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Effects of Age, APOE ε 4, Cognitive Reserve and Hippocampal Volume on Cognitive Intervention Outcome in Amnestic Mild Cognitive Impairment

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Abstract

Here we studied intervention outcome and potential predictors for cognitive intervention effects in patients with amnestic mild cognitive impairment (aMCI), a population at risk of Alzheimer's disease. We included 100 aMCI patients (cognitive intervention group, n=69; active control group, n=31) that underwent a previously established 6-month group-based multicomponent cognitive intervention or an active control condition. As a primary endpoint we defined changes in global cognition (Alzheimer's Disease Assessment Scale – Cognitive Subscale, ADAS-Cog). Secondary endpoints were changes in verbal and visual episodic memory (California Verbal Learning Test, CVLT; Face Name Learning Test, FNL). Overall, we found no improvements in our primary outcome ADAS-Cog. Group by time interactions were found for CVLT learning (p=0.031), with improvements in the intervention group and deteriorations in the control group. The intervention group deteriorated in FNL learning (p=0.001) and the control group deteriorated in FNL recall (p=0.048). The main focus of the study was, however, whether intervention outcome was predicted by factors that are known to affect disease progression. As predictors we selected age, *APOE* carrier status, cognitive reserve, and hippocampal volume. In linear regression analyses, lower hippocampal volume predicted deteriorations in ADAS-Cog (p=0.035) and CVLT recall (p=0.016), whereas younger age (p=0.011) and *APOE* ε4 non-carrier status (p=0.024) predicted improvements in CVLT learning. Lower cognitive reserve predicted deteriorations in FNL recall (p=0.008). Regarding the modest intervention effects, our results challenge a general recommendation of cognitive interventions in aMCI. Rather, our findings suggest that younger patients, *APOE* ε4 non-carriers, and patients with higher CR and higher hippocampal volume have a higher likelihood to benefit from a cognitive intervention, which could be useful for the selection of patients for future intervention trials.

Keywords: Alzheimer's disease; Mild cognitive impairment; Outcome predictors; Cognitive intervention; Memory

Introduction

The concept of amnestic Mild Cognitive Impairment (aMCI) enables clinicians to identify individuals at risk for developing Alzheimer's disease (AD), holding potential for secondary prevention of AD dementia [1,2]. As the efficacy of available drug therapies in aMCI is limited [3], non-pharmacological treatment approaches like cognitive interventions are investigated as a potential therapeutic approach. Previous cognitive intervention trials in aMCI report an attenuation of cognitive decline [4] or even improvements in episodic memory performance [5]. Yet, ongoing investigations of cognitive interventions also pose the question why some patients benefit from a cognitive intervention while others do not, i.e., whether therapeutic effects are modulated by factors that influence the general course of aMCI. Knowledge of factors predicting the outcome of cognitive interventions could foster more individualized treatment approaches by facilitating the identification of aMCI patients that have a high likelihood to benefit from participating in a cognitive intervention. Numerous studies have shown that carrying at least one copy of the APOE ε4 allele and hippocampal atrophy are related to a more rapid cognitive decline in MCI [6], hence they may also limit the efficacy of cognitive interventions [7,8]. On the other hand, both greater cognitive reserve [9,10] and neural plasticity (which is higher in younger patients) [11] have been shown to alleviate the impact of brain pathology onto cognitive performance and may thus favor positive effects of cognitive interventions. On these grounds, we investigated, whether age, the APOE genotype, hippocampal volume and cognitive reserve modulated the effects of a cognitive intervention paradigm that focuses on the training of episodic memory – the cognitive domain most severely affected in aMCI. Addressing this question, we conducted a previously established, controlled cognitive intervention [12] in a large sample of aMCI patients. Next, we assessed the overall treatment effects as a critical reappraisal of previously reported results [12]. In line with our pilot study [12] we used a measure of global cognition as a primary intervention outcome; secondary outcomes were more specific measures of verbal and visual episodic memory that better capture the core symptomatology of aMCI. However, the main aim of this study was to assess the predictive value of age, the APOE genotype, cognitive reserve and hippocampal volume on cognitive intervention outcome in subjects with aMCI. We expected younger age and higher cognitive reserve to favor intervention effects, whereas presence of

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the APOE ε4 allele and hippocampal atrophy were assumed to limit intervention effects. We included these specific predictors, since they are relatively easy to assess, widely available and could thus be used in clinical practice to identify subjects that are likely to benefit from a cognitive intervention.

