Long-Term Observation of a Multicomponent Cognitive Intervention in Mild Cognitive Impairment

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ABSTRACT

Background: Recent studies demonstrated benefits of cognitive intervention in mild cognitive impairment (MCI), but few studies have determined long-term effects on cognition, conversion rate to Alzheimer's disease, and the role of early intervention.

Method: A 6-month multicomponent cognitive group intervention was applied in participants with single- or multiple-domain amnestic MCI (defined according to Petersen's criteria). One group (n = 12) received the intervention at the beginning of the study period and was compared with an active control group (n = 12) who received it after an 8-month time lag. Follow-up assessments were conducted at 15 and 28 months (study period was August 2007–December 2009). The primary outcome was change in cognitive function as determined by changes in scores on the Mini-Mental State Examination and the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), and the secondary outcomes were change in specific cognitive and noncognitive functions and conversion to Alzheimer's disease (according to *DSM-IV*/NINCDS-ADRDA criteria and NAI-AA criteria for probable Alzheimer's dementia with increased level of certainty).

Results: Eighteen participants completed the study after 28 months. Long-term data revealed a stable intervention effect on the primary outcome ADAS-cog in the early-intervention group ($P = .024$). The participants in the later-intervention (control) group appeared to benefit to a lesser extent from the cognitive intervention compared to those who received it earlier. Only participants in the later-intervention group (6 of 12) converted to Alzheimer's disease during the 28-month study period.

Conclusions: Benefits of our 6-month cognitive intervention on global cognitive status appear to be preserved over extended follow-up periods. Early cognitive intervention may delay conversion to Alzheimer's disease. Findings in a small sample encourage the use of the intervention in larger-scale studies.

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Cognitive intervention is thought to be a beneficial therapeutic approach in Alzheimer's disease (AD) and its preclinical stage.[1–3] No pharmacologic treatment options are currently available for predementia stages of AD outside of clinical trials.[1] Delaying AD onset by 5 years—for example, by a distinct cognitive intervention in patients who would eventually develop this condition—would result in a decrease in the apparent prevalence of AD by 50% and lead to substantial personal, social, and economic benefits.[4] There is an urgent need for novel therapeutic strategies that may more efficiently affect disease progression and its related symptoms.

Beneficial effects of cognition-based interventions on cognitive decline have been reported in subjects with mild cognitive impairment (MCI).[3] MCI is defined as a subjective memory complaint with objective memory impairment that does not interfere notably with activities of daily life or psychosocial competence, excluding a clinical diagnosis of dementia as defined in *DSM-IV* or *ICD-10*.[5,6] Compared with healthy individuals, those with amnestic MCI (aMCI) can be regarded as being in a prodromal stage of AD and are at risk for dementia.[7]

Short-term effects of cognitive interventions in MCI have been shown on improved global cognitive functioning and specific cognitive and noncognitive functions.[3] However, most studies do not provide information on potential mid- to long-term effects after the intervention has ended. Moreover, data regarding the effects of cognitive intervention on the conversion to AD are still widely lacking. In MCI, some studies have investigated the effects of cognitive interventions beyond the main intervention being studied.[8–10] In a 1-year follow-up study,[10] the efficacy of a computer-assisted neuropsychological training program (Training NeuroPsicologico [TNP]) was evaluated in MCI participants in 3 groups: participants treated with TNP and cholinesterase inhibitors were compared to those treated only with cholinesterase inhibitors and to untreated participants. Untreated participants maintained their cognitive, functional, and behavioral status after 1 year, and participants treated only with cholinesterase inhibitors improved in depressive symptoms, whereas participants treated with TNP and cholinesterase inhibitors showed significant improvements in memory, abstract reasoning, and depressive symptoms. Troyer and colleagues[8] showed that a group intervention increased memory-strategy knowledge and use in MCI participants beyond 3 months postintervention relative to waitlist controls.

