THE ROLE OF VISUOSPATIAL AND VISUOMOTOR FUNCTIONS IN THE DIAGNOSIS OF ALZHEIMER'S DISEASE

PhD thesis

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I. Introduction

Alzheimer's disease (AD) is the most common type of major neurocognitive disorders (NCDs) in the elderly: two-thirds of dementia cases in this age group are attributed to the disease. Currently, there are around 55 million patients with dementia globally, and the number of patients is expected to triple by 2050. It is estimated that NCDs will be the leading cause of morbidity by then. Despite tremendous efforts, curative treatment options are not available as of now. Currently available treatment options are aimed at slowing the progression of cognitive decline. Furthermore, a model has estimated that a one-year delay in disease onset would result in a 11.8 million decrease in patients worldwide, while a 2-year delay would lead to 22.8 million cases fewer. Aging research is shifting to identifying cases as early as possible, preferably in prodromal phases such as mild cognitive impairment (MCI) that might represent a critical window for interventions. However, 50% of dementia patients remain undiagnosed despite the serious efforts aimed at timely diagnosis. There are many possible reasons for this. One might be the lack of population wide screening. Only 16 percent of older adults aged 65 years and over receive routine cognitive evaluation. Another potential reason is the limited availability of trained medical personnel and the location boundedness of these examinations since the patient must be physically present at the examinations. Additionally, due to lack of sensitivity, neuropsychological tests fail to identify early-stage cognitive impairment. A possible solution to tackle these problems could be telemedicine, making dementia screening more readily available to a greater number of patients, including those living at more remote locations. There is an increasing number of electronic cognitive appliances available for both at-home and clinical use. However, these appliances carry the risk of nonadherence due to unfamiliarity with digital tools, vision problems, and cognitive tests being too difficult and tiring

among others. These issues point to the possible benefit of an automated, electronic, self-administered screening tool that uses plain tasks aimed at evaluating few cognitive domains. Previous literature proposed that a computerized task based on evaluating visuomotor functions could find a faint alteration in visuomotor coordination that otherwise would remain unnoticed. It also suggested the possible benefit of using visuomotor ability-based tasks for identifying individuals at risk of AD prior to the onset of apparent cognitive decline, as well as for monitoring the conversion of preclinical AD to MCI. These findings point to the possible benefits of a visuomotor ability-based screening tool for the AD continuum.

II. Objectives

With a series of studies, we aimed to explore the alteration of the visuospatial and visuomotor functions in Alzheimer's disease patients and in mild cognitive impairment compared to age-matched, cognitively healthy control elderly participants, to better understand their association with disease stages and progression. These objectives served as the basis of our work towards establishing visuomotor ability-based screening methods for MCI and Alzheimer's disease.

Specific objectives:

- To assess the involvement of different cognitive domains—orientation, attention, memory, verbal fluency, language, and visuospatial skills—in the cognitive impairment of AD patients with different disease duration.
- To evaluate the possible role of the above cognitive domains in the early recognition of AD.
- To evaluate the possible benefit of assessing these cognitive domains in monitoring the progression of cognitive impairment.
- To analyse the structural integrity of the visuospatial network in a-MCI patients on structural MRI recordings.
- To characterize the functional connectivity of the visuospatial network in a-MCI via functional MRI recordings.
- To ascertain the discriminatory potential of small amplitude hand movements, recorded via a visuomotor ability-based paradigm, in distinguishing between cognitively healthy individuals and MCI patients in a clinical environment.