Methods

Subjects

We included subjects >55 years with a clinical diagnosis of aMCI as defined by the Petersen criteria [2] based on CERAD-Plus [13,14] test scores. In detail, subjects had to score below 1.5 standard deviations of the age and education adjusted norms in at least one of the memory subtests (immediate or delayed recall) of the CERAD-Plus battery, in order to be diagnosed with aMCI. If treated with anti-dementive or antidepressant drugs, subjects had to be on stable medication for at least 2 months prior to study start. Subjects had to score ≥ 86 IQ points on the MWT-B scale, to ensure average premorbid verbal IQ [15]. Exclusion criteria were defined as: Presence of depressive symptoms (a score >18 on the Beck Depression-Inventory II (BDI-II)), evidence for other DSM-IV axis 1 disorders, neurological disorders, uncontrolled arterial hypertension, diabetes mellitus or a history of alcohol or drug abuse, participation in a cognitive training 2 months before study inclusion and MRI contraindications.

Standard protocol approvals, patient consents, and registration

The study was approved in August 2010 by the ethics committee of the Ludwig Maximilian University Munich and registered at www.clinicaltrials.gov as NCT01525368 as "Outcome Predictors of a Cognitive Intervention in aMCI." All participants provided written informed consent.

Study design

The study design was a prospective non-randomized clinical trial, using a previously described cognitive intervention paradigm [12] and an active control condition (ACC) paradigm. Since our pilot study has revealed effect sizes of d=0.4 to 0.7, a sample size greater than 50 and an duration of 6 months (equivalent to the pilot study) were considered sufficient to detect intervention effects [12]. Also our sample size is in agreement with most cognitive intervention studies previously published, as shown by a recent meta-analysis that showed a mean sample size of 50 averaged across 27 cognitive intervention trials [5]. Due to the monocenter design of the study, subject recruitment was limited, hence only one group met at a time. To ensure sufficient group sizes, subjects were non-randomly assigned to the group currently recruited (CIG or ACC). After enrolment for the CIG was finished (7 separate groups), participants for the ACC were recruited (2 separate groups). Regarding season coverage of the study groups, the CIG's covered in total all 12 months from January to December; the ACC's covered the 9 months from December to August. Group sessions were held by a specially trained psychologist or social worker. Outcome measures (see below) were defined a priori.

Cognitive intervention

The intervention [12] consists of 20 group sessions, weekly applied for 120 min each. The program is based upon the theory of cognitive reserve and retrogenesis and has been described in detail in our earlier work [10,12,16]. Our intervention addresses mainly the training of verbal episodic memory, as well as attention and executive functions. Moreover, the program integrates stimulation of activities of daily living, as well as psychomotor and recreational exercises and promotes meta-cognition with information on cognitive changes in aging and AD.

Active control condition

To control for intervention effects, ACC participants met 6 times, once per month, and received paper-pencil exercises for self-study at home, addressing mainly sustained attention, which is thought to be relatively spared in aMCI [17]. Completion of the exercises was not monitored. During each meeting the next set of at-home exercises was provided.

Study cohort

Subjects were recruited between September 2010 and July 2014 in Memory Clinics at the University Hospital Munich (Institute for Stroke and Dementia Research and Department of Psychiatry). A study-flowchart is depicted in (Figure 1). To assess the patients' cognitive status, we used the CERAD-Plus Battery [13,14]. Patients who met inclusion criteria underwent additional comprehensive neuropsychological testing (see below) and MRI before and after the study period. Of 160 subjects screened, 122 met inclusion criteria. A total of 88 subjects were assigned to the CIG, and 34 subjects to the ACC. Overall, 69 patients of the CIG completed the intervention and were included in the statistical analysis. Eighteen patients dropped out of the CIG, either due to withdrawal of informed consent (n=5), insufficient attendance (defined as missing more than 4 sessions) (n=8), hearing impairment (n=1), development of primary progressive aphasia (n=1), surgery (n=1), refusal of follow-up examinations (n=2), or development of clinical depression (n=1). In the ACC, 31 of the 34 subjects completed the study. Reasons for drop out were withdrawal of informed consent (n=2) and refusal of follow-up examination (n=1).