The use of early intervention in oligosymptomatic patients is largely unexplored. Aspects of early cognitive intervention derive from the concept of cognitive reserve[11] hypothesizing that cognitive reserve might be better preserved in mildly impaired patients at risk for developing dementia than in patients who have already developed dementia.[12] Moreover, a meta-analysis[13,14] covering more than 29,000 individuals found a risk reduction for dementia of 46% in people with high "behavioral brain reserve," also referred to as "cognitive reserve," that was primarily due to participation in mentally stimulating activities. Additionally, a recent longitudinal cohort study[15] revealed that mentally stimulating activity in cognitively healthy persons appears to slow cognitive decline

before dementia onset. We assume that early direct modulation of behavioral brain reserve might help to delay the onset of dementia in AD. We further hypothesize that early participation in a cognitive intervention enhances its cognitive benefits.

We previously reported that participants with aMCI who received a 6-month cognitive intervention demonstrated improved cognitive and noncognitive functions compared to an active control group.[16] We found significant treatment effects in the cognitive intervention group for the primary outcome, global cognitive status (cognitive subscale of the Alzheimer's Disease Assessment Scale [ADAS-cog]), and for the secondary endpoint, mood (Montgomery-Asberg Depression Rating Scale [MADRS]). Gains in cognition were associated with attenuated decline in glucose metabolism, measured with fluorodeoxyglucose positron emission tomography, in cortical regions typically affected by AD.[17] The aim of the current study was to evaluate the effects of our multicomponent cognitive intervention in a long-term observation of participants in our previous study[16] with the active control group receiving the same cognitive intervention but with an 8-month time lag. We hypothesized that the early onset of a cognitive intervention may play an important role concerning cognitive benefits, progression of cognitive decline, and onset of AD.

As previously described, we could not detect significant effects in AD patients in our prior study.[16] Moreover, the increasing dropout rate in the already small AD patient sample in the course of the study substantially limited statistical power. Therefore, we studied long-term effects in the MCI group only.

Clinical Points

A 6-month multicomponent cognitive intervention in individuals with amnestic mild cognitive impairment:

- Appears to preserve immediate improvements in global cognitive status over an extended follow-up period for more than 2 years
- Seems to be more effective in those receiving it earlier compared to those receiving it after an 8-month time lag
- May delay conversion to Alzheimer's disease for more than 2 years in those who receive it early

METHOD

Participants

Twenty-seven participants were recruited at the Alzheimer Memorial Center of Ludwig-Maximilian University, Munich, Germany. Inclusion followed if participants met Petersen's criteria for single- or multiple-domain aMCI[6]; had no major physical illness, other mental disorder, or disability that could affect participation; and, if treated, had been receiving stable doses of drugs for at least 3 months prior to the start of the study (for more details, see Buschert et al[16]).

Design

Of the 27 screened participants, 24 with aMCI were randomly assigned to either a 6-month cognitive intervention (n = 12), consisting of weekly, 2-hour, cognitive training sessions (intervention group 1 [IG-1]), or an active control condition (n = 12), consisting of paper-and-pencil exercises for self-study (intervention group 2 [IG-2]) (Figure 1). The cognitive intervention builds on the theory of cognitive reserve[12] and was tailored to the cognitive and functional requirements of aMCI participants, following the theory of retrogenesis as the basis for the intervention task selection.[18] The specifics of these training sessions have been previously described.[16] In brief, the participants engaged in cognitive activities ranging from training in formal mnemonic memory techniques to informal activities fostering cognitive and social engagement. In contrast, the control condition focused on exercises of isolated, sustained attention, which is expected to be largely unimpaired, at least in beginning AD.[19]

Eight months after IG-1 began receiving the cognitive intervention, participants in the control condition (IG-2) crossed over to the intervention condition and received the same 6-month cognitive intervention, while participants in IG-1 received no more treatment. After the latter period, a waiting phase of 12 months without treatment followed for all participants.

Comprehensive neuropsychological testing was always conducted within a 4- to 6-week timeframe preintervention or postintervention at Baseline (beginning of the study period) and after overall 8 months (Post1), 15 months (Post2), and 28 months (Follow-up), with a total intervention period of 24 months. Raters were blinded to participant classification and treatment plan throughout the study; an instructor uninvolved in randomization and neuropsychological testing administered the intervention and control conditions. The study was approved by the Ethics Committee of the Medical Faculty of Ludwig-Maximilian University and officially registered (ClinicalTrials.gov identifier NCT00544856). All participants gave written informed consent prior to the start of the study. A complete design would have included an active control group maintained over the whole study period; however, this was deemed problematic because those participants would be systematically excluded from any treatment for more than 2 years. Figure 1 shows the study design.

