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Can olfactory training support improvement of memory functioning in patients with cognitive disorders?

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Summary

Aim. According to some theoretical interpretations of the olfactory training effects, the training may indirectly exert positive influence on cognitive functioning in patients with Alzheimer's dementia. The mechanism of action is stimulation of cerebral blood flow in areas of brain which are shared by olfactory and memory processes. The aim of this article is to verify a hypothesis that the olfactory training improves memory and attention functions in patients with amnestic mild cognitive impairment.

Method. Participants with amnestic mild cognitive impairment (N = 35; 17 males and 18 females) constituted their own control group. During the first 12 weeks from the baseline evaluation no therapeutic actions were performed. The subjects underwent control neuropsychological assessment and entered in the second stage of the study. In that stage they were subjected to a daily olfactory training, which included two a few-minute-long sessions per day, which were performed for the following 3 months. Subject's memory functioning was measured at three time points: at the baseline, after 3 months and after 6 months (from the baseline). Cross-over assignment was used as the intervention method – which means that the participants constituted their own control group. The scales employed in the study to measure memory and attention were: ACE–III, CVLT, and MMSE.

Results. Statistically significant improvement in memory functions measured with the CVLT, MMSE, ACE–III Memory, and ACE–III Total Score was obtained. It is considered an artefact related to practice effects, not true training results. Moreover, trend suggesting improvement on the ACE–III Attention was noted as well.

Conclusions. The authors review theoretical implications of the conducted study. Methodological challenges pertaining to the study design are discussed and future research directions are proposed.

Key words: olfactory training, mild cognitive impairment, neuropsychological rehabilitation

Introduction

In spite of intensive research, the cure for Alzheimer's disease (AD) has not been found yet. According to data provided by experts, the percentage of studies which brought negative or inconclusive results is 99.6% [1]. While most research is focused on pharmacological effect, there are also attempts of neuropsychological nature, e.g., errorless learning or methods of reminiscence therapy [2–4]. Multiple failed attempts to influence the fully developed Alzheimer's disease made researchers focus on its earlier stages, such as pre-clinical or prodromal stage, which is called mild cognitive impairment.

Mild cognitive impairment, which is called mild neurocognitive disorder in ICD-11, is diagnosed when patient complain about feelings of worsening of cognitive abilities and this worsening is confirmed by objective measures. The significant worsening of cognitive abilities may pertain to single or multiple domain of cognitive functioning, however, it does not interfere with patient's ability to perform activities of daily living. Such worsening cannot be explained in terms of normal aging [5].

The authors of this paper published results [6] of the research of olfactory training in patients with moderate cognitive disorders of amnestic type. It might be concluded there that the ability of the above-mentioned patients to recognize smells and differentiate between them can be improved to some extent. According to the authors' knowledge, no studies on cognitive effects of the olfactory training in patients with MCI have been published so far. Dalautzai in the review paper [7] points out that training olfactory functions in Alzheimer patients is an important therapeutic objective as it improves regional cerebral blood flow (rCBF), the condition of neural connections in areas associated with smell, and cognitive functioning. Stimulation of trigeminal nerve itself has positive influence on olfactory ability and may mitigate olfactory dysfunctions related to age and AD. The author quotes findings of research involving animals, which indicates that olfactory training has positive influence on neurophysiological changes in mice and rats. As for humans, olfactory training results in internal changes in pyramidal neurons creating favorable conditions for growth of synaptic connections based on activity. Dalautzai points out that continuous learning may hold the brain in the learning mode where olfactory memory is acquired quickly and effectively.

It is known that the olfactory performance quality is a reliable predictor of Alzheimer's disease development in patients with MCI. It has been confirmed empirically [8, 9] that olfactory impairments occur in a preclinical phase of AD, being ahead of cognitive and affective symptoms. Doty [10] adduces results of longitudinal studies according to which the olfactory impairment antedates the other clinical symptoms of AD for a few years. According to results obtained by Scalco and his team [11], worsening of the olfactory ability is associated with an increased risk of cognitive deterioration and may herald conversion to AD in patients with MCI. It has already been proven in the 1990s [12] that the olfactory identification ability and olfactory thresholds allow

to predict further development of the disease in 91% of patients with AD and 73% of MCI cases. Some researchers [13] find that the olfactory impairment may be a better predictor of dementia than outcomes of cognitive ability tests.

