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New management strategies for older adults with cognitive decline

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New management strategies for older adults with cognitive decline

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Editorial: New management strategies for older adults with cognitive decline

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Editorial on the Research Topic
New management strategies for older adults with cognitive decline

Introduction

Aging causes various chronic diseases such as heart disease, stroke, cancer, diabetes, and cognitive decline (1). A continued increase in the number of people with age-related cognitive decline and patients with pathological dementia, particularly Alzheimer's disease (AD), has been observed worldwide due to rapid population aging (2). A decline in cognitive function not only significantly limits functional independence, quality of life, and decision-making ability but also places a heavy burden on family members, caregivers, and the society (2). Therefore, measures to combat cognitive decline and dementia need to be established on a global scale.

New drugs (aducanumab and lecanemab) that can reduce amyloid-β plaques (a cardinal AD pathology) have been recently approved (3). Consequently, other novel drugs are presently being developed, further increasing the significance of the early detection of and intervention for cognitive decline and dementia.

Notably, recent efforts to integrate digital technology and neuroscience have led to advances in methods for the early detection of and intervention for cognitive decline and dementia (4, 5). Thus, this Research Topic aimed to collect studies on new management strategies for the early detection of and intervention for the aforementioned conditions in older adults.

Early detection of cognitive decline and dementia

Dementia can be caused by various diseases, with AD being the most common, accounting for 60–80% of all dementia cases (2, 6). AD forms a continuum spanning three stages: preclinical AD, mild cognitive impairment (MCI) due to AD, and AD dementia (6). The concept of subjective cognitive decline (SCD) also exists, which is the advanced stage of preclinical AD (7). Early detection of AD targets people with conditions at earlier stages

of the AD continuum. The currently available biomarkers for the early stages of the AD continuum include techniques such as electroencephalography (EEG), magnetic resonance imaging (MRI), positron emission tomography, and cerebrospinal fluid analysis (8).

This Research Topic includes two studies that applied digital technology to conventional methods. By employing structural MRI along with digital image processing, Rivas-Fernández et al. found that people with SCD exhibit patterns of structural changes similar to those with amnestic MCI or AD dementia despite the absence of clinical symptoms. This suggests that the aforementioned method is useful for the early detection of the AD continuum. Rutkowski et al. found that a machine learning approach could separate and classify the features of EEG network topology (node and edge count distributions) to diagnose early-onset dementia. This study is a step forward to the development of a low-cost, home-based neurobiomarker to monitor cognitive interventions and dementia care management.

Two other studies involved new screening methods using digital technology. Using a digital platform, van den Elzen et al. developed short versions of the first Dutch famous face test specifically for older adults based on systematic collection and selection of famous faces. This test may help distinguish the earliest stages of the AD continuum from normal aging. Igarashi et al. established an auxiliary assessment method for cognitive function through intake interviews integrated with natural language processing models. This method could classify cognitive functions (AD continuum severity) with high accuracy.

In summary, the application of digital technologies to conventional methods or the development of new biomarkers using digital techniques may contribute to advances in the early detection of cognitive decline and dementia.

Early intervention for cognitive decline and dementia

There are 12 risk factors for dementia, namely, low educational level, hearing loss, traumatic brain injury, hypertension, alcohol, obesity, smoking, depression, social isolation, physical inactivity, air pollution, and diabetes. Approximately 40% of dementia cases are believed to be preventable by ameliorating these risk factors (9). The WHO has published guidelines to prevent the aforementioned risk factors, which recommended 12 corresponding interventions: physical activity; tobacco cessation; nutritional, alcohol use disorder, and cognitive interventions; social activity; and weight, hypertension, diabetes mellitus, dyslipidemia, depression, and hearing loss management (10).

This Research Topic includes two studies related to the risk factors for dementia. A systematic review by Boccara et al. found that regional fat deposits (particularly visceral adipose tissues and hepatic fat), rather than central (or abdominal) obesity, may better explain the association between adiposity and the brain. This finding may lead to new personalized fat-reducing treatments. Liu et al. reported that sleeping 7–8 h per day was related to a low risk of cognitive impairment in mid- and late life. They also showed that the optimal post-lunch napping duration for these stable sleepers was 60 min. This study highlights the importance of optimal sleeping habits to cognitive function.

Two other studies reported on new interventions using digital technology. Bernini et al. developed HomeCoRe, a system for remotely supporting cognitive intervention. They found that the utility and user experience of this system are satisfactory for individuals at risk of dementia and their families. The authors encourage a wider and more systematic use of this system. Meanwhile, Chadjikyprianou and Constantinidou developed a multidimensional group online intervention designed to strengthen/improve cognitive and psychosocial functioning in healthy older adults. This intervention may be a valuable contribution to public healthcare and dementia prevention for older adults.

Two further studies addressed considerations when implementing interventions for people with dementia. Ocal et al. observed an inefficient object localization in patients with posterior cortical atrophy compared with patients with typical AD and the controls. These findings may have implications for considering the adverse effects of visual clutter in developing and implementing environmental modifications to promote functional independence in AD. McLaren et al. found that patients with MCI or early dementia have limited perspectives on the prediction of current and future functional abilities. Therefore, they emphasized that considering the patient's poor insights and future thinking is extremely important when implementing technological innovations and advanced care planning.

One study reported on the usefulness of pharmacological intervention. In a randomized, double-blind, single-center, placebo-controlled trial, Hermush et al. found that the medical cannabis oil "Avidekel" was useful in significantly reducing agitation in patients suffering from behavioral disturbances related to dementia.

In summary, this Research Topic presents new ideas for early intervention that could help revolutionize interventions for people with cognitive decline and dementia.

Conclusion

Advances in the integration of digital technology and neuroscience have led to the rapid development of new management strategies (early detection and intervention) for dementia. This Research Topic provides information on such strategies for older adults with cognitive decline, particularly at the early stages of the AD continuum. We believe that this Research Topic will provide valuable insights to guide future research efforts and clinical practice.

Author contributions

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Conflict of interest

GD was employed by NeuroTrax Corporation.

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Prospective association between sleep duration and cognitive impairment: Findings from the China Health and Retirement Longitudinal Study (CHARLS)

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Objective: The association between sleep duration and cognition are inconclusive. Our study aimed to comprehensively investigate the effects of sleep duration on the risk of cognitive impairment in the middle-aged and older Chinese population.

Methods: We used the longitudinal cohort data from waves 1–4 (2011–2018) of the China Health and Retirement Longitudinal Study (CHARLS). Self-reported exposures included total sleep duration, nocturnal sleep duration, post-lunch napping, and changes in sleep duration over time according to face-to-face interviews. Cognitive function was assessed by a Chinese version of the Modified Mini-Mental State Examination (MMSE).

Results: A total of 7,342 eligible participants were included. The mean age was 61.5 ± 6.5 years, and 48.9% (3,588/7,342) were male. We identified a U-shaped association of total sleep duration as well as nocturnal sleep duration with the risk of cognitive impairment. People with 7–8 h of total sleep duration and 6–7 h of nocturnal sleep had the lowest risk of cognitive impairment. Further results showed that post-lunch napping within 2 h was beneficial to cognition and 60 min was optimal. Moreover, analyses of changes in sleep duration further supported that sleeping less or more was harmful to cognition. Notably, those "excessive-change" sleepers (from ≤6 to ≥9 h, or from ≥9 to ≤6 h) had more risks.

Conclusions: Keeping 7–8 h per day was related to the lowest risk of cognitive impairment in midlife and late life, and an optimal post-lunch napping was 60 min for these stable sleepers. Especially, excessive changes

in sleep duration over time led to poorer cognition. Our work highlights the importance of optimal sleep habits to cognitive function. The self-reported sleep measures limited our findings, and further studies are needed for verification.

KEYWORDS

sleep duration, napping, cognitive impairment, risk, changes in sleep duration

Introduction

As a leading cause of disability for older adults, dementia is becoming a public health problem. The number of people with dementia is about 50 million worldwide and will increase to 152 million by 2050 (1). In China, there are 10 million people with dementia, accounting for 25% of the patients with dementia in the world (2). So far there is no effective treatment for dementia and thus prevention strategy has become a top priority. Cognitive impairment is a cardinal feature during the long preclinical period of dementia. Therefore, to identify modifiable risk factors of cognitive impairment is essential for dementia prevention (3).

Several risk factors including age, sex and marital status are confirmed in the development of cognitive impairment or dementia (4–7). Nowadays, an increasing number of studies have reported a strong association between sleep and cognition. Experimental studies found the effects of sleep and circadian rhythm on cognitive impairment (8, 9). Population studies also supported the role of sleep duration in cognitive function. It is estimated that about 15% of Alzheimer's disease in the population may be due to sleep problems (10). One study showed that both self-reported short and long sleep durations were risk factors for cognitive aging (11). Two dose-response meta-analyses showed a U-shaped association between total sleep duration and the risk of cognitive disorders (12, 13). Ma et al. identified an inverted U-shaped association of nocturnal sleep duration with global cognitive decline (14). Napping is another important sleep behavior. It is estimated that 22–69% of older adults have habitual daytime napping in the world (15–17). Previous studies explored the short- or long-term effects of daytime napping on cognition, but findings are inconsistent (15, 18–20). In addition, the association between changes in sleep duration and cognition is attracting more and more attention. However, some cohort studies (21, 22) observed that both increased and decreased sleep duration were related to poor cognition, whereas other studies (23–25) did not support this conclusion. Two recent studies exhibited an association of excessive changes in sleep duration with lower cognitive function (26, 27). Although sleep duration is associated with cognition, few studies focus on the effects of different types of sleep duration.

Previous studies often focused on the effect of one behavior of sleep on cognition, and possibly limited by sample size or methodology. Even in the large cohort studies, results are not fully consistent and need more verification. Therefore, we performed this study to comprehensively examine the association between different types of sleep behaviors and cognitive function, using the data from a large population-based prospective cohort, the China Health and Retirement Longitudinal Study (CHARLS) (28). Based on data from four waves of CHARLS, we aimed to explore the following issues: (1) the dose-response association of total and nocturnal sleep duration with the risk of cognitive impairment; (2) effects of nocturnal sleep and napping on cognitive function; and (3) longitudinal associations between changes in total sleep duration and cognitive impairment risk.

Materials and methods

Study population

This study used the publicly available data from the CHARLS[1] (28). CHARLS is an ongoing national longitudinal survey, covering 450 urban and rural areas from 28 provinces of China. Demographic characteristics, health outcomes and family information were assessed in this cohort. At baseline, a total of 17,708 participants were recruited. Ethical approval for the data collection of the CHARLS was obtained from the Institutional Review board of Peking University (IRB00001052-11015). All participants provided written informed consents during the investigation. We collected the data four waves of CHARLS, including 2011 wave 1 (baseline), 2013 wave 2, 2015 wave 3, and 2018 wave 4 (28).

The inclusion criteria in this study were as follows: (1) participants at baseline attended the Modified Mini-Mental State Examination (MMSE) in 2018 wave 4; and (2) age $\geq$60 years old at 2018 wave 4. Hence a total of 9,106 subjects were included. Then the following exclusion criteria were applied: (1) reporting unusual values of sleep duration ($<$3 or $>$18 h

1 http://charls.pku.edu.cn

per night) (n = 392); (2) missing data of sleep duration at baseline or MMSE scores (n = 1,217); and (3) self-reported diagnoses of mental illness or neurological disease (n = 155). Finally, we included 7,342 eligible participants for analyses (**Supplementary Figure 1**).

Measurements

Cognitive assessment

Cognitive function was measured using the Chinese version of the MMSE test. It is a good tool to evaluate cognitive function, which has good validity and reliability in Alzheimer's disease patients as well as in the general population (29–31). MMSE items include memory, orientation, language, and attention and computation, with a total score of 30. The lower score indicates the poorer cognitive function. Cutoffs were described as 18 for illiterate individuals, 21 for participants with ≤6 years of education, and 25 for participants with >6 years of education (31). Cognitive impairment was considered as participants who had the MMSE scores lower than cutoffs based on the years of education above.

Sleep variables

Four sleep variables were investigated: nocturnal sleep duration, post-lunch napping, total sleep duration, and changes in sleep duration over time. The nocturnal sleep duration and post-lunch napping were collected from two questions at each wave by face-to-face interviews: (1) "During the past month, how many hours of actual sleep did you get at night?" (2) "During the past month, how long (minutes) did you take a nap after lunch?" Total sleep duration was the sum of nocturnal sleep and post-lunch napping. When describing the characteristics of participants, both of total sleep duration and nocturnal sleep duration at baseline were divided into six groups: ≤5, 6, 7, 8, 9, and ≥10 h. Post-lunch napping was divided into four groups: <30, 30–90, and >90 min. The cut points for sleep durations and post-lunch napping were according to previous studies (15, 32). Changes in sleep duration over time were evaluated from baseline to 2013 wave 2, and from baseline to 2015 wave 3.

Covariates

Demographic characteristics and other potential confounders were considered as covariates in this study. They included age, sex, marital status, education level, socioeconomic groups, urbanization, smoking, drinking, Activities of daily living (ADL), social activity scores, and chronic disease comorbidity status.

Marital status was divided into two groups: married and others (divorced, widowed, or never married). Education was categorized as illiterate, primary school (≤6 years of education), and secondary school or higher (>6 years of education). The annual household consumption spending per capita was used as a proxy for socioeconomic status, as described by Zhao et al. (33). We considered four socioeconomic groups based on the quartiles of annual household consumption spending per capita stratified by provinces. Smoking status was categorized as current smokers and non-smokers (e.g., never smokers or ex-smokers). Drinking status was categorized as current drinkers and non-drinkers (e.g., never drinkers or ex-drinkers). Chronic disease comorbidity referred to 11 kinds of non-communicable diseases, including self-reported diagnosed hypertension, diabetes, heart disease, chronic lung disease, digestive disease, live disease, kidney disease, dyslipidemia, stroke, cancer, and arthritis. In addition, participants who did not report hypertension but have systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg were also considered as hypertension. Participants who did not report diabetes but have glycated hemoglobin ≥6.5% were also considered as diabetes. According to the number of these diseases, disease status was defined as three groups: none, one or two, and three or more. ADL included six items: eating, dressing, bathing, transferring, continence, and using the toilet. Participants were classified as two groups: without difficulty (not needing assistance for all items of ADL), and with difficulty (needing assistance for any item of ADL). Based on the number of social activities, social scores were divided into three groups: 0, 1, and ≥2. Social activities were as follows: (1) communicating with friends; (2) playing Ma-jong, chess, or cards, or going to community club; (3) volunteering to help family, friends, or neighbors who do not live with you; (4) going to a sport, social or other kinds of club; (5) taking part in a community-related organization; (6) doing voluntary work for a charity; (7) volunteering to take care of a sick or disable person who do not live with you; (8) attending an educational or training course; (9) investing in stock market; and (10) using the internet. The frequency of the activities above should be daily or almost every week in the last month.

Statistical analyses

Baseline characteristics were shown as mean ± standard deviation (SD) or frequency/percentages. Group differences were examined using Student's t-test or Kruskal–Wallis test for continues variables and Pearson's χ^2 test for categorical variables. Multiple logistic regression models were used to investigate the associations between baseline sleep variables and the risk of cognitive impairment after adjustment of covariates. In the characteristics description, sleep variables were roughly shown as categorical data. For deeply explore their association with the risk of cognitive impairment, they were treated as continuous data in further restricted cubic spline functions. We used the restricted cubic spline function with 3 knots

TABLE 1 Baseline characteristics of the participants according to the cognitive function.