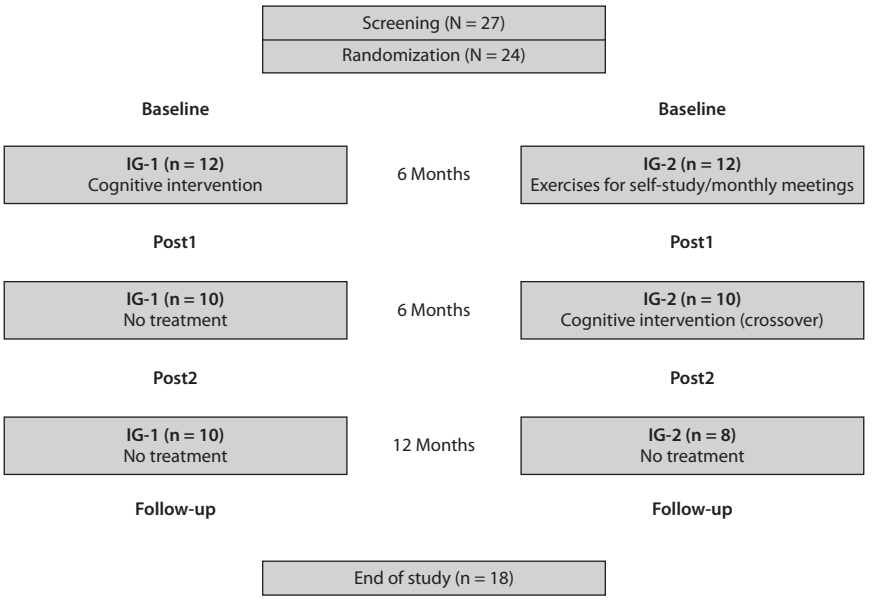
Assessments

The main outcome measure was change in cognitive function as determined by changes in scores on the Mini-Mental State Examination (MMSE)[20] and ADAS-cog (version B at Baseline, version C at Post1, version D at Post2, and version B at Follow-up).[21]

Secondary outcome parameters included change on the following assessments:

- story memory and story recall subtests of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), versions A (Baseline and Post2) and B (Post1 and Follow-up)[22];
- Trail Making Test (TMT), parts A and B[23];

Figure 1. Trial Profile: Early and Later Cognitive Intervention in Individuals With Amnestic Mild Cognitive Impairment



Abbreviations: IG = intervention group, RCT = randomized controlled trial.

- MADRS[24]; and
- Quality of Life-Alzheimer's Disease scale.[25]

Another secondary outcome measure was conversion to AD meeting *DSM-IV*[26]/National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[27] and revised National Institute on Aging-Alzheimer's Association workgroups (NAI-AA) criteria for probable AD dementia with increased level of certainty.[28]

Analysis

Data were entered into the Statistical Package for the Social Sciences (SPSS) Statistics 19 (IBM; Armonk, New York). Chi-square and *t* tests, analyses of variance (ANOVAs), and correlations were used for comparisons of sociodemographic parameters between IG-1 and IG-2 and for testing possible covariates such as age, gender, education, MCI subtype, and time since onset of symptoms for the measured scales. IG-1 had higher scores on RBANS story recall ($P = .033$), so for this scale the Baseline score was included as a covariate. Furthermore, as gender differences could be detected for RBANS story memory ($P = .036$), RBANS story recall ($P = .030$), and MADRS ($P = .043$) at Baseline, gender was included as a covariate if appropriate. To test for differences between the scale scores and the 2 groups (IG-1 and IG-2) for all time points, the following new scores were calculated: (Post1 – Baseline, Post2 – Baseline, and Follow-up – Baseline). For each of these scores, an ANOVA was performed that included covariates as described above. Furthermore, a repeated-measures ANOVA was performed to study main effects. Results represent differences in changes from Baseline in measures of efficacy at postbaseline time points (see analysis strategy[29]).