Outcome measures

All subjects underwent comprehensive neuropsychological examination before and after the 6 month study period. Baseline and follow-up neuropsychological examinations were performed in a standardized manner by specially trained psychologists who were not blinded concerning the subjects' group membership. To ensure comparability with our pilot study [12] regarding the intervention effects, we used changes in global cognition in terms of the total score of the Alzheimer's disease Assessment Scale - Cognitive Subscale (ADAS-

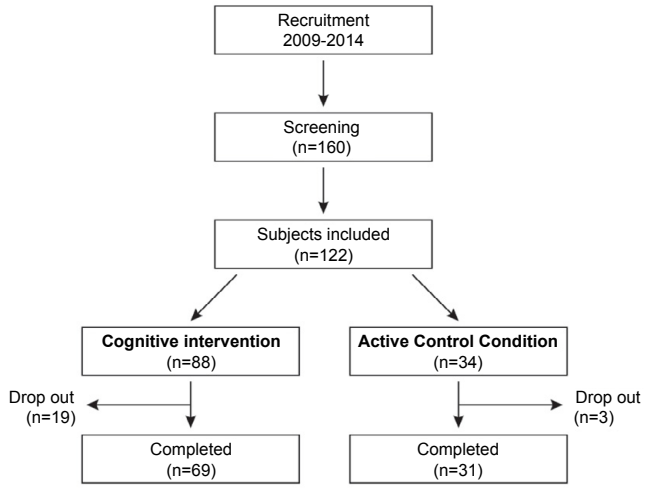

Figure 1: Study flowchart.

Cog) as a primary outcome measure. The ADAS-Cog comprises subtests on naming, word recall, constructional praxis, orientation and language functions and is validated for cognitive assessment in aMCI [18]. Due to the complex nature of episodic memory – the domain mainly affected in aMCI and early AD - secondary outcome measures of episodic memory were assessed, namely the German versions of the California Verbal Learning Test (CVLT) [19] and the Face Name Learning Test (FNL) [20]. In both tests, we assessed subscales for learning and delayed free recall. As a tertiary outcome measure, BDI-II was used to assess effects on mood and depressive symptoms that were observed in previous cognitive intervention trials [4].

MRI acquisition

All patients underwent cranial MRI before and after the study using a 3T scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) with a 12 channel head coil. We assessed a 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence with whole brain coverage (TR/TE=2100/3.06 ms, inversion time=900 ms, flip angle=9°) and 1mm isotropic voxel resolution. All MRI datasets were inspected by a neuroradiologist to exclude structural lesions prior to the intervention.

Assessment of potential predictors for cognitive changes

Potential predictors (age, APOE genotype, hippocampus volume, cognitive reserve) were selected based on theoretical considerations since they are relatively easy to assess and show consistent associations with the disease course in previous studies (see discussion).

APOE genotyping

We assessed the APOE genotype via Single Nucleotide Polymorphism (SNP) analysis of SNPs rs7412 and rs429358 using TaqMan SNP genotyping assays by Applied Biosystems. For all analyses the genotype was dichotomized in APOE ε4 carriers (when at least one €4 Allele was present) and in APOE ε4 non carriers (when no €4 Allele was present).

Hippocampus volumetric assessment

Image processing was performed in Statistical Parametric Mapping 8 (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK). T1w images were segmented in gray matter, white matter, and cerebrospinal fluid via a unified segmentation approach [21] implemented in SPM8. For segmentation, we used preexisting tissue probability maps from a population of 662 healthy elderly subjects [22]. The images were subsequently smoothed with an 8 mm FWHM Gaussian kernel and normalized to the T1 Montreal Neurological Institute (MNI) template using the DARTEL Toolbox implemented in SPM8. The segmented and normalized images were modulated to preserve the volume of the images and multiplied with binary hippocampal masks in MNI space picked from the SPM anatomy toolbox [23]. Hippocampal volume was obtained by cumulating the grey matter volume within the bilateral hippocampus masks.

Cognitive reserve

In line with previous studies, we used an estimate of premorbid verbal IQ as assessed by the German multiple vocabulary test as a proxy measure for cognitive reserve [15,24].