Baseline characteristics	Number	Cognitive impairment group (%)	Cognitive normal group (%)	t/χ^2	*P* value
Total	7,342	3,675 (50.0)	3,667 (50.0)		
Age (years)	7,342	62.2 ±7.0	60.8 ±5.8	9.20	<0.001
Sex					
Male	3,588	1,540 (42.9)	2,048 (57.1)	142.84	<0.001
Female	3,754	2,135 (56.9)	1,619 (43.1)		
Urbanization					
Rural	4,666	2,587 (55.4)	2,079 (44.6)	148.72	<0.001
Urban	2,676	1,088 (40.7)	1,588 (59.3)		
Marital status					
Married	6,438	3,104 (48.2)	3,334 (51.8)	70.87	<0.001
Other	904	571 (63.2)	333 (36.8)		
Education level					
Illiterate	2,220	1,567 (70.6)	653 (29.4)	557.74	<0.001
Primary school	4,427	1,877 (42.4)	2,550 (57.6)		
Secondary school or higher	692	229 (33.1)	463 (66.9)		
Socioeconomic status					
Quartile 1	1,844	1,063 (57.7)	781 (42.4)	111.90	<0.001
Quartile 2	1,831	975 (53.3)	856 (46.8)		
Quartile 3	1,826	883 (48.4)	943 (51.6)		
Quartile 4	1,787	731 (40.9)	1,056 (59.1)		
Smoking status					
Non-smokers	4,995	2,585 (51.8)	2,410 (48.3)	18.01	<0.001
Current smokers	2,347	1,090 (46.4)	1,257 (53.6)		
Drinking status					
Non- drinkers	5,493	2,831 (51.5)	2,662 (48.5)	19.21	<0.001
Current drinkers	1,849	844 (45.7)	1,005 (54.4)		
Chronic disease comorbidity status					
0	2,253	1,133 (50.3)	1,120 (49.7)	0.61	0.736
1∼2	3,811	1,915 (50.3)	1,896 (49.8)		
>2	1,278	627 (49.1)	651 (50.9)		
ADL					
With difficulty	1,145	681 (59.5)	464 (40.5)	48.17	<0.001
Without difficulty	6,197	2,994 (48.3)	3,203 (51.7)		
Social scores					
0	4,738	2,537 (53.6)	2,201 (46.5)	89.78	<0.001
1	1,984	921 (46.4)	1,063 (53.6)		
2	620	217 (35)	403 (65)		
Nocturnal sleep duration (h)					
≤5	2,124	1,143 (53.8)	981 (46.2)	62.14	<0.001
6	1,607	752 (46.8)	855 (53.2)		
7	1,433	632 (44.1)	801 (55.9)		
8	1,587	794 (50)	793 (50)		
9	299	181 (60.5)	118 (39.5)		
≥10	292	173 (59.3)	119 (40.8)		
Post-lunch napping (min)					
0	3,460	1,859 (53.7)	1,601 (46.3)	43.52	<0.001
1∼29	1,216	591 (48.6)	625 (51.4)		
30∼90	1,860	826 (44.4)	1,034 (55.6)		
>90	806	399 (49.5)	407 (50.5)		

(Continued)

TABLE 1 (Continued)

Baseline characteristics	Number	Cognitive impairment group (%)	Cognitive normal group (%)	t/χ^2	*P* value
Total sleep duration (h)					
≤5	1,625	908 (55.9)	717 (44.1)	47.67	<0.001
6	1,259	620 (49.3)	639 (50.8)		
7	1,417	649 (45.8)	768 (54.2)		
8	1,490	687 (46.1)	803 (53.9)		
9	832	419 (50.4)	413 (49.6)		
≥10	719	392 (54.5)	327 (45.5)		

Data was shown as mean ± standard deviation (SD) for continues variables or frequency (percentage) for categorical variables. Three participants had missing values for education level, and 54 had missing values for socioeconomic status.

of "6, 8, and 10 h" in the multiple logistic regression model to explore the dose-response association between total sleep duration at baseline and cognitive impairment risk in the whole and subgroup participants. Then we used the knots of "5, 7, and 9 h" to explore the dose-response association between nocturnal sleep duration at baseline and cognitive impairment risk. Moreover, we explored the effects of post-lunch napping on cognition based on different nocturnal sleep durations using a multiple logistic regression with restricted cubic spline function ("0, 30, and 90 min" as knots). For analyses of changes in sleep duration, we classified participants into five groups according to total sleep duration between baseline and wave 2, and between baseline and wave 3 as follows: stable moderate sleepers (always 7–8 h), moderate-to-unhealthy sleepers (from 7–8 h to ≤6 or ≥9 h), unhealthy-to-moderate sleepers (from ≤6 or ≥9 h to 7–8 h), short or long sleepers (always ≤6 or ≥9 h), and "excessive-change" sleepers (from ≤6 to ≥9 h, or from ≥9 to ≤6 h). The changes in total sleep duration from baseline to Wave 2, and from baseline to Wave 3 were explored separately. Odds ratio (OR) and 95% confidence interval (CI) were used to measure the association strength of risk. Statistical analyses were conducted by Stata 15.0 (College Station, TX, United States). A two-sided *P* value <0.05 was considered statistically significant.

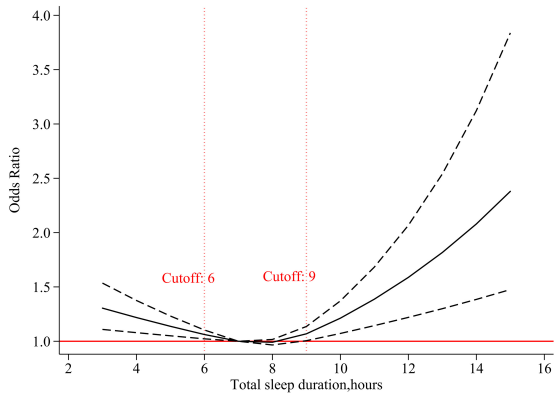

FIGURE 1
The adjusted dose-response association between total sleep duration at baseline and risk of cognitive impairment. Total sleep duration at baseline was modeled *via* a restricted cubic spline function with knots of 6, 8, 10, and 7 h was as the reference value.

Results

Sample characteristics

A total of 7,342 eligible participants at baseline were included for analyses. The mean age was 61.5 ± 6.5 years, and 48.9% (3,588/7,342) were male. Of these, 3,675 (50.0%) participants had cognitive impairment based on the MMSE scores in the 2018 wave 4. Nocturnal sleep duration, post-lunch napping and total sleep duration demonstrated significant associations with cognitive impairment. Among other baseline factors, older age, female, not married, smoking, and ADL with difficulty increased the risk of cognitive impairment. Living in urban, higher level of education, higher socioeconomic status, and more social scores played a protective role of cognitive function. These cognition-related covariates were adjusted in the following analyses dealing with sleep variables. Details are shown in **Table 1** and **Supplementary Table 1**.

Association of total sleep duration with risk of cognitive impairment

A U-shaped association was observed between total sleep duration at baseline and risk of cognitive impairment, based on the restricted cubic spline logistic regression model. As shown in **Figure 1**, the moderate sleep duration was 7–8 h per day, and sleep less (≤6 h) or more (≥9 h) significantly increased the risk of cognitive impairment. Similar U-shaped patterns were also observed in the subgroup analyses by sex and age, and females and younger age seemed to be more affected by sleep duration (**Supplementary Figure 2**).

Association of nocturnal sleep duration and post-lunch napping with risk of cognitive impairment

As shown in Figure 2A, a U-shaped association suggested that 6–7 h of nocturnal sleep duration at baseline had the lowest risk of cognitive impairment. Short (≤5 h) or long (≥8 h) nocturnal sleep duration was harmful to cognitive function.

Based on these results, the role of post-lunch napping at baseline was further explored. We identified that post-lunch napping significantly decreased the risk of cognitive impairment in participants sleeping 6–7 h at night (OR = 0.77, 95% CI = 0.66–0.90, P = 0.001, Table 2). Dose-response analysis showed that less than 110 min of post-lunch napping helped decrease the risk of cognitive impairment, and 60 min was likely to be the best duration (Figure 2B). However, the significant effects of post-lunch napping on cognition were not found among participants with short (≤5 h) or long (≥8 h) nocturnal sleep duration (Table 2).

Further analysis revealed that post-lunch napping was significantly related to nocturnal sleep duration (All $P < 0.001$, Supplementary Table 2). Overall, participants who reported less nocturnal sleep duration tended to have less napping, and vice versa (Figure 2C).

Association of changes in total sleep duration with risk of cognitive impairment

For changes in total sleep duration over time, we analyzed the data from baseline to 2013 wave 2, and from baseline to 2015 wave 3 (Table 3). Overall, compared with stable moderate sleepers (always 7–8 h), other sleepers showed an increased risk of cognitive impairment or similar tendency. Compared with stable moderate sleepers (always 7–8 h), short or long sleepers (always ≤6 or ≥9 h) had an increased risk of cognitive impairment (from baseline to wave 2: OR = 1.22, 95% CI = 1.04–1.42, P = 0.012; from baseline to wave 3: OR = 1.19, 95% CI = 1.02–1.38, P = 0.027). Notably, those "excessive-change" sleepers (from ≤6 to ≥9 h, or from ≥9 to ≤6 h) likely had more risks (from baseline to wave 2: OR = 1.63, 95% CI = 1.30–2.03, $P < 0.001$; from baseline to wave 3: OR = 1.58, 95% CI = 1.27–1.96, $P < 0.001$).

Discussion

In this nationally representative community-based cohort including 7,342 middle-aged and older subjects, we identified a significant U-shaped association between total sleep duration and cognitive function. A similar U-shaped pattern was also observed in nocturnal sleep. We also found that 7–8 h of total sleep duration and 6–7 h of nocturnal sleep had the lowest risk of poor cognition. Post-lunch napping within 2 h could decrease the risk of cognitive impairment, and 60 min might be an optimal choice. Longitudinal analysis highlighted that excessive changes in sleep duration over time had more risk of cognitive impairment than sleeping less or more. The unhealthy sleep patterns over time were significantly modified by some factors including social activities.

Previous cohort studies have investigated the association between sleep duration and cognitive disorders but had inconsistent results, such as the US Nurses' Health Study by Tworoge et al. (34), the Finnish Twin Cohort by Virta et al. (35), and Screening Across the Lifespan Twin study by Bokenberger et al. (36). Possible reasons included not large sample size (n < 2,000), short follow-up period (<3 years), or weak in representativeness (e.g., only one sex or twin study). Several meta-analyses were performed and found a U-shaped pattern of sleep duration in cognition, but they did not distinguish total sleep duration from nocturnal sleep duration (12, 13). Recently, Ma, et al. combined data from the English Longitudinal Study of Ageing (ELSA) and CHARLS, also reported a U-shaped association between nocturnal sleep duration and cognitive function (14). Consistently, we identified a U-shaped association of total sleep duration as well as nocturnal sleep duration with the risk of cognitive impairment. Compared with the studies by Ma et al. (14), we evaluated more sleep variables based on the data from more waves of survey and information from a new comprehensive assessment tool of cognitive outcome in the CHARLS. Moreover, we recommended 7–8 h for total sleep or 6–7 h for nocturnal sleep per day, because such sleep durations had the lowest risk of cognitive impairment. A recent study with sleep duration measured by polysomnography also supported our results (37). Lucey et al. investigated the relationship between cognitive performance and sleep duration measured by the single-channel EEG device, and showed that individuals with sleeping less than 4.5 or more than 6.5 h at night had declined cognitive scores (37). Because the sleep time is about one hour shorter measured by EEG than by self-reported, the results corresponded to 5.5–7.5 h per night of self-reported sleep time to have the lowest risk (34, 37). Although the biological mechanisms of extreme sleep durations on cognition is still unclear, putative pathways included circadian dysfunction (38), increased accumulation of amyloid-β in the brain (39), and elevate levels of systemic inflammatory markers (e.g., C-reactive protein, interleukin-6) (40–42). In addition, we observed that sleep seemed to affect females more than males on cognition, possibly due to the hormonal and biological differences between the sexes (43). We also observed that the effects of total sleep duration on the risk of cognitive impairment decreased with age, suggesting that it is better to perform sleeping intervention as early as possible.

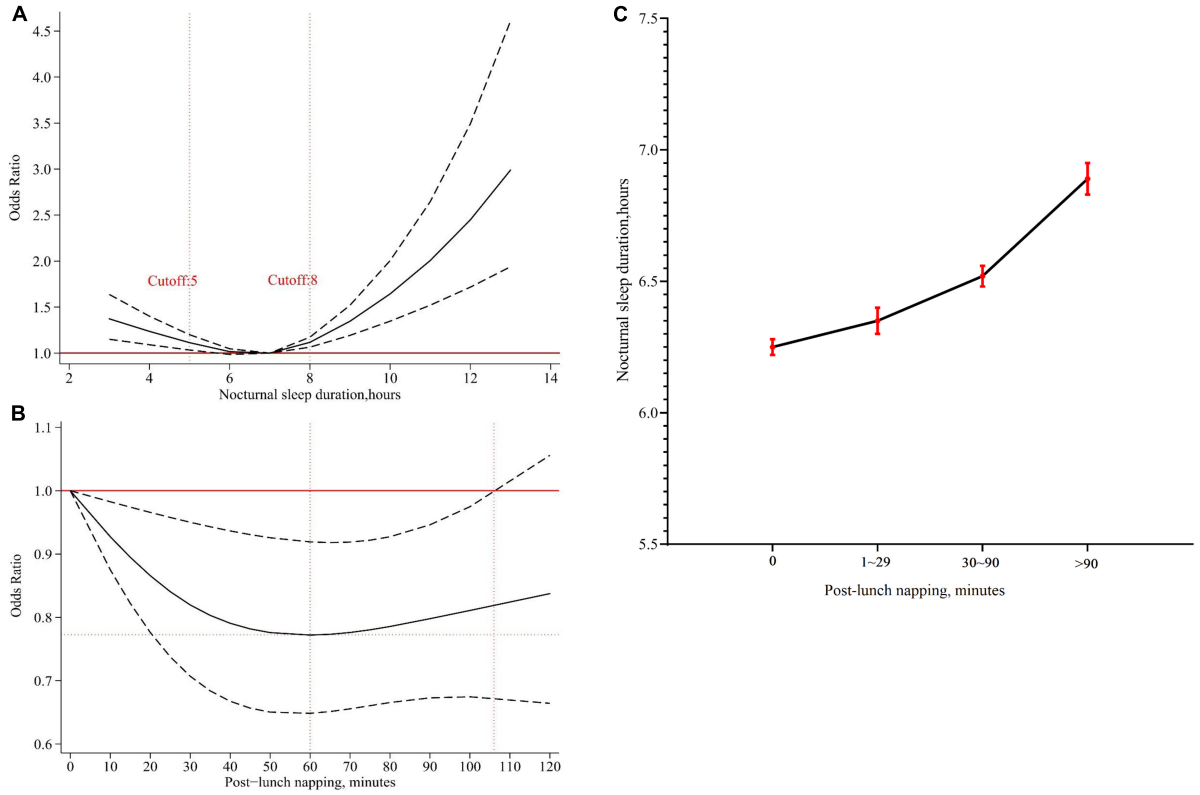

FIGURE 2
The effects of nocturnal sleep duration or post-lunch napping at baseline on cognition. **(A)** The adjusted dose-response association between nocturnal sleep duration at baseline and risk of cognitive impairment. Nocturnal sleep duration at baseline was modeled *via* a restricted cubic spline logistic regression model with knots of 5, 7, 9, and 7 h was as the reference value. **(B)** The adjusted dose-response association between post-lunch napping at baseline and risk of cognitive impairment among participants sleeping 6–7 h at night. Post-lunch napping at baseline was modeled *via* a restricted cubic spline logistic regression model with knots of 0, 30, and 90 min, and non-napping was as the reference value. **(C)** Association between post-lunch napping and nocturnal sleep duration. The black dots represented mean nocturnal sleep duration, and the red error bars represented 95% confidence intervals.

TABLE 2 The association between post-lunch napping at baseline and risk of cognitive impairment stratified by nocturnal sleep duration.

Nocturnal sleep duration (h)	Post-lunch napping	Number of participants (%)	OR (95% CI)	*P* value
≤5	No	1,134 (53.4)	Reference	
	Yes	990 (46.6)	1.12 (0.93, 1.35)	0.247
6∼7	No	1,378 (45.3)	Reference	
	Yes	1,662 (54.7)	0.77 (0.66, 0.90)	0.001
≥8	No	948 (43.5)	Reference	
	Yes	1,230 (56.5)	0.85 (0.71, 1.02)	0.085

Multiple logistic regression models were used to investigate the associations between post-lunch napping at baseline and the risk of cognitive impairment stratified by nocturnal sleep duration with adjustment of potential confounders: age, sex, marital status, education level, socio-economic status, urbanization, smoking, drinking, ADL, social activity score, and chronic disease comorbidity status.

Daytime napping is prevalent in Asians. Previous studies have reported that moderate daytime napping could improve cognitive performance in the ageing people (15, 44, 45). Daytime napping can regulate the inflammatory response and reduce fatigue in the day (46), but excessive napping may develop sedentary habit and be considered a risk marker of amyloid-β accumulation (47). Consistently, our work also supported the benefits of post-lunch napping on cognition, and had more details in moderate napping time. We found that in the participants with 6–7 h of nocturnal sleep, post-lunch napping within 2 h led to better cognition, and the optimal napping time was 60 min. Further results showed that short nappers often slept less at night, and vice versa. That might imply that different types of nocturnal sleep have certain napping habits,

TABLE 3 The association between change of total sleep duration and risk of cognitive impairment.

