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D15 Report on elderly-tailored on-line games with measurement capabilities

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Acronyms

Acronym	Description
ACE	Addenbrooke's Cognitive Examination
AD	Alzheimer Disease
CNS	Central Nervous System
GLM	General Linear Model
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
PAL	Paired Associates Learning
RAVLT	Rey Verbal Learining Test
SD	Standard Deviation
TIV	Total Intracranial Volume

1 Introduction

It is well documented that an aging society is a general tendency in Europe as well as in the United States (USA). The number of people belonging to the population aged 65 or over has tripled in the last 50 years and this tendency is expected to continue in the next 50 years [1]. Data on the prevalence of dementia are varying but studies are consistent in indicating the increasing prevalence of the disease in older age. Total payments for health care, long-term care, and hospices for people with Alzheimer Dementia (AD) and other dementias in the USA are forecasted to increase from $203 billion in 2013 to $1.2 trillion in 2050 (in 2013 dollars) [1].

Since there is no effective treatment for dementia, the early detection of symptoms and the identification of methods for slowing the progression of the disease have been the main focus of medical research on the subject in recent years.

The transitory condition between physiological aging and dementia known as 'mild cognitive impairment' (MCI) has gained a significant focus of interest. In MCI mild impairment of cognitive skills can be revealed by neuropsychological tests [2], while global cognitive functions and everyday activities are preserved. The clinical significance of the pre-disease conditions is based on the increased conversion rate of affected patients compared to the average. While dementia occurs annually in 1–4% of average elderly population, this rate is 10–15% in case ofMCI [3,4]

In view of the above it is understandable that several studies target the symptoms and differences from the average population that are closely linked to the development of dementia and can therefore be used to assist the early diagnosis.

At present cerebral imaging methods, especially MR imaging of the temporal brain regions and neuropsychological tests are considered to be the most sensitive tools for the early detection of risk [5]. In the latter case literature emphasizes the importance of the tests assessing visuospatial memory targeting the most frequent type of dementia, Alzheimer's disease [6,7].

This is consistent with the fact that the neuropathological changes in Alzheimer's dementia start in the entorhinal cortex and in the hippocampus years before the occurrence of clinical symptoms, and then they spread to further parts of the brain [8]. Hippocampus is the area where information on space and objects converges [9,10], therefore its functioning in visuospatial memory is crucial.

Long term follow-up studies suggest that subjects who achieved worse results in visuospatial memory tests such as the Paired Associates Learning (PAL) test compared to

peer groups had a higher risk of developing dementia in later life [6]. Literature supports the importance of risk population screening, demonstrating that treatment, specifically cognitive training, started in pre-dementia stage prolongs the duration of this stage and subsequently the duration of independent living [11]. Several studies showed that cognitive training can produce moderate to large beneficial effects on memory related outcomes [12,13], enhance cognitive control [14] and reduce the risk of dementia [15] based on the brain plasticity [16,17]. The difficulty of screening arises from the fact that these neuropsychological tests (the basis of diagnosis) were developed for clinical use. Therefore they are available only for a limited number of patients, since their application requires the active participation of an expert. Contrary to this, cognitive games provided by web pages dedicated to maintain and improve mental functions are accessible for a wider range of the population. The games on these web pages can entertain a participant, many of them have concurrently demonstrated a benefit on the development of various cognitive domains, therefore on maintaining mental wellbeing [18,19]. The widespread availability of these games and the fact that they don't require extensive expertise can make them suitable for fulfilling the screening function [20]. Another issue with clinical neuropsychological testing is that in most cases, when subjects visit a psychologist or a psychiatrist, the symptoms of the cognitive decline are manifest and interfere with everyday functioning, i.e. the dementia has already developed. Unlike europsychological tests, cognitive games are played by healthy, well functioning elderly people, subjects who should be monitored for early signs. Additionally the games can be played regularly, daily or weekly, which make them a repetitive measurement, and thus ideal for screening.

Therefore it is always important to emphasize toward participants in such programs, that the result of the screening is not equal to the clinical diagnosis, it is rather a recommendation to seek further professional help, and that it may be prudent to undergo detailed neuropsychological testing and neuroimaging.

The primary objective of this study was to show the suitability of similar computer games developed in the framework of the M3W project in the detection of preclinical signs of later cognitive decline. Therefore the correlation between the results of the computer games and the size of CNS structures were analyzed. Furthermore the perfromance differences in these games between healthy controls and subjects with MCI were also analyzed.