Statistical analysis

All statistical analyses were conducted using R (R software package, version 2.13.2; R Foundation for Statistical Computing, Vienna, Austria). To compare baseline demographics and clinical characteristics of the CIG and ACC, we used chi-square test for categorical variables and T-test for independent samples to compare means of continuous measures. Group differences were considered significant when meeting a p value below €=0.05.

To determine treatment effects we conducted analyses of covariance (ANCOVA) using group (CIG vs. ACC), time (baseline vs. follow-up) and an interaction term (group X time) as the independent variables and post-intervention cognitive test scores as dependent variables. To control for potential confounds, age, gender and premorbid verbal IQ were entered as covariates.

To test the effect of potential predictors on the cognitive outcome in the CIG, we used univariate multiple regression. In a first step, we analyzed these predictive effects in the CIG only. For each outcome measure, all potential predictors were entered in a linear model and served as regressors to predict post-intervention test scores, controlling for effects of gender and pre-intervention test scores. Predictors that revealed significant beta weights for cognitive changes in the CIG were subsequently entered in linear models with interaction terms (group by predictor) on post-intervention test scores controlling for gender and pre-intervention test scores to analyze whether their predictive value was specific for the CIG. All statistical tests were conducted 2-tailed.

Results

Characteristics of the study cohort

Descriptive statistics for both groups are displayed in (Table 1) significantly larger number of CIG patients took Acetyl cholinesterase inhibitors (p=0.018) plus CIG patients had significantly higher hippocampal volume (p=0.016) and higher premorbid verbal IQ (p=0.044)

Changes in outcome measures

The ANCOVA models showed no overall effects of the intervention on ADAS-Cog, contrasting the results of our pilot study [12]. A significant group by time interaction was found for CVLT learning (p=0.041), with improvements in the CIG, but deteriorations in the ACC. Furthermore, we found significant main effects of time on FNL learning (p<0.001) and FNL recall (p=0.003) outcomes, suggesting deteriorations in both FNL subtests independent of the group. Changes in primary outcome measures between pre- and post-intervention in both groups are displayed in (Table 2).

Predictors of intervention effects

To investigate our main question, we tested whether hippocampal volume, the APOE genotype, age or cognitive reserve had an effect on treatment efficacy. For ADAS-Cog, lower hippocampal volume predicted deteriorations (p=0.035). Regarding CVLT learning, younger age (p=0.011) and APOE 4 non-carrier status (p=0.024) predicted a better outcome. Presence of the APOE ε4 allele also showed a trend (p<0.1) towards predicting deteriorations in FNL learning and recall. Besides, higher hippocampal volume predicted improvements in CVLT recall (p=0.016). In FNL recall, lower premorbid verbal IQ predicted deterioration (p=0.008). The significant predictor associations for cognitive changes in the CIG were additionally tested for group (CIG vs. ACC) by predictor interactions. None of these interactions was significant at a significance threshold of €=0.05. Detailed results of multiple regression analyses for cognitive changes in the CIG are displayed in (Table 3).

	CIG (n = 69)	ACC (n = 31)	Total (n = 100)	
Demographics				
Age	73.4 (5.2)	74.8 (6.6)	73.8 (5.7)	p = 0.247
min/max	61/87	57/85	57/87	
Gender f/m	34/35	12/19	46/54	p = 0.327
Premorbid verbal IQ	118.58 (14.4)	113.19 (11.0)	116.91(13.7)	p = 0.044
min/max	91/145	93/136	91/145	
Cognitive status				
MMSE	27.4 (1.7)	27.1 (1.9)	27.3 (1.8)	p = 0.373
min/max	23/30	22/30	22/30	
Clinical characteristics				
aMCI subtype single-domain/multi-domain	24/45	14/17	38/62	p = 0.376
AChE-I intake	11	0	11	p = 0.018[a]
APOE status				
ε4 carriers/non-carriers	38/31	12/19	50/50	p = 0.130
HV				
Volume	3.6 (0.7)	3.2 (0.7)	3.5 (0.7)	p = 0.016[a]
min/max	2.1/5.3	2.2/4.3	2.1/5.3	

Differences in continuous variables were compared using T-Test for independent samples. categorical variables were checked using Chi-Squared test. Abbreviations: CIG = Cognitive Intervention Group; ACC = Active Control Condition; MMSE = Mini Mental State Examination; BDI-II = Beck Depression Inventory II; $HV_{adjusted}$ = Volume of bilateral hippocampi adjusted to total intracranial volume in ml; Values represent mean ± standard deviation in ( ); min/max = range of scores.
[a] Significant values (p < 0.05).