Changes in total sleep duration*	From baseline to 2013 Wave			From baseline to 2015 Wave		
	Number of participants (%)	OR (95% CI)	*P* value	Number of participants (%)	OR (95% CI)	*P* value
Stable moderate sleepers	1,220 (19.2)	Reference		1,183 (18.1)	Reference	
Moderate-to-Unhealthy sleepers	1,315 (20.7)	1.19 (1.01, 1.41)	0.039	1,434 (21.9)	1.05 (0.89, 1.24)	0.538
Unhealthy-to-Moderate sleepers	1,297 (20.4)	1.24 (1.05, 1.47)	0.010	1,316 (20.1)	1.12 (0.95,1.32)	0.193
Short or Long sleepers	2,011 (31.6)	1.22 (1.04, 1.42)	0.012	2,063 (31.1)	1.19 (1.02, 1.38)	0.027
"Excessive-change" sleepers	512 (8.1)	1.63 (1.30, 2.03)	<0.001	571 (8.8)	1.58 (1.27, 1.96)	<0.001

*Stable moderate sleepers: always 7–8 h, Moderate-to-Unhealthy sleepers: from 7–8 h to ≤6 or ≥9 h, Unhealthy-to-Moderate sleepers: from ≤6 or ≥9 h to 7–8 h, Short sleepers: always ≤6 h, Long sleepers: always ≥9 h, "Excessive-change" sleepers: from ≤6 to ≥9 h, or from ≥9 to ≤6 h. Multiple logistic regression models were used to investigate the associations between change of total sleep duration and the risk of cognitive impairment with adjustment of potential confounders: age, sex, marital status, education level, socio-economic status, urbanization, smoking, drinking, ADL, social activity score, and chronic disease comorbidity status.

which possibly play different roles on cognition. Supportive evidence was that a national survey determined the beneficial effect of long nap durations on cognitive performance only in elderly adults with a morning chronotype, rather than in those with other chronotypes (48). Another explanation was that the nocturnal sleep habit probably masked the beneficial effect of napping on cognition for participants who slept less (≤5 h) or more (≥8 h) at night.

Recently, some studies have focused on associations of changes in sleep duration and cognitive function, but results are conflicting (21–25). Our work demonstrated that short or long sleepers (always ≤6 or ≥9 h) had more risk of cognitive impairment than no-change moderate sleepers (always 7–8 h). This result was in line with the recommendation by the National Sleep Foundation that 7–8 h of sleep is good for the elderly (49). Moreover, we further found that the highest risk of cognitive impairment was in those who had excessive changes in sleep duration (from ≤6 to ≥9 h, or from ≥9 to ≤6 h). Supportive evidence can be found in the latest studies (26, 27, 50). Hua et al. used the nocturnal sleep data of three waves of CHARLS (2011–2015) and found that an increased or decreased change of ≥2 h in sleep duration correlated with poorer cognition (26). Wu et al. reported that substantial changes in sleep duration (e.g., from ≤5 to ≥9 h) was associated with a higher risk of cognitive impairment (27). Even for the mild cognitive impairment, keeping stable sleep duration in a normal range is essential for better cognition (50). A possible explanation that shifts of sleep duration may increase the levels of inflammatory markers and contribute to the decline cognition (41). Other interpretations included amyloid-β deposition and circadian dysfunction (38, 39), but exact mechanisms are not very clear and need more investigations.

Actually, abnormal sleep durations are common health problems rather than simple behaviors among the middle-aged and older adults. For example, excessive daytime sleepiness (EDS) can cause falls, depression and cognitive impairment, and was estimated to occur in about 20% of the older people (51). A recent study investigated the association between malnutrition and excessive daytime sleepiness (EDS) in patients with and without dementia, and found that malnutrition, dysphagia, and vitamin D deficiency were significantly related to EDS (52). Interestingly, nutritional status was also reported to be closely associated with insomnia or insomnia severity in older adults (53). These issues should be considered in the association between sleep behaviors and cognitive function in the future.

This study has major strengths in a large and nationally representative sample, many waves of follow-ups, multiple adjustment of potential confounders, and comprehensive analyses of sleep behaviors. However, several limitations should also be acknowledged. First, the sleep variables were collected by self-reported data rather than objective measurements, which might be influenced by recall bias and lead to exposure misclassification. Second, although we adjusted for a number of potential confounders, residual confounding still possibly occurred due to unmeasured covariates, including other sleep disturbances (e.g., parasomnias), napping frequency and nutrition conditions. Influences of these factors should be considered in future studies. Third, MMSE is a good screening tool to identify dementia, but it is insensitive to detect mild cognitive impairment or early-stage dementia, which could not replace the clinical diagnosis. Fourth, the cognitive assessment based on MMSE in this study was only performed in the latest follow-up. Although we excluded participants with self-reported diagnoses of mental illness or neurological disease, we could not obtain the object measurements of cognitive function at baseline and also not capture the cognition decline over time. At last, cognitive impairment has many types (e.g., Alzheimer's disease and dementia with Lewy bodies) (54), which may be associated with types of sleep problems and subgroup analyses may provide more information for clinicians. Due to insufficient information collected in this study, we could not perform such analyses. Based on these limitations above, our findings should be cautiously interpreted and more detailed studies are still warranted in the future.

In summary, keeping 7–8 h per day in midlife and late life was related to the lowest risk of cognitive impairment, and an optimal post-lunch napping was 60 min for these stable sleepers. Moreover, excessive changes in sleep duration could result in poorer cognition. To date, "sleep" has not mentioned as a lifestyle intervention for dementia, and three large multi-domain trials (FINGER, MAPT and PreDIVA) regarding interventions to prevent cognitive disorders did not include sleep duration (55). Our findings provide new evidence for lifestyle intervention studies on cognitive impairment in the future.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary material**.

Ethics statement

Ethical approval for the data collection of the CHARLS was obtained from the Institutional Review board of Peking University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NS conceived, designed, and supervised the study. WL and QW performed the formal analyses and wrote the first draft of the manuscript. MW and PW collected and reviewed the data. All authors critically revised successive drafts of the manuscript and approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.971510/full#supplementary-material

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Effects of rich cannabidiol oil on behavioral disturbances in patients with dementia: A placebo controlled randomized clinical trial

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Background: Almost 90% of patients with dementia suffer from some type of neurobehavioral symptom, and there are no approved medications to address these symptoms.

Objective: To evaluate the safety and efficacy of the medical cannabis oil "Avidekel" for the reduction of behavioral disturbances among patients with dementia.

Materials and methods: In this randomized, double-blind, single-cite, placebo-controlled trial conducted in Israel (ClinicalTrials.gov: NCT03328676), patients aged at least 60, with a diagnosis of major neurocognitive disorder and associated behavioral disturbances were randomized 2:1 to receive either "Avidekel," a broad-spectrum cannabis oil (30% cannabidiol and 1% tetrahydrocannabinol: 295 mg and 12.5 mg per ml, respectively; n = 40) or a placebo oil (n = 20) three times a day for 16 weeks. The primary outcome was a decrease, as compared to baseline, of four or more points on the Cohen-Mansfield Agitation Inventory score by week 16.

Results: From 60 randomized patients [mean age, 79.4 years; 36 women (60.0%)], 52 (86.7%) completed the trial (all eight patients who discontinued treatment were from the investigational group). There was a statistically significant difference in the proportion of subjects who had a Cohen-Mansfield Agitation Inventory score reduction of $\geq$ 4 points at week 16: 24/40 (60.0%) and 6/20 (30.0%) for investigational and control groups, respectively (χ^2 = 4.80, P = 0.03). There was a statistically significant difference in the proportion of subjects who had a Cohen-Mansfield Agitation Inventory score reduction of $\geq$ 8 points at week 16: 20/40 (50%) and 3/20 (15%),

respectively (χ^2 = 6.42, P = 0.011). The ANOVA repeated measures analysis demonstrated significantly more improvement in the investigational group compared to the control group at weeks 14 and 16 (F = 3.18, P = 0.02). Treatment was mostly safe, with no significant differences in the occurrence of adverse events between the two groups.

Conclusion: In this randomized controlled trial, 'Avidekel' oil significantly reduced agitation over placebo in patients suffering from behavioral disturbances related to dementia, with non-serious side-effects. Further research is required with a larger sample size.

KEYWORDS

medical cannabis, cannabidiol, dementia, behavioral disturbances, agitation, randomized controlled trial (RCT), neuropsychiatric symptoms

Introduction

Dementia, characterized by a progressive decline in cognitive and functional abilities and challenging behavioral symptoms (1, 2), is one of the major causes of disability and dependency among older adults (3). Neuropsychiatric symptoms (NPS) occur in up to 90% of patients with dementia (4–6), and are associated with a reduced quality of life (7, 8). Symptoms contributing to decreased quality of life include agitation, mood disorders, hallucinations and delusions (psychosis), and sleep disorders (7, 9, 10). Agitation, a common NPS in dementia, is associated with an increased rate of cognitive and functional decline (11), rapid disease progression (12, 13), and an earlier death (14) compared to patients with dementia without agitation. In addition, patients with agitation are more likely to be admitted to institutions (15–18), and to require more antipsychotics and antidepressants (19), increasing the overall cost of care. Meta-analyses on the reasons patients with dementia are placed in nursing homes confirm the significant role of NPS symptoms that are ineffectively managed (20, 21).

In the absence of approved medications for NPS, antipsychotics are typically used off-label to treat agitation in dementia, although evidence for their efficacy is limited and usage may involve dangerous side-effects (22–26). A recent meta-analysis found an increased odds of cerebrovascular events, fracture, and death associated with antipsychotics; increased odds of falls associated with dextromethorphan-quinidine; and increased odds of death associated with anticonvulsants (22). Guidelines recommend the use of antipsychotics for the treatment of NPS in patients with dementia only when symptoms are dangerous or cause significant patient distress (22). Identifying an effective, low-risk therapeutic alternative for NPS, and specifically agitation, in patients with dementia is essential.

Cannabinoids work by interacting with receptors in the endocannabinoid system (ECS), especially cannabinoid 1 receptor (CB1R) and cannabinoid 2 receptor (CB2R). CB1Rs are extensively distributed throughout the body, with a significant presence in the central nervous system, whereas CB2Rs are found in immune cells and tissues (27). The ECS is an important neuromodulatory system linked to a variety of psychiatric, neurodegenerative, and motor illnesses, including schizophrenia, anorexia, Alzheimer's disease, Parkinson's disease, and Huntington disease (28, 29). Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most common cannabinoids found in the cannabis plant (30). CBD has anti-inflammatory, neuroprotective, antipsychotic, anxiolytic, and antidepressant properties (31). While THC is the primary psychoactive ingredient (32), CBD is non-intoxicating (30); and when combined with THC, may counterbalance the psychoactivity of THC (33). While each of the two main cannabinoids has been linked to clinical and physiological effects on its own, researchers have hypothesized that the main cannabinoid and minor cannabinoids operate synergistically (34). Several controlled studies suggest that CBD is safe and effective for the treatment of anxiety (35–38), Parkinson's disease (37, 39), post-traumatic stress disorder (38), autism (40), epilepsy (41), and schizophrenia (42). Some clinical data supports the beneficial therapeutic effects of cannabinoids on behavioral symptoms, particularly on agitation in patients with dementia (43–45); however, reviews concluded that it is uncertain whether cannabinoids have any beneficial or harmful effects on behavioral disturbances related to dementia. All included studies tested THC and synthetic THC analogs; none of them examined the effect of CBD on agitation (46, 47). Although treatment with cannabinoids appears to be safe in patients with dementia (47), cancer (48), and older patients (49); overall evidence for the management of dementia-related NPS with medical cannabis has been equivocal (50).

As CBD cannabis oils are becoming increasingly available, the need for further evaluation of CBD cannabis oils as a possible treatment option for agitation and identification of the treatment characteristics is increasing.

The primary objective of this trial was to evaluate the safety and efficacy of cannabis oil extracted from one chemovar "Avidekel" (30% CBD and 1% THC: 295 mg and 12.5 mg per ml, respectively), for behavioral disturbances in patients with dementia.

Materials and methods

Study design

This was a single-center, randomized (2:1), placebo-controlled, double-blind trial. Patients were recruited nationally by the principal investigator (VH). During enrollment, written informed consent was provided by the legal representatives of all participants, and an application for a cannabis treatment license was arranged (issuance took an average of seven weeks). Over 16 weeks of the treatment period, participants came in for follow-up every two weeks, with the option to terminate their participation. After completing the study, all trial participants were offered the option to renew their cannabis treatment license. The trial took place in a tertiary hospital in Israel from December 2017 to September 2019.

The trial, registered in ClinicalTrials.gov: NCT03328676, was approved by the Laniado Hospital Ethics Committee (project LND 0111-16) and the clinical trials department at the Israel Ministry of Health (project 20173138). Study procedures were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Consolidated Guidelines on Good Clinical Practice and followed the CONSORT reporting guideline (51).

Participants

During screening, participants were evaluated for eligibility criteria, which included an age of 60 years or older, diagnosis of a major neurocognitive disorder according to the DSM-5 criteria (all types of dementia), Mini–Mental State Examination (MMSE) (52) score of < 26 for cognitive impairment measurement, clinically relevant neuropsychiatric behaviors defined as Neuropsychiatric Inventory–Nursing Home Version (NPI-NH) (53–55) sub-score of agitation ≥ 3, a stable medication regimen for at least two weeks prior to baseline visit, and residence in either an institutionalized setting or in a non-institutionalized setting subject to 24-h supervision. Exclusion criteria included severe heart disease [New York Heart association (NYHA) class IV] (56), epilepsy, anxiety disorder; psychotic conditions in the present or in the past (not related to dementia), family history of schizophrenia, current substance use disorder, recent cannabis experience, or scheduled surgery during the trial.

Randomization

Eligible participants were randomly assigned by a computerized random-number generator system in a 2:1 ratio to receive either 'Avidekel' oil or a placebo. Patients with dementia are required to have consent of legal representatives in order to enroll in clinical trials. To encourage caregivers' interest in enrollment of this trial, the 2:1 ratio was employed (57). The randomized list of patients was set before the trial was initiated, and the investigational product (IP) and placebo were prepared. Patients, families, and the medical teams were masked to the individual patients' treatment assignment. To ensure masking was maintained, "Avidekel" and placebo oils were manufactured to have an identical appearance and smell.

Investigational product

The IP or placebo was added to the routine medication regimen (**Table 1**). Subjects received the IP or the placebo as drops applied under the tongue three times a day. Participants in the investigational group received "Avidekel" (made in Israel by Tikun-Olam Cannbit Pharmaceuticals), an ethanol extraction of rich CBD (∼15%), low-THC (∼0.5%) cannabis chemovar dissolved in olive oil. The IP contained 30% CBD, 1% THC, 1% Cannabichromene (CBC), 0.5% Cannabigerol (CBG), and 0.5% Cannabidivarin (CBDV). One drop of 0.04 ml contains 11.8 mg CBD and 0.5 mg THC. Patients in the control group received a placebo containing olive oil and chlorophyll.

Caregivers were instructed to shake the oil bottle, place the drops of oil with a tablespoon under the patient's tongue, and wait one minute before swallowing to enhance oil absorption. The initial dose was one oil drop in the morning, afternoon, and evening, for two days. They were instructed to increase each dose by one drop in increments of two days. The dose was titrated gradually depending on the tolerance of each patient, to a maximum dose of 21 drops per administration or until an adverse reaction occurred. The caregivers were instructed to then taper down one level to a pre-adverse reaction dose. The time for each patient to "find" the therapeutic dose: a balance between maximum reduction in agitation and minimum side-effects, lasted up to six weeks. After the titration phase, patients entered a ten-week treatment phase of fixed-dose (**Supplementary Table 1**).

We selected this specific chemovar "Avidekel" aiming to minimize side-effects. This was based on earlier clinical experience with 39 patients with indications for dementia and on 93 patients with pediatric autism spectrum disorder with

TABLE 1 Characteristics of the patient population at baseline.

Characteristic	Avidekel oil (n = 40)	Placebo oil (n = 20)	P value
Age (years), mean ± SD	78.8 ± 9.3	80.5 ± 9.6	0.51
Gender, n (%)			
Females	22 (55)	14 (70)	0.26
Males	18 (45)	6 (30)	
Country of birth, n (%)			
Israel	12 (30)	6 (30)	0.95
Other	28 (70)	14 (70)	
Residence, n (%)			
Institution	7 (17)	2 (10)	0.66
Home	33 (83)	18 (90)	
Years since diagnosis, mean ± SD	4.24 ± 2.91	3.27 ± 2.42	0.27
Comorbidities, n (%)			
Cardiovascular diseases	33 (83)	17 (85)	0.81
Hypertension	17 (43)	9 (45)	0.85
Diabetes-type 2	11 (28)	6 (30)	0.84
Neurologic[1]	10 (25)	8 (40)	0.23
Endocrine[2]	5 (13)	2 (10)	0.78
Eye/ear	5 (13)	2 (10)	0.78
Depression	3 (8)	1 (5)	0.71
Renal	2 (5)	2 (10)	> 0.99
Other	16 (40)	9 (45)	0.71
Medication, n (%)			
Antihypertensive	21 (53)	12 (60)	0.85
Antidepressant	21 (53)	7 (35)	0.14
Antipsychotic	17 (43)	9 (45)	> 0.99
Sedative	12 (30)	10 (50)	0.46
Other	31 (78)	20 (100)	0.47
Questionnaires, mean ± SD			
MMSE[3] score	12.4 ± 6.8	15.2 ± 6.2	0.13
CMAI[4] score	59.3 ± 20.3	58.7 ± 22.3	0.92
NPI-NH[5] score	41.7 ± 19.1	42.5 ± 20.1	0.88
GDS[6] score	4.9 ± 3.3	2.8 ± 3.1	0.02
PAINAD[7] score	0.1 ± 0.4	0.1 ± 0.4	0.99
CGI-S-A/A[8] score	2.6 ± 3.3	2.9 ± 3.3	0.74

Data are presented as mean ± standard deviation for continuous data and No. (%) for categorical data.
SD, Standard Deviation.
[1]Neurologic co-morbidities include cerebrovascular disease and epilepsy.
[2]Endocrine co-morbidities include hypothyroidism and hyperthyroidism.
[3]MMSE – Mini–Mental State Examination. Range and scaling: 0–30 points (≤ 9 meaning severe cognitive impairment).
[4]CMAI – Cohen-Mansfield Agitation Inventory. Range and scaling: 29–203 points (29 meaning no symptoms).
[5]NPI-NH – Neuropsychiatric Inventory–Nursing Home Version. Range and scaling: 0–144 points (0 meaning no symptoms).
[6]GDS – Geriatric Depression Scale. Range and scaling: 0–30 points (0 meaning no symptoms).
[7]PAINAD – Pain Assessment in Advanced Dementia Scale. Range and scaling: 0–10 points (0 meaning no symptoms).
[8]CGI-S-A/A – Clinical Global Impression for Agitation and Aggression. Range and scaling: 0–10 points (0 meaning no symptoms).

behavioral disturbances (58). In both cases, patients receiving this product showed improvement in agitation with low-frequency side-effects. This type of sublingual administration (59) is more accurate with fewer fluctuations than other routes of administration. A similar product was tested for pharmacokinetics parameters in Crohn's disease patients and demonstrated blood concentrations of the main active ingredients and their metabolites (60).