Olfactory ability tests successfully differentiate between AD patients and healthy individuals and their results correlate with the performance on the delayed recall task in the CVLT (California Verbal Learning Test) memory test [11]. Anosmic patients experience atrophic changes in such brain areas as medial prefrontal cortex (MPC), anterior cingulate cortex (ACC) and middle cingulate cortex (MCC). Some volume changes are also detected in dorsolateral prefrontal cortex (dlPFC), cerebellum and superior occipital gyrus (SOG). Atrophy was also found in piriform cortex (PC), insular cortex (IC), orbitofrontal cortex (OFC), supramarginal gyrus (SMG), precuneus (Prec), hippocampus (HPC), and parahippocampal region [7]. The above-mentioned atrophic changes are a time function of anosmia duration – anosmia lasting longer than two years has a more devastating effect as compared to one lasting shorter than two years. Importantly, olfactory stimulation increases local cerebral brain flow in OFC, piriform cortex, amygdala, parietal lobe cortex and insular cortex [7].

According to Gates et al. [14], all the reports up-to-date stating no effect in MCI patients undergoing cognitive training might result from failure to provide a clearly defined definition of intervention. According to the authors, cognitive exercise brings about moderate or even big benefits in terms of cognitive competence of patients as measured by memory tests. Lustig et al. [15] state that the so-called multimodal approaches, based on the transfer phenomenon, might facilitate cognitive functioning of the elderly. One of the examples is aerobics, as its positive influence on neurogenesis and angiogenesis was confirmed by research conducted on animals [16] and people [17]. The latter confirmed improved competence in many cognitive areas, especially in the case of executive functions.

All things considered, the authors of this paper decided to examine whether participation in olfactory training will bring about cognitive benefits. In other words, can olfactory training be treated as cognitive ability training? The term cognitive training refers to programs which, based on a given theory, develop skills or strategies by, among others, suggesting specialized exercises that are supposed to refer to particular cognitive functions [18]. The goal of cognitive training is preventing, delaying or minimizing cognitive decline, restoring lost ability or learning to cope with deficiencies [19, 20]. Olfactory training might be regarded as a tool used to delay or minimize the degree of dementia, which is nothing but cognitive training itself.

The aim of this paper is to verify the hypothesis that olfactory training improves functioning of memory and attention in MCI patients.

Methodology

The research protocol was approved by the Bioethics Committee of the Medical University of Wroclaw. The patients expressed their consent to take part in the research in writing. The research did not entail any negative side effects in any of the participants. The subjects were recruited from the patients of the Alzheimer Centre in Scinawa and the "Neuron" Neuropsychological Centre in Wolow. The intervention method applied was cross-over assignment with patients being their own reference group. During the first three months they were not undergoing the training. Then the training was started and lasted another three months. The patients were subjected to training procedures at the Alzheimer Centre in Scinawa and in the outpatient mode. The subjects underwent a thorough neuropsychological examination during three stages of the research: 1) Baseline – setting the reference point to monitor changes; 2) After three months without olfactory training – "Month 3"; 3) After three months of olfactory training – "Month 6").

Olfactory training description

So-called 'Smell Quarter' training, developed by Burckhardt (Germany), was applied. The patients participating in the training stage for four weeks, twice a day, were exposed to four smells: lemon, rose, eucalyptus, and clove. Each session lasted 1 – 2 minutes.

Characteristics of the subject group

Out of 200 patients who had been selected after documentation analysis, 60 were qualified for the research. The selection was based on results of medical (internal, neurological and psychiatric) examination and neuropsychological assessments. Patients' medical documentation was reviewed and the following assessments were performed: 1) interview (with the patients and their caregivers); 2) Mini Mental State Examination (MMSE); 3) California Verbal Learning Test (CVLT) – an assessment of the auditory verbal memory; 4) Benton Visual Memory Test (BVMT) – an evaluation of visual memory and process of visual-spatial analysis and synthesis; 5) Verbal Fluency Test – phonemic and semantic one, an assessment of thinking organization/executive functions; 6) Ruff Figural Fluency Test (RFFT) – an evaluation of executive functions: initiation, planning and divergent reasoning; 7) Wisconsin Card Sorting Test (WCST) – a global evaluation of executive functions; 8) Raven Progressive Matrices Test – a global assessment of the cognitive ability; 9) Color Trails Test (CTT) – an assessment of the ability to sustain attention and sequential thinking; 10) D2 Test of Attention – an evaluation of the attention parameters and visual field scanning; 11) selected items of the Luria-Nebraska battery – an evaluation of expressive speech, receptive speech, motor abilities, and presence of partial deficits. The employed tests

are commonly used in neuropsychology and they allow to evaluate memory, language, executive and visual-spatial abilities [21].