The major cause of dementia is Alzheimer's disease, where the visuospatial memory is the earliest function affected [6,7]. Therefore for the purpose of this study the well-known 'Find the Pairs' memory game (computer version) was chosen, since this game assesses

this memory function. Based on the results of previous longitudinal follow-up studies it is a well known fact that the volume of the hippocampus and the related structures, such as the volume of the temporal lobes, and the entorhinal cortex are the best predictors of cognitive decline and the later conversion to dementia [21–23]. Therefore the primary endpoint of the present investigation was to show correlation between the volumes of these Central Nervous System (CNS) structures and the results of the memory game. A further endpoint was to show differences between subjects with MCI and healthy controls in the results of the memory game. While neuropsychological tests such as the Rey verbal learning test are also good predictors of pathological cognitive decline in elderly people, our secondary endpoint was to show correlations between these neuropsychological measures and the memory game. An implementation of the Paired Assocaites Learning test (PAL) has also been developed in the framework of the project, and a similar validation to the memory game was done and described here.

In other types of dementia such as frontoteporal and vascular dementia the decline of executive functions are often observed. Therefore the results of the 'Rabbit game', which intends to assess executive functions, are analyzed together with neuropsychological tests assesing executive functions and the thickness of the frontal cortex strongly linked to planning and executive functioning. Again a further endpoint was to show differences between the study groups in the game results.

2 Participants

Altogether 50 subjects participated in the study (70% female), aged between 58 and 86. The average age was 67.2. Patients with record of stroke or head injury with loss of consciousness are excluded from the study. Patients with epilepsy, or active phase psychiatric disorder, or drug, or alcohol abuses and those who suffered with dementia were also excluded. According to the neuropsychological tests there were 22 healthy controls and 28 patients with MCI.

3 Methods

3.1 Differentiation among participants

The Petersen criteria include subjective memory complaint corroborated by an informant together with preserved everyday activities, a memory impairment based on a standard neuropsychological test, preserved global cognitive functions and finally the exclusion of dementia. It does not specify a neuropsychological test for the assessment of memory

impairments, therefore we applied the Rey Auditory Verbal Learning Test (RAVLT), which is the most frequently used test based on the literature [5]. For the differentiation between MCI and healthy controls we applied a cutoff score of 1 SD under population mean standardized for age and gender. If a given subject scored under this cutoff value either in the total score or in the delayed recall subscore, he or she was put into the MCI group. These criteria are based on the recommendations of the National Institute on Aging—Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [12].

The Petersen criteria allow the recognition of amnestic MCI, when decline of memory is observed in Neuropsychological tests. With another group of MCI, memory loss is not as significant as the impairment of their cognitive functions. This type is called the Amnestic Mild Cognitive Impairment, where executive functions are mostly involved. In the study non-amnestic MCI patients were separated, based on the data of age and education adjusted, standard Trail making tests, so that their results of the mainly non-memory increasing games could be examined separately.

3.2 Neuropsychological tests

The Mini Mental State Examination (MMSE) is a standard test; its effectiveness was proven by several studies, as a useful method in differentiating between subjects with dementia and healthy controls [5,31]. The subtasks of the test assess orientation, central executive function, rapid association formation, verbal identification ability and the ability to analyze and synthesize.

The Addenbrooke's Cognitive Examination (ACE) was used to assess the global cognitive performance, including orientation, attention, memory, verbal fluency, verbal and visuospatial skills [32,33].

The Rey Auditory Verbal Learning Test (RAVLT) was used for the detailed assessment of memory functions based on Petersen criteria. Rey test evaluates verbal learning and memory [34]. A list of 15 words (list A) should be repeated by the subject immediately. This test is repeated 5 times. Then another list of 15 words (list B or interference list) is presented once that should be recalled. Then list A should be recalled without repeating, and then this task is repeated after 30 minutes.

The Trail Making test, Part A and Part B (number connection) [33,35,36] is used to evaluate selective attention, cognitive flexibility and executive functions. In Part A, randomly distributed numbers should be connected in numerical order, while in Part B randomly distributed numbers and letters are displayed. The subject is instructed to connect them in a

pre-defined order. The time required to complete the test is the dependent variable. Part A of TMT measures attention and executive functions, while Part B is also affected by cognitive flexibility.

