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Differential Response to Cognitive Stimulation in Moderate Versus Moderately Severe Alzheimer's Disease

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Alzheimer's disease (AD) is characterized by impairments across several neurocognitive domains, particularly memory and executive function. The study explored the effectiveness of an individual cognitive stimulation (iCS) program on cognitive outcomes in older adults with moderate to moderately severe AD. A multicentre randomized controlled trial was conducted with 80 Portuguese older adults (M_{age}: 83.0 ± 7.1 years) with AD. Participants were randomly assigned to either iCS (n = 39; 49%) or treatment as usual (n = 41; 51%). Alzheimer's Disease Severity (ADS) categorized two groups based on Mini-Mental State Examination score: 10–14 in the *ADS moderately severe* group and 15–20 in the *ADS moderate* group. In participants with moderate AD, iCS led to significant improvements in memory-related outcomes (particularly Memory Assessment Test) and a trend toward improvement in global cognition. In contrast, no significant effects were observed in participants with moderately severe AD. Meta-analytic comparisons and meta-regression confirmed a significant difference in intervention effectiveness between severity levels. iCS was significantly more effective in individuals with moderate AD than in those with moderately severe AD. This difference in responsiveness between severity levels was statistically confirmed ($Q = 11.29$, $p < .001$). iCS was effective in enhancing memory in individuals with moderate AD, with additional indications of global cognitive benefit. However, no meaningful effects were observed in participants with moderately severe impairment, suggesting diminished responsiveness to iCS as disease severity increases.

Public Significance Statement
This study found that a cognitive stimulation program improved memory in people with moderate Alzheimer's disease. The findings also highlight the challenges and limitations of cognitive interventions in more advanced stages of the disease.

Keywords: Alzheimer's disease, cognitive function, cognitive stimulation therapy, executive function, memory impairment

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Alzheimer's disease (AD) is characterized by alterations in several neurocognitive domains including complex attention, executive function, learning, memory, language, perceptual-motor, and social cognition, in addition to impairment in functional daily living activities (American Psychiatric Association [APA], 2022).

The prevalence of AD is expected to double by 2050 (Alzheimer's Association, 2022) with numbers estimated to reach over half of a million Portuguese citizens by that time (Alves et al., 2024).

Treatments for AD can vary and broadly include pharmacologic and nonpharmacologic options. While there is substantial efficacy data around pharmacological therapies, exploring nonpharmacologic options either as adjunctive treatments to medication or alternatives for those who cannot access or tolerate medications is imperative. Nonpharmacological interventions offer several advantages, including the reduced adverse effects and, in some cases, greater cost-effectiveness than pharmacological treatments. In older adults, nonpharmacological interventions also have shown to enhance brain plasticity (Cabeza, 2002; Nagamatsu et al., 2012), further reinforcing the effectiveness of these treatment options. One common nonpharmacologic treatment for AD is cognitive stimulation (CS). This approach includes activities and discussion aimed at enhancing cognitive and social functioning through therapies such as reminiscence and reality orientation (Woods et al., 2012). Reality orientation reviews temporal and spatial information and related activities, with primary emphasis on reviewing basic personal and current information (location, date, weather, current events) to all participants (Woods et al., 2023). A meta-analysis revealed that reality orientation therapy shows positive results in cognition in older adults with AD (Chiu et al., 2018). Reminiscence therapy guides participants through past experiences and events (often by using prompts such as photos, audio, or visual recordings) and has shown to improve cognition (Woods et al., 2018) as well as depression, functional activities, and quality of life (Cuevas et al., 2020) in older adults with AD. Even simple reminiscence has shown to be an effective strategy for preserving and enhancing adaptive recall functions in older adults with mild cognitive impairment due to AD (Soria-Urios et al., 2025).

Several systematic reviews focusing on the cognitive effects of CS in older adults with moderate AD revealed objective improvements in general cognition, memory, orientation, calculation, and praxis (Cafferata et al., 2021; Chao et al., 2020; Gómez-Soria et al., 2023; Lobbia et al., 2018; Saragih et al., 2022). Similar findings of cognitive benefits have also been reported in a review of reviews (Meyer & O'Keefe, 2020).

A Cochrane review conducted by Woods et al. (2023) revealed successful CS treatments in older adults with mild-to-moderate dementia over and above any medication effects. CS therapies have shown consistent positive intervention effects that persist up to 3 months posttreatment (McDermott et al., 2019; Woods et al., 2012).

Individual cognitive stimulation (iCS) is a less explored approach compared to group cognitive stimulation, distinguished by its personalized, one-on-one format. While less widely studied and offering reduced social benefits, iCS offers several potential advantages such as greater personalization and flexibility and enhanced engagement and focus by the participant. Furthermore, iCS may be more effective for people needing personalized attention, with complex needs and/or who cannot access group interventions.

The iCS intervention explored in the present study is an adaptation of Spector et al.'s (2006) cognitive stimulation intervention that has been thoroughly detailed elsewhere (Justo-Henriques, 2021). In short, it integrates elements of cognitive stimulation, reminiscence, and reality-oriented therapies. This iCS has demonstrated benefits on global cognition and mood in participants with mild cognitive impairment (Justo-Henriques et al., 2019, 2021; Justo-Henriques, Silva, Carvalho, et al., 2025), on memory and executive functions in participants with mild AD (Justo-Henriques, Lemos, et al., 2025), and on memory in participants with mild-to-moderate AD (Justo-Henriques, Pérez-Sáez, et al., 2025). The intervention was designed

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with particular attention to variations in cognitive functioning across disease stages, allowing for flexibility in task demands, pacing, and facilitation to accommodate individual needs. Although the current iCS program has been extensively studied across various contexts and populations, its effectiveness in individuals with more advanced cognitive impairment remains less clear. This study aims to deepen our understanding of iCS efficacy by evaluating its impact on cognitive outcomes in older adults with moderate and moderately severe AD.

Method

Study Design

This study reported the results of a subsample from a larger multicentre, single-blind, randomized controlled trial (RCT) evaluating the effects of iCS in older adults with AD (Clinicaltrials.gov ID: NCT05433493; Justo-Henriques, Pérez-Sáez, et al., 2025). The trial followed a parallel two-arm design, with participants randomly assigned in a 1:1 ratio to either the intervention group (iCS plus treatment as usual [TAU]) versus the control group (TAU only). Participants were assessed at baseline (T0), end of intervention (T1), and 12-week follow-up (T2). This study adheres to the Consolidated Standards of Reporting Trials statement guidelines and the extension for randomized trials of nonpharmacologic treatments (Boutron et al., 2017; Schulz et al., 2010).

Participants

Overall inclusion criteria were as follows: a diagnosis of probable AD according to *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, text revision (APA, 2022) criteria (confirmed via institutional health records; no biomarker data were available), age 65 or older, native Portuguese speaker, preserved communication skills, and receipt of care and support services for at least 3 months (including those living in long-term care centres, attending day and social programs, and receiving home-based services). Participants (or their legal representatives) provided signed informed consent.

Exclusion criteria included severe communication impairment; significant sensory and physical limitations; acute or chronic illness preventing participation; aggressive and disruptive behaviour; and recent initiation (within 2 months) of neuroleptics, antipsychotics, or other psychoactive medications.

The Consolidated Standards of Reporting Trials diagram (Boutron et al., 2017; Schulz et al., 2010) shown in Figure 1 details the flow of participants recruited to the study and reasons for ineligibility. Recruitment took place through a public invitation to social care institutions in Portugal to participate in an RCT on CS for older adults with AD. After the research team explained the study, 13 institutions agreed to collaborate. The institutions then identified participants who met the inclusion criteria, resulting in 167 participants completing the eligibility assessment. A total of 142 participants were selected for the RCT: 72 participants were allocated to the iCS and 70 participants to the TAU group.