Finally, the results of 35 subjects who followed the training regime were taken into consideration. The age of 35 subjects ranged from 55 to 89. (M = 69.7, SD = 7.7). The inclusion criteria are described in Table 1. The group was balanced in terms of gender (17 women and 18 men). The average value of the MMSE was 25.85 (SD = 1.35; dispersion from 23 to 28). 5 patients were diagnosed with anosmia, 23 – with hyposmia and 7 – with normosmia (total result of Sniffin' Sticks: M = 23.7; SD = 7.4; min = 9.5; max = 35.5).

Table 1. **Research inclusion/exclusion criteria**

Inclusion criteria
– at least 55 years old – MMSE = 25–28 – interdisciplinary diagnosis of aMCI
Exclusion criteria
– record of craniocerebral trauma with loss of consciousness – diagnosis of neurological disease other than MCI – diagnosis of other chronic somatic diseases affecting cognitive functioning – diagnosis of mental disorder – MMSE ≤24 and ≥29 – somatic disease likely to affect the sense of smell (upper respiratory tract infections, diabetes, polyneuropathies)

Screening assessments were conducted throughout 6 months before commencing the project and was part of diagnosis carried out at the Alzheimer Centre. The battery of memory tests included the Mini Mental State Examination (MMSE), Addenbrooke Cognitive Examination III (ACE-III) and California Verbal Learning Test (CVLT – VII trial, after postponing, was subject of analysis). These methods of neuropsychological examination have been popular for years. Due to the size of the article they will not be described here. For more information, please refer to an article by Arevalo-Rodriguez et al. [22] about the MMSE, an article by Bruno [23] about the ACE-III and an article by Alioto et al. [24] about the CVLT.

Statistical analysis

The completed data were analyzed by means of the General Linear Model Repeated Measures, (GLMRR) using SPSS v.25 (IBM Inc., USA). GLMRR was selected as the best one for the measure strategy based on repetitive measurements in the same group of subjects and collecting data of interval nature. The chi-squared test was used to analyze nominal and ordinal data. CVLT results were analyzed with Friedman's test due to frequent failure to meet the criterion of normal distribution of data.

Result analysis

Statistical analysis of results revealed statistic differences yielded in the CVLT, MMSE and ACE-III subscales: Attention, Memory and Total Score. No changes were recorded in the range of ACE-III subscales: Fluency, Language and Visual-Spatial Skills (see Tables 2, 3, 4, and 5).

Table 2. **Descriptive characteristics of memory tests: ACE-III and MMSE during research**

	N	MMSE		ACE – Attention		ACE – Memory		ACE – Fluency		ACE – Language		ACE – Visual-Spatial Skills		ACE – Total Score	
		M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Baseline	35	25.91	1.27	17.71	9.70	18.00	4.35	9.94	3.52	24.20	3.88	14.77	1.86	81.29	15.07
Month 3	35	26.45	1.23	15.87	2.01	19.86	3.34	10.03	2.05	24.67	1.65	14.91	1.03	85.35	6.63
Month 6	35	26.58	1.50	17.14	1.15	20.64	3.03	9.85	1.60	25.12	1.24	14.40	1.90	87.14	5.59

M – mean

SD – standard deviation

Table 3. **Statistical significance of changes in cognitive ability measured by the ACE-III and MMSE during research**

Wilks' Lambda						
Variable	Value	F	Hypothesis df	Error df	Significance	Partial eta squared
MMSE	0.769	40.954	20.000	330.000	p<0.05*	0.231
ACE–Attention	0.567	120.626	20.000	330.000	p<0.05*	0.433
ACE –Memory	0.663	80.399	20.000	330.000	p<0.05*	0.337
ACE–Fluency	0.989	0.175	20.000	330.000	p=0.840	0.011
ACE–Language	0.880	20.251	20.000	330.000	p=0.121	0.120
ACE–Spatial/Visual Skills	0.906	10.717	20.000	330.000	p=0.195	0.094
ACE–General Score	0.810	30.876	20.000	330.000	p<0.05*	0.190