III. Methods

Study 1

To examine the diagnostic potential of assessing visuospatial abilities in the early detection of Alzheimer's disease, we included 110 AD patients and 45 cognitively healthy elderly control individuals in this study from the AlzEpi Cohort Observational Library (ACOL database) of the National Institute of Mental Health, Neurology and Neurosurgery, Budapest, Hungary. Patients with Alzheimer's Disease were diagnosed based on the guidelines of the National Institute on Aging and the Alzheimer's Association. Every participant gave their informed written consent. Every participant underwent detailed neurological and neuropsychological evaluation, including the Mini Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination (ACE) tests. We created three groups based on disease duration and assigned the participants accordingly. Group 1 included 36 individuals with a disease duration of up to two years, Group 2 comprised 44 participants with a disease duration of 2 to 4 years, while patients with a disease duration of at least four years (n=30) belonged to Group 3. Furthermore, we created a fourth group, Group 0 containing the 45 cognitively healthy control participants. Regarding statistical analysis, we used ANCOVA for parametric data with age, sex, and disease onset as covariates and Kruskal-Wallis test for non-parametric data to perform intergroup comparisons. We then applied Tukey's post-hoc test. We tested the association between the ACE total score and its subscores and disease duration (in years) with Spearman's rho. We normalized the ACE subscores after which within-group analysis was completed with Wilcoxon signed-rank test. Normalization was carried out by dividing each subscores by the maximum score of the given subscore. For the statistical analysis, we used the IBM SPSS 20 software.

Study 2

To assess the alteration of the visuospatial system as a potential early marker of cognitive decline, we included 78 individuals in our study: 32 patients with multidomain amnestic MCI (a-MCI) and 46 cognitively healthy control individuals. Every participant gave their informed written consent. We obtained the data by the collaboration of two independent research centres through the Euro- Fingers Consortium (www.eufingers.com). The two centres used an established, identical protocol for medical imaging examination for clinical and research purposes. We included data of 19 MCI patients and 26 healthy control individuals from the aforementioned ACOL database, and data of 33 individuals (13 MCI patients and 20 healthy controls) from the Semmelweis MCI Neuroimaging Cohort (SMNC) database of the Department of Psychiatry and Psychotherapy, Semmelweis University. The diagnosis of MCI patients was determined by a multidisciplinary team based on the Petersen criteria. Every participant in this study underwent detailed neurological and neuropsychological examination, including the ACE, MMSE, Rey Auditory Verbal Learning Test (RAVLT), and Trail-making Test (TMT). They were also involved in a 3 T high resolution structural and functional MRI acquisition (sMRI and fMRI, respectively). We applied the open source FreeSurfer 6.0 software package for the analysis of T1-weighted anatomical images. We used the CONN MATLAB toolbox for the analysis of resting-state fMRI data. We used the independent sample t-test for continuous variables with parametric distribution, whereas we used the Mann-Whitney U test for non-parametrically distributed data. We applied the Chi-square test for categorical variables. We analysed the intergroup differences in structural MRI recordings and neuropsychological test results with ANCOVA test (covariates: age, sex). Benjamini-Hochberg correction was applied to counteract multiple comparisons. We reported the effect sizes with Cohen's d. We used the IBM SPSS

20 software for statistical analysis, excluding the analysis of functional MRI results.

Study 3

To investigate the diagnostic potential of a paradigm assessing visuomotor function, we involved 68 participants, 46 cognitively healthy individuals, and 22 patients with MCI. Every participant gave their informed written consent. The diagnosis of MCI was given based on the revised Petersen criteria. We only recruited right-handed regular computer and internet user participants. Every participant underwent a detailed neurological and neuropsychological evaluation. The neuropsychological test battery included the ACE, MMSE, RAVLT, TMT, Clinical Dementia Rating scale (CDR), Beck Depression Inventory (BDI), and Spielberger State-Trait Anxiety Inventory (STAI) and completed the Precognize paradigm. In close collaboration with researchers and medical professionals from the National Institute of Mental Health, Neurology and Neurosurgery, Precognize Ltd. developed a visuomotor paradigm called Precognize in the framework of the National Brain Research Program II (2017–2021). The paradigm was developed based on part A of the Trail-Making Test. To complete the paradigm, the participants are asked to click on each number on the screen with a computer mouse in ascending order as speedily as they can. The numbers (1–9) are presented in circles in fixed positions on the screen. Solely correct clicks are accepted, that are the next in order and are on the margin of or within the circle surrounding the number (Figure 1.).
The process starts with entering research codes to the program for both the participant and the examiner. This ensures that the data is anonymized. The visuomotor tasks are preceded by a thorough description followed by a simplified trial version.