To test for differences between the intervention groups at the beginning of the respective cognitive interventions (IG-1 at Baseline, IG-2 at Post1) and for differences between Post1 and Post2, with Post1 scores serving as baseline scores, we conducted further ANOVAs with primary and secondary outcome variables as described above.

RESULTS

Feasibility and Acceptance of Program

The study was conducted from August 2007–December 2009, with the 8-month time-lagged cognitive intervention (received by IG-2) being conducted from April 2008–September 2008. Two participants in IG-2 did not attend the intervention (lack of motivation, conversion to AD). The mean attendance of the remaining participants was 17.5 (88.5%) out of 20 sessions (range, 15–20 sessions). None of the participants dropped out of the study in the course of the crossover intervention.

Sample Characteristics

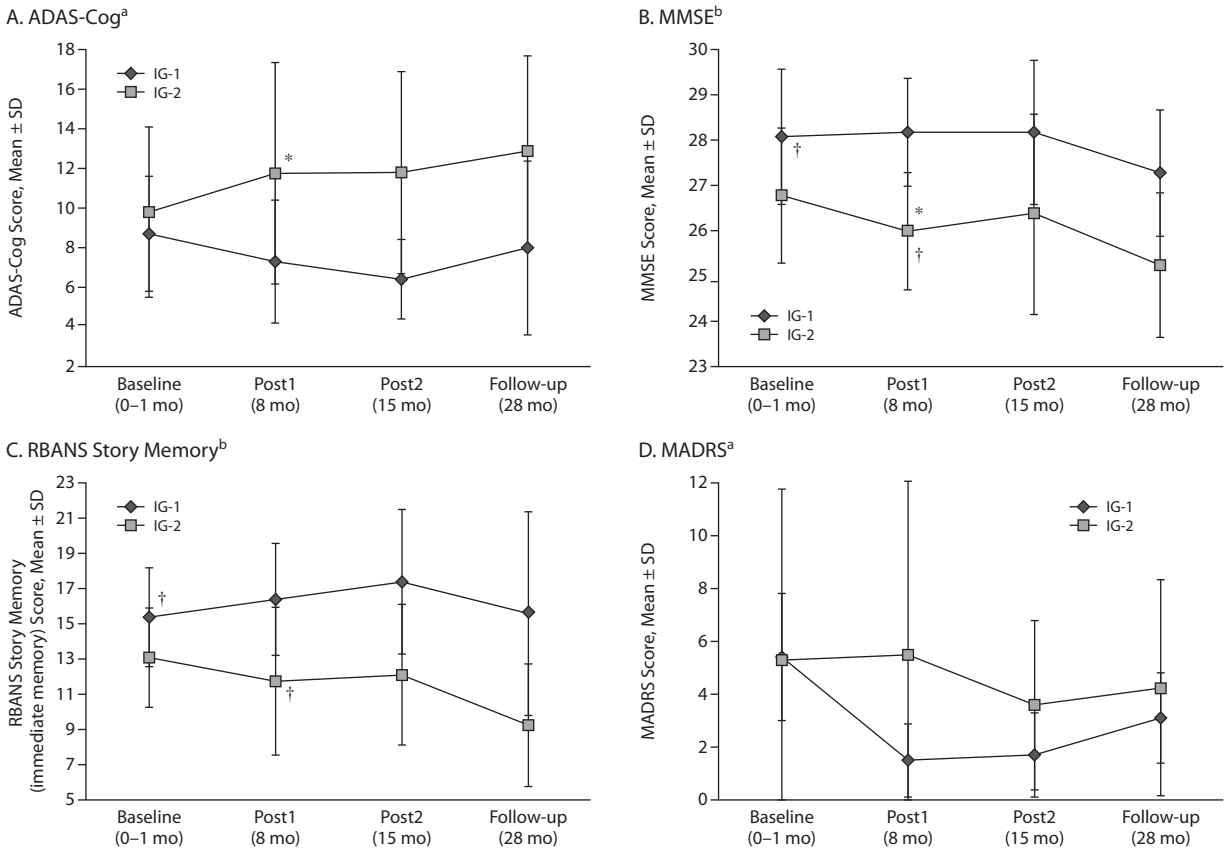
The initial sample consisted of 27 participants with amnestic single- or multiple-domain MCI. Three participants withdrew consent because they found participation in the study too demanding. Twenty-four participants were randomly assigned to the early (IG-1; n = 12) and later (IG-2; n = 12) intervention groups. The groups did not differ with regard to gender, age, educational level (for descriptive data at Baseline, see Buschert et al[16]), aMCI subtype ($\chi^2_1 = 1.510$, $P = .219$), or time since onset of symptoms of cognitive decline ($t_{22} = 1.720$, $P = .099$) (Table 1). Furthermore, no differences between aMCI subtypes regarding cognitive status or onset of symptoms could be detected.