* statistically significant changes

df – degrees of freedom: training (main effect) and error (error variance)

F – F statistics of the analysis

Partial eta-squared – main effect measure

Wilks' Lambda analysis results indicate statistical significance of changes in attention ability in the course of the study ($F(2, 33) = 8.399$, $p < 0.005$) (Table 2 and 4). The subjects scored on average M = 17.71 at first measurement; after three months it dropped to M=15.87, and after another three months, during which the subjects took part in ol-

factory training, it increased to M=17.14. The values of standard deviation during first measurement (SD = 9.70) are worth pointing out, as compared with corresponding values at second measurement (SD = 2.01) and third measurement (SD = 1.15). Probably, during initial research one or more of the subjects scored higher for a reason. It was confirmed by intra-object effect analysis which indicated that rejecting the zero hypothesis would be premature ($F(2, 68) = 0.863$; $p = 0.427$; Mauchley's sphericity: $\chi^2(2) = 94.523$; $p < 0.005$).

Table 4. **Descriptive characteristics of CVLT results during research**

	N	Trial A1		Trial A2		Trial A3		Trial A4		Trial A5		Trial B		Trial A6		Trial A7	
		M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Baseline	35	4.29	1.90	5.89	2.17	6.91	3.06	7.49	3.18	8.38	3.18	4.09	1.54	5.66	3.14	6.03	3.41
Month 3	35	4.60	2.00	6.89	2.25	7.52	2.28	8.21	2.35	8.83	2.69	4.01	1.21	6.75	2.39	6.32	2.88
Month 6	35	6.38	1.92	8.22	2.12	8.75	2.21	8.53	2.65	10.44	2.26	4.47	1.03	8.04	3.04	7.82	3.09

M – mean

SD – standard deviation

Table 5. **Statistical significance of changes in cognitive ability measured by the CVLT during research**

Variable	Trial A1	Trial A2	Trial A3	Trial A4	Trial A5	Trial B	Trial A6	Trial A7
χ^2	21.206	22.992	15.697	8.773	17.055	4.032	11.863	12.687
df	2	2	2	2	2	2	2	2
Significance	p<0.005*	p<0.005*	p<0.005*	p<0.05*	p<0.005*	p=0.133	p<0.005*	p<0.005*

χ^2 – chi-squared

df – degrees of freedom

* statistically significant changes

Statistically significant differences were found in subjects' performance in all seven trials A of the CVLT in the course of the study (results in Table 4 and 5). The subjects achieved better scores at successive measurements. Noteworthy, trial B results were almost identical (see Chart 1).

Discussion

Based on theoretical considerations quoted in the introduction to this paper, olfactory activity might be stimulating for brain operation and support improvement of cognitive abilities. It is therefore worth considering practical implications of the aforementioned theory. Following the conducted research it was concluded that participation in olfactory training is not related to improvement in memory skills in people with mild cognitive impairment.

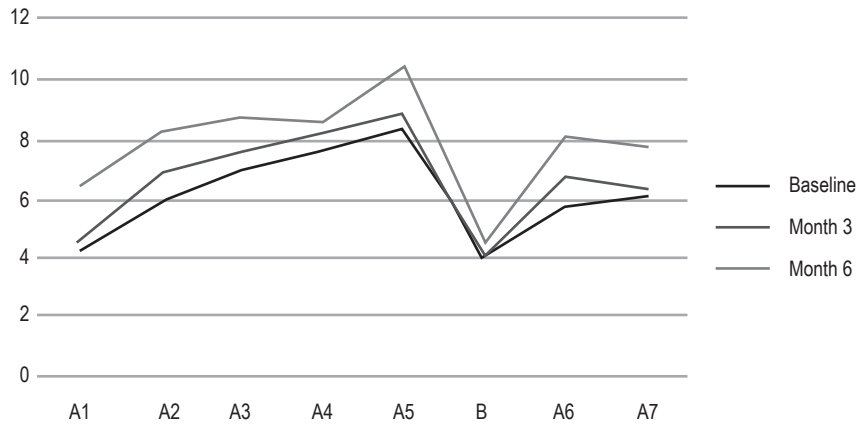

Chart 1. **Changes in memory level measured with the CVLT**

In the case of scores in the MMSE, CVLT, ACE-III Memory, and ACE-III Total Score (see Table 2, 3, 4, and 5) the result curves suggest that most probably the improvement of cognitive skills measured by the tests is an artefact associated with the effect of learning. The argument in favor of the above is the fact that the improvement at the trend level was observed in measurement 2, after three months without therapy. Spontaneous improvement of cognitive skill should not be detected in population with MCI, which is a prodromal phase of Alzheimer's disease. A useful explanation is the one where patients unintentionally acquired the rules of performing the above-mentioned tests and as a result they did better and better in subsequent ones.