Eligible participants completed baseline assessments and were randomized at a 1:1 ratio within each institution to iCS or TAU, using a nonstratified permuted block design with variable block sizes generated using the DatInf RandList software. Group allocation was concealed from participants and therapists until the intervention began. Trained evaluators (clinical psychologists) were blinded to group allocation and were not involved in intervention sessions. All assessments were conducted individually in a quiet and controlled environment at three time points: baseline (T0), end of intervention (T1), and 12-week follow-up (T2).

For the present analysis, a subsample of 80 participants with moderate to moderately severe AD was selected from 12 institutions. Of these, 39 participants were allocated to the iCS group and 41 to the TAU group (see Figure 1). Cognitive severity was classified using Mini-Mental State Examination (MMSE): Scores of 15–20 indicated moderate AD, and 10–14 indicated moderately severe AD. These cutoffs are widely used in clinical research and referenced in guidelines such as the National Institute for Health and Care Excellence Guidelines (2018). Pharmacological treatment for AD was documented for each participant, including donepezil, memantine, rivastigmine, and/or galantamine intake. Randomization is presumed to have balanced medication effects between groups, although no formal statistical comparison was conducted. None of the participants had previously undergone this intervention program.

Sixty-eight of 80 older adults completed the three assessments time points and were included in the final analysis. In the iCS group, nine participants dropped out (four moderate and three moderately severe). Reasons included lack of interest (one moderate and another moderately severe) and hospitalization (three moderate and four moderately severe). In the TAU group, three did not complete the follow-up assessment (two with moderate and one moderately severe), due to hospitalization (one moderate and one moderately severe) and death (one moderate). Full participant flow is detailed in Figure 1.

The study was approved by the ethics committee of the Health Sciences Research Unit: Nursing of Nursing School of Coimbra (Code Number: P876_05_2022), and all ethical guidelines were strictly followed. Participants were informed about the study's objectives and methods and assured that their participation was entirely voluntary. All participants were informed of their right to withdraw from the study at any time. Informed consent was signed prior to the intervention. The therapists regularly monitored participants' engagement levels to identify potential disinterest or willingness to withdraw from the study.

Intervention

The intervention was conducted at the participants' sites (day care or long-term care centre). The intervention lasted 12 weeks, from March 6 to May 26, 2023. The current iCS program is described in detail elsewhere (Justo-Henriques et al., 2019, 2021; Justo-Henriques, Pérez-Sáez, et al., 2025; Justo-Henriques, Silva, Carvalho, et al., 2025; Justo-Henriques, Lemos, et al., 2025; Justo-Henriques, 2021). Participants in the iCS group received two sessions of the cognitive program per week for 12 weeks in addition to their usual activities. Each iCS session lasted 45 min and was structured into four moments: welcome (5 min), orientation to time and place (10 min), main activity (25 min), and debrief/review and closure (5 min). The iCS sessions were individually administered and led by previously trained therapists. Activities were based on iCS principles, with difficulty increasing progressively across sessions. The program addressed multiple cognitive domains at each session, namely, executive function, learning and memory, complex attention, language, and perceptual-motor function. Details about each session are described elsewhere (Justo-Henriques, 2021). The program

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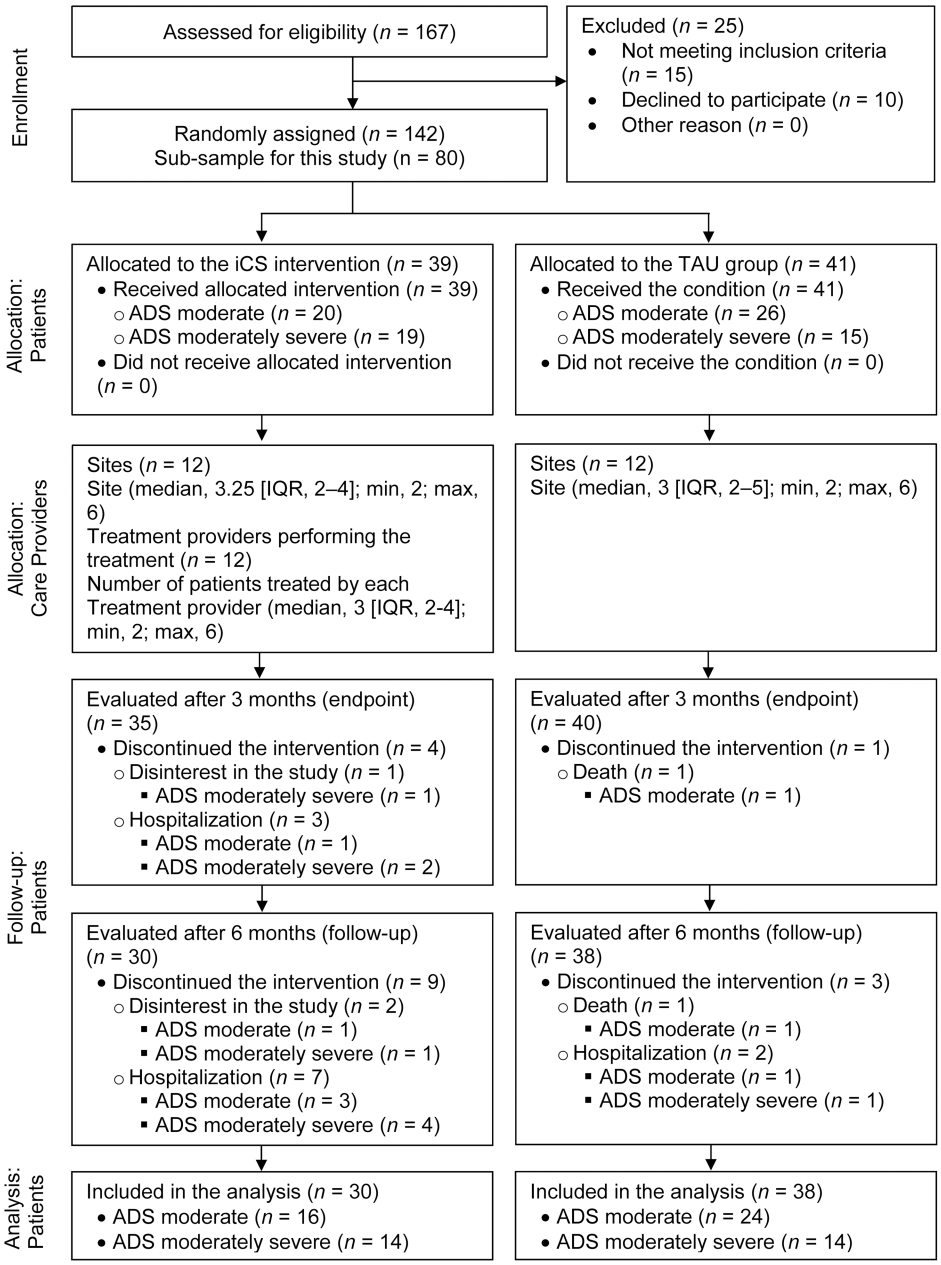
Figure 1

The Consolidated Standards of Reporting Trials Diagram (Boutron et al., 2017; Schulz et al., 2010) of Participant Flow Through the Study



Abbreviations: ADS = Alzheimer's Disease Severity; IQR = Interquartile Range; iCS = Individual Cognitive Stimulation; TAU = Treatment As Usual.

included activities based on the therapeutic tools of CS, *Roletas da Memória* (Memory Roulettes), which targeted specific cognitive functions through themed exercises in the Portuguese language (attention, language, short-term memory, semantic memory), mathematics (attention, reasoning, calculation), and daily living activities (attention, semantic memory, language, gnosis). In addition, *Bingos Seniores* (Senior Bingos) included bingo games on topics of fruit (episodic memory), travel to the past (short-term and semantic memory), and sounds/music (sensory and semantic memory, gnosis, attention, eye–hand coordination). Therapists completed an adherence questionnaire after each session and were encouraged to contact the principal researchers if they had any concerns about the intervention.