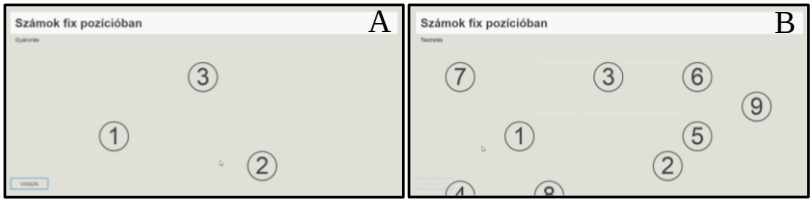

Figure 1. Screenshot images of the Precognize paradigm. The paradigm starts with a mock part (A) to confirm that participants understand the task, followed by the live test (B).

The participants are asked to complete the task with both dominant and subdominant hands, one after the other. The primary mouse button is adjusted so that the participants control it with the index finger of each hand. During the task solving the program records every mouse action made by the participants. For data analysis, we extracted the computer mouse movement parameters for the two hands separately. We divided the task completion into 9 sections: each section represents the interval between two numbers. This adds up to 18 sections altogether, considering both hands. We extracted the following parameters: entropy, distance, time, number of tries, velocity, and speed. We then averaged the values of these parameters from the 9 sections for both hands separately. Regarding the statistical analysis, we analysed the distribution of the data with the Kolmogorov-Smirnov test. We applied the Mann-Whitney U test or independent sample t-test to assess continuous variables. We used the Chi-square test for categoric variables. ANCOVA test was applied to assess group effect on motor data with gender, age, and anxiety level as covariates. We used the Benjamini Hochberg correction to counteract the effect of multiple comparisons. We determined the effect sizes in Cohen's d. We used Pearson correlation to analyse the relation between neuropsychological test results and visuomotor characteristics.

IV. Results

Study 1

Spearman's rho revealed a significant negative correlation between ACE total score and disease duration ($p<0.001$; $r= -0.643$). Intergroup analysis of ACE subscores presented significant differences in memory ($F=69.11$; $p<0.001$), visuospatial abilities ($\chi2=113.96$; $p<0.001$), language ($\chi2 = 100.38$; $p<0.001$), orientation ($\chi2=96.27$; $p<0.001$), attention ($\chi2=87.11$; $p<0.001$), and verbal fluency ($\chi2=61.12$; $p<0.001$). No significant modifying effect of sex, age, and disease duration was found. Tukey's post-hoc test revealed that, from the six subscores, visuospatial abilities were the only subscore in which all four groups differed significantly (all p-values <0.001). Compared to healthy controls (Group 0) the difference was highest in Group 1, the earliest disease stage. We used Spearman's rho to assess the interrelation between the six subscore of the ACE and disease duration. Every subscores of the ACE showed a significant negative correlation with disease duration (all p-values < 0.05). The most prominent association presented between disease duration and visuospatial abilities ($r= -0.85$). We used the Wilcoxon signed rank test to analyse within-group differences in ACE subscores. In group 0, verbal fluency had the lowest normalized score (0.87), followed by memory (normalized score: 0.9), but the two did not differ significantly. The third lowest normalized score was that of visuospatial abilities, with a normalized score of 0.96. Visuospatial abilities' subscore differed significantly from both verbal fluency ($Z= -3.75$; $p<0.001$) and memory ($Z= -3.61$; $p<0.001$). The lowest normalized score in Group 1 belonged to verbal fluency (0.64), followed by attention (0.77) and memory (0.78). The normalized subscore of verbal fluency was significantly lower than attention ($Z= -4.14$; $p<0.001$), memory ($Z= -4.41$; $p<0.001$). The normalized subscore of attention and memory were not