3.3 Games

Visuospatial memory was measured by an implementation of the PAL test used in several neuropsychological test batteries [37]. In the PAL test windows open up in random positions on the screen after each other for 3 seconds with abstract shapes shown in one or more windows.

Other windows remain blank depending on the difficulty level. When all squares were shown, the previously shown shapes appear in the centre of the screen and the participants have to decide in which window they saw that shape before. The test consist of five different levels in eight stages in total, the number of shapes increases from 1 to 8 on the different stages. The subjects had 10 trials to complete a given stage, otherwise the test ended. The arrangement of windows was asymmetrical in the test and it changed from stage to stage. [37]

The '**Find the Pairs**' memory game requiring mainly visuospatial memory was selected from a set of computer games developed in the framework of the 'M3W' project (http://www.m3wproject.eu), dedicated to maintaining and measuring mental wellness among elderly people. In the beginning of the game, cards are laid face down. Two cards can be flipped face up in each turn by clicking on them. If the shapes (pictures) on the cards match, they disappear. The task is to clear all the cards from the table by finding the pairs. First there was a tutorial run on a table of 3x4 cards, afterwards participants had to complete a practice run on a table with 3x6 cards, and finally the measurement was done on a table of 4x6 cards. The position of the cards was the same for all participants.

The '**Rabbit game**' assesses planning and executive functions. The numbered figures should be placed in numerical order following these rules: A figure can only move to an empty slot, can only jump one other figure or move to an adjacent empty place. Players should solve the puzzle using the least possible moves and the game also has a time limit.

3.4 MRI images

All patients underwent a routine brain MR examination, including high resolution anatomical images, which were used for further analysis. Image acquisitions were done at the MR Research Center, Semmelweis University, Budapest on a 3 Tesla Philips Achieva clinical MRI scanner equipped with an 8-channel SENSE head-coil. The high resolution, whole brain

anatomical images were obtained using a T1 weighted 3 dimensional spoiled gradient echo (T1W 3D TFE) sequence.

Cortical reconstruction and volumetric segmentation were performed by Freesurfer 5.3 image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications; we made no changes to this pipeline. Briefly, image processing includes motion correction [24], removal of non-brain tissue using a hybrid watershed/surface deformation procedure , automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate,putamen, ventricles) [25] intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class [26,27]. Once the cortical models were completed, Freesurfer performed a number of deformable procedures for in further data processing and analysis. Steps included surface inflation [28], registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects [29], parcellation of the cerebral cortex into units based on gyral and sulcal structure [25], and creation of a variety of surface based data including maps of curvature and sulcal depth. Segmentation and cortical models were checked and corrected manually on each subject, however correction showed no significant changes to the results.

3.5 Statistical analysis

Correlations between the results of the memory game and the size of the temporal structures were analyzed by General Linear Model Analysis (GLM in SAS 9.2) with age, gender and Total Intracranial Volume (TIV) as covariates, and are given in terms of partial correlation R. In the correlation analysis of the results of the memory game and the result of the neuropsychological test only age and gender were the covariates. For the evaluation of the game the following output variables were used: clicks per picture and total time used. Correlations with the number of stages completed in the PAL test were analyzed by Spearman Correlation, since the distribution of this variable deviated largely from the normal distribution. In order to quantify uncertainty for the correlational analyses we calculated the 95% confidence intervals.

In case of the PAL test we used the adjusted number of total trials, instead of the raw total trials since this measure takes into account that several subjects failed to complete all the stages of the test and thus have fewer opportunity to make errors. In order to calculate the adjusted measure we added the maximum score of 10 trials for each stage not attempted due to an earlier failure to the raw total trials. We used also the number of stages completed as an outcome measure.

With the Rabbit-game standardized values of the number of correct clicks and the time needed to complete the game were used for evaluation. In this case 'Standardized' means that time results and the number of clicks were divided by the difficulty level (on the power of 3), so that results on different leveles are comparable and can be evaluated together.

Differences between healthy controls and subjects with MCI have been analyzed by GLM with age and gender as covariates (results are presented as bar graphs).