Table 1: Characteristics of the study cohort at baseline assessment.

Outcome measures	Timepoint	CIG	ACC	ANCOVA
Primary				
ADAS-Cog (↓)	Baseline	10.7 (4.6)	11.6 (3.2)	n.s.
	Follow-Up	11.0 (4.7)	11.1 (4.4)	
longitudinal change		p = 0.372	p = 0.572	
Secondary				
CVLT-learning (↑)	Baseline	29.5 (11.7)	27.1 (12.4)	Main effect group (F = 4.312, p = 0.041[a]), Main effect time (F = 3.964, p = 0.049), Interaction Group X Time (F = 4.777, p = 0.031)
	Follow-Up	32.5 (13.8)	25.9 (12.9)	
longitudinal change		p = 0.040[a]	p = 0.429	
CVLT- recall (↑)	Baseline	4.8 (4.2)	3.0 (3.8)	Main effect group (F = 6.934, p=0.010[a])
	Follow-Up	5.1 (5.0)	2.8 (3.8)	
longitudinal change		p = 0.792	p = 0.773	
FNL-learning (↑)	Baseline	20.5 (7.7)	16.3 (7.7)	Main effect group (F = 6.459, p = 0.013[a]), Main effect time (F = 15.62, p < 0.001)
	Follow-Up	18.3 (8.2)	14.8 (7.9)	
longitudinal change		p < 0.001[a]	p = 0.575	
FNL- recall (↑)	Baseline	3.9 (2.2)	2.7 (2.2)	Main effect group (F = 9.713, p = 0.002[a]), Main effect time (F = 9.344, p = 0.003)
	Follow-Up	3.5 (2.5)	2.0(2.2)	
longitudinal change		p = 0.208	p = 0.048[a]	
Tertiary				
BDI-II (↓)	Baseline	7.7 (4.2)	7.9 (6.5)	n.s.
	Follow-Up	7.7 (4.9)	7.7 (5.4)	
longitudinal change		p = 0.938	p = 0.836	

Abbreviations: ANCOVA = Univariate Analysis of Covariance; CIG = Cognitive Intervention Group; ACC = Active Control Condition; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; CVLT = California Verbal Learning Test; FNL = Face Name Learning Test; BDI-II = Beck Depression Inventory II; Values represent means ± standard deviation in ( ).
(↑) = higher better; (↓) = lower better.
[a] Significant values (p < 0.05).
n.s. = non-significant.

Table 2: Analysis of intervention effects.

Discussion

In the current study, we investigated predictors of cognitive intervention outcome in aMCI. More precisely, we examined whether factors that modulate the disease course of aMCI in general also modulate the effects of a previously established cognitive intervention paradigm [12]. Regarding our primary outcome measure ADAS-Cog, we found no significant effects of the cognitive intervention, contrasting our previous findings [12]. In terms of our secondary outcome measures, we found significant group by time interactions on verbal teach, with improvements in the CIG and deteriorations in the ACC. Regarding visual learning and recall, both groups (ACC and CIG) deteriorated significantly.

Even though the overall treatment effects were modest, we found a considerable variance in individual rates of change in primary and secondary outcome measures to investigate our main question – the predictors of intervention outcome. In brief, we expected younger age and higher cognitive reserve (as assessed via premorbid verbal IQ) to favor intervention effects, whereas presence of the APOE ε4 allele, and lower hippocampal volume were assumed to limit intervention effects. We focused on these predictors, since they are relatively easy to assess and widely used in clinical practice. Overall, we found effects in the directionality that we initially hypothesized. For the ADAS-Cog, lower hippocampal volume predicted deteriorations. Regarding the verbal learning subtest of the CVLT, younger age and APOE ε4 non-carrier status predicted improvements, whereas higher hippocampal volume predicted improvements in the recall subtest of the CVLT. In visual memory (FNL) lower premorbid verbal IQ (cognitive reserve proxy) predicted deteriorations in recall. In a second analysis step, group by predictor interactions on cognitive changes were non-significant. Thus, in accordance with previous research, the predictive associations delineated here apply for the disease course of aMCI in general but also modulate the effects of a cognitive intervention.