Table 1. Demographic and Clinical Characteristics of Participants at Baseline Assessment With Regard to Single- and Multiple-Domain aMCI Subtypes (N = 24)

Variable	Early Intervention: IG-1 (n = 12)	Later Intervention: IG-2 (n = 12)	Group Differences	
			Test Result	*P* Value
aMCI subtype, single/multiple domain, n	7/5	4/8	$\chi^2_1 = 1.510$	.219
Time since onset of symptoms of cognitive decline, mean (SD), mo	34.6 (14.5)	26.0 (9.4)	$t_{22} = 1.720$	.099
	Single-Domain aMCI (n = 11)	Multiple-Domain aMCI (n = 13)		
MMSE score, mean (SD)	27.7 (2.0)	27.2 (1.5)	$F_{1,22} = 0.501$	.486
ADAS-cog score, mean (SD)	9.7 (2.3)	9.2 (4.6)	$F_{1,22} = 0.104$	.750
Time since onset of symptoms of cognitive decline, mean (SD), mo	33.7 (12.7)	27.4 (12.5)	$F_{1,22} = 1.511$	.232

Abbreviations: ADAS-cog = cognitive subscale of the Alzheimer's Disease Assessment Scale, aMCI = amnestic mild cognitive impairment, IG = intervention group, MMSE = Mini-Mental State Examination.

Figure 2. Results at All Time Points for the Early Intervention Group (IG-1) and Later Intervention Group (IG-2)



[a]Lower scores indicate improvement. [b]Higher scores indicate improvement.
*Significant *t* test results refer to post hoc comparison testing for the effect of progression (Baseline vs Post1) within IG-2 (ADAS-cog: $t_{11} = 2.8$, $P = .02$; MMSE: $t_{11} = 3.1$, $P = .01$).
†Significant difference in cognitive function for IG-2 at Post1 versus IG-1 at Baseline (MMSE: $F_{1,20} = 10.390$, $P = .004$; RBANS story memory (immediate memory): $F_{1,20} = 5.410$, $P = .031$).
Abbreviations: ADAS-cog = cognitive subscale of the Alzheimer's Disease Assessment Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

As 2 participants in the IG-1 group dropped out at the very beginning of the study (intercurrent illness, lack of compliance), a total of 22 participants were finally followed up; these participants had no differences with regard to gender, age, educational level, MCI subtype, or onset of cognitive decline. However, IG-1 showed higher scores on RBANS story recall ($F_{1,20} = 5.263$, $P = .033$; mean [SD] scores, IG-1: 7.50 [2.59] vs IG-2: 4.75 [2.96]). Thus, the baseline score of this scale was included as a covariate. Furthermore, because gender had a significant impact on memory, as seen on RBANS story memory ($F_{1,20} = 5.057$, $P = .036$) and RBANS story recall ($F_{1,20} = 5.435$, $P = .030$), as well as on mood, as seen on the MADRS ($F_{1,20} = 4.692$, $P = .043$), gender was also added as a covariate.