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The sessions were held at the participants' respective institutions, with the therapists conducting each session, preferably in a room with minimal distractions and in accordance with intervention deadlines (Justo-Henriques et al., 2020).

The iCS sessions were delivered by therapists at each institution. Sessions were conducted by 12 therapists and/or other rehabilitation professionals (psychologists, occupational therapists, social educators, social workers, gerontologists) who received a 6-hr training program which included session objectives and schedules, all intervention protocols and materials, and implementation guidelines. This training was developed by two of the principal investigators for standardization. Detailed demographics of the professionals involved are provided in Supplemental Table S1.

The TAU group only carried out their usual site-based activities, which were not restricted, provided they were distinct from the intervention program. These activities typically included socialization, cognitive games, light physical exercises, stimulation of personal skills, self-care, and medications administration. Some TAU participants may have engaged in some form of CS activity during data collection, since this is a popular intervention, though none of the institutions offered a structured iCS program during the study period. Those in the treatment group also had access to these same activities.

Outcomes' Instruments

The study used validated instruments to measure outcomes across three domains: global cognitive function, memory, and executive function. All instruments were administered by trained and blinded evaluators at three time points: baseline (T0), end of intervention (T1), and at 12-week follow-up (T2). At T0, a structured questionnaire was administered to obtain participants' sociodemographic data (i.e., age, gender, educational level, marital status), type of institution attended, use of antidepressant medication, and clinical condition/diagnoses.

Cognitive functioning was assessed using the Portuguese version of the MMSE and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog). MMSE (Cronbach's $\alpha = .89$) is a widely used screening tool that evaluates cognitive domains of orientation, attention, memory, language, and visual–spatial skills. Scores range from 0 to 30, with higher scores indicating better cognitive functioning (Folstein et al., 1975; Guerreiro et al., 1994; Morgado et al., 2009). ADAS-Cog (Cronbach's $\alpha = .554$) was designed to evaluate cognitive functioning in persons with AD in the domains of memory, orientation, language, praxis, and visuoconstruction. ADAS-Cog is composed of 11 subtests, ranging from 0 to 68 points, with higher scores reflecting worse performance (Mohs et al., 1983; Nogueira et al., 2018; Rosen et al., 1984). Notably, this relatively low Cronbach's α value may be due to the variability among subtests. ADAS-Cog is commonly used in clinical trials to evaluate the cognitive effects of dementia medications (Moniz-Cook et al., 2008). The present study administered an adapted Portuguese version of the ADAS-Cog (Guerreiro et al., 2008).

Memory function was assessed using the Memory Alteration Test (MAT; Cronbach's $\alpha = .93$) and the Free and Cued Selective Reminding Test (FCSRT; Cronbach's $\alpha = .915$ for the immediate recall [IR] and .879 for the delayed recall [DR]). MAT is a brief and easy-to-administer instrument that evaluates five memory domains: temporal orientation, encoding, semantic memory, free recall, and cued recall. Total scores range from 0 to 50, with higher scores indicating better memory performance. It has good psychometric properties and is highly sensitive to detecting mild cognitive decline (Rami et al., 2007; Sousa et al., 2015). FCSRT is a verbal learning and memory test that facilitates encoding and retrieval conditions by using semantic cues on learning and recall trials. It is composed of 16 semantically categorized, unrelated items/words (Buschke, 1984; Lemos et al., 2012, 2015).

Executive function was assessed with the Frontal Assessment Battery (FAB; Cronbach's $\alpha = .83$) which includes six subtests: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. Total scores range from 0 to 18, with higher scores indicating better executive functioning (Dubois et al., 2000; Lima et al., 2008).

Data Analysis

Categorical variables were reported as frequencies and percentages, and the chi-square or Fisher's exact test was applied as appropriate. The Shapiro–Wilk test was used to assess the normality of continuous variables, which were expressed as mean and standard deviations. Student's t test was used to compare group means for continuous variables when the normality assumption was met. When normality was violated, the nonparametric Mann–Whitney U test was applied to compare median values. Levene's test was used to assess the homogeneity of variance for continuous individual variables. No imputation was performed for missing data; therefore, only data from participants who completed the follow-up assessment were analyzed. The effects of iCS on outcomes (MMSE, ADAS-Cog, MAT, FCSRT, FAB) were analyzed using 2×3 repeated measures mixed analysis of variance (ANOVA), with group assignment (iCS, TAU) as the between-subjects factor and time (baseline [T0], postintervention [T1], follow-up [T2]) as the within-subjects factor. The primary effects of interest were the Group × Time ($G \times T$) interactions. Post hoc pairwise comparisons with Bonferroni correction were conducted to compare groups (iCS vs. TAU) at each time point (T0, T1, T2) and within-group changes across time points (T0 vs. T1, T0 vs. T2, and T1 vs. T2) for both iCS and TAU groups. The Greenhouse–Geisser correction was applied when Mauchly's test indicated a violation of sphericity. The Bonferroni adjustment was applied for multiple comparisons to identify significant factor effects. A significance level of 5% was set, with a two-tailed p value $< .05$ considered statistically significant. The effect size in ANOVA was assessed using partial η squared.

Forest plots were employed, a graphical tool widely used in meta-analyses, observational studies, and clinical trials (Li et al., 2020). Given their relevance to clinical trials, examples of their application can be found in studies by Connolly et al. (2011), Cummings et al. (2010), and the POISE Study Group (2008). In this study, forest plots provide a concise and structured comparison of baseline assessments across two groups (iCS vs. TAU) and two subscales, yielding a pooled effect estimate.

This comparison is based on the standardized mean difference (SMD), allowing for the assessment of the direction and magnitude of the effect between the iCS and TAU groups. Hedges' g correction (Borenstein et al., 2009) was applied to the SMD to reduce potential

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bias, particularly in small sample sizes. The interpretation of the SMD point estimate follows these criteria: SMD > 0: favours iCS; SMD < 0: favours TAU; SMD = 0: no difference.

At the bottom of the forest plot, a diamond symbol (♦; pooled effect estimate) represents the overall effect across subscales and groups. A narrower diamond indicates a more precise estimate, whereas a wider diamond reflects greater uncertainty. Heterogeneity and variance between assessments were examined using I^2 and τ^2 statistics. The I^2 statistic, expressed as a percentage, quantifies heterogeneity among studies and is interpreted as follows: 0%–25%: low; 25%–50%: moderate; 50%–75%: high; ≥75%: very high heterogeneity.

Additionally, tau-squared measures true variance across assessments that cannot be explained by sample size or other factors. A low tau-squared value suggests minimal variability, meaning all assessments measure the same effect and any variation is due to chance.

The *p* value displayed in the forest plot corresponds to the *Q*-test for heterogeneity (Cochran's *Q*-test). The null hypothesis states no significant heterogeneity among assessments (i.e., all measure the same effect). If the null hypothesis is not rejected, the results are considered consistent across assessments.

Since the forest plots do not explicitly separate subscales, they do not determine whether one subscale differs significantly from the other. To further investigate this, a subgroup analysis and a meta-regression were conducted. The subgroup analysis examined each subscale separately, while the meta-regression directly assessed whether subscale severity moderated the intervention effect, determining whether SMD varied based on Alzheimer's disease severity. Statistical analyses were conducted using IBM SPSS Statistics (Version 29) and R (R Core Team, 2024).

Results

Sociodemographic and Clinical Characteristics

The sociodemographic and clinical characteristics of the participants are briefly described below. As shown in Table 1, the sample with moderate AD consisted of 46 older adults, with a mean age of 82.8 ± 6.8 years, and 76.1% were female. Most participants had an educational level of 1–4 years, were widowed, and resided in long-term care centre. Regarding moderately severe AD (Table 2), the sample consisted of 46 older adults, with a mean age of 82.8 ± 6.8 years, and 76.5% were female. Most participants had an educational level of 1–4 years, resided in long-term care centre, and half were widowed.