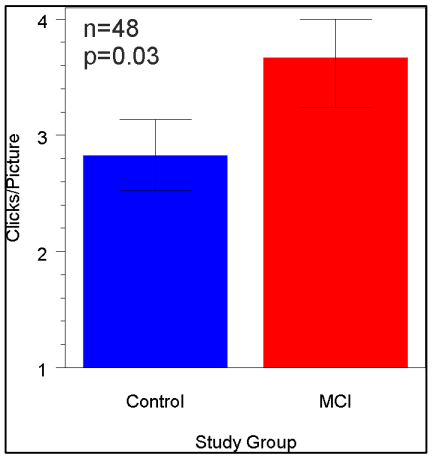
4 Results

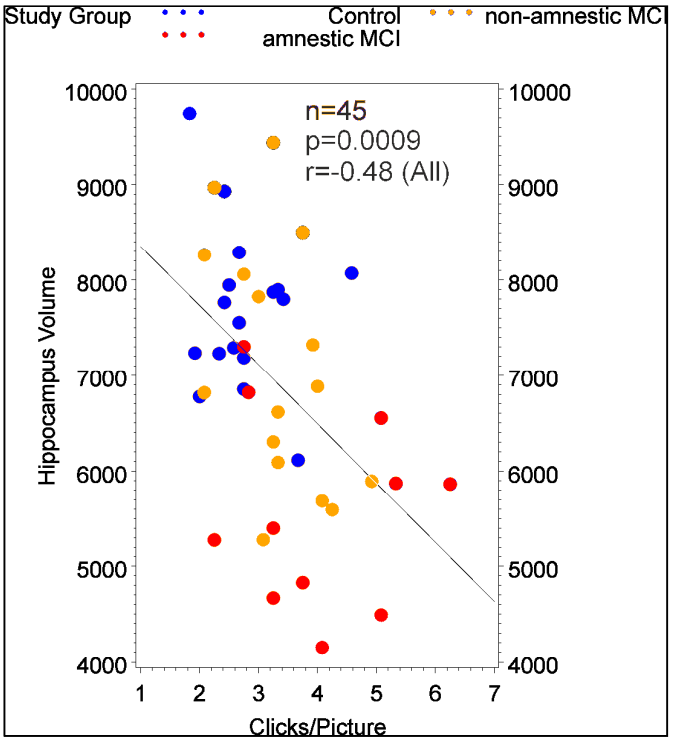
4.1 'Find the Pairs' game

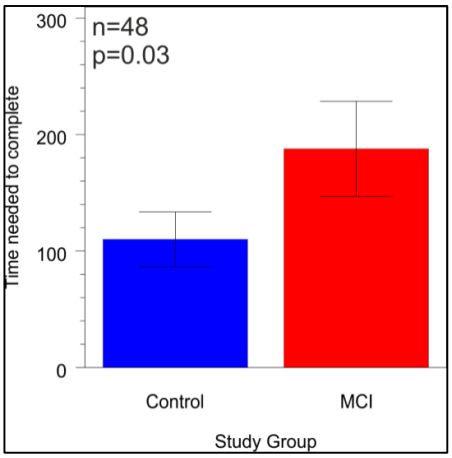
The aim of the investigation was to show that widely used computer games can help to identify subjects at risk. In order to show this, analysis was conducted of the correlations between the results of the **'Find the Pairs'** game and the volumes of those CNS structures previously found to be good predictors of later cognitive decline. The study found that subjects with smaller hippocampus volumes needed more trials and more time to complete the game (**Figure 1**).

Furthermore subjects with MCI needed significantly more time and trials to complete the game (**Figure 1**). Thus, the results support the initial hypothesis that healthy individuals achieving worse results in the **'Find the Pair'** game have increased level of atrophy in the predefined brain structures.

A similar correlation was found between the results of the Rey test and the above mentioned parameters of the game (**Figure 2**).