As seen in Figure 2, significant differences between the 2 groups at the beginning of the cognitive intervention (IG-1 at Baseline, IG-2 at Post1) appeared in global cognitive status (MMSE: $F_{1,20} = 10.390$, $P = .004$) and immediate and delayed

Table 2. Change in Measures of Efficacy From Baseline to Post2 (15 months) and From Baseline to Follow-Up (28 months) for the Early Versus Later Intervention Groups as Well as Change Over All Time Points in Participants With aMCI[a]

	Change From Baseline to Post2				Change From Baseline to Follow-Up				Change Over All Time Points	
	Early Intervention:	Later Intervention:	ANCOVA		Early Intervention:	Later Intervention:	ANCOVA		ANCOVA	
Measure	IG-1 (n = 10)	IG-2 (n = 10)	$F_{1,18}$	P	IG-1 (n = 10)	IG-2 (n = 8)	$F_{1,16}$	P	$F_{1,16}$	P
ADAS-cog[b]	−2.30 (3.27)	+2.10 (4.43)	6.382	**.021**[d]	−0.70 (4.78)	+4.13 (4.32)	4.913	**.041**[e]	6.169	**.024**[f]
MMSE[c]	+0.20 (1.81)	−0.50 (1.58)	0.846	.370	−0.70 (2.26)	−1.63 (1.68)	0.922	.351	1.643	.218
RBANS story memory (immediate memory)[c]	+2.00 (1.21)	−1.71 (1.21)	4.671	**.046**[g]	+0.17 (1.22)	−4.25 (1.34)	5.934	**.029**[h]	7.051	**.019**[i]
RBANS story recall (delayed memory)[c]	+0.53 (0.90)	−1.23 (0.94)	1.669	.216	−0.25 (0.93)	−1.78 (1.06)	1.089	.316	2.158	.166
TMT-A[b]	−7.10 (27.83)	−0.40 (17.62)	0.414	.528	−5.60 (27.50)	+6.50 (19.48)	1.100	.310	0.134	.719
TMT-B[b]	−29.10 (33.52)	+3.00 (50.43)	2.810	.111	−2.50 (59.69)	+29.88 (59.93)	1.303	.270	1.624	.221
MADRS[b]	−3.92 (1.23)	−1.87 (1.23)	1.371	.259	−2.50 (2.05)	−1.12 (2.24)	0.205	.658	1.384	.259
QoL-AD[c]	+0.96 (3.87)	−2.04 (4.39)	2.625	.123	+2.12 (1.72)	−0.62 (5.21)	2.468	.136	2.620	.125

[a]Values expressed as mean (SD) unless otherwise noted. Boldface indicates significance. [b]Negative difference indicates improvement. [c]Positive difference indicates improvement. [d]Partial $\eta^2 = 0.262$. [e]Partial $\eta^2 = 0.235$. [f]Partial $\eta^2 = 0.278$. [g]Partial $\eta^2 = 0.226$. [h]Partial $\eta^2 = 0.298$. [i]Partial $\eta^2 = 0.342$.
Abbreviations: ADAS-cog = cognitive subscale of the Alzheimer's Disease Assessment Scale, aMCI = amnestic mild cognitive impairment, ANCOVA = analysis of covariance, IG = intervention group, MADRS = Montgomery-Asberg Depression Rating Scale, MMSE = Mini-Mental State Examination, QoL-AD = Quality of Life-Alzheimer's Disease, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, TMT-A/B = Trail Making Test, part A/B.

Table 3. Dropout and Conversion to Alzheimer's Disease From Baseline to Follow-Up (28 months) in aMCI Participants Receiving Early or Later Intervention (N = 24)

	Total		Dropout		Converted to Alzheimer's Disease[a]	
Time Point	Early Intervention: IG-1, n	Later Intervention: IG-2, n	Early Intervention: IG-1, n (%)	Later Intervention: IG-2, n (%)	Early Intervention: IG-1, n (%)	Later Intervention: IG-2, n (%)
Baseline	12	12	0 (0)	0 (0)	0 (0)	0 (0)
Post1 (8 mo)	10	12	2 (8.3)	0 (0)	0 (0)	1 (4.2)
Post2 (15 mo)	10	10	0 (0)	2 (8.3)	0 (0)	3 (12.5)
Follow-up (28 mo)	10	8	0 (0)	2 (8.3)	0 (0)	2 (8.3)
Total			2 (8.3)	4 (16.7)	0 (0)	6 (25.0)