Comparing the cognitive intervention effects of the current cohort with our previous findings [12], we did not find changes on ADAS-Cog and episodic memory improvements were smaller as compared to our pilot study [12] or other previously published CIs [25-28]. Since our pilot study [12] comprised a smaller study cohort (12 CIG vs. 12 ACC) with younger (on average 3 years) as well as less impaired patients at baseline (2 points difference on average on the ADAS-Cog scale compared to the current cohort), these sample differences might partially explain the differences in treatment efficacy [12]. This explanation is also in line with results of previous cognitive interventions in aMCI [25-28], in which patients were on average 3 to 10 years younger, but memory improvements due to the cognitive intervention were larger. We have shown, that younger age predicted stronger improvements in verbal learning (CVLT) and similarly other authors have shown associations between younger age and larger intervention gain in aMCI [25,29]. Hence, we argue that the benefit of cognitive interventions partially depends on a patients' age, with younger patients showing better outcome. Translating this into clinical practice, we argue that especially younger patients that show aMCI symptomatology should be motivated to participate in cognitive interventions. Since the current sample was older than in our pilot study [12] and intervention effects were lower, it is also possible that longer intervention duration would have increased intervention efficacy. In contrast to other studies [4], we found no intervention effects on the level of depressive symptoms. Since our exclusion criterion for depression (BDI-II score<18) was very conservative, we did not expect significant affective improvements due to floor effects. As the CIG was lacking changes in depressive symptoms over time, we can also exclude a mediating effect of depression improvement on cognitive performance; such an effect was suggested in previous studies where depressive symptoms negatively affected cognitive performance [30].

Interestingly, we observed discordant effects on progression of verbal and visual memory with verbal learning improvements in the CIG, but deteriorations in visual learning in the CIG and visual recall in the ACC as assessed by the FNL. This may be explained by a clear focus of our intervention on the training of strategies supporting memory in the verbal domain. A similar trend towards improvements in verbal, but deteriorations in visual memory was reported before in a controlled cognitive intervention trial [27] in aMCI focusing on the training of episodic memory. Besides, there is evidence that deficits in face-perception occur early in aMCI; hence visual memory deterioration can also reflect impaired face-perception and thus a bottleneck for memory performance in cognitive tests using a face-name paradigm [27]. However, our findings of deteriorations in visual memory in aMCI patients underscore the need to further study visual face-name memory, especially due to its' relevance for every-day life [31,32].

Addressing the main aim of this study to identify predictors of cognitive changes in the CIG, we found APOE ε4 non-carriers to show improvements in verbal learning (CVLT learning). A similar trend was found for visual learning (FNL learning). The APOE ε4 allele is a

	Predictors							
	Age		***APOE***		**HV**		**IQ**	
Outcome	β	p	β	p	β	p	β	p
Primary								
ADAS-Cog (↓)	-0.055	0.650	0.095	0.392	**-0.271**[a]	**0.035**	0.138	0.239
Secondary								
CVLT learning (↑)	**-0.322**[a]	**0.011**	**-0.276**[a]	**0.024**	-0.022	0.881	-0.067	0.590
CVLT recall (↑)	-0.044	0.733	-0.081	0.537	**0.347**[a]	**0.016**	0.167	0.192
FNL learning (↑)	-0.113	0.391	-0.227	0.070	0.075	0.611	0.085	0.519
FNL recall (↑)	-0.067	0.598	-0.172	0.153	0.062	0.661	**0.335**[a]	**0.008**

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; CVLT = California Verbal Learning Test; FNL = Face Name Learning Test; HV = Hippocampal Volume
Beta values are standardized to a z-scale.
(↑) = higher better; (↓) = lower better;
[a] Significant values ($p < 0.05$).