Safety assessments

For safety evaluation, serious adverse events (SAEs; defined as: death, life-threatening events, hospitalization, debilitation, or immobility), and all adverse events (AEs), with a severity score on a Likert scale of 1 to 10, were collected in all trial visits. In this population with many comorbidities and medications, the symptom list of main AEs was also evaluated at baseline and documented as a non-IP-related AE report. An AE was defined as any unfavorable symptom, sign, syndrome, or disease that occurred during the study, having been absent at baseline, or, if present at baseline, appeared to worsen. Clinical data included vital signs and physical examination information collected in all trial visits, as well as blood chemistry and hematology labs collected every other visit.

Outcomes measures

The primary efficacy endpoint was the proportion of subjects achieving a 4-point decrease in the Cohen-Mansfield Agitation Inventory (CMAI) at week 16 compared to baseline (61–65). A total CMAI score was obtained by summing all items from a caregivers' rating questionnaire consisting of 29 agitated behaviors, each rated on a 7-point scale of frequency, with higher scores indicating greater severity. A total score of > 45 was regarded as clinically significant agitation, and a total reduction of 8 points or more was considered a clinically significant change (65). We determined that a 4-point decrease in CMAI score represents a better outcome compared to a similar randomized controlled trial that used oral THC (in which a 2.3 points reduction in the active group was not significant) (66), and above the placebo effect of two points decrease in the CMAI (67).

Secondary outcomes included: The proportion of subjects achieving an 8-point decrease in mean CMAI score, proportion of patients achieving 30% and 50% reduction in CMAI scores, the time necessary to achieve a 4-point reduction in CMAI, mean change in NPI-NH agitation/aggression sub-score. In the NPI-NH, the higher the score, the more severe and frequent the behavioral disturbances. The following questionnaires were also administered: the Geriatric Depression Scale (GDS), the Pain Assessment in Advanced Dementia Scale (PAINAD), the Clinical Global Impression for Agitation and Aggression (CGI-S-A/A), and the MMSE.

At each visit, a geriatrician and a trained occupational therapist examined the patients. All study questionnaires were administered and completed on paper by the trained staff and answered by the patient's main caregiver (a family member or

a hired caregiver) on every visit and recorded to an electronic Case Report Form.

Statistical analysis

Sample size was calculated using the Power and Precision version 4 software (68), for a power of 80% and for two-sided α level of 0.05 to detect a difference in the proportion of successful reduction in CMAI scores between the investigational group compared to control at week 16. Success was defined as at least a 4-point reduction. For an expected difference of 35% in the proportion of success between the groups, an unbalanced sample of 42 and 22 was selected for the investigational and placebo group, respectively. Thus, 64 patients were randomly assigned to the investigational or control group (4 patients withdrew immediately after randomization, leaving 60 patients who started treatment to be included in the analysis). A 35% difference in proportion between the two groups was selected based on findings from an un-published report on the IP that was used to treat 14 patients with dementia-related behavioral disturbances.

The efficacy analyses were performed according to the intention-to-treat (ITT) principle, in order to provide unbiased comparisons among groups. The ITT analysis was done in all patients randomized and receiving treatment, with missing data imputation for patients who did not complete the trial (using last-observation-carried-forward method). We further performed a per protocol (PP) analysis (for 52 patients) as a sensitivity analysis, in which only patients who completed the trial according to protocol and had data available from all time points were counted toward the results. The primary outcome, CMAI reduction of >8 points and proportion of patients achieving 30% and 50% reduction in CMAI scores, were analyzed with the chi-square test including Yates' corrected chi-square (continuity correction).

The baseline CMAI distribution was tested for normality using the Kolmogorov-Smirnoff test. The Mauchly's Test of Sphericity was used to test whether the variances of the differences were equal. Baseline characteristics between groups are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Chi-square tests and independent *t*-tests were performed to compare groups for categorical and continuous baseline variables, respectively.

The GLM (general linear models) ANOVA Repeated Measures procedure was used to provide an analysis of variance for repeated CMAI measurements for nine visits on each subject. The analyses involve one within factor (time) and one between factor (groups). Changes over time and differences within groups were calculated (time*group), including contrasts tests to test differences among factor levels (1 factor, 9 levels), with a total significant level of 5%. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated [$\chi^2(35) = 353.4$, $P < 0.001$ for ITT and $\chi^2(35) = 299.4$, $P < 0.001$ for PP], meaning the F-statistic is positively biased rendering it invalid and increasing the risk of Type I error. To overcome this problem, we corrected the degrees of freedom using the Greenhouse-Geisser correction to obtain a valid critical F-value. The contrast was compared by method: difference, each level was compared to baseline. Analyses were performed on two full data sets (without missing data), the ITT set (n = 60) and the PP set (n = 52). In addition, the GLM test was performed again with a *post hoc* analysis based on the MMSE score to compare the change in CMAI in patients with higher or lower score than the median MMSE score.

Kaplan Meier survival analysis was performed to compute the time to achieve a CMAI ≥ 4-point reduction (success) for each group and the group difference was tested using the log rank chi-square test. Comparison of CMAI mean score between the two groups was analyzed by the independent *t*-test.

Comparison between groups in NPI-NH frequencies of all sub-categories (as dichotomous variables: yes/no) were analyzed by the Fisher's exact test for baseline and end of study. NPI-NH factors scores, total NPI-NH, and all other variables were tested by independent *t*-test. Frequency of AEs and medications consumption between the two groups was compared by using the Fisher's exact test.

Data were analyzed with IBM SPSS statistics software version 27.0 (SPSS Inc. Headquarters, Illinois, United States). Significance levels were set at 0.05.

Results

Of 67 patients screened for a possible enrollment, three patients were not eligible and four opted not to participate in the trial. Among the 60 randomized patients initiating treatment, the mean age was 79.4 ± 9.4 years; 36 (60.0%) were female and 52 (86.7%) completed 16 weeks of trial (**Figure 1**).

Upon enrollment, no meaningful differences were found. At baseline, all recruited patients presented MMSE scores of ≤ 25 (**Table 1**). In the repeated measures analysis, there was no difference in MMSE change from baseline to week 16 between the two groups (F = 1.58, P = 0.21). Overall, 32 of 40 participants in the investigational group (80.0%) and all participants in the control group completed the 16-week treatment. Two patients died of non-product-related causes. For the remaining six patients, attrition seemed due to personal and caregiver difficulties. AEs were not reported as a reason to leave the trial. At baseline, there were no statistically significant differences between completers and those who did not completed the trial.

Participants in the active and control groups consumed on average 14.9 and 17.9 drops per administration, respectively (44.7 and 53.7 drops per day, respectively)

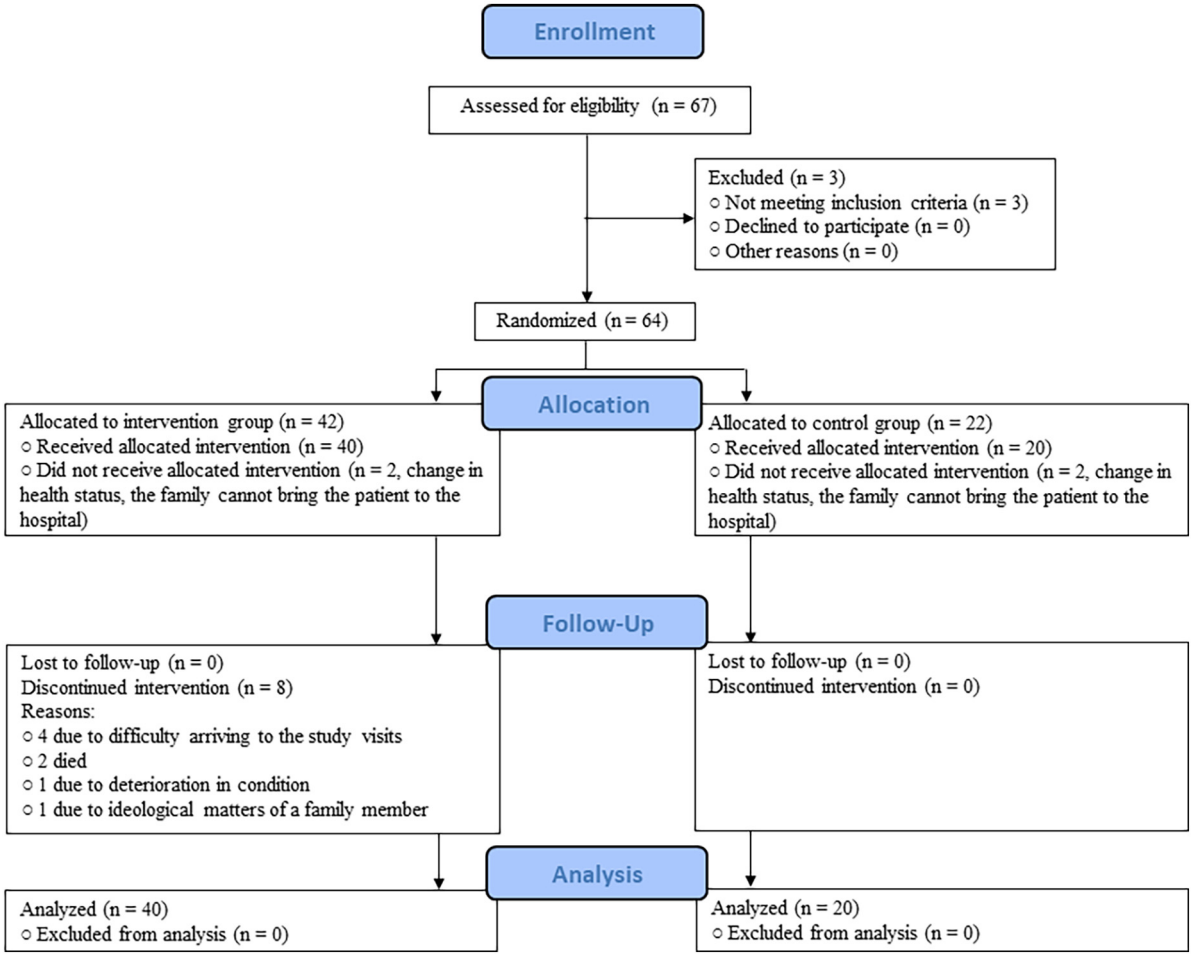

FIGURE 1
CONSORT diagram.

(Supplementary Figure 1). Mean CBD and THC consumption per administration was 175.8 mg and 7.4 mg, respectively (527.5 mg and 22.3 mg per day, respectively) (Supplementary Figure 2). Dose was not correlated with age (r = –0.17, P = 0.28) or with the outcome, both the change in CMAI (r = –0.23, P = 0.21), and the reductions of ≥ 4 point (t = 0.21, P = 0.83).

Primary outcome

The primary endpoint of the trial was the proportion of subjects achieving a CMAI ≥ 4-point decrease during the treatment period. For the ITT set, the proportions observed were 24/40 (60.0%) and 6/20 (30.0%) for investigational and control groups, respectively (χ^2 = 4.80, P = 0.03; with continuity correction χ^2 = 3.67, P = 0.06). For the PP set (52 completers), the proportions observed were 22/32 (68.7%) and 6/20 (30.0%) for investigational and control groups, respectively (χ^2 = 7.44, P = 0.006; with continuity correction χ^2 = 5.96, P = 0.01).

Secondary outcomes

The main hypothesis that the consumption of the IP will reduce behavioral disturbances and restlessness in older patients with dementia was tested by the CMAI reduction over time between groups (Figure 2). The CMAI baseline measures were slightly skewed, but we were unable to observe a significant skewed distribution when splitting into groups (Kolmogorov-Smirnoff P > 0.05). We compared the CMAI reduction from baseline to week 16 in both ITT and PP sets. Both demonstrate a significantly greater reduction in the investigational group, compared to the control group. In the ITT set, the reduction in CMAI scores at week 16 was of 10.7 ± 15.2 and 2.5 ± 9.4 points (t = –2.20, P = 0.03) for the investigational and control group, respectively. In the PP set, the reduction was of 13.3 ± 15.3

and 2.5 ± 9.4 (t = –2.85, P = 0.006) for the investigational and control group, respectively. The average CMAI score in the last visit for the investigational group was 44.03 ± 13.21. The CMAI aggressive behavior sub-score also showed significantly greater improvement in the investigational group compared to the control group (t = 1.30, P = 0.02 for the PP set). There was a statistically significant difference in the proportion of subjects who had a CMAI score reduction of ≥ 8 points at week 16: 20/40 (50%) and 3/20 (15%), respectively (χ^2 = 6.425, P = 0.011). To test the reduction of CMAI over time, we used two full data sets: an ITT set and a PP set of completers. The GLM ANOVA repeated measures over time of CMAI scores for the ITT data demonstrate a significant decrease over time in the multivariate test for both groups (within-subject effect F = 4.74, P = 0.001). Analysis demonstrated a significantly greater improvement in the investigational group compared to the control group, for tests of week 14 (F = 6.13, P = 0.01) and week 16 (F = 7.07, P = 0.01) compared to baseline. The same analysis for the PP data demonstrates a significant decrease over time (F = 6.45, P < 0.001) and with different reduction trends between the two groups (F = 3.18, P = 0.02). Results present a wide confidence interval; however, tests of difference between groups at week 14 (F = 4.83, P = 0.03) and at week 16 (F = 4.84, P = 0.03) were significantly different.

We tested whether patients with lower MMSE scores (14 and below) were different from patients with MMSE scores of 15 or higher in the CMAI change through time. We could not find a significant difference in either the entire group (F = 1.73, P = 0.12) or within the interventional group alone (F = 1.23, P = 0.33). For patients in the investigational group who achieved a ≥ 4-point decrease in CMAI (60.0%), it took a mean of 8.8 weeks (95% CI: 6.7–11.1 weeks), whereas patients who received the placebo and achieved a ≥ 4-point decrease in CMAI (30.0%) took 12.9 weeks (95% CI: 10.2–15.6). This difference was significant (log rank χ^2 = 5.19, P = 0.02).

Table 2 demonstrates the differences between groups in clinical parameter scores for completers at baseline and at the end of the trial. NPI-NH results demonstrate a significant reduction (29.4%) in agitation/aggression (χ^2 = 5.98, P = 0.01) and a significant reduction (22.5%) in sleep disturbances (χ^2 = 5.19, P = 0.03) in the investigational group compared to the control group, as well as a significant difference in the mean NPI-NH Agitation/Aggression factor score at week 16 (t = 2.01, P = 0.03). Chang was from 12.1 ± 5.8 to 6.7 ± 6.9 in the investigational group, and from 15.5 ± 7.8 to 11.4 ± 8.7 in the control group. There was no statistically significant difference in the GDS, PAINAD, CGI-S-A/A or MMSE questionnaires. An improvement of < 30% in CMAI total score was achieved by 24.3% of patients in the investigational group, and 10% in the control group (χ^2 = 0.94, P = 0.30). Similarly, an improvement of < 50% in CMAI total score was achieved by 8% of patients in the investigational group and 0% in the control group (χ^2 = 0.24, P = 0.54). The most improved behaviors of the CMAI questionnaire that improved in all patients in the investigational group included making physical sexual advances, throwing things, spitting, hurting themselves or others, tearing things or destroying property, intentional falling, eating/drinking inappropriate substances, and making verbal sexual advances.

There was no statistically significant difference in medications used between groups and over time, demonstrating stable medication consumption throughout the trial in both groups (Supplementary Table 2).

Adverse events

All withdrawals occurred in the investigational group. The reported reasons for withdrawals were: four patients discontinued treatment due to difficulty commuting to the study appointments (one patient completed baseline visit, two patients completed 2 weeks, and one completed 4 weeks); one patient left after 4 weeks due to the ideological concerns of her son; one patient withdrew after the baseline visit due to a deterioration in his condition (dialysis patient).