significantly different. The cognitive domain with the lowest normalized score in Group 2 was visuospatial abilities (0.5). Verbal fluency (0.6) was the second, while orientation (0.68) was the third most impaired domain. The normalized subscore of visuospatial abilities was significantly lower than orientation ($Z= -4.38$; $p<0.001$) and verbal fluency ($Z= -3.31$; $p=0.001$). The normalized subscore of verbal fluency was significantly lower than orientation ($Z= -3.62$; $p<0.001$). The cognitive domain with the lowest normalized score in Group 3 was visuospatial abilities (0.25). The second most impaired domain was memory (0.51) followed by verbal fluency (0.52). The normalized subscore of visuospatial abilities was significantly lower than memory ($Z= -4.46$; $p<0.001$) and verbal fluency ($Z= -4.47$; $p<0.001$). The normalized subscores of memory and verbal fluency did not differ significantly.

Study 2

Compared to the HC group, we found reduced cortical thickness in the a-MCI group in several cortical areas. The cortical thickness of the right superior temporal gyrus and the left temporal pole showed the greatest F values ($F=8.04$ and $F=5.26$, respectively). These are the only areas where intergroup differences of cortical thickness remained significant after Benjamini-Hochberg correction ($p<0.001$ and $p=0.034$, respectively). Age had a significant modifying effect on cortical thickness of several regions. The largest effect was on the right superior temporal gyrus ($F=21.81$). However, this effect disappeared once Benjamini-Hochberg correction was applied ($p>0.05$). Sex had no significant modifying effect ($p>0.05$). Regarding fMRI data, we found that the right middle frontal gyrus had decreased functional connectivity to the left superior frontal gyrus, left middle frontal gyrus, and left precentral gyrus. Moreover, the right middle frontal gyrus had impaired functional connectivity to the left temporal pole, left inferior

temporal gyrus, and the left precentral gyrus. However, the a-MCI group had stronger functional connectivity between the left inferior temporal gyrus and the triangular part of the left inferior frontal gyrus and left middle frontal gyrus compared with the HC group.

Study 3

We found significant intergroup differences in computer mouse movement characteristics for both the right and left hand. Regarding the left hand, we detected the most significant difference in movement entropy ($F=5.24$; $p=0.001$, Cohen's $d=0.94$) while the time required for task completion and the distance of the hand movements were also significantly different ($F=4.32$; $p=0.005$ and $F=1.16$; $p=0.0134$, respectively). In regard to the right hand, entropy of the computer mouse movements proved to be the most significantly different characteristic between the groups ($F=8.46$; $p<0.001$, Cohen's $d=0.9$), while time of task completion and the distance of the movements also proved to be significantly different ($F=4.626$; $p=0.003$ and $F=1.03$; $p=0.019$, respectively) Out of the six measures the significance was lost for distance of computer mouse movements for both hands after Benjamini Hochberg correction ($p>0.05$). No significant modifying effect of age, sex, and state anxiety was detected ($p>0.05$). After applying Pearson's correlation, we found significant correlations between movement parameters and the scores of RAVLT, ACE, MMSE, CDR and TMT tests, while results for tests such as BDI and STAI—measuring mood and anxiety—were not significant. The correlation was positive for the tests where higher scores indicate worse performance, e.g. TMT and CDR scale. We detected the most significant correlation between the CDR scale and movement parameters (average $r=0.36$, all p's < 0.001). Regarding the tests where higher scores indicate better cognitive performance, such as the ACE, MMSE, and RAVLT, we found

negative correlations to the computer mouse movement features with r values of -0.14 to -0.5. We detected the most significant correlation between the ACE total score and the movement parameters (average r= -0.37, all p's < 0.05).