Table 3: Regression Models to predict cognitive changes in the CIG (controlling for gender and baseline cognition).

well-known risk factor for developing aMCI and AD. Presence of the APOE ε4 allele is associated with increased amyloid-beta deposition in the brain [33] and studies have reported faster rates of memory decline even in non-demented APOE ε4 carriers. Moreover, the effect of APOE ε4 on cognitive decline has been shown to be modulated by age, with older patients showing faster rates of decline when possessing at least one APOE ε4 allele [34]. Taken together, APOE ε4 carriers are likely to show more AD related pathology and faster cognitive decline as compared to APOE ε4 non-carriers. Regarding the known effects of the APOE ε4 allele, our results of larger improvements in APOE ε4 non-carriers thus appear plausible. A further possible explanation for larger improvements in the APOE ε4 non-carriers is that APOE ε4 non-carriers in our sample show aMCI due to non-amyloid pathology. Recent studies showed, that aMCI subjects with suspected non-amyloid pathology show an overall slower progression of cognitive symptoms as compared to subjects with aMCI due to underlying AD pathology [35,36]. Hence, a further possibility is that intervention related improvements are greater in subjects with aMCI caused by non-AD pathology. Besides the effects of the APOE ε4 allele, previous cognitive interventions [25,29] showed younger age to be associated with better intervention outcome. In line with these findings, our analysis showed younger age to predict larger improvements in CVLT learning in the CIG. One factor potentially explaining this observation is neural plasticity that has been shown to decline with age especially in medial temporal lobe areas [11], which are crucial for memory performance and also typically affected in MCI and early AD [37]. Thus, our finding is concordant with previous publications suggesting that younger patients show a more favorable outcome in verbal learning [25,29]. In measures of global cognition (ADAS-Cog) and verbal recall memory (CVLT recall), higher hippocampal volume predicted overall improvements due to the intervention. A recent study [38] showed a correlation between higher hippocampal volume and better performance in CVLT recall in healthy young men, emphasizing the importance of the hippocampus for memory recall in general and for this CVLT subscale in particular. During AD pathogenesis, volume loss of the hippocampus as an indicator of AD related neurodegeneration is present in pre-symptomatic stages and in aMCI, continues with AD progression and progresses fastest in individuals that later convert to AD-dementia [6,39,40]. In line with these findings, MCI patients of our sample with higher hippocampal volume show a better outcome in CVLT recall. However, considering the role of hippocampal atrophy as a surrogate for AD pathology, subjects with relatively high hippocampal volume are less likely to show aMCI due to AD pathology [36]. Given that aMCI due to non-AD pathology is associated with slower cognitive decline, this further supports the notion that aMCI subjects with non-AD pathology show greater improvements due to a cognitive intervention.

Ultimately, lower cognitive reserve as assessed by the premorbid verbal IQ predicted deteriorations in face-name (FNL) recall, implying greater cognitive reserve to guard against cognitive deteriorations, congruent with previous research [10]. The list of predictors analyzed in this study is of course not exhaustive and other factors, comorbidities (i.e. cardiovascular health, diabetes) or more sensitive markers of brain pathology (i.e., AV45- or FDG-PET) might contribute to intervention outcome as well. However, this goes beyond the scope of this exploratory study and should be addressed by future studies.

Limitations of the study regarding the analysis of intervention effects are a missing subject randomization and examiner blinding and different group sizes. Since, both groups differed in AChE-I intake, we cannot exclude effects on intervention outcome, albeit a meta-analysis showed no beneficial effects of AChE-I on cognition in aMCI. [3] Also noticeable are different drop-out rates in both groups (19 in the CIG vs. 3 in the ACC), which occurred most likely due to different time expenditure (CIG: 1 meeting per week; ACC: 1 meeting per month). The different time expenditure of the CIG and the ACC could also be a factor potentially influencing intervention effects, since there is evidence that social activities positively impact cognitive function in elderly subjects [41].

In conclusion our results provide evidence that intervention effects were higher in aMCI subjects that showed higher hippocampal volume and were APOE ε4 non-carriers, indicating that they had a lower probability of AD related pathology as an underlying cause of aMCI. In line with this interpretation, we found no intervention related improvements in patients with AD dementia in our pilot study [12]. However, facing our moderate treatment results, the current results challenge the notion of a general recommendation of cognitive interventions in aMCI. Rather, our current results suggest that specific characteristics may render aMCI patients likely to benefit from a cognitive intervention. We argue, that aMCI patients who are relatively young, APOE ε4 non-carriers, show little hippocampal atrophy, and have a high IQ might be especially suitable for cognitive intervention trials. Accordingly, knowledge of these predictors could help assign aMCI patients to cognitive interventions in clinical practice and future cognitive intervention trials.

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