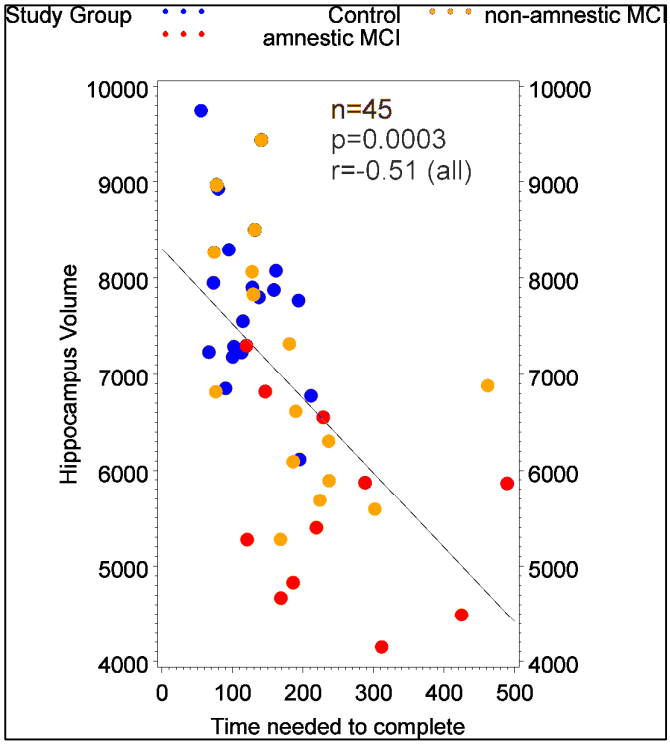


Figure 1

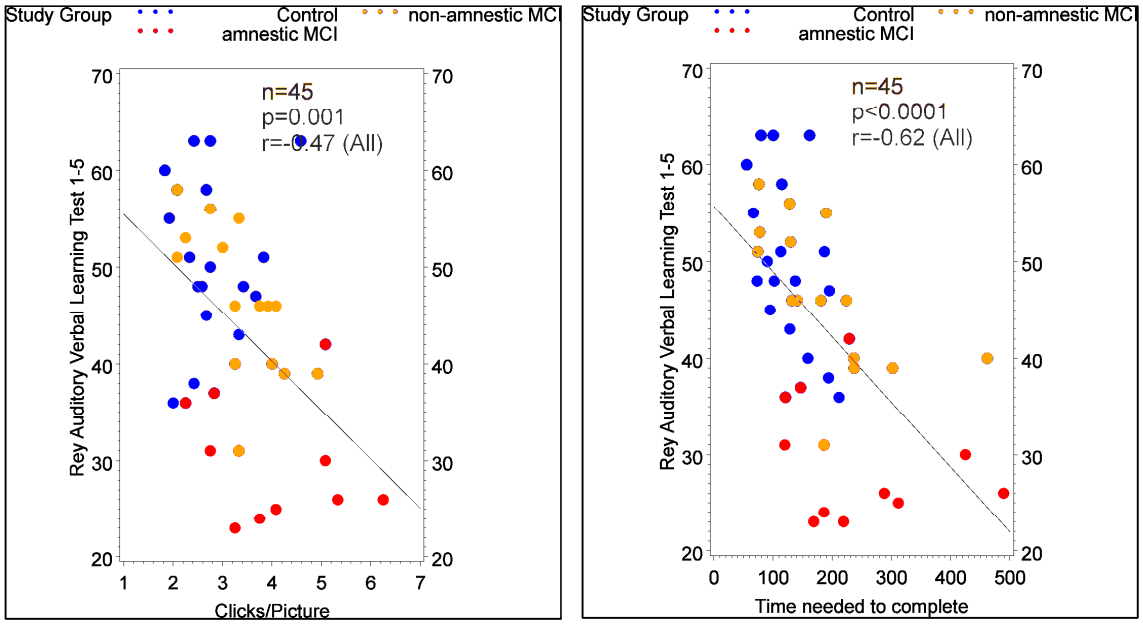


Figure 2

Furthermore there was no correlation between the results of the game and the total intracranial volume, the total cortex volume, and the amount of the cerebrospinal fluid, which shows the specificity of the above correlations. In other words this verifies that the above correlations are not due to general atrophy rather a consequence of a more specific process starting in the temporal regions. The results of the Trail Making Test part A and B, assessing mainly selective attention and executive functions respectively, did not correlate with the game results, which indicate that decreased performance in the memory game is not part of a general cognitive slowing.

4.2 The PAL test

The **PAL Test** developed in the framework of the M3W project was included to assess associative learning between visual stimuli and different spatial locations [37]. The total adjusted number of trials and stages completed in the PAL test were significantly worse in the MCI group compared to the control group (**Figure 3**). Furthermore the same parameters of the **PAL test** also showed significant correlations with the thickness of entorhinal cortex (temporal CNS structure responsible for memory functions and affected in the early stage of Alzheimer disease, **Figure 3**) and the results of the RAVLT (memory test to setting up the diagnosis of Alzheimer and MCI, **Figure 4**).