V. Conclusions

1. Rigorous neuropsychological assessment contributes to early detection of cognitive decline.
2. Verbal fluency seems to be the most affected cognitive domain in early AD; thus, its evaluation could have a central role in early diagnosis of AD.
3. The decline of visuospatial abilities follows a linear trajectory over the AD continuum; thus, visuospatial abilities could have a possible role in tracking the advancement of cognitive impairment.
4. Due to the linear trajectory of visuospatial abilities' decline, they could have a role in validating drug trials.
5. Visuospatial abilities were the most impaired cognitive domain in our cohort of multiple domain a-MCI patients.
6. We demonstrated—after rigorous statistical correction—that reduced cortical thickness of the superior temporal gyrus and temporal pole are distinctive structural features of a-MCI.
7. The fMRI-based analysis of visuospatial network pointed to reduced functional connectivity between left and right frontal areas, whereas functional connectivity was increased between left frontotemporal regions.
8. Simultaneously, increased and decreased levels of functional connectivity of different brain regions might represent a compensatory mechanism of the visuospatial network.
9. With the possibility of automatized data analysis, alteration of visuospatial abilities detectable by resting state fMRI could be a sensitive and non-invasive early

biomarker for cognitive impairment with low need of man-hour.

10. Fine motor control is impaired early in MCI.
11. Characterizing fine movement entropy could be applied for the early detection of cognitive impairment.
12. Considering the opportunity for self-administration, automatization and the potential use of artificial intelligence, fine movement analysis could serve as a population-wide cognitive screening tool for older adults.

VI. Bibliography of the candidate's publications

VI.1. Publications related to the thesis:

1. Horvath AA, **Berente DB**, Vertes B, Farkas D, Csukly G, Werber T, Zsuffa JA, Kiss M, Kamondi A. Differentiation of patients with mild cognitive impairment and healthy controls based on computer assisted hand movement analysis: a proof-of-concept study. Sci Rep. 2022;12(1):19128. (**IF:4.6**)
2. **Berente DB**, Zsuffa J, Werber T, Kiss M, Drotos A, Kamondi A, Csukly G, Horvath AA. Alteration of Visuospatial System as an Early Marker of Cognitive Decline: A Double-Center Neuroimaging Study. Front Aging Neurosci. 2022;14:854368. (**IF:4.8**)
3. **Berente DB**, Kamondi A, Horvath AA. The Assessment of Visuospatial Skills and Verbal Fluency in the Diagnosis of Alzheimer's Disease. Front Aging Neurosci. 2021;13:737104. (**IF:4.8**)

Cumulated impact factor of publications related to the thesis: **14.2**

VI.2 Publications not related to the thesis:

1. Csukly G, Tombor L, Hidasi Z, Csibri E, Fullajtár M, Huszár Z, Koszovácz V, Lányi O, Vass E, Koleszár B, Kóbor I, Farkas K, Rosenfeld V, **Berente DB**, Bolla G, Kiss M, Kamondi A, Horvath AA. Low Functional network integrity in cognitively unimpaired and MCI subjects with depressive symptoms: results from a multi-center fMRI study. Translational Psychiatry. 2024;14(1):179. (**IF:6.8****)
2. Zsuffa JA, Katz S, Koszovacz V, **Berente DB**, Kamondi A, Csukly G, Mangialasche F, Rocha ASL, Kivipelto M, Horvath AA. Lifestyle and behavioural changes in older

adults during the Covid-19 pandemic are associated with subjective cognitive complaints. Sci Rep. 2024;14(1):2502. (**IF:4.6****)

3. Bolla G, **Berente D**, Andrássy A, Zsuffa J, Hidasi Z, Csibri E, Csukly G, Kamondi A, Kiss M, Horváth A. Comparison of the diagnostic accuracy of resting-state fMRI driven machine learning algorithms in the detection of mild cognitive impairment. Sci Rep. 2023;13. (**IF:4.6***)
4. Zsuffa J, Koszovácz V, **Berente D**, Bálint Z, Katz S, Kamondi A, Csukly G, Horváth A. A COVID-19-pandémia harmadik hullámának hatása a 60 év feletti magyar lakosság életmódjára, mentális és fizikai egészségére. Orvosi hetilap. 2022;163:1215-1223. (**IF:0.6**)

Cumulated impact factor of publications not related to the thesis: **16.6**

**,* Expected IF