Tables 1 and 2 show the participants' characteristics and assessment scores at baseline, as well as the results of between-group comparisons. For both severity subgroups, no significant differences were found between iCS and TAU in age, marital status, type of institution attended, and antidepressants (all $p \geq .351$). However, significant differences were found between iCS and TAU regarding educational level ($p = .050$) for *ADS moderate* (Table 1) and gender ($p = .011$) for *ADS moderately severe* participants (Table 2). For both subsamples, no significant differences were found between iCS and TAU regarding baseline mean scores in MMSE, ADAS-Cog, MAT, FCSRT IR, FCSRT DR, and FAB (all $p \geq .471$).

Effects of iCS at End Point and Follow-Up

Global Cognitive Functioning (MMSE and ADAS-Cog)

ADS Moderate. A repeated measures ANOVA (Table 3) revealed a trend toward a significant $G \times T$ interaction for MMSE scores, $F(2, 76) = 2.964$, $p = .058$, $\eta_p^2 = .072$. Although post hoc comparisons revealed no significant differences in the multiple comparisons, the TAU group showed similar MMSE scores across the three assessments, while the iCS group showed progressive improvement (T0, T1, and T2). No significant $G \times T$ interactions were found across MMSE cognitive domains—orientation, retention, attention and calculation, verbal recall, language, and visuoconstruction (all $p \geq .162$; Supplemental Table S2).

Regarding the ADAS-Cog, repeated measures ANOVA (Table 3) revealed no significant $G \times T$ interaction, $F(1.657, 62.967) = 2.116$, $p = .134$, $\eta_p^2 = .053$. Repeated measures ANOVAs for ADAS-Cog components—including word recall, naming objects and fingers, commands, constructional praxis, ideational praxis, orientation, word recognition, remembering test instructions, language, word finding difficulty, and comprehension of spoken language—revealed no significant $G \times T$ interactions (all $p \geq .074$; Supplemental Table S4).

ADS Moderately Severe. Repeated measures ANOVA (Table 4) revealed no significant $G \times T$ interaction on the MMSE, $F(2, 52) = 1.087$, $p = .345$, $\eta_p^2 = .040$. Repeated measures ANOVAs for MMSE cognitive domains revealed a trend toward significant $G \times T$ interaction in visuoconstruction, $F(2, 52) = 3.120$, $p = .053$, $\eta_p^2 = .107$. No significant differences were found in the other domains (all $p \geq .159$; Supplemental Table S3).

Repeated measures ANOVA revealed no significant $G \times T$ interaction on the ADAS-Cog, $F(2, 52) = 0.322$, $p = .726$, $\eta_p^2 = .012$ (Table 4). Repeated measures ANOVAs for ADAS-Cog components revealed no significant $G \times T$ interactions (all $p \geq .140$; Supplemental Table S5).

Memory Function (MAT and FCSRT)

ADS Moderate. Repeated measures ANOVA (Table 3) revealed a significant $G \times T$ interaction on MAT, $F(1.671, 63.509) = 4.123$, $p = .027$, $\eta_p^2 = .098$. Multiple comparisons indicated that the iCS group showed significant improvement from T0 to T2 ($p = .028$), whereas the TAU group showed no change from T0 to T1 but declined by T2. Analysis of MAT subscales revealed significant improvements in encoding, $G \times T$ interaction: $F(1.632, 62.030) = 4.126$, $p = .028$, $\eta_p^2 = .098$. A trend toward significant improvement was observed in semantic memory, $G \times T$ interaction: $F(2, 76) = 3.076$, $p = .052$, $\eta_p^2 = .075$, with pairwise comparisons showing improvements in the TAU group from T0 to T1 ($p = .020$) and from T1 to T2 ($p = .010$). Significant improvements were also found in free recall, $G \times T$ interaction: $F(2, 76) = 3.143$, $p = .049$, $\eta_p^2 = .076$. No significant improvements were observed in cued recall and temporal orientation (Supplemental Table S6).

For the FCSRT, the following measures were chosen for analysis: Total IR, defined as the sum of free and cued recall across the three trials, and Total DR, defined as the sum of free and cued recall in the delayed trial. Repeated measures ANOVA did not reveal a significant $G \times T$ interaction for either IR, $F(1.455, 55.277) = 1.798$, $p = .183$, $\eta_p^2 = .045$, or DR, $F(1.328, 50.480) = 1.210$, $p = .291$, $\eta_p^2 =$

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Table 1

Moderate AD[a]: Sociodemographic, Clinical Characteristics of the Sample, and Baseline Scores of the Outcomes

Baseline characteristic	Overall sample ($N = 46$)	iCS group ($n = 20$)	TAU group ($n = 26$)	t, χ^2	p value	Fisher exact test	d, φ, U
Age in years, mean (*SD*) [range]	82.8 (6.8) [67–96]	82.7 (7.6) [67–96]	82.8 (6.2) [68–93]	$t = 0.05$	.958		$d = 6.87$
Gender (%)							
Male	11 (23.9)	4 (20.0)	7 (26.9)			.732	φ = .08
Female	35 (76.1)	16 (80.0)	19 (73.1)				
Educational level (%)							
1–4 years	40 (87.0)	18 (90.0)	22 (84.6)			.050	φ = .35
5–12 years	4 (8.7)	0 (0.0)	4 (15.4)				
Higher education	2 (4.3)	2 (10)	0 (0.0)				
Marital status (%)							
Single	2 (4.3)	2 (10.0)	0 (0.0)			.415	φ = .27
Married	15 (32.6)	6 (30.0)	9 (34.6)				
Divorced	1 (2.2)	0 (0.0)	1 (3.8)				
Widowed	28 (60.9)	12 (60.0)	16 (61.5)				
Type of institution attended (%)							
Day care	18 (39.1)	9 (45.0)	9 (34.6)	$\chi^2 = 0.51$	.474		φ = .11
Long-term care centre	28 (60.9)	11 (55.0)	17 (65.4)				
Antidepressants (%)							
Yes	22 (47.8)	8 (40.0)	14 (53.8)	$\chi^2 = 0.87$	.351		φ = .14
No	24 (52.2)	12 (60.0)	12 (46.2)				
Outcome							
MMSE score, mean (*SD*) [range]	17.63 (1.70) [15–20]	17.55 (1.79) [15–20]	17.69 (1.67) [15–20]		.744		$U = 245.50$
ADAS-Cog score, mean (*SD*) [range]	29.67 (7.43) [14–42]	29.15 (6.85) [14–39]	30.08 (7.96) [14–42]	$t = 0.42$	.680		$d = 0.12$
MAT score, mean (*SD*) [range]	15.15 (7.82) [2–35]	14.90 (7.23) [3–33]	15.35 (8.39) [2–35]	$t = 0.19$	.850		$d = 0.06$
FCSRT IR score, mean (*SD*) [range]	12.28 (10.94) [0–42]	11.75 (8.80) [0–28]	12.69 (12.50) [0–42]		.859		$U = 252.00$
FCSRT DR score, mean (*SD*) [range]	4.30 (4.23) [0–14]	4.70 (3.91) [0–10]	4.00 (4.51) [0–14]		.591		$U = 236.00$
FAB score, mean (*SD*) [range]	6.28 (2.84) [2–15]	6.15 (2.18) [3–10]	6.38 (3.30) [2–15]		.780		$U = 272.50$

Note. ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive; ADS = Alzheimer's Disease Severity; FAB = Frontal Assessment Battery; FCSRT IR = Free and Cued Selective Reminding Test Immediate Recall; FCSRT DR = Free and Cued Selective Reminding Test Delayed Recall; iCS = individual cognitive stimulation; MMSE = Mini-Mental State Examination; MAT = Memory Alteration Test; TAU = treatment as usual; AD = Alzheimer's disease.