[a]According to *DSM-IV*[26]/National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association[27] and revised National Institute on Aging-Alzheimer's Association workgroups criteria for probable Alzheimer's disease dementia with increased level of certainty[28] due to cognitive decline as determined by increase of 3 points or more on ADAS-cog total score and/or significant impairment in social or occupational functioning as assessed with Global Deterioration Scale and verified by a caregiver.
Abbreviations: ADAS-cog = cognitive subscale of the Alzheimer's Disease Assessment Scale, aMCI = amnestic mild cognitive impairment, IG = intervention group.

memory (RBANS story memory: $F_{1,20} = 5.410$, $P = .031$; RBANS story recall: $F_{1,20} = 11.410$, $P = .003$).

After Post1 testing, 2 participants in IG-2 dropped out (lack of motivation, conversion to AD), so that 10 participants attended the late intervention. Hence, 20 participants were tested at Post2. During the 12-month Follow-up period, another 2 participants dropped out of the study due to conversion to AD. Therefore, 18 participants completed the study and received 28-month Follow-up assessment. Figure 1 shows the trial profile and attrition.

Effects of Treatment

The significant effect on ADAS-cog scores in IG-1 that had been observed between Baseline and Post1 (see Buschert et al[16]) was seen for the duration of the study period (Table 2): change from Baseline to Post2: $F_{1,18} = 6.382$, $P = .021$, $\eta^2 = 0.262$; change from Baseline to Follow-up: $F_{1,16} = 4.913$, $P = .041$, $\eta^2 = 0.235$; repeated-measures effect over all time points: $F_{1,16} = 6.169$, $P = .024$, $\eta^2 = 0.278$. Furthermore, significant effects on immediate memory (RBANS story memory) in IG-1 became apparent at Post2 ($F_{1,18} = 4.671$, $P = .046$, $\eta^2 = 0.226$) and Follow-up ($F_{1,16} = 5.934$, $P = .029$, $\eta^2 = 0.298$) and remained stable over these time points (repeated measures: $F_{1,16} = 7.051$, $P = .019$, $\eta^2 = 0.342$). A previously evaluated significant effect on MADRS in IG-1 as well as a tendency toward a significant effect on MMSE and TMT-B in IG-1 (see Buschert et al[16]) disappeared after Post1 (all $P > .1$). No other effects were associated with $P < .1$ (see Table 2).

Concerning differences between groups (IG-1, IG-2) between Post1 and Post2, all effects were associated with $P > .1$ (RBANS story memory: $P = .13$) or $P \geq .2$ (MMSE: $P = .20$, TMT-B: $P = .84$, MADRS: $P = .47$), with the exception of ADAS-cog ($P = .04$).

Regarding progression to AD, 6 of 12 participants in IG-2 (25% of the initial sample of 24 participants) converted to AD in the course of the 28-month study period (Table 3).

DISCUSSION

In the current study, we evaluated long-term effects of a multicomponent cognitive intervention in aMCI on cognitive and noncognitive function and the impact on conversion rate to AD in an early treatment group (IG-1) compared to a group receiving an 8-month time-lagged intervention (IG-2). Findings in IG-1 revealed stable significant effects on

global cognitive functioning over the whole study period and a time-lagged effect on memory between Post2 and end of the study. No participant in IG-1 converted to AD during the study.

Feasibility and Acceptance of Program and Study

As with the early treatment,[16] the time-lagged program was well accepted. We again achieved a very high level of participation. Participants were highly compliant, and the dropout rate was relatively low (see Table 3), in spite of the fact that the intervention was quite demanding, as mentioned previously.

Long-Term Effects of the Cognitive Intervention

The significant intervention effect on global cognitive status seen on ADAS-cog between Baseline and Post1 (see Buschert et al[16]) remained stable over all time points (see Table 2). This finding appears to be clinically important, especially because a previous number-needed-to-treat analysis of ADAS-cog revealed that 5 MCI participants needed to be treated in order for 1 to benefit compared to controls when a decrease of 4 or more points was calculated as improvement.[29]

In contrast to IG-1,[16] we could not detect significant intervention effects in IG-2 for either primary (MMSE, ADAS-cog) or secondary (RBANS memory, TMT-B, MADRS, Quality of Life-Alzheimer's Disease scale) outcomes. However, cognitive and noncognitive functions in IG-2 appear to have stabilized due to participation in the cognitive intervention (see Figure 2). In contrast, performance on the main outcome variables ADAS-cog and MMSE had significantly declined in the prior control condition, as seen on *t* test results referring to post hoc comparisons testing for the effect of progression (Baseline vs Post1) within IG-2 (ADAS-cog $t_{11} = 2.8$, $P = .02$; MMSE $t_{11} = 3.1$, $P = .01$) (see Figure 2).