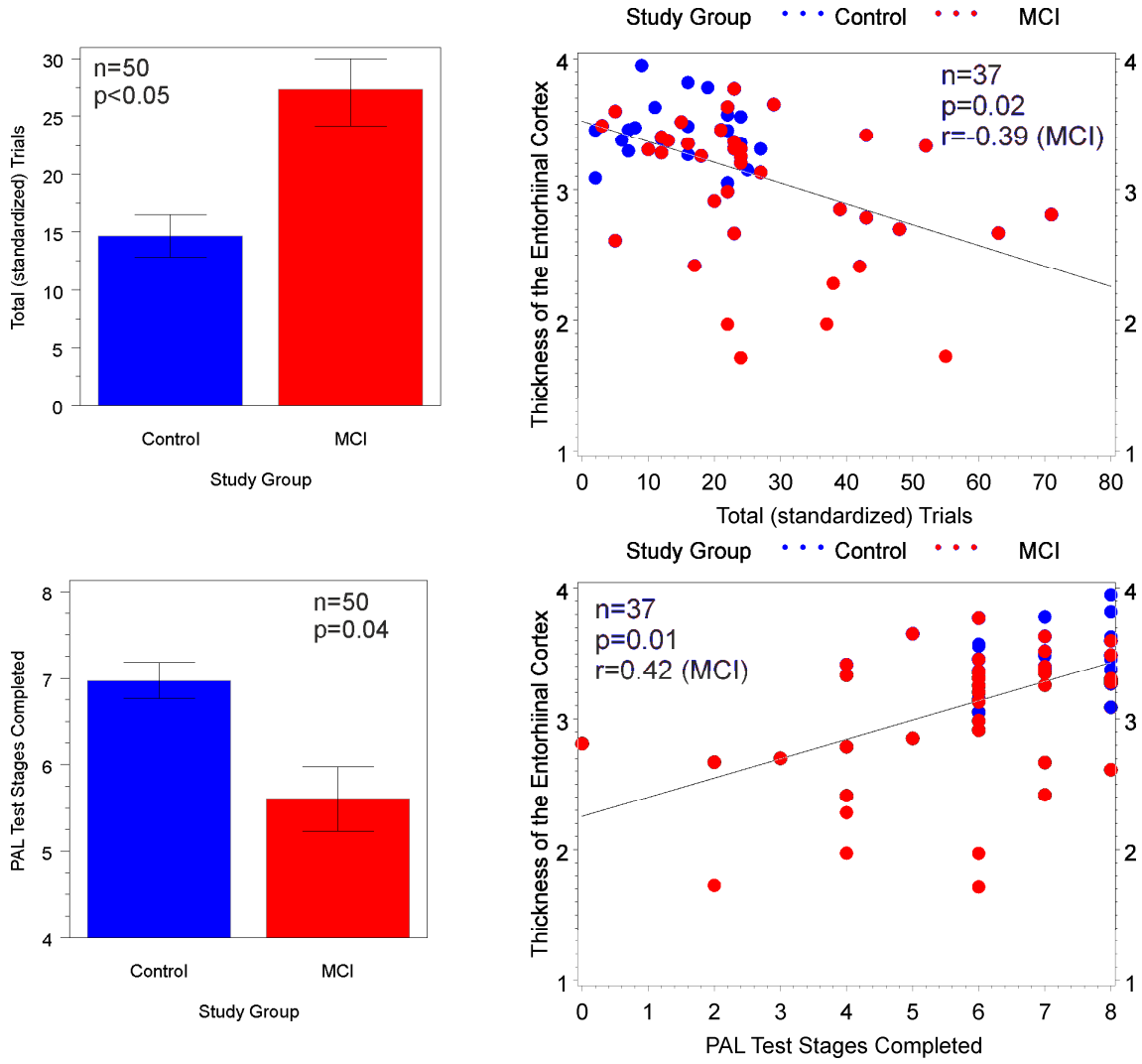


Figure 3

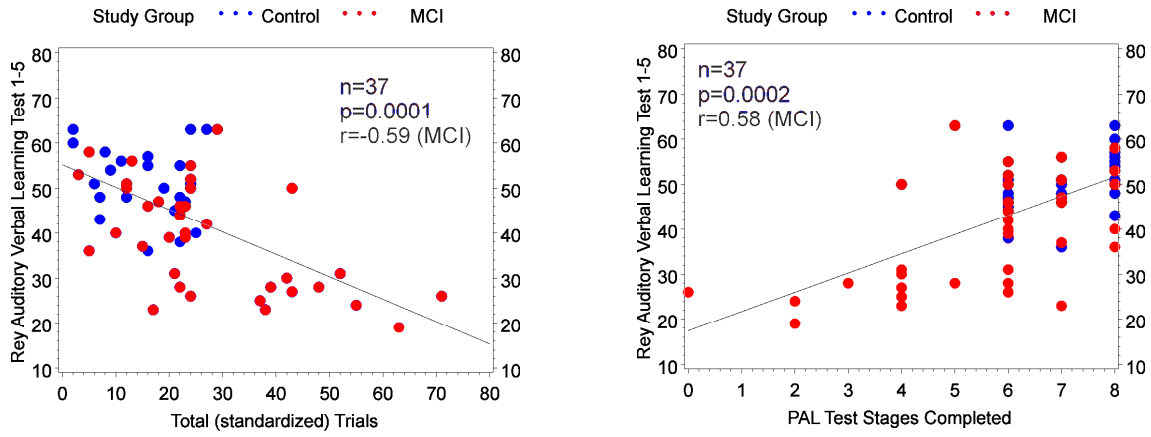


Figure 4

4.3 The 'Rabbit game'

The time and moves needed to complete the **'Rabbit game'** differed significantly between subjects with MCI and healthy controls (**Figure 5**).