Thirteen SAEs included two deaths and eleven hospitalizations (Table 3). There were no significant differences in the occurrence of SAEs (9 and 4 in the investigational and control groups, respectively). The two deaths were in the investigational group. The first patient, 94 years old, suffering from colonic cancer and chronic renal failure, died from septic shock after completion of 4 weeks in the study. The second patient, 87 years old, experienced recurrent hospitalizations due to severe hyponatremia and anemia, for which he was recurrently intubated, and died from breathing difficulties (only baseline results were recorded). There was no statistically significant difference in the death rate between the two groups (active group 6.25% versus placebo group 0.0%, χ^2 = 1.28, P = 0.52). We did not see a direct link between the SAEs and the IP.

Sleepiness (48.6%), confusion and disorientation (45.9%), and decreased memory (32.4%) were the most frequent complaints among participants in the investigational group. No significant differences were observed in the occurrence of AEs between groups (Table 3). However, in the investigational group there were notably higher rates of decreased memory (χ^2 = 3.52, P = 0.06), hallucinations (χ^2 = 2.72, P = 0.08), sleepiness (χ^2 = 1.85, P = 0.17), and confusion and disorientation (χ^2 = 1.42, P = 0.18). No change in pulse or blood pressure were observed throughout the study.

Discussion

In this randomized placebo-controlled trial, we aimed to test the hypothesis that broad-spectrum rich CBD

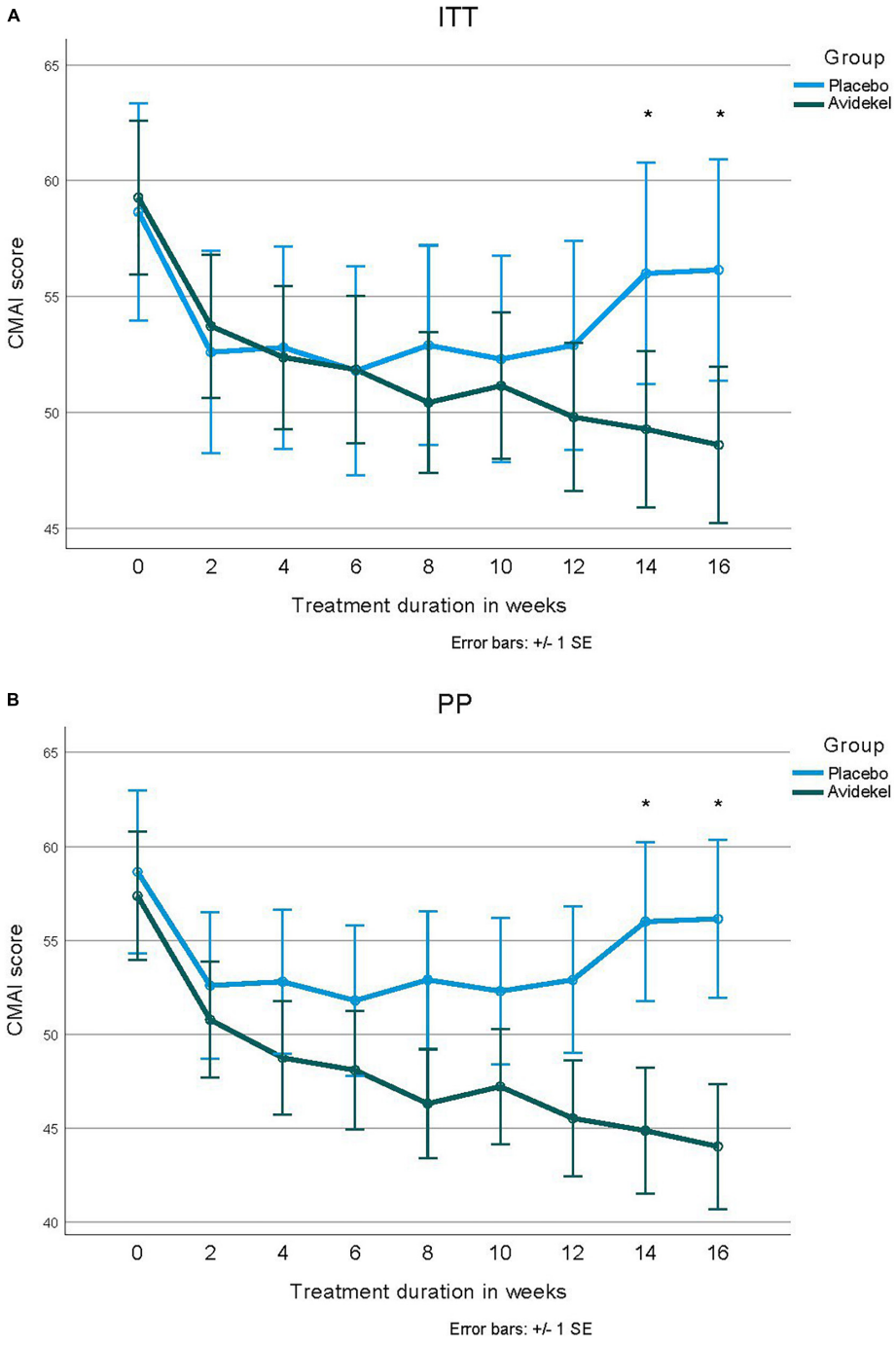

FIGURE 2
The Cohen-Mansfield Agitation Inventory score reduction over time between groups. Panels **(A,B)** present mean CMAI scores in the two groups, throughout the trial visits both in intention-to-treat analysis of all randomized patients that initiated treatment (n = 60), and per protocol analysis of patients who completed the trial according to protocol (n = 52). **(A)** Intention-to-treat analysis. **(B)** Per-protocol analysis.

medical cannabis oil differs from a placebo in alleviating behavioral disturbances in patients with dementia. Patients in the investigational group experienced a significantly greater reduction in sleep disturbances, and in agitation and aggression sub-score using two different measurement tools. The improvements were accompanied with non-serious side-effects.

Agitation CMAI scores decreased significantly in the investigational group over the course of treatment. Over the years, CBD has been suggested to have a positive clinical effect

TABLE 2 Effects on neuropsychiatric signs and symptoms for completers, at baseline and end of trial.

Variable	Baseline – week 0			End of trial – week 16		
	Avidekel (n = 32)	Placebo (n = 20)	P	Avidekel (n = 32)	Placebo (n = 20)	P
CMAI[1] Sub-cores, mean ± SD						
Aggressive behavior	14.0 ± 4.4	14.7 ± 5.0	0.60	12.0 ± 3.2	16.0 ± 8.6	0.02
Physically non-aggressive behavior	23.7 ± 9.1	22.9 ± 9.1	0.76	17.3 ± 7.4	21.0 ± 9.7	0.13
Verbally agitated behavior	19.7 ± 9.9	21.1 ± 10.4	0.63	14.7 ± 6.8	19.2 ± 10.6	0.07
CMAI total score, mean ± SD	57.4 ± 17.4	58.7 ± 22.3	0.81	44.0 ± 13.2	56.2 ± 25.5	0.03
NPI-NH[2] sub-categories, n (%)						
Delusion	16 (50)	9 (45)	0.78	6 (19)	6 (30)	0.35
Hallucinations	12 (38)	6 (32)	0.77	6 (19)	5 (25)	0.59
Agitation/Aggression	32 (100)	20 (100)	–	21 (66)	19 (95)	0.01
Depression/Dysphoria	24 (75)	15 (75)	0.26	18 (56)	9 (45)	0.43
Anxiety	21 (66)	14 (70)	0.89	14 (44)	11 (55)	0.43
Elation/Euphoria	2 (6)	7 (35)	0.02	2 (6)	2 (11)	0.61
Apathy/Indifference	25 (78)	14 (70)	0.53	21 (66)	14 (74)	0.55
Disinhibition	11 (34)	12 (60)	0.09	9 (28)	11 (55)	0.08
Irritability/Lability	25 (78)	15 (75)	0.87	21 (66)	13 (65)	0.96
Aberrant Motor Behavior	19 (59)	11 (55)	0.78	19 (59)	8 (40)	0.17
Sleep disturbances	21 (66)	15 (75)	0.55	9 (28)	12 (60)	0.03
Appetite and eating disturbances	18 (56)	10 (50)	0.78	9 (28)	8 (40)	0.37
NPI-NH Factors Scores, mean ± SD						
Agitation/Aggression	12.1 ± 5.8	15.5 ± 7.8	0.08	6.7 ± 6.9	11.4 ± 8.7	0.03
Depression	7.1 ± 4.8	8.0 ± 6.2	0.56	4.1 ± 4.7	5.8 ± 6.1	0.26
Psychosis	5.4 ± 7.3	3.4 ± 4.3	0.27	1.3 ± 2.3	2.7 ± 4.5	0.14
Psychomotor agitation	7.9 ± 6.3	9.1 ± 6.6	0.51	3.6 ± 4.1	6.5 ± 6.7	0.06
Apathy	8.7 ± 5.8	6.7 ± 5.1	0.21	5.8 ± 5.5	4.9 ± 3.8	0.52
NPI-NH Total score, mean ± SD	41.2 ± 18.4	42.5 ± 20.1	0.81	21.4 ± 16.9	31.2 ± 22.0	0.08
MMSE[3] Total score, mean ± SD	12.2 ± 6.3	15.2 ± 6.2	0.10	10.4 ± 6.8	13.7 ± 7.5	0.21
GDS[4] Total score, mean ± SD	5.5 ± 3.3	2.8 ± 3.1	0.01	4.9 ± 4.0	3.3 ± 4.4	0.18
PAINAD[5] Total score, mean ± SD	0.1 ± 0.4	0.1 ± 0.4	–	0.0 ± 0.0	0.1 ± 0.2	–
CGI-S-A/A[6] Total Score, mean ± SD	2.8 ± 3.5	2.9 ± 3.3	0.84	1.3 ± 2.4	2.0 ± 2.9	0.35

SD, Standard Deviation.
[1]CMAI – Cohen-Mansfield Agitation Inventory. Range and scaling: 29–203 points (29 meaning no symptoms). Analysis was performed on all patients.
[2]NPI-NH – Neuropsychiatric Inventory–Nursing Home Version. Range and scaling: 0–144 points (0 meaning no symptoms). Analysis was performed on all patients.
[3]MMSE – Mini–Mental State Examination. Range and scaling: 0–30 points (≤ 9 meaning severe cognitive impairment). Analysis was performed on 46 patients, 29 patients in the Avidekel group and 17 in the control group.
[4]GDS – Geriatric Depression Scale. Range and scaling: 0–30 points (0 meaning no symptoms). Analysis was performed on 42 patients, 26 patients in the Avidekel group and 16 in the control group.
[5]PAINAD – Pain Assessment in Advanced Dementia Scale. Range and scaling: 0–10 points (0 meaning no symptoms). Analysis was performed on 46 patients, 29 patients in the Avidekel group and 17 in the control group.
[6]CGI-S-A/A – Clinical Global Impression for Agitation and Aggression. Range and scaling: 0–10 points (0 meaning no symptoms). Analysis was performed on all patients.

in patients suffering from neurological conditions. It has been found to be effective in reducing anxiety (69), Parkinson's disease related symptoms (39), disruptive behavior, and other autism related symptoms (40). CBD has been also found to be effective as an anticonvulsant (41). There are no studies describing the effect of CBD on behavioral disturbances in dementia patients. Existing studies only tested THC and its analogs. In our study, 31% of patients in the investigational group reached the maximum dose allowed of 10.5 mg THC and another 15.6% reached 10 mg THC per administration; therefore, a direct effect of THC contributing to the decrease of behavioral disturbances cannot be ruled out. On the other hand, controlled studies with THC administration as a single active compound for the management of behavioral disturbances in dementia patients showed no significant decrease (66, 70, 71). Some pre-clinical studies demonstrated that the compounds in Avidekel work synergistically and that the combination of active ingredients in the IP is responsible for the observed effect. If this is the case, administering one component as an isolated material would not reproduce the same effect (72, 73). The difference in the average CMAI scores between groups only became significant at week 14, highlighting the importance of patience in the first few months of treatment based mainly on CBD.

In one study on the effects of antipsychotic drugs (74) on behavioral disturbances in dementia, the primary end point proportions in the antipsychotic group compared to the control resemble the numbers we received. In some other antipsychotics

studies using the CMAI tool (75–77), results were different, and they did not find significant improvement in agitation compared to placebo. There was an improvement in behavioral symptoms in 30% of patients in the control group. This improvement may be explained by the placebo effect and by the non-specific benefit of being enrolled in a trial (78), with thorough bi-weekly medical monitoring. In the NPI-NH, the results of our study demonstrate a significant reduction in agitation/aggression total scores and are close to the NPI-NH total scores obtained in the investigational and control groups from other antipsychotic drugs studies (74). Further investigation is required to explore rich CBD cannabis oil as a treatment option for agitation in patients with dementia, especially because the average CMAI score in the Avidekel group at 16 weeks was below the definition of clinically significant agitation.

Although the etiology of dementia-related agitation involves psychological and social components, it is often predominantly characterized by anatomical and neurochemical changes in the brain (79). In a review on the pharmacological treatment addressing the etiology of dementia-related agitation and aggression, pharmacological modulation of specific molecular targets was suggested as management options (80). Some of the proposed molecular targets are affected by CBD, which acts on more than 65 targets [for a review, see (81–83)]. The mechanisms of action underlying the direct and indirect effects of CBD on agitation involve the regulation of the serotonin 1A receptor, CB1Rs, the hypothalamic-pituitary-adrenal axis, anandamide, CB2Rs, and GABAA receptors (81, 82, 84). Animal models showed that chronic administration of CBD led to a reduction in inflammation and increased clearance of amyloid beta (85), while also reducing anxiety, depression, and stress-related behaviors (86).

TABLE 3 Patients experiencing adverse events[1].

Variable	Avidekel ($n = 37$)	Placebo ($n = 20$)	P
Serious adverse events, n (%)			
Hospitalization	7 (19)	4 (20)	0.74
Death	2 (5)	0 (0)	–
Adverse events, n (%)			
Decreased memory	12 (32)	2 (10)	0.06
Hallucinations	8 (22)	1 (5)	0.08
Sleepiness	18 (49)	6 (30)	0.17
Dry mouth	5 (14)	5 (25)	0.17
Confusion and disorientation	17 (46)	6 (30)	0.18
Fear	9 (24)	3 (15)	0.34
Restlessness	10 (27)	7 (35)	0.39
Blurred vision	4 (11)	1 (5)	0.41
Dizziness	6 (16)	2 (10)	0.47
Weakness	8 (22)	5 (25)	0.54
Red/Irritated eyes	2 (5)	1 (5)	0.61
Increased heart rate	3 (8)	1 (5)	0.65
Psychoactive effects	3 (8)	1 (5)	0.65
Headaches	3 (8)	2 (10)	0.66
Slurred speech	6 (16)	3 (15)	0.99
Decreased concentration	0 (0)	1 (5)	–
Other	21 (57)	9 (45)	0.29
Patients experiencing any adverse event	34 (91)	18 (90)	0.99

[1]The analysis was performed on an intention-to-treat population. In three patients, there were no visits after treatment initiation and side-effect reports were not available.

Sleep disturbances in the NPI-NH were significantly lower in the investigational group at week 16 compared to baseline. This finding is in line with the published literature demonstrating the positive effect of THC on sleep, in the context of different medical indications, both in controlled (87–89) and uncontrolled studies (45, 90–92). Similar results were found in controlled studies on a combination of THC and CBD (93–95). As for the effect of CBD on sleep, one study showed that CBD does not impair sleep (96), and several uncontrolled studies have shown that CBD improves sleep (69, 97). In this study, 49% of the investigational group reported drowsiness as a side-effect. The improvement in behavioral disturbances along with the reduction in sleep disturbances raises concerns regarding the anesthetizing characteristics of the IP. However, IP consumption does not appear to be related to increased apathy, as there were no differences between groups in NPI-NH apathy scores.

The treatment appears to be relatively safe. Common adverse events included sleepiness, confusion and disorientation, restlessness, fear, weakness, and hallucinations, among others. The safety profile of CBD cannabis oil appeared to be high in other studies as well (98, 99), including in pediatric populations (100–102). Although not statistically significant, the higher rates of decreased memory, sleepiness, and hallucinations in the investigational group should be further explored. It may indicate that the dose of 10 mg THC per administration for patients with dementia may be too high, even when combined with an increased presence of CBD. The occurrence of reported AEs in patients who discontinued treatment were not different from the rest of the cohort. Although we did not find a link between the IP and the study discontinuation, we cannot exclude the possibility that the IP might have a tolerability barrier.

