Methods on the screening of mild cognitive impairment and the slow down of progression – establishment of an online platform's medical background

Doctoral thesis

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The social and economic consequences of the aging society

According to the Council of the European Union, currently 47.5 million people in the world are affected by dementia (Supporting people living with dementia, 2015). It is predicted that the number of people suffering from dementia will double every twenty years and most of newly diagnosed cases will occur in developing countries (Ferri et al., 2005).

By applying the international epidemiological data on dementia to Hungary, 250,000 affected patients are estimated out of 2,000,000 elderly people over the age of 65 (Alzheimer's World Report, 2014).

As far as healthcare costs are concerned, estimates currently account for EUR 180 billion per year in the EU, which is expected to increase to EUR 250 billion by 2030. In Hungary, this amounted to about EUR 1 billion in 2008, 75% of which were direct health care costs and 25% indirect ones, such as time and money spent for home care (Alzheimer Europe, 2009).

To the aging of the population, the development of medical science and the consequent reduction in mortality caused by various physical diseases greatly contributes. However, against dementia, which is affecting the elderly generation, currently no effective cure is available.

In the absence of this, the early detection of the process and the mapping of the methods of slowing the progression are of the utmost importance.

The significance of early detection is supported by the literature data that the treatment initiated in the pre-dementia phase lengthens the duration of this stage and, in this connection, the time of the ability to live independently (Budd et al., 2011).

As the focus was placed on prevention, more and more attention has been paid to the mild cognitive impairment that has been defined as a temporary state between physiological aging and dementia in recent years.

The clinical relevance of mild cognitive impairment lies in its conversion rate higher than the average of those affected. While 1 to 4% of the average elderly population converts into dementia, this ratio is 10-15% for mild cognitive impairment (Bischkopf et al., 2006).

Mild cognitive impairment includes memory complaints occurring during retention of daily activity as a definition. Objective memory damage, which results in 1-2 SD deviations in neuropsychological tests compared to the adjusted age and education group. Retained global cognitive functions and excludability of the diagnosis on dementia (Petersen et al., 1999).

In recent years, one of the main goals of the research is to determine the predictors of conversion in order to predict the patients with MCI who are more likely to develop dementia later.

In the course of a longitudinal study that is based on *Alzheimer's Disease Neuroimaging Initiative's* database , 320

participants were evaluated for markers' conversion predictor ability such as MR assayed local cerebral cortex thickness, neuropsychological tests, liquor amyloid β_{1-42} and total tau protein levels as well as individual risk factors.

According to their results, the performance deterioration in neuropsychological tests was the best predictor of the two-year conversion (Gomar et al., 2011).

Under the above circumstances, the AAL-M3W project was launched in 2011, under the auspices of the European Union, within its framework we strive for the development of an *online platform*, which can be used both to detect the early deterioration of cognitive functions and to slow down the progression (m3w-project.eu).

Objectives

During our studies, we aimed to develop methods screening for mild cognitive impairment, tracking and maintaining cognitive abilities of the affected population, and to evaluate their effectiveness.

It was also our goal to create an effective, easy-to-use screening test to assess the risk population.

Subsequently, we aimed to design a toolkit that is able to maintain cognitive abilities and track their changes.

In the following, we set the goal of creating a targeted training, to this end, we studied different subtypes of the risk population.

Questions

Is the PAL test we have developed able to screen for mild cognitive impairment?

Did the results achieved on the developed games adequately reflect the cognitive status?

Does playing games help to maintain / improve cognitive abilities?

Can subgroups separated within mild cognitive impairment objectively be separated within our sample?

Hypothesis

Based on our hypothesis, the screening for mild cognitive impairment and cognitive training can be effectively implemented via an *online platform*.

Methods

Participants

Our study included 63 participants; aged 52-95, the male/female ratio was 2:3. Out of the involved patients, eight were permanent residents of a retirement home, while the others lead independent living.

Exclusion criteria

We did not select those into the study who suffered from dementia based on the age and education adjusted standardized data of MMSE, were alcohol or drug addicts, suffered head traumas, from epilepsy, or from acute phase psychiatric illness.

Recruitment

The determination of the MCI was done according to the Petersen criteria (Petersen et al 2009). According to these, fourteen out of sixty-three people got in the MCI group, forty-nine in the healthy control group.

The Rey Auditory Verbal Learning Test served as the basis for separating amnestic mild cognitive impairments from the healthy population as the most commonly used instrument in the literature (Gomar et al., 2011; Reuter et al., 2010; Segonne et al., 2004).

Paper and computer-based tests - the course of the examination

The study consisted of recording pencil and computer-based neuropsychological tests and computer games.

Recorded tests

The Mini Mental Test is a standard test, the effectiveness of which for separating a healthy population from a population with dementia is demonstrated by a number of studies (Gomar et al., 2011; Petersen et al., 1999).

The Addenbrooke Cognitive Examination was used to assess global cognitive functions.

The Rey Auditory Verbal Learning Test was used for the detailed examination of memory (Rey, 1958).