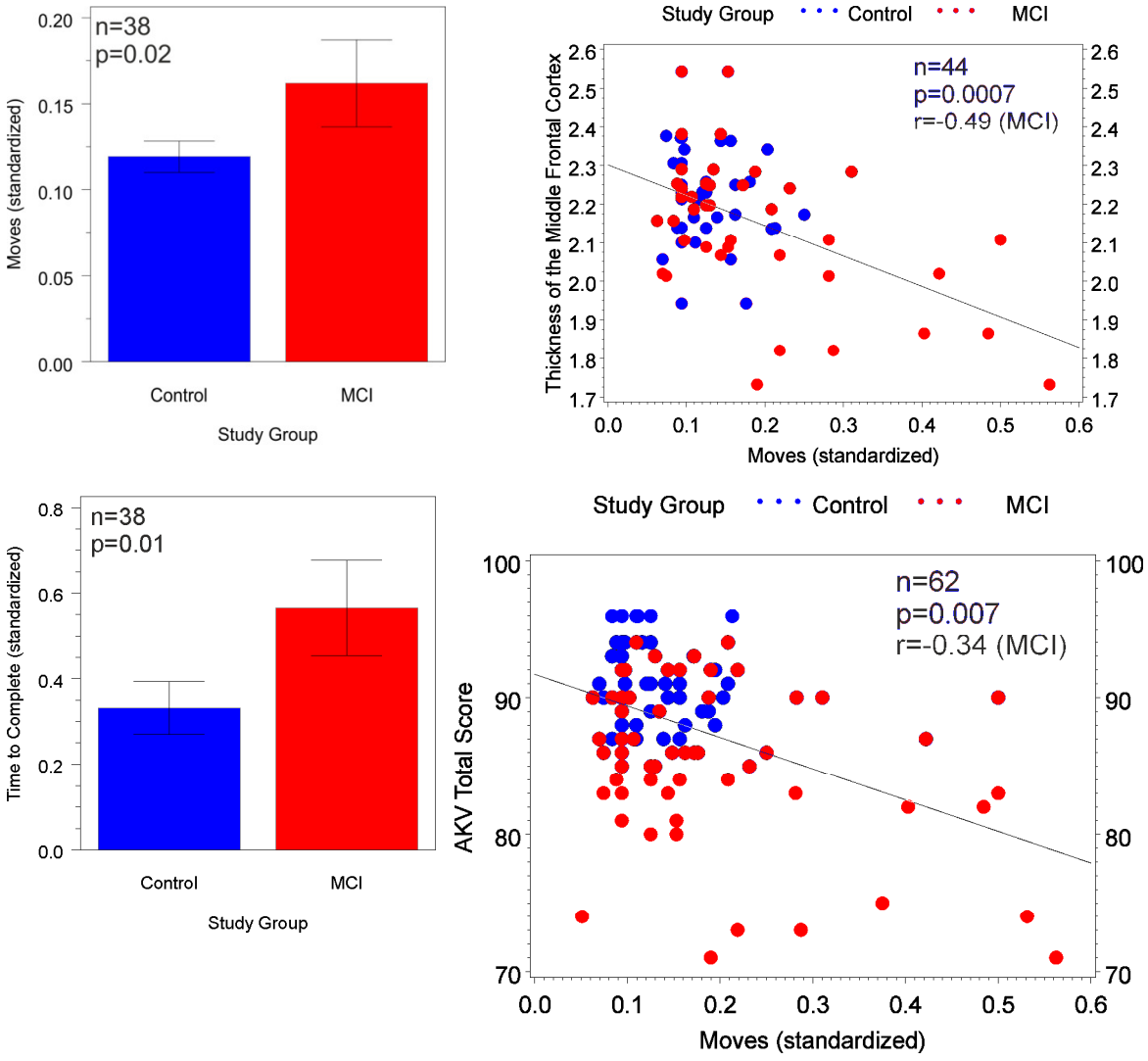


Figure 5

Furthermore the same outcome measures of the game show significant corellations with the thickness of middle frontal cortex and orbital gyrus (CNS regions responsible for planning and executive functioning) in the MCI group. A further significant correlation was found

between the moves to complete the **'Rabbit game'** and the results on the ACE test (a neuropsychological test to detect MCI) (**Figure 6**).

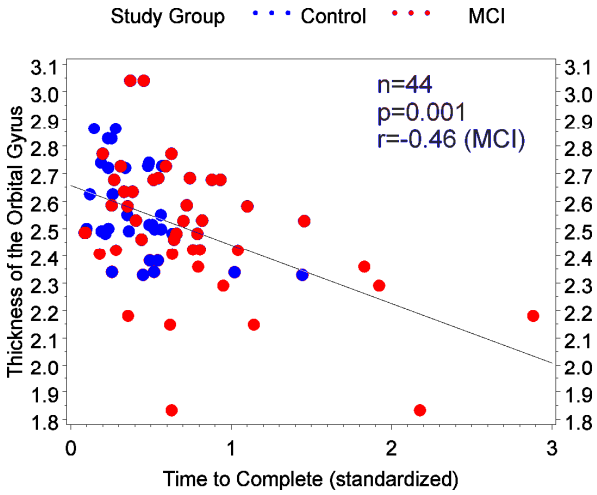


Figure 6

5 Conclusions

Our results support the initial hypothesis that the games developed in the framework of the M3W project can measure cognitive functions in elderly and can detect the early signs of MCI and dementia. Healthy controls and subjects suffering from MCI achieving worse results in the **'Find the Pair'** game and in the **PAL test** have increased level of atrophy in the temporal brain structures such as the hippocampus and the entorhinal cortex and showed decreased performance in the RAVLT, which were previously extensively validated and considered to be sensitive tools in the prediction of dementia. Additionally, subjects with MCI who performed worse on the '**Rabbit game**' showed stronger atrophy in the frontal regions responsible for executive functions and planning. Subjects with MCI achieved significantly worse in the '**Find the Pair**' game, on the **PAL test**, and in the '**Rabbit game**' compared to healthy controls. Based on these results it can be concluded that computer games such as the '**Find the Pairs**' game or the '**Rabbit game**' are useful in detecting the early signs of cognitive decline.

Compared with MRI and neuropsychological testing, the benefits of computer games are their accessibility, their cost-effectiveness, and the involvement of healthy subjects, or subjects with MCI. Furthermore cognitive games can be played at home, where anxiety caused by the clinical environment is not present and does not reduce performance. However their lower sensitivity and specificity are definite drawbacks. Therefore they can be

used to give feedbacks to the players, and may give a hint to them that it might be useful to seek professional help.

This may help people to seek help in the beginning of the cognitive decline far earlier than they currently do. It must be emphasized toward the users, that these computer games are not appropriate for diagnosing and therefore they cannot replace the detailed neuropsychological investigation in clinical practice. However the findings of this study support the idea that such games can help people at risk to seek professional help in time.

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