Moreover, observed differences between groups at Baseline and Post1 seemed to attenuate considerably after IG-2 also attended the cognitive intervention (see Figure 2). This suggests that IG-2 might also have benefited from the cognitive intervention, but that this effect did not offset the disadvantages of the delayed beginning. Given the progressive nature of prodromal MCI[5] and considering that IG-2 started with the cognitive intervention about 8 months later compared to IG-1, one can assume that this time delay may be responsible for the lack of significant intervention effects. As previously hypothesized,[12] the capability to enhance or compensate for impaired cognitive functions declines in the course of prodromal cognitive impairments and frank AD. Indeed, IG-2 appears to have been more impaired in global cognitive status and memory at the beginning of the later cognitive intervention at Post1 compared to IG-1 at Baseline (see Figure 2). This assumption may have important clinical implications for early diagnosis and treatment of cognitive impairments due to prodromal AD, with the assumption being, the earlier the intervention, the better the effectiveness.[30]

The strong, immediate intervention effect on mood in IG-1[16] disappeared after the end of the intervention. This suggests that improvement in mood is primarily due to participation in the group setting. Given that benefits to mood disappeared after the end of the early intervention, whereas those to global cognitive status remained stable, it is unlikely that improvements in global cognitive status are largely due to reduction of depressive symptoms.

As with mood, modest improvements in higher attentional functions, seen on TMT-B, in IG-1 could not be preserved beyond the cognitive group intervention,[16] which suggests that global cognitive benefits are not just a by-product of short-term increase of attentional function.

Immediately after the early cognitive intervention, we detected only modest gains for immediate memory, seen on RBANS story memory in IG-1 (see Buschert et al[16]), which reached significance only at follow-up testings. Participants in IG-1 may have needed some sort of consolidation phase after the cognitive intervention to incorporate practical memory strategies into daily routines.[8]

Conversion to Alzheimer's Disease

According to *DSM-IV*[26]/NINCDS-ADRDA[27] criteria as well as revised NAI-AA criteria for probable AD dementia with increased level of certainty,[28] none of the participants in IG-1 converted to AD within 28 months, but 50% (n = 6) of the IG-2 participants did (see Table 3). This finding is in accordance with our findings of stable improvements in global cognitive status over the 28-month study period in IG-1 (see Table 2) and leads to the hypothesis that early participation in our cognitive intervention might delay onset of AD. This hypothesis should be tested in future larger-scale studies.

Limitations

Our study has some limitations. It included a relatively small number of participants, which limited the statistical power. Theoretically, one would want to include an additional control group that did not receive a specific cognitive intervention over the whole study period. It is, however, very difficult to motivate affected people to participate for more than 2 years in a study without receiving any treatment. High attrition rates would very likely render it impossible to gain clinically relevant information from a nonactive control group.

CONCLUSION

Benefits of our early 6-month multicomponent cognitive intervention on global cognitive status appear to have been preserved over an extended period of 20 months after the intervention. In contrast, participants receiving the late intervention appear to have benefited to a lesser extent. Furthermore, early participation in the program may delay conversion to AD. Results indicate that the time point to start participation in a cognitive intervention is crucial for further benefits in cognition and function. Given that this is a multicomponent intervention, it is not clear from this study

whether one specific component of the intervention might be more important than another with respect to influencing the outcome. This would be an area for further study.

Our encouraging results regarding cognitive intervention in aMCI may have important clinical implications for further therapeutical approaches. The expected enormous increase in the number of dementia patients[31] makes it mandatory to advance the development and implementation of cognition-based interventions in prodromal AD.

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