Limitations

Our trial has several limitations. All eight patients who discontinued the treatment belonged to the investigational group and the sample size of 60 participants for our main outcome in an ITT analysis has a power of only 60%. The small number of participants, recruited in a single medical center, with no comparison between sub-types of dementia

(Alzheimer's disease, Lewy body and vascular dementia), made the study group highly heterogenous, providing limited ability to define the safety profile of the IP. However, heterogeneity, specifically in dementia patients, increases the importance of the results. Outcome measures did not include measures that would rule out functional impairment following treatment with a product containing THC, and pharmacokinetic indices of the IP were not collected in this trial. Although the GDS questionnaire has been shown to retain acceptable qualities when applied to older patients with dementia, it is a less sensitive questionnaire compared to the Cornell Scale for Depression in Dementia (103). Due to the limited availability of "Avidekel" in most countries, there is a lack in necessary research required to compare chemovars and to identify which specific compounds in "Avidekel" resulted in the superior effect "Avidekel" has shown over other chemovars in the clinic, with similar concentrations of THC and CBD. Subsequent research should also aim to identify new efficacious chemovars.

Conclusion

Our findings suggest that rich-CBD cannabis oil may alleviate agitation in older patients with dementia. One trial is not enough to make conclusions on the safety and efficacy of broad-spectrum CBD. We recommend conducting a large scale randomized controlled trial on behavioral disturbances related to dementia and to compare clinical sub-types of dementia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the principal investigator, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Laniado Hospital Ethics Committee (project LND 0111-16) and the Clinical Trials Department at the Israel Ministry of Health (project 20173138). The patients/participants provided their written informed consent to participate in this study.

Author contributions

VH and LB-L conceived the study, wrote the protocol, and drafted the manuscript. VH was the guarantor. All authors acquired, analyzed, or interpreted the data, and critically revised the manuscript for important intellectual content.

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Conflict of interest

LB-L and VL report employment at Tikun-Olam Cannbit Pharmaceuticals Ltd., with stock options in the company. LB-L reports consulting role with TO Pharmaceuticals LLC. As a consultant of the company, LB-L was registered as an inventor on a patent on the investigational product for behavioral disturbance in patients with dementia.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.951889/full#supplementary-material

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Neuroanatomical and neurocognitive changes associated with subjective cognitive decline

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Introduction: Subjective Cognitive Decline (SCD) can progress to mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia and thus may represent a preclinical stage of the AD continuum. However, evidence about structural changes observed in the brain during SCD remains inconsistent.

Materials and methods: This cross-sectional study aimed to evaluate, in subjects recruited from the CompAS project, neurocognitive and neurostructural differences between a group of forty-nine control subjects and forty-nine individuals who met the diagnostic criteria for SCD and exhibited high levels of subjective cognitive complaints (SCCs). Structural magnetic resonance imaging was used to compare neuroanatomical differences in brain volume and cortical thickness between both groups.

Results: Relative to the control group, the SCD group displayed structural changes involving frontal, parietal, and medial temporal lobe regions of critical importance in AD etiology and functionally related to several cognitive domains, including executive control, attention, memory, and language.

Conclusion: Despite the absence of clinical deficits, SCD may constitute a preclinical entity with a similar (although subtle) pattern of neuroanatomical changes to that observed in individuals with amnestic MCI or AD dementia.

KEYWORDS

Alzheimer's disease, subjective cognitive decline (SCD), structural magnetic resonance imaging, brain structural changes, subjective cognitive complaints

1. Introduction

The neuropathological onset of Alzheimer's disease (AD), the most common cause of dementia, may occur several decades before the emergence of clinical symptoms. Regarding cognitive impairment, the following cognitive stages have been proposed: cognitively unimpaired (CU, corresponding to a control group), subjective cognitive decline (SCD), mild cognitive impairment (MCI), and AD dementia.

Within the AD continuum, SCD has been proposed as a possible preclinical stage that includes a subset of CU individuals with normal performance in standardized cognitive tests

(adjusted for age, sex, and education), who report subjective cognitive complaints and who have an increased risk of future objective cognitive decline (1). SCD is characterized by two main criteria: (1) a self-experienced persistent decline in cognitive capacity, relative to a previously normal cognitive status, which is unrelated to an acute event; and (2) normal performance on standardized cognitive tests used to classify MCI, adjusted for age, sex, and education (1, 2). As the disease progresses, cognitive deficits arise and can lead to MCI, a syndrome in which cognitive impairment can be objectively measured by neuropsychological examinations (3), and daily life activities are preserved, although cognitive difficulty may have a mild functional impact on more complex activities of daily life (4).

In recent years, there has been growing interest in assessing the rate of conversion of people diagnosed with preclinical AD to dementia. It has been demonstrated that people with subjective memory complaints, but not objective impairment, are two times more likely to develop dementia than individuals without subjective memory complaints. The annual conversion rates in these individuals are 6.6% to MCI and 2.3% to dementia, compared with 1% in those without subjective memory complaints (5). Thus, the early detection of individuals at risk of converting to AD dementia will have important implications for the early prevention of cognitive impairment through the implementation of pharmacological and/or non-pharmacological interventions. SCD thus represents a pre-symptomatic stage of interest and in which it may be possible to identify early brain changes that emerge before the onset of clinical symptoms.

Neuroimaging techniques with high spatial resolution, such as structural magnetic resonance imaging (sMRI), enable accurate *in vivo* examination of subtle changes that may affect the brain structure of individuals with preclinical AD. Thus, Schwarz et al. (6) proposed the "AD signature index," a neuroimaging biomarker that covers brain regions that are highly vulnerable to displaying neurodegenerative changes related to AD dementia. Assessment of the AD signature in possible preclinical stages such as SCD is of interest for examining the potential association between SCD and the development of AD dementia.

However, sMRI studies on SCD have reported inconsistent findings. Some studies have shown that individuals with SCD display a pattern of structural changes similar to those observed in subjects with amnestic MCI or AD dementia and involving medial temporal lobe (MTL, e.g., hippocampus, entorhinal cortex), frontal and posterior parietal regions (7–9), suggesting that SCD may represent a preclinical stage between normal aging and MCI. By contrast, other studies did not find any significant neuroanatomical differences between individuals with SCD and control subjects (10, 11), suggesting that microstructural changes in SCD may not be easy to detect.

These inconsistent findings have been attributed to several factors, including variations in study settings (community-recruited volunteers or participants from memory clinics), the use of different diagnostic criteria/methods of assessing SCD and differences in MRI strength and/or methodological approaches (e.g., voxel or surface based morphometry, manual or automatic segmentations) (12, 13).

Regarding the variations in study settings, it has been pointed out that, despite some common aspects, the pattern of neuroanatomical changes differs between SCD community-recruited volunteers and individuals with SCD who are recruited from memory clinics (13). Evidence from SCD-community samples indicates an AD-specific pattern of neurostructural changes involving MTL structures (e.g., hippocampus and entorhinal cortex) (14–17) as well as the temporo-parietal cortex (18–20). Individuals from SCD-clinical samples also exhibit neurostructural changes in MTL. In particular, it has been demonstrated that these individuals have reduced hippocampus volume (7, 21–26), although other studies did not replicate these findings (11, 27–34). Moreover, these subjects also have volume reductions and/or cortical thinning in the parahippocampus and the entorhinal cortex (28, 32, 33, 35), but again these findings have not been replicated in other studies (26, 34, 36, 37). In addition to these MTL neuroanatomical changes, there is evidence suggesting that SCD-clinical samples also display neurostructural changes that affect the frontal and parietal lobe as well as subcortical structures such as the thalamus, corona radiata and cholinergic basal nuclei (37, 38). Regarding the frontal and parietal lobe, it has been found that SCD-clinical samples have volume reductions in parietal and frontal lobe regions (21, 29), although these findings have not been replicated in other studies (34). Interestingly, direct comparison of SCD-community and SCD-clinical samples revealed more widespread structural changes in frontal, parietal, temporal (including hippocampus and parahippocampus) lobe regions and the bilateral insula in SCD-clinical samples (39, 40).

Another important factor contributing to the differences in findings is the difficulty in differentiating individuals with cognitive complaints who are undergoing normative aging from those in preclinical (41) stages of AD. In this regard, considering the recommendation by Jessen et al. (2) of the usefulness of "validated cut-off for classifying specific groups of individuals and for quantifying the severity of SCD in a research setting," Pereiro et al. (42) recently showed that considering a cut-off point in a questionnaire to assess the severity of SCCs, in addition to the two main diagnostic SCD criteria, improves the validity of prediction of progression from SCD to MCI and/or AD dementia (42). Regarding the neuropsychological assessment of SCD, Jessen et al. (2) also pointed out that comprehensive neuropsychological test batteries that assess multiple cognitive domains, for which age, sex, and education-adjusted normative data are available, are preferable to short psychometric tests with limited diagnostic accuracy (2). It is therefore possible that cognitive examination by use of comprehensive neuropsychological test batteries may be more appropriate than short psychometric tests for detecting subtle cognitive changes that may occur in preclinical stages such as SCD.

Finally, as mentioned above, another important source of variability in the findings reported in SCD-related literature may be at least partly due to differences in the neuroimaging methods used. It has been highlighted that, although voxel-based morphometry and surface-based morphometry are the most commonly used, other imaging methods such as manual segmentation of brain structures represents 21% of studies in both SCD-community and SCD-clinical samples (13). By comparing the hippocampal findings obtained using different neuroimaging methods and reported in the SCD literature, Pini and Wennberg (13) concluded that voxel-based morphometry may be more sensitive than manual segmentation for detecting atrophy in the earliest stages of dementia and therefore that these procedures may reveal more consistent evidence regarding gray matter (GM) differences in the hippocampus, a critical region in AD dementia.

Taking all of the above considerations into account, the present study is intended to evaluate the neurocognitive and neuroanatomical

changes in clinical sample of individuals who meet the two main diagnostic criteria for SCD, as proposed by the SCD-initiative (SCD-I) Working Group (1), relative to a group comprising control individuals, by extensive neuropsychological evaluation and validated sMRI procedures, respectively. The specific aims were to evaluate the following: (1) between-group differences in gray/white matter volume and cortical thickness; and (2) structural changes in the AD signature index proposed by Schwarz et al. (6). Considering previous findings, we hypothesized that, relative to the control group, individuals with SCD would display reduced volume and cortical thinning in MTL structures, parietal areas and frontal brain regions.

2. Materials and methods

2.1. Participants

The study included 98 individuals over 50 years old (73 women and 25 men), already participating in the Compostela Aging Study (CompAS) and recruited between June 2016 and January 2018. The CompAS is an ongoing longitudinal project (43) which has as its general objective the early detection and progression of cognitive impairment in patients aged + 50 years attending Primary Care Health Centers in Galicia (an autonomous community in NW Spain) with subjective cognitive complaints (SCCs). To date, the CompAS is composed of two cohorts. The first (from 2008 to 2014) included 878 individuals as eligible participants, of which 435 were excluded on the basis of the following exclusion criteria: prior diagnosis of depression or other psychiatric disturbances, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (44); prior diagnosis of neurological disease, including probable AD or other types of dementia, according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (45) and DMS-5 criteria (44); previous brain damage or brain surgery; previous chemotherapy; prior diagnosis of diabetes type II; sensory or motor disturbances; and consumption of substances that might affect normal performance of the tasks. The second cohort is composed of 505 eligible individuals, 178 of whom were excluded according to the exclusion criteria. The participants of the current study belong to the second cohort.

Participants gave their written informed consent prior to taking part in the study. The research project was approved by the Galician Clinical Research Ethics Committee (Xunta de Galicia, Spain) and was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki (46). Ninety-two participants were right-handed, three were left-handed and three were ambidextrous, as evaluated by the Edinburgh Handedness Inventory (47). All participants had normal audition and normal or corrected-to-normal vision.

2.2. Neuropsychological assessment

The participants underwent clinical, neurological and neuropsychological examination conducted respectively by general practitioners, cognitive neurologists and psychologists specialized in aging and dementia. The Spanish version of the Mini Mental State Examination (MMSE) (48) was administered to all participants in order to evaluate their general cognitive functioning, and the Spanish version of the Geriatric Depression Scale (GDS-15) (49) was administered to evaluate depressive symptoms (50). Other clinical instruments frequently used to assess the early cognitive manifestations of AD and other types of dementia were also administrated. Most of these instruments have been used to diagnose impairments in several domains or cognitive processes in MCI (2, 51–54). To evaluate attentional processes, we included the Trail Making Test A (55), which assesses attentional visual-perceptive searching and perceptive-motor processing speed, and the Attention and Calculation CAMCOG-R subscale (Cambridge Cognitive Assessment-Revised) which assesses attentional control (56). In order to assess executive functioning, we used the Trail Making Test B (55), which evaluates working memory and cognitive flexibility (57), the Phonological verbal fluency test (say words starting with "p" in 1 min), which assesses working memory and inhibition (58), and the Executive Function CAMCOG-R subscale, which assesses abstract thinking and categorization. For memory processes, we used the List A Total Recall (immediate memory of words), the Long-Delay Free Recall (long term verbal memory of words) from the California Verbal Learning Test (CVLT) (59; Spanish version by 60) and the Memory CAMCOG-R subscale, which together give a joint measure composed by short delay visual memory for objects and recognition, and recent and remote memory. To evaluate language processes, we included the Boston naming test (BNT) (61), the Spanish version of the Semantic verbal fluency (animals) (58) and the Language CAMCOG-R subscale, which together provide a joint measure of oral comprehension, repetition, naming, and reading comprehension. The Lawton and Brody Index (maximum possible scoring = 8) was used to evaluate Instrumental Activities of Daily Living (IADL) (62).

2.3. Assessment of SCCs and diagnosis of SCD

To evaluate the severity of SCCs, we used a short Spanish version of the Questionnaire for Subjective Memory Complaints (QSMC) (63, 64). This version comprises 7 items each scored on a Likert scale ranging from 1 to 5 (maximum score 35) and was administered to participants and to a family member to assess prospective and retrospective forgetfulness, distractions and difficulties in lexical access and spatial orientation. The QSMC items were as follows: (1) "Do you forget where you left your things?"; (2) "Do you forget names of people you just met?"; (3) "Do you forget names of close relatives or friends?"; (4) "Do you often have a word on the tip of your tongue?"; (5) "Are you lost in familiar places where you have been before?"; (6) "Are you lost in unfamiliar places where you have been a few times?"; and (7) "Do you forget things you planned to do?" The reliability of this QSMC short version, tested in participants from the first cohort of the CompAS (N = 878) was 0.69 (Cronbach's alpha) for patient score and 0.78 for informant scoring. The cut-off point, which corresponds to the 5% percentile of the total QSMC scoring adjusted for age, has been shown to be a valid measure of SCC severity to predict progression from SCD to MCI and dementia (predictive validity values: Sensitivity = 0.56;

Specificity = 0.95; Accuracy = 0.86; NPV = 0.82) and from MCI to dementia (Sensitivity = 0.89; Specificity = 0.87; Accuracy = 0.88; NPV = 0.94) (42).

Study participants were classified according to clinical, neurological and neuropsychological data as SCD (n = 49) or Control (n = 49), at a special meeting of the research team. Participants were diagnosed as SCD when they met the two main criteria proposed by the SCD-initiative (SCD-I) Working Group (1, 2): (1) self-experienced persistent decline in cognitive capacity, especially in memory, relative to a previously normal cognitive status, which is unrelated to an acute event; and (2) normal performance in standardized cognitive tests used to classify MCI, adjusted for age and education. For the first criterion, we asked the participants if they were worried about their failures in attention and memory in the last few years, and we asked the informants for confirmation (or otherwise) of the yes/no answers. In addition, to determine whether the level of SCCs was higher than in other people of the same age, we established the 5% percentile of the total QSMC scoring (patient) adjusted for age as cut-off point. Participants who reported SCCs but did not fulfill the previous SCD criteria and did not exhibit objective cognitive impairment in the neuropsychological tests, according to norms for aged and education, were categorized as controls. Both groups were matched regarding age, gender and years of education. Demographics and between-group differences in the neuropsychological measures (calculated by the corresponding analyses) are summarized in **Table 1**.

2.4. MRI acquisition and data analysis

For structural MRI analysis, a sagittal T1-weighted 3D-MPRAGE sequence (repetition time/echo time = 7.45 ms/3.40 ms, flip angle = 8°; 180 slices, voxel size = 1 × 1 × 1 mm, field of view = 240 × 240 mm^2, matrix size = 240 × 240 mm) was acquired with a Philips 3T Achieva scanner (Philips Medical System, Best, The Netherlands), in the University Hospital Complex, Santiago de Compostela, Galicia (Spain).

In order to evaluate differences in gray matter (GM) and white matter (WM) volume between groups, a voxel-based morphometry analysis was conducted in Matlab R2016a by using the Computational Anatomy Toolbox[1] implemented in the Statistical Parametric Mapping software (SPM12[2]). After visual quality control, T1-weighted images were manually reoriented to the anterior-posterior commissure, segmented in GM and WM tissues (65) and normalized to the Montreal Neurological Institute space using a customized template built with the DARTEL toolbox (66). Normalized and modulated GM/WM images were then spatially smoothed with a Gaussian kernel of 8 mm Full Width at Half Maximum (FWHM).