The *Trail Making Test A and B* (Tombaugh et al., 2004) were used to examine selective attention, cognitive flexibility and executive functions.

The *Clinical Dementia Rating Scale* (Morris, 1993) is a five-point scale used to measure cognitive and functional performance in order to measure Alzheimer's disease.

The Geriatric Depression Scale and the Addenbrooke Cognitive Examination were used to exclude depression (Yesavage, 1988; Dudás et al., 2005). Anxiety symptoms were measured with the Spielberger State-Trait Anxiety Inventory (Spielberger et al., 1970).

The study included the recording of an own implementation of the *Paired Associates Learning Test* which is a visuo-spacial memory test.

Memory game

During the memory game developed under the M3W project, out of many downside cards two can be turned over in a round. After that, the cards will be reversed and a new round will follow. The goal is to find the card pairs by remembering the location of drawings on the cards, which will remain upside once found. The test is mainly used for examining spatial visual memory. The number of cards displayed can be changed by the difficulty level.

For the games and the corresponding neuropsychological functions see in the following table:

M3W games	Developped cognitive functions	kognitív.hu games	Developped cognitive functions
Hashi	executive functions	**Flasher**	visuo-spatial memory
Rotate	executive functions	**Jeweler**	visuo-spatial memory
Corsi	visuo-spatial memory	**Odd one out**	executive functions
Connection	executive functions	**Suspicious guy**	working memory
Sudoku	executive functions	**New take off**	visuo-spatial memory
Planar-game	executive functions / visuo-spatial memory		
Memory game	visuo-spatial memory		
Gopher	attention/psycho-motor speed		

MR imaging

All participants took part in a routine MRI testing. The study was conducted at the Semmelweis University MR Center via a *3 Tesla's Philips Achieva MR* scanner.

Statistical Methods

The results of the neuropsychological tests were analyzed by covariance analysis (ANCOVA) in the two diagnostic groups, with covariates on the sex, age, qualification and Geriatric Depression Scale results.

Linear logistic regression was used to determine whether neuropsychological tests (PAL, ACE, MMSE) were able to separate healthy elderly people from those suffering from MCI. The results were displayed via an ROC curve (*Receiver Operating Characteristics curve*).

Analyzes were carried out using the SAS 9.2 program.

MR data was evaluated by using the *Freesurfer*, resp. SAS program.

Between memory game results and temporal structures, a correlation analysis was performed by a *General Linear Model* analysis (GLM in SAS 9.2). The age, sex and the total intracranial volume were included as covariant. Regarding the correlation between the neuropsychological tests and the memory game, we corrected for sex and age. Spearman analysis was performed on the number of levels performed in

the PAL test, since the distribution of the data showed no normal distribution. We used a confidence interval of 95%.

The difference between the groups was analyzed by logistic regression analysis (PROC LOGISTIC in SAS) with the groups as independent variables.

The memory game was represented as a predictor variable, with sex and age as a covariant. We chose logistic regression because of the relatively small number of the group (Peduzzi et al., 1996).

During cognitive training, performance improvement was measured by the primary output variable of relevant tests of the CogState test package.

Results

The results of logistic regression: how much the individual neuropsychological tests were able to differentiate between the two experimental groups

Based on the PAL test (limit = 25 points) the MCI group could be separated from the control group with a sensitivity of 71.4% and a specificity of 91.8% (chi^2= 11.9, n = 63, p = 0.0005, OR = 1.12 (CI = 1.05-1.2)).

Correlation between the temporal structures and the memory game.

The number of attempts needed to complete the memory game has correlated with the size of the *hippocampus* (R = -0.4, 95%CL = (R = -0.4, 95%CL = [-0.65 -0.04], n = 34, p = 0.03), with the volume of the *entorhinal cortex* (R = -0.41, 95%CL = [-0.66 -0.05], n = 34, p = 0.02) and the temporal pole (R = -0.44, 95%CL = [-0.68 -0.09], n = 34, p = 0.01). In addition, the time to finish the game has correlated with the volume of the *hippocampus* (R = -0.54, 95%CL = [-0.75 -0.22], n = 34, p = 0.002), the *entorhinal cortex* (R = -0.54, 95%CL = [-0.75 -0.22], n = 34, p = 0.02), and the temporal pole (R = -0.42, 95%CL = [-0.67 -0.07] 0002).

Correlation between neuropsychological tests, clinical measurements and the memory game

The number of corrected attempts of the PAL test (R = 0.4, 95%CL = [0.05 0.66] n = 33, p = 0.03), the number of elements found upon the first attempts (R = -0.42, 95%CL = [-0.67 -0.07] n = 33, p = 0.02), and the number of completed levels

(Spearman R = -0.47, 95%CL = [-0.70 -0.13] n = 33, p = 0.008) has correlated with the time required to complete the memory game.