[a] Scored between 15 and 20 on the MMSE. Results of between-group comparisons at baseline.

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Table 2

Moderately Severe AD[a]: Sociodemographic, Clinical Characteristics of the Sample, and Baseline Scores of the Outcomes

Baseline characteristic	Overall sample ($N = 34$)	iCS group ($n = 19$)	TAU group ($n = 15$)	t, χ^2	p value	Fisher exact test	d, φ, U
Age in years, *M* (*SD*) [range]	83.3 (7.59) [66–94]	84.6 (7.29) [70–94]	81.5 (7.86) [66–94]	$t = -1.19$	.243		$d = 7.54$
Gender (%)							
Male	8 (23.5)	1 (5.3)	7 (46.7)			.011	φ = .49
Female	26 (76.5)	18 (94.7)	8 (53.3)				
Educational level (%)							
1–4 years	27 (79.4)	15 (78.9)	12 (80.0)			.651	φ = .21
5–12 years	6 (17.6)	4 (21.1)	2 (13.3)				
Higher education	1 (2.9)	0 (0)	1 (6.7)				
Marital status (%)							
Single	6 (17.6)	3 (15.8)	3 (20.0)			.814	φ = .18
Married	9 (26.5)	4 (21.1)	5 (33.3)				
Divorced	2 (5.9)	1 (5.3)	1 (6.7)				
Widowed	17 (50.0)	11 (57.9)	6 (40.0)				
Type of institution attended (%)							
Day care	5 (14.7)	2 (10.5)	3 (20.0)			.634	φ = .13
Long-term care centre	29 (85.3)	17 (89.5)	12 (80.0)				
Antidepressants (%)							
Yes	22 (64.7)	12 (63.2)	10 (66.7)	$\chi^2 = 0.05$	.831		φ = .04
No	12 (35.3)	7 (36.8)	5 (33.3)				
Outcome							
MMSE score, *M* (*SD*) [range]	12.41 (1.35) [10–14]	12.42 (1.39) [10–14]	12.40 (1.35) [10–14]		.945		$U = 145.00$
ADAS-Cog score, *M* (*SD*) [range]	38.18 (10.66) [12–58]	38.26 (11.22) [20–58]	38.07 (10.29) [12–56]	$t = 0.05$	.958		$d = -0.02$
MAT score, *M* (*SD*) [range]	9.00 (6.73) [1–26]	8.47 (6.02) [1–22]	9.67 (7.71) [1–26]	$t = 0.51$	.616		$d = 0.18$
FCSRT IR score, *M* (*SD*) [range]	9.09 (9.34) [0–34]	9.53 (10.71) [0–34]	8.53 (7.60) [0–23]		.918		$U = 145.50$
FCSRT DR score, *M* (*SD*) [range]	2.47 (3.36) [0–11]	2.26 (3.14) [0–10]	2.73 (3.71) [0–11]		.471		$U = 163.50$
FAB score, *M* (*SD*) [range]	4.68 (1.39) [2–9]	4.68 (1.53) [2–9]	4.67 (1.23) [2–7]		.784		$U = 134.50$

Note. ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive; ADS = Alzheimer's Disease Severity; FAB = Frontal Assessment Battery; FCSRT IR = Free and Cued Selective Reminding Test Immediate Recall; FCSRT DR = Free and Cued Selective Reminding Test Delayed Recall; iCS = individual cognitive stimulation; MMSE = Mini-Mental State Examination; MAT = Memory Alteration Test; TAU = treatment as usual; AD = Alzheimer's disease.

[a] Scored between 10 and 14 on the MMSE. Results of between-group comparisons at baseline.

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Table 3
Moderate AD: Results of Repeated Measures ANOVA

	iCS group (n = 16)			TAU group (n = 24)			Group × Time				Pairwise comparison								
											iCS			TAU			iCS versus TAU		
	T0	T1	T2	T0	T1	T2													
Outcome measure	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*df*	*F*	*p* value	η_p^2	T0 versus T1	T0 versus T2	T1 versus T2	T0 versus T1	T0 versus T2	T1 versus T2	T0	T1	T2
MMSE	17.44	19.19	19.38	17.71	17.00	17.21	2, 76	2.964	.058	.072									
	(1.75)	(3.08)	(3.84)	(1.68)	(4.13)	(4.65)													
ADAS-Cog[a]	29.19	27.44	29.13	30.17	32.58	33.92	1.657, 62.967	2.116	.134	.053									
	(6.89)	(9.59)	(12.43)	(8.21)	(11.64)	(11.87)													
MAT[a]	15.00	17.06	19.50	15.29	15.21	14.75	1.671, 63.509	4.123	**.027**	.098	.268	**.028**	.162	1.00	1.00	1.00	.908	.517	.167
	(5.97)	(5.94)	(10.41)	(8.70)	(10.21)	(10.46)													
FCSRT IR[a]	12.63	14.06	17.19	12.54	9.96	12.42	1.455, 55.277	1.798	.183	.045									
	(8.82)	(10.82)	(14.37)	(13.02)	(13.35)	(14.29)													
FCSRT DR[a]	4.88	5.44	6.13	4.00	3.38	3.92	1.328, 50.480	1.210	.291	.031									
	(3.95)	(4.91)	(5.43)	(4.69)	(4.84)	(5.10)													
FAB	6.31	6.00	6.31	6.42	6.29	5.92	2, 76	0.610	.546	.016									
	(2.24)	(2.28)	(2.65)	(3.39)	(3.28)	(3.19)													

Note. AD = Alzheimer's disease; ANOVA = analysis of variance; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive; FAB = Frontal Assessment Battery; FCSRT IR = Free and Cued Selective Reminding Test Immediate Recall; FCSRT DR = Free and Cued Selective Reminding Test Delayed Recall; iCS = individual cognitive stimulation; MMSE = Mini-Mental State Examination; MAT = Memory Alteration Test; TAU = treatment as usual; T0 = baseline assessment; T1 = end point assessment; T2 = follow-up.
[a] Greenhouse–Geisser correction. Results of pairwise comparisons (Bonferroni correction) for baseline (T0), end point (T1), and follow-up (T2) assessments (iCS vs. TAU). Results of pairwise comparisons (Bonferroni correction) for iCS and TAU groups (T0 vs. T1, T0 vs. T2, and T1 vs. T2). The information in bold is statistically significant at an α level of 5%.

.031; Table 3. Multiple comparisons showed no significant differences, despite the iCS group improving from T0 to T1 and from T1 to T2, while the control group worsened from T0 to T1 and maintained its baseline score at T2. Repeated measures ANOVAs for FCSRT subscales (IR free, IR cued, DR free, DR cued) revealed no significant $G \times T$ interactions (all $p \geq .095$).

ADS Moderately Severe. Repeated measures ANOVA (Table 4) revealed no significant $G \times T$ interaction on the MAT, $F(2, 52) = 0.462$, $p = .632$, $\eta_p^2 = .017$. Analysis of MAT subscales revealed significant improvements only in free recall, $G \times T$ interaction: $F(2, 52) = 3.804$, $p = .029$, $\eta_p^2 = .128$ (Supplemental Table S7). No significant $G \times T$ interaction was found for FCSRT IR or DR, $F(1.599, 41.576) = 0.458$, $p = .592$, $\eta_p^2 = .017$; $F(2, 52) = 0.145$, $p = .865$, $\eta_p^2 = .006$. Repeated measures ANOVAs for FCSRT subscales revealed no significant $G \times T$ interactions (all $p \geq .338$, Supplemental Table S9).

Executive Function (FAB)

ADS Moderate. Repeated measures ANOVA revealed no significant $G \times T$ interaction on the FAB total scores, $F(2, 76) = 0.610$, $p = .546$, $\eta_p^2 = .016$ (Table 3). Repeated measures ANOVAs for FAB subscales revealed no significant $G \times T$ interactions (all $p \geq .205$, Supplemental Table S10).