Statistical analyses were conducted using the General Linear Model (GLM) approach, and between-group analysis was performed *via* two sample t-tests including the total intracranial volume and the GDS scores as covariates (the SCD group displayed higher depressive symptoms, but below the 5–7 cut-off score for mild depression, see **Table 1**). Statistical analyses were conducted considering the whole brain as the volume of interest. Finally, voxel-wise permutation testing (10,000 permutations) was conducted by the Threshold Free Cluster Enhancement (TFCE) method with the TFCE toolbox.[3] Results were considered significant at $p < 0.05$ Family-Wise Error (FWE).

Cortical thickness differences were evaluated by surface-based morphometry analysis, with FreeSurfer 6.0 software.[4] The automated default preprocessing pipeline was used for cortical reconstruction and volumetric segmentation (67, 68). The preprocessing pipeline included motion correction, skull stripping, transformation into the Talairach space, segmentation of cortical and subcortical GM/WM volumetric structures, intensity normalization, tessellation of the boundary between GM and WM, and topology correction. A quality control protocol was conducted over the FreeSurfer segmentations with the Freeview program. FreeSurfer segmentations were visually inspected on a slice-by-slice basis by an experienced technician, to enhance the reliability of the cortical thickness measurements. Pial surface misplacement errors that included meninges and the skull were manually corrected in all subjects. Moreover, erroneous white matter segmentation due to intensity normalization errors was fixed in seventy-four participants by using control points. All manual editions were conducted following the technical instructions included in the Freeview Guide.[5] Final segmentations were supervised by a senior researcher (SGA). Between-group analysis was performed by a GLM including the GDS scores as covariate and applying a Monte Carlo simulation to correct for multiple comparisons with 10,000 iterations, a cluster-forming threshold set at $p < 0.005$ and a smoothing kernel of 15 mm FWHM. Additionally, p-values were adjusted for both hemispheres applying the Bonferroni correction, and results were considered significant at $p < 0.05$.

A follow-up ROI analysis was performed over MTL. Hippocampal subfields were automatically segmented with FreeSurfer (69). The following volume measurements were visually inspected before being exported: whole hippocampus including head, body and tail; the parasubiculum; the head and body of the presubiculum, subiculum, CA1, CA3 (CA2 is included in CA3), CA4, granulate cell of the molecular layer of dentate gyrus, hippocampal molecular layer, hippocampal fissure, fimbria and the hippocampus-amygdala transition area. The entorhinal cortex and parahippocampal gyrus volume and all hippocampal subfield volume measurements were adjusted using the estimated total intracranial volume (eTIV) by the residual approach: adjusted_volume = volume_observed–b × (eTIV–mean_eTIV), where mean_eTIV is the average eTIV of all subjects, and b is the coefficient of regression between the observed volume and the eTIV. In comparison with other approaches, the residual adjustment method proved optimal for discriminating between Control subjects and individuals with AD dementia and also between individuals with MCI and patients with AD (70). Between-group analysis was performed using a multivariate GLM including Group as the fixed factor, the adjusted volume measures as dependent variables and the GDS scores as covariate. The Bonferroni method was used to correct for multiple comparisons, and the significance level was set at $p < 0.05$.

Finally, the AD signature index was computed by averaging the thickness estimates from the entorhinal cortex, inferior temporal

1 http://www.neuro.uni-jena.de/cat/

2 https://www.fil.ion.ucl.ac.uk/spm/

3 http://www.neuro.uni-jena.de/tfce/

4 http://surfer.nmr.mgh.harvard.edu/

5 https://surfer.nmr.mgh.harvard.edu/fswiki/FreeviewGuide

TABLE 1 Mean values and standard deviations (SD, in brackets) of demographic and neuropsychological measures in the control (cognitively unimpaired individuals) and the subjective cognitive decline (SCD) groups.

	Control *N* = 49	SCD *N* = 49	*p* = *	Cohen's d effect sizes
Age	65.80 (6.75)	68.12 (8.63)	0.140	0.30
Years of education	11.88 (5.26)	10.39 (5.11)	0.158	0.29
Gender (Female/Male)	38/11	35/14	0.487[a]	
GDS-15 score	2.49 (2.68)	3.63 (2.56)	0.033	0.44
Subjective cognitive complaints				
Patient	15.53 (2.24)	20.10 (1.99)	< 0.001	2.16
Informant-caregiver	14.00 (3.27)	16.03 (3.85)	0.006	1.20
General functioning				
MMSE	28.53 (1.69)	28.02 (1.56)	0.123	0.31
Attention				
TMT-A (seconds)	51.20 (26.91)	51.76 (20.83)	0.910	0.02
CAMCOG-R (Attention and calculation)	7.69 (1.61)	7.43 (1.37)	0.382	0.17
Executive function				
TMT-B (seconds)	132.78 (77.85)	137.94 (63.10)	0.719	0.07
Phonological verbal fluency (letter p)	14.59 (4.84)	13.12 (5.19)	0.150	0.29
CAMCOG-R (Executive function)	21.20 (4.21)	21.24 (11.43)	0.981	0.005
Memory				
CVLT (Long-delay free recall)	12.04 (2.29)	11.41 (2.39)	0.184	0.27
CVLT (List A immediate total recall)	53.06 (8.24)	50.82 (9.70)	0.220	0.25
CAMCOG-R (Memory)	22.61 (2.33)	21.74 (2.50)	0.075	0.36
Language				
BNT	50.82 (6.94)	50.33 (6.78)	0.725	0.07
Semantic verbal fluency (Animals)	20.10 (5.27)	17.39 (5.14)	0.011	0.52
CAMCOG-R (Language)	27.02 (2.00)	26.27 (2.36)	0.090	0.34
Instrumental activities of daily living				
IADL (Lawton and Brody index)	7.89 (0.36)	7.56 (0.91)	0.015	0.48

Two sample *t*-test; *$p < 0.05$. GDS-15, geriatric depression scale; MMSE, mini-mental state examination; TMT-A/B, trail making test (version A/B); CVLT, California verbal learning test; CAMCOG-R, Cambridge cognitive examination; BNT, Boston naming test; IADL, Lawton and Brody index; SCD, subjective cognitive decline. *a* = Chi squared test.

gyrus, middle temporal gyrus, inferior parietal lobe, fusiform gyrus and precuneus (6). Between-group differences in the AD signature index were evaluated using a univariate GLM including the Group as fixed factor, the AD signature index as a dependent variable and the GDS scores as covariate. Results were considered significant at $p < 0.05$.

3. Results

3.1. Between group analysis

The demographic data and results of the neuropsychological examinations are summarized in Table 1. There were no significant differences between the groups regarding age, years of education or gender, but, as expected, there were significant differences in the SCCs. Moreover, there were no significant differences in any cognitive test except in one neuropsychological language test (Semantic Verbal Fluency test). Relative to IADL, both groups scored next to the maximum, but the control group scores were significantly higher than those of the SCD group.

Volume and cortical thickness data are summarized in Table 2 and illustrated in Figure 1. Relative to control subjects, individuals with SCD displayed significant reductions in GM volume in the triangular part of the inferior frontal gyrus, the orbital part of the middle frontal gyrus, the superior and middle frontal gyrus and the superior medial frontal gyrus of both hemispheres, the orbital part of the medial frontal gyrus of the left hemisphere, the bilateral anterior and the right middle cingulate cortex, and the left precentral/postcentral gyrus. Moreover, relative to the control group, the SCD group displayed reductions in WM volume in the left triangular part of the inferior frontal gyrus and the left precentral/postcentral gyrus, as well as cortical thinning in the left inferior and the right middle temporal gyrus, the left entorhinal cortex and the right lateral orbitofrontal cortex.

The follow-up ROI analysis revealed that, relative to controls, individuals with SCD displayed a significantly reduced volume in the left hippocampus tail, left head of the subiculum, right fimbria and right parahippocampal gyrus, as well as significant thinning of

TABLE 2 Brain regions showing significant differences in gray matter (GM) and/or white matter (WM) volume and cortical thickness in the between-group analyses.

	Combined peak-cluster level								
	Brain region	Cluster size	L/R	MNI coordinates			TFCE-FWE *p*-value		
				X	*Y*	*Z*			
Gray matter Control > SCD									
Volume	Anterior cingulate cortex	7390	R	16	46	19	0.018		
	Anterior cingulate cortex*		L	1	42	22	0.025		
	Midcingulate cortex		R	10	23	36	0.037		
	Superior medial frontal gyrus		R	7	42	37	0.038		
	Superior frontal gyrus		R	13	40	33	0.038		
	Middle frontal gyrus		R	27	34	36	0.038		
	Middle frontal gyrus	6792	L	−28	42	20	0.030		
	Middle frontal gyrus (orbital part)		L	−36	45	−8	0.037		
	Superior frontal gyrus		L	−27	54	2	0.039		
	Medial frontal gyrus (orbital part)		L	−14	56	−2	0.041		
	Superior medial frontal gyrus		L	−14	60	10	0.043		
	Inferior frontal gyrus (triangular part)	1519	R	41	22	15	0.033		
	Postcentral gyrus	1650	L	−54	−5	42	0.034		
	Precentral gyrus		L	−44	5	42	0.046		
	Middle frontal gyrus (orbital part)	569	R	33	50	−2	0.041		
	Inferior frontal gyrus (triangular part)	491	L	−47	16	31	0.041		
White matter Control > SCD									
	Inferior frontal gyrus (triangular part)	1142	L	−37	18	32	0.028		
	Postcentral gyrus	718	L	−42	−13	39	0.047		
	Precentral gyrus		L	−49	−5	49	0.048		
	Brain region	Cluster size (mm^2)	L/R	MNI coordinates			Max-log10(*p*-value)	CWp	Cohen's D
				X	*Y*	*Z*			
Control > SCD									
Thickness	Inferior temporal gyrus	1506.29	L	−46.8	−36.1	−23.6	4.59	0.0002	1.06
		842.93	L	−50	−63.8	−3.6	4.84	0.009	1.03
	Entorhinal cortex	848.82	L	−26.5	−9.3	−33.7	3.62	0.008	1.03
	Middle temporal gyrus	1236.69	R	57.4	−1.2	−28.1	5.21	0.0004	1.02
	Lateral orbitofrontal	708.99	R	30.8	33.5	−7.8	3.94	0.029	0.99

L/R, left or right hemisphere; MNI, montreal neurological institute coordinates; TFCE, threshold free cluster enhancement; FWE, family wise error; Max-log10(*p*-value), maximum-log10(*p*-value) at each cluster; CWP, clusterwise *p*-value; Cohen's D, effect sizes. *According to the Automated Anatomical Labeling (AAL) atlas, this coordinate ($X = 1$; $Y = 42$; $Z = 22$) is located in the left anterior cingulate cortex even though the x-coordinate is positive. However, other left coordinates of the anterior cingulate are also significant within this cluster.

the left entorhinal cortex and the right parahippocampal gyrus (see Table 3).

Moreover, between-groups comparisons revealed that the AD signature index was significantly lower ($p = 0.005$) in the SCD group (mean: 2.53; SD: 0.10) than in the control group (mean: 2.57; SD: 0.10).

4. Discussion

The present study aimed to evaluate neuroanatomical differences between individuals with SCD and control subjects. The results revealed that individuals with SCD showed subtle structural changes in similar brain regions to those observed in amnestic MCI and AD dementia including MTL, frontal cortex and parietal regions (7–9). These neurostructural changes are located in some regions with important functional roles in several cognitive domains such as executive function, attention, episodic memory and language.

The cognitive performance was generally similar in both groups. However, the SCD group performed the semantic verbal fluency test less well than the control group. This result is consistent with previous evidence of poorer performance in semantic verbal fluency measures in people with SCD relative to control subjects

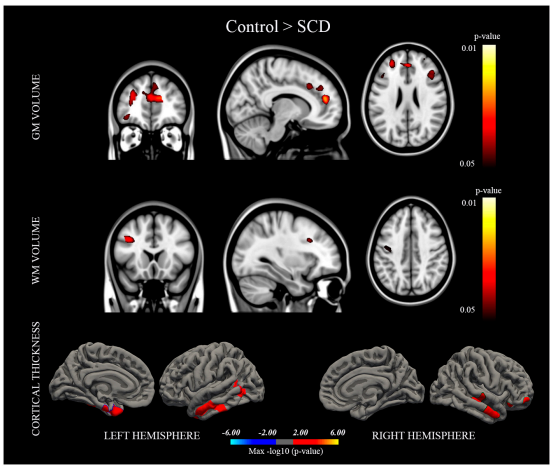

FIGURE 1
Brain regions in which the control group displayed significantly higher gray matter/white matter (GM/WM) volume and cortical thickness than the subjective cognitive decline (SCD) group. Results were considered statistically significant at $p < 0.05$.

(71). Moreover, the absence of extensive cognitive differences between the two groups was not unexpected. SCD has, by definition, been proposed as a possible preclinical stage of AD in which people display subjective cognitive complaints (SCCs), but in whom objective evidence of cognitive impairment is not usually detected by neuropsychological assessment (1). As Jessen et al. (2) pointed out, neuropsychological assessments for screening SCD are usually conducted using short psychometric tests with limited diagnostic accuracy. However, the use of comprehensive neuropsychological test batteries that assess multiple cognitive domains, and for which age, sex, and education-adjusted normative data are available (2) is preferable. We therefore hypothesized that the exhaustive cognitive assessment conducted in the present study would successfully detect the subtle cognitive differences revealed by the semantic verbal fluency test performance in the SCD group.

The need for accurate detection of neuroanatomical changes before the onset of extensive cognitive deficits in individuals with SCD highlights the importance of using techniques with high spatial resolution (e.g., sMRI) to locate early neurostructural changes in people with SCCs who are at risk of developing AD dementia. This, in turn, could be of interest in regard to implementing future non-pharmacological interventions aimed at preventing cognitive impairment. This is of particular importance if we take into account previous studies demonstrating, for example, that people with subjective memory complaints, but not objective impairment, are two times more likely to develop dementia than individuals without subjective memory complaints (5).

Several of the present study findings suggest that SCD may be related to neurophysiopathological changes that occur in AD. First, SCD participants displayed reduced cortical thickness in the AD signature index. This AD neuroimaging marker captures the cortical thinning of AD vulnerable regions and is therefore consistent with the brain atrophy characteristic of the early stages of AD onward (72). Atrophy in those regions including the AD signature is observed in MCI patients with presence of beta-amyloid deposits (6, 73, 74). Therefore, the results suggest that the psychometric criterion of SCC severity proposed by Pereiro et al. (42) for diagnosis of SCD may be appropriate for early detection of AD, consistent with the prognostic value of progression from preclinical and prodromal stages to AD dementia (42).

The present findings have indeed shown a pattern of neurostructural changes in the SCD group congruent with that described for AD (72). Within the MTL, brain changes were located in the hippocampal tail, the head of subiculum, the entorhinal cortex of the left hemisphere and also in the fimbria and the parahippocampal gyrus of the right hemisphere. Neurodegeneration of MTL is a characteristic feature in the etiology of AD dementia. According to Braak and Braak (72), the earliest presence of neurofibrillary tangle deposition takes place in MTL areas, including the entorhinal cortex, hippocampus and the parahippocampal gyrus. Moreover, MTL plays an essential role in episodic memory, the cognitive domain most affected in AD dementia. Previous studies aimed at evaluating structural changes in the hippocampus and its subfields revealed atrophy in CA1 and the subiculum subfields of individuals with SCD or AD dementia (7, 33). In addition to the hippocampus and the subiculum, structural changes also affected the entorhinal cortex, and the parahippocampal gyrus. Neurostructural changes in both MTL areas were observed in SCD (33) and in MCI and AD dementia (75, 76); in addition, these changes may represent a biomarker of progression in AD (77, 78).

Beyond the MTL, SCD individuals displayed cortical thinning of the left inferior and the right middle temporal gyrus. Synaptic loss in the inferior temporal gyrus has been demonstrated in amnestic MCI (79), and neurodegeneration in these regions is considered a good predictor of decline in conversion to AD dementia (80). Convit et al. (80) demonstrated that, together with some occipito-temporal areas (fusiform gyrus), the inferior and middle temporal gyrus are the neocortical regions that are first affected in the progression toward AD dementia. These researchers observed that structural changes in MTL, occipito-temporal areas and temporal regions may predict the decline of control subjects and individuals with MCI toward AD dementia.

Thus, in the light of these findings regarding the temporal lobe, the present results seem to indicate that SCD is associated with structural changes in regions of critical importance in AD etiology and with an essential role in episodic memory.

Regarding the frontal lobe, individuals with SCD displayed reductions in GM volume in the triangular part of the inferior frontal gyrus, the orbital part of the middle frontal gyrus, the superior and middle frontal gyrus and the superior medial frontal gyrus of both hemispheres, as well as in the orbital part of the medial frontal gyrus and the precentral gyrus of the left hemisphere. In addition, the SCD group displayed cortical thinning in the right lateral orbitofrontal cortex. These results are consistent with the findings of previous studies reporting structural changes in the frontal lobe of individuals with SCD (9, 29, 39).

