)			78.00	(7.92)		
Education	16.67	(0.82)			18.33	(1.51)		
MMSE	29.33	(1.21)			27.83	(2.32)		
RBANS at baseline								
List learning	20.50	(2.59)	84	(13)	21.83	(3.25)	88	(12)
Story memory	14.17	(3.87)	88	(14)	15.17	(3.19)	92	(11)
Figure copy	19.17	(0.75)	110	(6)	17.83	(2.48)	102	(16)
Line orientation	17.17	(2.48)	103	(11)	17.50	(1.87)	106	(10)
Picture naming	9.83	(0.41)	107	(9)	9.83	(0.41)	109	(5)
Semantic fluency	15.83	(3.76)	90	(14)	15.50	(5.05)	91	(18)
Digit span (forward)	10.00	(2.28)	99	(14)	11.50	(2.88)	112	(19)
Coding	36.33	(4.13)	90	(8)	34.17	(5.42)	94	(15)
List recall	1.33	(1.21)	79	(15)	1.17	(2.86)	77	(13)
List recognition	16.33	(1.37)	66	(17)	16.00	(2.45)	68	(27)
Story recall	4.67	(3.08)	78	(26)	7.17	(3.25)	93	(15)
Figure recall	6.83	(7.03)	81	(26)	9.17	(7.68)	84	(27)
Index Scores								
Immediate memory			80	(6)			92	(9)
Visual constructional functioning			111	(14)			107	(17)
Language			94	(9)			97	(13)
Attention			94	(10)			104	(18)
Delayed memory			66	(13)			77	(22)
Total			85	(8)			94	(13)
Sum of index scores	443.83	(33.1)			477.33	(48.45)		
fMRI								0.19
Visit 1								
Accuracy (percent)	90.43	(7.46)			91.83	(5.35)		0.74
Novel reaction time (ms)	1072.48	(116.93)			1110.41	(253.14)		0.79

	Experimental			Control		
	Mean Raw	SD	Mean SS	SD	Mean SS	p (raw) p (SS)
Repeated reaction time (ms)	830.43	(100)		750.84	(110.44)	0.28
Novelty effect (ms)	242.05	(33.05)		359.57	(199.44)	0.29
Visit 2						
Accuracy (percent)	91.84	(6.27)		88.27	(8.15)	0.52
Novel reaction time (ms)	1098.44	(102.8)		1157.57	(185.41)	0.75
Repeated reaction time (ms)	699.53	(42.59)		716.48	(80.49)	0.87
Novelty effect (ms)	398.91	(99.67)		441.08	(146.27)	0.76

Note. Top of the table displays demographic and baseline neuropsychological test data (RBANS) for all subtests and index scores. Standard scores (SS) are displayed next to the raw subtest scores and these characterize relative strengths and weaknesses of the participant. Normative data were made available by the test author after the publication of the measure (Randolph, 2002. Test Supplement)1. Data from both pre and post functional MRI task sessions are displayed on the bottom of the graph including accuracy and reaction time.