ADS Moderately Severe. Repeated measures ANOVA revealed no significant $G \times T$ interaction on the FAB scores, $F(2, 52) = 0.951$, $p = .393$, $\eta_p^2 = .035$ (Table 4), including its subtests (all $p \geq .135$, Supplemental Table S11).

ADS Analysis

ADS Moderate. The SMD across the six assessed outcomes was .485, 95% confidence interval, CI [.222, .747]. The effect was positive (favouring iCS) and statistically significant, as the CI did not include zero. Heterogeneity analysis indicated no variability across outcomes ($I^2 = 0\%$), supported by the Q-test result ($Q = 1.20$, $p = .944$), suggesting the absence of significant heterogeneity (Figure 2).

ADS Moderately Severe. The SMD was −.204, 95% CI [−.509, .100]. The effect was slightly negative (favouring TAU), but not statistically significant, since the confidence interval includes zero. Heterogeneity analysis again indicated no variability across outcomes ($I^2 = 0\%$), supported by the Q-test ($Q = 1.82$, $p = .878$), suggesting the absence of significant heterogeneity (Figure 2).

ADS: Moderate Versus Moderately Severe. A direct comparison between the *ADS moderate* and *ADS moderately severe* subgroups revealed a statistically significant difference in effect sizes ($Q = 11.29$, $p < .001$). The moderate ADS subgroup showed a positive and significant effect, while the moderately severe subgroup exhibited a negative but nonsignificant effect (Figure 2, Figure 3).

Meta-Regression Analysis

The explanatory variables (moderators) in the meta-regression model included ADS levels (moderate vs. moderately severe), with the SMD corrected by Hedges' g as the outcomes variable. The meta-regression intercept was .485, representing the average SMD for the reference category (*ADS moderate*). The model coefficient

Table 4
Moderately Severe AD: Results of Repeated Measures ANOVA

	iCS group (n = 14)			TAU group (n = 14)			Group × Time			
Outcome measure	T0 *M* (*SD*)	T1 *M* (*SD*)	T2 *M* (*SD*)	T0 *M* (*SD*)	T1 *M* (*SD*)	T2 *M* (*SD*)	*df*	*F*	*p* value	η_p^2
MMSE	12.43 (1.45)	11.36 (3.18)	11.57 (3.65)	12.57 (1.22)	13.21 (4.87)	13.07 (4.27)	2, 52	1.087	.345	.040
ADAS-Cog	37.00 (8.11)	40.50 (12.45)	42.00 (11.61)	36.79 (9.36)	39.21 (9.48)	39.79 (8.74)	2, 52	0.322	.726	.012
MAT	9.00 (5.08)	7.36 (7.22)	8.21 (8.07)	10.29 (7.60)	10.57 (7.12)	10.57 (5.49)	2, 52	0.462	.632	.017
FCSRT IR[a]	10.36 (11.81)	6.07 (9.72)	6.57 (10.02)	9.14 (7.49)	7.14 (7.82)	6.21 (7.98)	1.599, 41.576	0.458	.592	.017
FCSRT DR	2.57 (3.46)	1.93 (3.79)	1.93 (3.41)	2.93 (3.77)	2.14 (3.44)	1.86 (2.63)	2, 52	0.145	.865	.006
FAB	4.86 (1.70)	4.14 (1.79)	3.71 (1.94)	4.64 (1.28)	4.86 (2.41)	4.50 (1.87)	2, 52	0.951	.393	.035

Note. AD = Alzheimer's disease; ANOVA = analysis of variance; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive; FAB = Frontal Assessment Battery; FCSRT IR = Free and Cued Selective Reminding Test Immediate Recall; FCSRT DR = Free and Cued Selective Reminding Test Delayed Recall; iCS = individual cognitive stimulation; MMSE = Mini-Mental State Examination; MAT = Memory Alteration Test; TAU = treatment as usual; T0 = baseline assessment; T1 = end point assessment; T2 = follow-up; AD = Alzheimer's disease.
[a] Greenhouse–Geisser correction.

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was −.689 (95% CI [−1.091, −0.287], $p < .001$), indicating that transitioning from moderate to moderately severe AD is associated with a decrease of .689 units in SMD average, and the R^2 value was 100%. No significant residual variability remained after accounting for the severity effect ($\tau^2 = 0$), and no unexplained heterogeneity was observed ($I^2 = 0\%$). Additionally, baseline heterogeneity between assessments was absent ($H^2 = 1$).

Adherence to Intervention

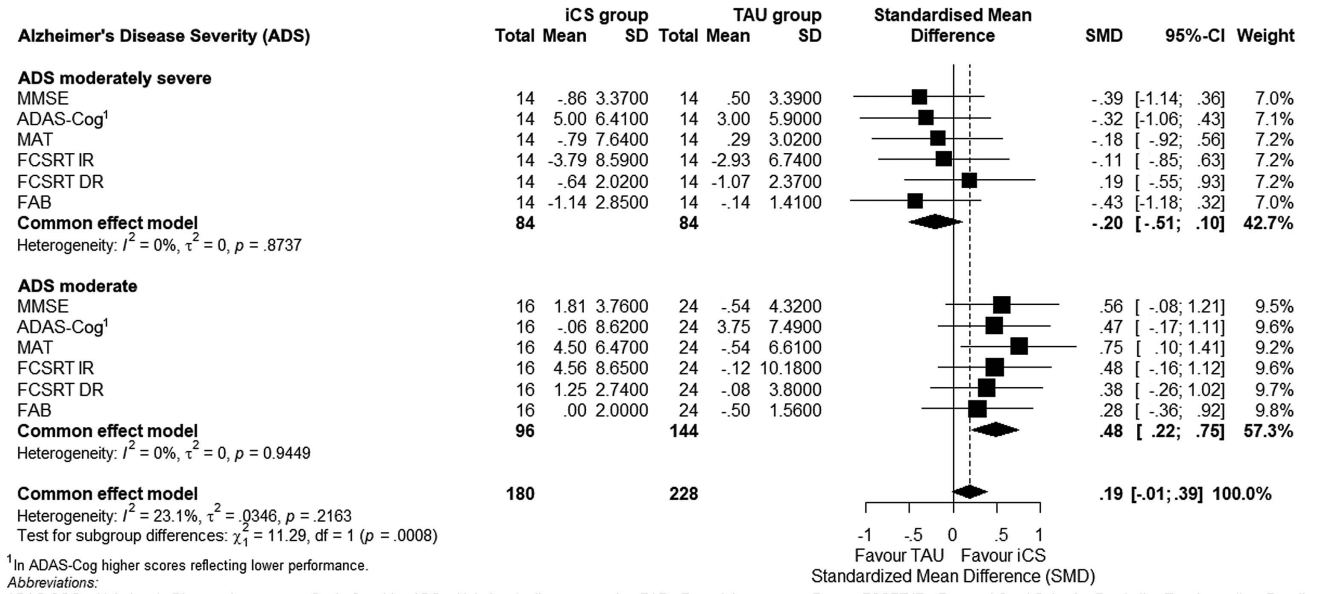
ADS Moderate. Adherence to iCS sessions was high (Table 5). Mean attendance of participants was 22.85 sessions (out of 24 sessions), with 90.0% of participants attending more than 20 sessions, and 75.0% of participants attended 24 (i.e., all) sessions. The reasons for not attending the 23 sessions were hospitalization due to physical illness or a physical acute illness (65.2%), refusal to participate (26.1%), and absence (8.7%).

ADS Moderately Severe. Adherence to iCS sessions was high (Table 5). Mean attendance of participants was 22.68 sessions (out of 24 sessions), with 89.4% of participants attending more than 20 sessions, and 68.4% of participants attended 24 (i.e., all) sessions. Twenty-five scheduled sessions were not held. The reasons for nonattendance were hospitalization due to physical illness or a physical acute illness (28.0%), refusal to participate (36.0%), dropping out of the study (32.0%), and medical appointments (4%).