Differentiation between those affected by mild cognitive impairment and the healthy group by the memory game

The healthy group has needed fewer tries (Chi^2 = 6; n = 46, p = 0.02, Odds Ratio = 2.9, 95% CI = 1.2-7.9, Sensitivity = 83%, Specificity = 62%, Cut-off = 4.5 Tries / Picture) and less time (Chi^2= 6.2; n = 46, p = 0.01, Odds Ratio = 1.2, 95% CI = 1.1-1.5, Sensitivity = 82%, Specificity = 67%, Cut-off = 250sec) to complete the memory game than those suffering from mild cognitive impairment.

Examining the effectiveness of cognitive training:
Following the cognitive training, we found a significant improvement from the baseline results in the results of the following tests: One Card Learning Task, One Card Back Learning Task, Groton Maze Learning Task, Social Emotion Task. These tests examine visuo-spacial memory, attention and executive functions, working memory, and emotional recognition features.

Differentiation in Cortical Volume, Cortical Thickness and Cognitive Performance in the aMCI, naMCI and the healthy control group

Significant difference was found in the volume of the *hippocampus* [F (2.61) = 9.2, p = 0.0002] and the *entorhinal cortex* within experimental groups [F (2.61) = 4.3, p = 0.02]. Based on post hoc tests, the volumes in the aMCI group were

significantly smaller than in the other two groups. Among the covariates, sex had a significant effect on the volume of the *hippocampus*. The *hippocampus* of men was significantly smaller than that of women [F (2, 61) = 7.9, p = 0.007]. The average thickness of the *entorhinal cortex* [F (2, 61) = 13.1, p <0.0001], the *fusiform gyrus* [F (2, 61) = 6.7, p = 0.002], the *isthmus of the cingulate gyrus* [F (2, 61) = 5.4, p = 0.007] and the *precuneus* [F (2, 61) = 10.4, p = 0.0001] were all significantly different between the experimental groups. Based on *post hoc* tests, a decrease in cortical thickness was found in the aMCI group in all four structures compared to the controls, *while the thickness of the entorhinal cortex* and the *fusiform gyrus* was also significantly reduced in the aMCI group compared to the naMCI group. There was a significant difference between the experimental groups in the anterograde memory [F (2, 60) = 12.9, p <0.0001], retrograde memory [F (2, 60) = 6.1, p = 0.004], category fluency [F (2, 60) = 22.9, p <0.0001) and letter fluency [F (2, 60) = 4.9, p = 0.01]. In the case of anterograde memory and category fluency, the performance of both the control and the naMCI group have exceeded the aMCI group's performance.

Group differences between central nervous system structures and neuropsychological tests.

Regarding retrograde memory, the controls performed better than the aMCI group, but worse than the naMCI group. In the verbal fluency test, the controls performed better than the naMCI group, but worse than the aMCI. The two MCI groups did not differ significantly from each other. (p > 0.05).

Furthermore, in the category fluency test, women performed better than men F (1, 60) = 9.8, p = 0.003]. Age did not have a significant effect on performance.

Correlation analysis

We found a strong correlation between neuropsychological tests and the cortical thickness and volume of temporal structures. In the MCI group, the Rey Auditory Verbal Learning Test showed a significant positive correlation with the size of the *amygdala* (r = 0.47, n = 20, p = 0.03) and the thickness of the *entorhinal cortex* (r = 0.46, n = 20, p = 0.04). Subjects who had a smaller *amygdala* size and a lower *entorhinal* thickness, performed worse on the memory test. In addition, the reduced *entorhinal* volume (r = 0.49, n = 19, p = 0.03), the reduced volume of *fusiform gyrus* (r = 0.48, n = 19, p = 0.04) and the cortical thickness of *fusiform gyrus* (r = 0.53, n = 19, p = 0.02) was paired with worse test results on the retrograde memory test.

Conclusion

According to our results, both the Addenbrooke Cognitive Examination and the self-developed PAL test can effectively differentiate between the healthy and the cognitively affected group. The recording time of the PAL test is shorter and the test does not require significant assistance or professional knowledge. Its advantage compared to the ACE test lies within its independence from education and its ability to be repeated within a short period of time, which allows the follow-up of progression. All of these properties make it suitable for the prescreening of larger populations in doctor's offices, which is of paramount importance for the prevention of dementia.

Our further findings support the initial hypothesis that healthy elderly people who have achieved worse results in the memory game have shown greater temporal atrophy. In addition, they had a worse result in tests sensitive in the early detection of dementia, such as PAL, ACE and RAVLT.

In addition, the memory test results of those with mild cognitive impairment was significantly worse than that of healthy controls. Based on the above results, we can conclude that the memory game can be used to detect signs of mild cognitive impairment.

Since in online cognitive training, participants did not play other games or did not perform any excessive intellectual activity, thus the progress experienced in cognitive functions is due to the effect of the training.

One of the possible reasons for the lack of progress in similar cognitive functions for other tests is the complexity of the tests and their higher level of difficulty. With well-designed, individualized training, cognitive functions can be developed and maintained.

MCI types can be separated by both neuropsychological and MR imaging examination, enabling early differentiation and the possibility of early screening examinations for the type of predicted dementia, respectively the follow-up or targeted medication, if needed.

Publications on which the dissertation is based

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