There is a possibility that the results of the ACE-III Attention are related to participation in olfactory training. There was no improvement recorded in measurement 2. These were the tests carried out after completed training that indicated improved attention (measured with the ACE-III Attention). Although the results do not confirm statistical significance of changes, their ambiguity leaves a lot of room for repeated research on a larger scale.

The results might be interpreted in the following ways: 1) olfactory training does not improve cognitive abilities in people with MCI, which was documented by the conducted research; 2) olfactory training does not improve cognitive ability of people with MCI, though the question whether its application could be effective in other disorders or with healthy individuals remains open; 3) olfactory training might improve cognitive ability of people with MCI, though methodological limitations of the conducted research prevented that from being proven.

Accepting the first explanation assumes recognizing Dalautzai's approach [7] – according to whom improving olfactory functions in AD patients makes sense due to stimulated cerebral blood flow, increased synaptic connectivity and stimulation of angiogenesis and neurogenesis processes – as not useful. Taking into account the

theoretical and empirical data, such uniform conclusion is, according to the authors, premature. It might be assumed that the regions where the above-mentioned processes are stimulated are not engaged in mnemonic functions. Moreover, a number of methodological aspects of the conducted research do not allow such explanation to be accepted, which is going to be discussed soon.

The second interpretation, where cognitive skill training might not work in MCI population but might be effective with other diseases (e.g., Parkinson's disease) or with healthy geriatric population, has some theoretical grounds. Lack of positive effects of training is consistent with lack of positive results or clinical research on various pharmacological substances [1]. It is possible that neurodegenerative changes in MCI are too advanced or located in such areas that even when we stimulate them by increased cerebral brain flow, it does not bring about any real changes. However, it might not be excluded that in the case of healthy elderly people or suffering from other neurodegenerative diseases, such training might cause positive results. It is known that Parkinson patients respond well to olfactory training, so it is worth finding out how such training can affect cognitive functions in this group [25–28]. Just like in the case of previous interpretation, we might bring up the argument that unequivocal report of no cognitive improvement due to olfactory training is premature, especially if it is compared to vast scientific data suggesting that such changes are plausible.

The third interpretation assumes that methodological limitations of conducted research do not allow zero hypothesis to be accepted. The following arguments speak in favor of restraining from final verdict:

(1) There were 35 subjects. Failure to meet the criterion of sphericity suggests that it would be worth examining a larger number of people in order to reduce the impact of individual results on data parameters and to increase the power of statistical analysis.
(2) Ambiguous nature of the results – in the case of confirmed, statistically significant changes in the CVLT, MMSE, ACE-III Memory and ACE-III General score tests, we deal with the practice effect. The scores in the ACE-III Attention test are much more complex and on the trend level they reflect the dynamics of changes that might be expected in the case of MCI subjects, that is no changes or slight deterioration of memory ability and attention during the first three months without treatment and minor improvement after three months of participation in training. It is worth pointing out that multivariate analysis using Wilk's Lambda indicated statistical significance of changes. Once a more rigorous analysis was applied, taking into account Mauchley's sphericity coefficient, the results were not confirmed.
(3) The applied theoretical model, assuming improved cognitive functioning in subjects with MCI as a result of olfactory training, might not be optimal. In clinical research investigating Alzheimer's medications similar difficulties

had to be tackled with and as a result the notion of clinical effectiveness of medication had to be altered. Instead of operationalizing it as improving ability compared to the initial result, it is viewed as slowing down the process of deterioration of cognitive ability [29]. It is possible that olfactory training does not contribute to improving memory, though it might support delaying the progress of cognitive deficiency. The question calls for further longitudinal prospective research.

Recapitulation

The results suggest lack of expected therapeutic effects of olfactory training. However, assuming that such effects do not occur is premature. Having analyzed the strong and weak points of the applied methodology, the authors point out that further research in this area is necessary. Empirical reports and theoretical analysis suggesting the possibility of neuropsychological rehabilitation of cognitive functions by means of olfactory stimulation are a strong argument to do so.

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