Degree of Participation During the Intervention

ADS Moderate. After analyzing the individual records of each session, we were able to obtain data regarding the level of collaboration

Figure 2
Forest Plot Illustrating the Subgroup Analysis for Each Subscale Individually and Overall, Using SMD Values, Considering Patient Groups (iCS vs. TAU), Baseline Assessment, and ADS Subscales (Moderately Severe vs. Moderate)

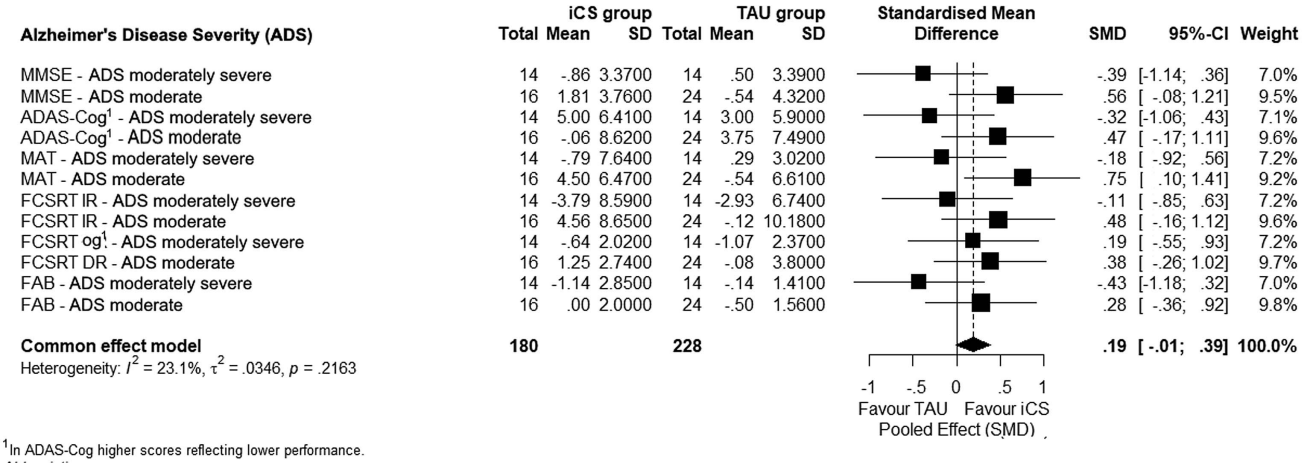


[1] In ADAS-Cog higher scores reflecting lower performance.
Abbreviations:
ADAS-COG= Alzheimer's Disease Assessment Scale-Cognitive;ADS= Alzheimer's disease severity; FAB= Frontal Assessment Battery;FCSRT IR= Free and Cued Selective Reminding Test Immediate Recall; FCSRT DR= Free and Cued Selective Reminding Test Delayed Recall; iCS= Individual Cognitive Stimulation; MMSE= Mini-Mental State Examination; MAT= Memory Alteration Test; TAU = Treatment As Usual.

Note. ADS = Alzheimer's Disease Severity; SMD = standardized mean difference; TAU = treatment as usual; iCS = individual cognitive stimulation; CI = confidence interval.

Figure 3

Forest Plot Illustrating the Pooled Analysis Using SMD Values, Considering Patient Groups (iCS vs. TAU), Assessment Baseline, and ADS Subscales (Moderately Severe vs. Moderate)



[1]In ADAS-Cog higher scores reflecting lower performance.
Abbreviations:
ADAS-COG= Alzheimer's Disease Assessment Scale-Cognitive;ADS= Alzheimer's disease severity; FAB= Frontal Assessment Battery;FCSRT IR= Free and Cued Selective Reminding Test Immediate Recall; FCSRT DR= Free and Cued Selective Reminding Test Delayed Recall; iCS= Individual Cognitive Stimulation; MMSE= Mini-Mental State Examination; MAT= Memory Alteration Test; TAU = Treatment As Usual.

Note. ADS = Alzheimer's Disease Severity; SMD = standardized mean difference; TAU = treatment as usual; iCS = individual cognitive stimulation; CI = confidence interval.

of participants throughout the intervention program, operationalized by active participation in the iCS activities. Participation was very high. Of the 480 iCS sessions (including all participants in the intervention group), the participants completed 457 (95.2%) of them. Participants appeared engaged in 389 (85.1%) sessions, minimally engaged in 66 (14.4%) sessions, and not engaged in only two (.4%) sessions (in these cases, drowsiness or minimal attention and concentration prevented meaningful participation), according to the qualitative judgment provided by the therapists at the end of each session.

ADS Moderately Severe. After analyzing the individual records of each session, we were able to obtain data regarding the level of collaboration of participants throughout the intervention program, operationalized by active participation in the iCS activities. Participation was very high. Of the 456 iCS sessions (including all participants in the intervention group), the participants completed 431 (94.5%) of them. Participants appeared engaged in 328 (76.1%) sessions, minimally engaged in 98 (22.7%) sessions, and not engaged in only five (1.2%) sessions (in these cases, drowsiness or minimal attention and concentration prevented meaningful participation), according to the qualitative judgment provided by the therapists at the end of each session.

Table 5

Attendance Statistics for the iCS Sessions

Attendance	Moderate AD, n = 20	Moderately severe AD, n = 19
Sessions attended		
M (*SD*)	22.85 (2.82)	22.68 (2.93)
Median [IQR]	24 [22.5–24]	24 [22–24.0]
Number of sessions attended (%)		
From 0 to 5	0 (0.0)	0 (0.0)
From 6 to 10	0 (0.0)	0 (0.0)
From 11 to 15	1 (5.0)	1 (5.3)
From 16 to 20	1 (5.0)	1 (5.3)
From 21 to 24	18 (90.0)	17 (89.4)

Note. AD = Alzheimer's disease; iCS = individual cognitive stimulation; IQR = interquartile range.

Discussion

This study presents the results of an RCT examining the efficacy of an iCS program for older adults with AD, including both moderate and moderately severe stages, conducted over a 12-week period. The original trial included participants with a wide range of cognitive functioning—that is, from mild to moderate AD (Justo-Henriques, Pérez-Sáez, et al., 2025)—with MMSE baseline scores differing by as much as 14 points. To reduce heterogeneity and allow for clearer interpretation, this analysis focused on a subsample of participants with moderate to moderately severe AD (baseline MMSE scores between 10 and 20). Within this range, two distinct severity levels were analyzed separately: moderate AD (MMSE 15–20) and moderately severe AD (MMSE 10–14). The present study revealed differential outcomes for the iCS program based on MMSE cutoff scores, which were used to categorize cognitive severity in the AD sample.

The findings of differences between moderate and moderately severe ADS subgroups were statistically significant, suggesting that the severity of the disease may influence the effect of the intervention. Specifically, significant group differences in memory functioning (as measured by the MAT) were observed in the moderate AD group between baseline and follow-up assessment. These results indicate that the intervention may be more effective for older adults with moderate AD, and the therapeutic approach could be adjusted based on the severity of AD. These findings align with our prior studies that have also found similar effects in a small sample with mild cognitive impairment (Justo-Henriques et al., 2019), a large mixed dementia sample of older adults living in

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residential care facilities (Justo-Henriques et al., 2021), and in a year-long randomized controlled mixed dementia sample (Justo-Henriques et al., 2023, Justo-Henriques, Silva, Pérez-Sáez, et al., 2025). These results are consistent with prior research highlighting the responsiveness of memory to cognitive stimulation in earlier stages of the disease. For instance, González-Moreno et al. (2022) reported improvements in immediate and delayed memory following a structured stimulation program in individuals with moderate AD, although gains diminished after a 3-month follow-up (González-Moreno et al., 2022). Similarly, Devita et al. (2021) showed that cognitive stimulation, either alone or combined with pharmacological treatment, significantly improved both IR and DR in individuals with mild AD, often outperforming acetylcholinesterase inhibitors alone (Devita et al., 2021). These findings support the view that memory remains a malleable and therapeutically responsive domain in moderate AD. Although no statistically significant effects were observed in global cognition measures, a positive trend was noted on the MMSE for the iCS group.

Conversely, the lack of observed benefits in the moderately severe group may reflect diminished cognitive plasticity, underscoring the limited efficacy of such interventions in more advanced stages of AD. This interpretation is supported by Woods et al. (2023), who, in a comprehensive Cochrane meta-analytic review, found that the effectiveness of CS interventions tends to decrease with increasing disease severity. The authors noted that cognitive improvements were more substantial in individuals with mild dementia compared to those with moderate stages, suggesting that disease severity moderates intervention outcomes. These findings reinforce the importance of initiating cognitive stimulation during earlier phases of cognitive decline, when the brain may retain a greater capacity for functional adaptation. Regarding the meta-regression analysis, the intervention was effective only in older adults with moderate AD, primarily through improvements in memory-related outcomes. In contrast, no significant cognitive gains were observed in participants with moderately severe AD, and a direct comparison confirmed a statistically significant difference in intervention effectiveness between the two groups. The meta-regression further showed that increased disease severity was associated with a substantial reduction in treatment effect, indicating that cognitive stimulation may be less effective as disease progresses. The meta-regression results suggest that disease severity significantly influences intervention outcomes, with older adults in the moderately severe group showing a significantly smaller effect compared to those with moderate AD. The negative and statistically significant coefficient indicates that the intervention was less effective in participants with more advanced disease severity. The R^2 value reveals that ADS was a strong and relevant moderating factor, suggesting that intervention effectiveness, as measured by the SMD, varies according to the level of severity. These findings highlight the importance of early-stage intervention, suggesting that individualized CS is most beneficial when applied before cognitive decline becomes too advanced. This has important implications for treatment timing strategies, emphasizing the importance of early-stage intervention within the disease process. Regarding participant adherence and engagement in both ADS groups, 90.0% of participants with moderate AD participants attended between in 21 and 24 sessions (average was 22.85 of 24 sessions attended), and 89.4% of the moderately severe AD participants engaged in 21–24 sessions (average was 22.68 of 24 sessions attended), notably high for a clinical trial and points to good participant satisfaction with the protocol regardless of the severity of the disease. A personalized intervention, implemented by trained professionals using a structured and validated program adapted to the cultural context, can encourage participant engagement and improve adherence to the program (Justo-Henriques et al., 2023; Justo-Henriques, Silva, Pérez-Sáez, et al., 2025).

These findings also have important research implications including focusing efforts on adapting and optimizing the intervention for the subgroups who have demonstrated the most effective outcomes, but also considering restructuring our protocols for those whose cognitive status is milder and more severe. For example, future studies may consider a briefer iCS program for those in the moderately severe group to explore for any beneficial outcomes. Generally, our protocol has high levels of adherence throughout most of our studies with very regular engagement from most participants. Continuing to refine this generally well-accepted protocol has the potential for great benefits to other Portuguese persons with AD.

This study is not without limitations. Notably, the short length of the intervention and follow-up may have limited the capacity to detect any cognitive changes potentially possible in a longer intervention period. Additionally, the small size of the ADS subgroups, which was not representative of the general population (although participants in both groups were well-matched), limits the generalizability of the findings. The samples were primarily composed of women, with limited education (the majority with 3–4 years, which was the standard for that generational cohort; Vieira, 1985), and the majority were in residential care. Further, about half of our participants were on antidepressant medications, and baseline mood and quality of life ratings were not collected (though those placed on antipsychotic medications prior to 2 months before recruitment or demonstrating aggressive or agitated behaviour were excluded from the study). An additional limitation is the fact that participant diagnoses were obtained from medical health records and not confirmed via biomarkers. Thus, we relied on diagnosis made by each participant's health provider, which were not confirmed by the research team, potentially resulting in the presence of some mixed or non-AD dementia participants in the sample. Although not being able to establish the reliability of participant diagnosis presents a critical limitation in this study, the absence of gold standard diagnostic criteria in Portugal presents a nationwide issue that interferes with accurate establishment of dementia diagnoses (Alves et al., 2024). Most health care providers, though, rely on *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, text revision criteria for establishing the diagnosis of probable AD, which constituted a central eligibility criterion for this study.

Moreover, a formal sample size calculation or power analysis was not conducted prior to data collection, which we recognize as a limitation of the present study. In addition, in the meta-regression model, the limited number of observations and the inclusion of a moderator variable with only two levels may have led to an artificial inflation of the model's explanatory power, potentially contributing to overfitting. Consequently, the results derived from this meta-regression should be interpreted with due caution and regarded as exploratory in nature. Finally, we must be cautious of the possibility of generalizing the results of this trial to other demographic and clinical groups beyond the study population. Although the predominance of women and low educational attainment in our sample reflects the demographic reality of the Portuguese older adult population—where older women and individuals with limited formal education are overrepresented—these factors, combined with the institutionalized setting that the intervention

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took place, still call for caution when generalizing results to broader and community-dwelling groups.

Conclusion

In summary, this study provides evidence that individualized CS can significantly improve memory in older adults with moderate AD. However, its benefits did not extend to those with more advanced impairment. These findings underscore the importance of early-stage intervention and suggest that iCS may be most valuable as part of a proactive, stage-sensitive treatment strategy. Future research should investigate how intervention timing, intensity, and combination with other therapies can optimize cognitive outcomes across disease stages

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Résumé

La maladie d'Alzheimer (MA) se manifeste par des déficiences dans plusieurs domaines neurocognitifs, en particulier la mémoire et les fonctions exécutives. L'étude a évalué l'efficacité d'un programme de stimulation cognitive individuelle (iCS) sur les performances cognitives chez des personnes âgées présentant une maladie d'Alzheimer aux stades modéré et modérément sévère. Un essai contrôlé randomisé multicentrique a été mené auprès de 80 personnes âgées portugaises atteintes de la MA (âge moyen : 83,0 ± 7,1 ans). Les participants ont été répartis aléatoirement soit dans le groupe de stimulation cognitive individuelle (n = 39; 49 %), soit dans le groupe recevant les soins habituels (n = 41; 51 %). La sévérité de la maladie d'Alzheimer (ADS) a permis de classer les participants en deux groupes selon le score au Mini-Mental State Examination : 10 à 14 pour le groupe ADS modérément sévère et 15 à 20 pour le groupe ADS modéré. Chez les participants atteints de MA modérée, l'iCS a entraîné des améliorations significatives des résultats liés à la mémoire (en particulier le test d'évaluation de la mémoire) et une tendance à l'amélioration de la cognition globale. En revanche, aucun effet significatif n'a été observé chez les participants atteints de MA modérément sévère. Les analyses statistiques, y compris les méta-analyses et la régression, ont mis en évidence une différence significative dans l'efficacité de l'intervention en fonction du degré de gravité. L'iCS était significativement plus efficace chez les personnes atteintes de MA modérée que chez celles atteintes de MA modérément sévère. Cette différence de réactivité entre les niveaux de sévérité a été confirmée statistiquement (Q = 11,29, p < 0,001). L'iCS s'est avérée efficace pour améliorer la mémoire chez les individus atteints de MA modérée, avec des indications supplémentaires d'un bénéfice cognitif global. Cependant, aucun effet significatif n'a été observé sur les participants présentant une atteinte modérément sévère, ce qui suggère que la réactivité à l'iCS diminue avec l'aggravation de la maladie. Mots-clés : maladie d'Alzheimer, fonctions cognitives, thérapie de stimulation cognitive, fonctions exécutives, troubles de la mémoire.

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