We also observed structural changes in the bilateral anterior and the right middle cingulate cortex in individuals with SCD. Prior evidence suggests that, while the midcingulate cortex is functionally related to successful episodic memory retrieval (81),

TABLE 3 Mean values and standard deviations (SD in brackets) of the adjusted hippocampal subfields measures and the surrounding medial temporal lobe areas.

Brain region			Control *N* = 49		SCD *N* = 49		*p*		Cohen's D	
			Left	Right	Left	Right	Left	Right	Left	Right
Volume (mm^3)										
Hippocampus	Whole hippocampus		3106.63 (293.33)	3199.74 (297.82)	3024.21 (344.62)	3169.10 (346.94)	0.172	0.543	0.26	0.10
	Hippocampus	Head	1523.10 (158.68)	1600.42 (164.84)	1497.46 (197.21)	1590.13 (198.96)	0.435	0.715	0.14	0.06
		Body	1068.03 (106.79)	1081.15 (96.91)	1040.69 (118.82)	1068.35 (118.29)	0.205	0.455	0.24	0.12
		Tail	515.49 (60.80)	518.17 (69.59)	486.06 (66.79)	510.61 (58.64)	**0.016**	0.442	**0.46**	0.12
	Presubiculum	Head	133.50 (17.74)	128.09 (17.84)	126.89 (18.10)	126.68 (18.20)	0.069	0.679	0.37	0.08
		Body	148.44 (25.57)	135.30 (23.42)	141.50 (21.93)	130.09 (20.69)	0.179	0.247	0.29	0.24
	Subiculum	Head	177.57 (23.20)	178.72 (22.09)	167.83 (25.40)	175.75 (27.64)	**0.048**	0.516	**0.40**	0.12
		Body	223.61 (24.29)	221.21 (23.02)	215.47 (28.49)	217.39 (25.85)	0.134	0.328	0.31	0.16
	Parasubiculum		63.91 (14.44)	61.07 (11.17)	60.22 (13.88)	59.16 (13.85)	0.254	0.466	0.26	0.15
	CA1	Head	454.03 (48.14)	485.54 (49.74)	454.17 (60.99)	486.57 (62.94)	0.957	0.993	0.003	0.02
		Body	108.71 (19.89)	118.03 (17.67)	109.88 (22.92)	120.34 (22.38)	0.894	0.694	0.06	22.38
	CA3*	Head	105.03 (16.12)	116.98 (16.06)	106.23 (19.02)	117.40 (18.80)	0.831	0.958	0.07	0.02
		Body	75.97 (13.08)	86.94 (11.83)	77.85 (14.95)	89.90 (16.23)	0.661	0.385	0.13	0.21
	CA4	Head	110.57 (12.76)	119.67 (13.68)	110.73 (17.06)	119.49 (15.85)	0.919	0.872	0.01	0.01
		Body	107.70 (12.14)	112.29 (11.86)	105.63 (13.61)	113.46 (13.89)	0.401	0.695	0.16	0.09
	GC.ML.DG	Head	131.79 (16.31)	143.44 (17.12)	131.89 (21.34)	143.41 (20.34)	0.902	0.905	0.005	0.002
		Body	121.83 (14.57)	125.23 (13.33)	118.04 (15.16)	125.48 (15.37)	0.200	0.983	0.26	0.02
	Molecular layer HP	Head	294.13 (30.47)	309.50 (32.44)	287.92 (38.42)	306.59 (39.33)	0.350	0.631	0.18	0.08
		Body	201.90 (22.95)	207.35 (21.35)	195.00 (25.23)	204.63 (24.79)	0.137	0.483	0.29	0.12
	Hippocampal fissure		152.12 (25.10)	168.58 (22.16)	152.23 (25.32)	176.38 (29.68)	0.890	0.145	0.004	0.30
	Fimbria		79.87 (16.88)	74.80 (18.20)	77.31 (19.13)	67.08 (19.28)	0.422	**0.032**	0.14	**0.41**
	HATA		52.57 (10.16)	57.40 (10.42)	51.58 (9.65)	55.08 (11.25)	0.494	0.222	0.10	0.21
PHG			1930.67 (263.16)	1845.76 (234.86)	1880.51 (287.25)	1728.77 (190.88)	0.509	**0.005**	0.19	**0.55**
Entorhinal C.			1518.16 (260.16)	1560.71 (217.92)	1524.64 (272.26)	1569.70 (277.70)	0.865	0.699	0.02	0.04
Thickness (mm)										
PHG			2.63 (0.24)	2.56 (0.23)	2.58 (0.26)	2.48 (0.15)	0.354	**0.044**	0.20	**0.41**
Entorhinal C.			3.18 (0.27)	3.14 (0.32)	3.05 (0.34)	3.12 (0.35)	**0.009**	0.668	**0.42**	0.06

SCD, subjective cognitive decline; PHG, parahippocampal gyrus; Entorhinal C, entorhinal cortex; CA, cornu ammonis; GC.ML.DG, granule cell of the molecular layer of dentate gyrus; Molecular layer HP, molecular layer of the hippocampus; HATA, hippocampus-amygdala-transition-area; Cohen's D, effect sizes. *CA2 is included in the CA3 subfield. Regions in which the analyses revealed statistically significant between-group differences for the volume and thickness are highlighted in bold.

the anterior cingulate and the dorsolateral prefrontal cortex support retrieval monitoring, a control process that evaluates retrieval outcomes in relation to behavioral goals (82). Therefore, considering the functional relationship between frontal lobe and cognitive processes, such as attention, executive functioning and language (83), and the involvement of the cingulate system in the aforementioned cognitive control processes, the present results suggest that individuals with SCD display subtle changes that may affect the structure of brain networks supporting attention, executive function, language, successful episodic memory retrieval, and cognitive control processes (e.g., retrieval monitoring).

The SCD group also displayed reductions in GM in the left postcentral gyrus. Parietal lobe atrophy has been demonstrated in subjects with amnestic MCI or AD dementia (84, 85) and also in earlier stages, such as SCD (86). Considering that parietal lobe is highly interconnected with several brain areas, structural changes in this lobe may be related to the progressive neuropsychological decline in several cognitive domains (e.g., attention, memory, language, and executive function) commonly displayed by patients along the AD continuum (87).

There is evidence to suggest that, despite some common features, individuals recruited from memory clinics and who reported concerns about their cognition (SCD-clinical samples) displayed more widespread neurostructural changes involving frontal, parietal, temporal (including hippocampus and parahippocampus) lobe regions and the insula, relative to population-based cohorts (SCD-community samples) (39, 40). Structural changes in SCD-clinical samples have been attributed to comorbid mood disorder symptomatology that may be related to a more complex neurodegenerative pattern than that observed in SCD-community samples (13).

However, we evaluated a SCD-clinical sample recruited from Primary Care Health Centers, and none of the participants had prior diagnosis of any psychiatric disorder. Nonetheless, the SCD group displayed higher levels of depressive symptomatology. Depressive symptoms are commonly observed in individuals with SCD, and it has been shown that depression and SCD are independently associated with the risk of developing MCI and dementia, with hazard ratios of 1.4 and 2.0, respectively (88). Importantly, the co-occurrence of SCD and depression was associated with the highest risk (hazard ratio = 2.8) of developing a neurocognitive disorder within 7.2 years of follow-up (compared to 12.2 years in participants without depression or SCD) (88). These findings were recently confirmed in a nationwide longitudinal study (89). Therefore, considering that neither of the two groups had scores compatible with mild depression and that depressive symptomatology was included as a covariate in the sMRI analyses, the neurostructural differences observed in the SCD group could not be explained either by differences in the study setting or comorbid effects of mood disorder symptomatology in the SCD group. Thus, one possible explanation for the neurostructural changes displayed by the SCD group in frontal brain areas and also in other regions of critical importance in AD dementia (especially those included in the AD signature) may be related to structural changes occurring during progression from SCD to prodromal stages (i.e., MCI) and AD dementia.

The present study has some limitations that are worth noting. Its cross-sectional nature, together with the relatively small sample size, limits evaluation of the clinical trajectory and the neuroanatomical changes that may take place in a hypothetical progression from SCD toward MCI or AD dementia. Moreover, future studies should consider examining other AD biomarkers (e.g., CSF, PET or blood-based) that may reveal where participants are in the AD continuum. In addition, despite the absence of significant differences between groups regarding age and gender, only 25% of the study population were men. Future studies should evaluate the neuroanatomical and cognitive differences in larger and better matched samples with an equal proportion of males and females within each group to enable generalization of the results.

5. Conclusion

In summary, application of the diagnostic criterion of SCD using the levels of SCC severity proposed by Pereiro et al. (42) revealed that individuals with SCD have an objective, measurable pattern of subtle neurostructural and neurocognitive changes consistent with those reported in prodromal and clinical stages of the AD continuum. Structural changes were located in MTL, frontal and parietal areas with a critical role in several cognitive domains affected in AD dementia, including executive control, attention, episodic memory and language. Thus, the results emphasize the need to focus future research on preclinical stages (i.e., SCD) of the AD continuum to assess the prognostic value of the structural and neurocognitive changes observed. The early detection of these neurostructural changes before the onset of clinical symptoms may have important implications for the application of pharmacological and/or non-pharmacological therapies to prevent cognitive impairment in those individuals at risk of progressing toward AD dementia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Galician Clinical Research Ethics Committee, Xunta de Galicia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MR-F: methodology, formal analysis, writing – original draft, visualization, and manuscript revision. ML and SG-Á: conceptualization, methodology, investigation, visualization, supervision, project administration, and manuscript revision. MZ and FD: conceptualization, investigation, resources, supervision, project administration, funding acquisition, and manuscript revision. CL-S: investigation, formal analysis, and manuscript revision. AP: conceptualization, methodology, investigation, formal analysis, project administration, and manuscript revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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HomeCoRe system for telerehabilitation in individuals at risk of dementia: A usability and user experience study

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Background: Telerehabilitation has enabled a broader application of cognitive rehabilitation programs. We have recently developed HomeCoRe, a system for supporting cognitive intervention remotely with the assistance of a family member. The main goal of the present study was to determine usability and user experience of HomeCoRe in individuals at risk of dementia and in their family members. The association between subjects' technological skills and main outcome measures was evaluated as well.

Methods: Fourteen individuals with subjective cognitive decline (SCD) or mild neurocognitive disorder (mNCD) were recruited to participate in this pilot study. All participants received a touch-screen laptop implemented with the HomeCoRe software. The intervention consisted of 18 sessions and included a patient-tailored adaptive protocol of cognitive exercises. Usability was assessed in terms of treatment adherence and participants' performance across sessions; user experience *via* self-reported questionnaires and a descriptive diary.

Results: Usability and user experience were overall satisfactory and suggested usability, pleasantness, and high motivation while using HomeCoRe. Technological skills correlated only with the perceived ability to start and/or perform exercises autonomously.

Discussion: These results, although preliminary, suggest that the usability and user experience of HomeCoRe are satisfactory and independent of technological skills. These findings encourage wider and more systematic use of HomeCoRe to overcome the current limitations of in-person cognitive rehabilitation programs and to reach more individuals at risk of dementia.

KEYWORDS

usability, user experience, neurocognitive disorder, cognitive rehabilitation, telerehabilitation

Introduction

Mild neurocognitive disorder (mNCD) (1) is defined as a transitional status between normal aging and possible development of early dementia. It is characterized by subjective cognitive complaints and objective cognitive decline greater than expected for individual's age and education levels, but not interfering with activities of daily life. Subjective cognitive decline (SCD) is a condition referring to the self-perception of worsening cognitive abilities relative to a previous level of performance (2). Existing literature suggests that SCD individuals are at greater risk for dementia than older adults without SCD, as their subjective cognitive decline would in part reflect subtle impairment that has not yet reached the criteria for mNCD diagnosis (3). Given the limited effectiveness of pharmacological treatments in slowing cognitive symptoms in all these "at risk" individuals, cognitive rehabilitation techniques have gained increasing attention in recent years (4–6).

Cognitive rehabilitation can be delivered using traditional paper-and-pencil techniques or by means of more innovative computer-based solutions (7), this thanks to the development of Information and Communication Technologies. Computer-based solutions overcome some limits of traditional approaches, such as time, costs, and individuals' accessibility, to name a few (8–11). In fact, computerized rehabilitation uses engaging motivational cues and provides real-time feedback; task complexity and response time demands may change frequently during and across sessions, in accordance with individual performance. This allows avoiding over- or under-stimulation and providing more training time in areas of relative weakness. Computer support also saves time for therapists in the preparation of the exercises and allows to record all session parameters for further statistics (12). Telerehabilitation (TR) represents a further development of computer-based rehabilitation, providing assistance to individuals at risk of dementia on a large scale and directly at home (13, 14). In this regard, it is of particular importance that TR tools have a person-centered design, involving final users into the creation, design, and refinement of the software (15). To the best of our knowledge, the available evidence about usability and user experience (UX) associated to cognitive TR in the field of neurodegenerative diseases is still poor and heterogeneous (16–22). For instance, Isernia and colleagues (23) evaluated participants' experience with iHEAD, which is a telerehabilitation program for both motor and cognitive abilities in Chronic Neurological Diseases (e.g., Parkinson's disease, multiple sclerosis, and stroke). Jelcic (24) explored the feasibility of a lexical-semantic stimulation *via* TR in early Alzheimer disease.

Usability is defined as the degree to which a particular system can be used with effectiveness, efficiency, and satisfaction by users (25). It can be measured with objective parameters, such as number of completed tasks, time to complete the tasks, number of interventions made by the therapist, and number of errors (26). UX refers to the perceptions, beliefs, emotions, and preferences related to the utilization of the TR system (25). UX can be considered as a subjective dimension assessed by means of validated questionnaires and scales or by non-standardized tools (26). Taken together, usability and UX are used to evaluate the effectiveness of TR system and they should be preliminary assessed (27). A major issue in the field of normal and pathological aging is the lack of familiarity/life experience with advanced technology, which could determine difficulties in the autonomous management of digital devices (28–30). Therefore, it has been stressed the need of accessible and user-friendly TR platforms in aged populations. As consequence, duration and frequency of cognitive rehabilitation sessions need to be adjusted according to participant's characteristics (31) as well as adherence to treatment and outcome measures must be monitored by the therapist remotely (32).

In the last years, a cognitive rehabilitation (CoRe) software was implemented for an in-person cognitive training (33, 34). CoRe has been shown to be effective in restoring lost brain function and slowing degenerative diseases in early cognitive decline, compared with traditional interventions (35–37). In view of the willingness of treated participants to start/continue CoRe program at distance (38), we have recently developed a "home" version (i.e., HomeCoRe), able to provide a cognitive intervention directly at home (39, 40).

In the present study, we aimed at determining the usability and UX of the HomeCoRe system in individuals at risk of dementia. To this end, we recruited a sample of 14 individuals with SCD or mNCD. Treatment adherence and performances across the treatment sessions were used as usability indicators; UX was evaluated by means of both self-reported quantitative questionnaires and a qualitative session diary exploring personal experience while using the system. In particular, we considered the percentage of completed sessions as primary outcome, while the other usability and UX scores as secondary outcomes. The association between participants' technological skills and main outcome measures was evaluated as well.

Methods

Participants and study design

Fourteen individuals with SCD ($n = 4$) or mNCD ($n = 10$) were recruited from the IRCCS Mondino Foundation of Pavia. This number met the most common sample size requirement for a usability assessment (41, 42). See Table 1 for participants' characteristics.

Inclusion criteria were: (a) age >50 years; (b) education >5 years; (c) a diagnosis of SCD (2) or mNCD (1) based on clinical history, neurological and neuropsychological assessment; (d) clinical dementia rating (CDR) (43) score ≤0.5; and (e) mini-mental state examination (MMSE) (44) adjusted score ≥23.8. Exclusion criteria were the presence of sensory impairments and/or of motor functioning deficits in dominant upper limb. In general, participants were supported in the use of the device and software by a family member. In case they felt particularly independent, the involvement of the family member was not requested.

Individuals once enrolled underwent an in-person baseline assessment concerning clinical questionnaires and neuropsychological measures of about 90 min (T0) using the below-listed tests. Then, they were addressed to the HomeCoRe intervention program consisting in 18 remote at-home sessions (3 sessions/week for 6 weeks, each lasting approximately 45 min/day). Finally, at the end of the 6-week rehabilitation program, participants and family members underwent a final (T1) assessment evaluating usability and UX. We did not collect any neuropsychological assessment at T1, as we were interested in evaluating usability and UX data before carrying out an effectiveness study.

The study was approved by the Institutional Review Board of the San Matteo Hospital, Pavia, and it was carried out in compliance with the Helsinki Declaration. Written consent was obtained from all participants (and possible family members).

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TABLE 1 Participants' characteristics.

	SCD (*n* =4)		mNCD (*n* =10)		Total (*n* =14)	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Age in years	61.5	6.5	71.0	7.6	68.2	8.4
Gender (% female)	100	-	50	-	65	-
Years of education	12.2	3.7	12.2	4.6	12.2	4.3
CDR	0.0	0.0	0.4	0.1	0.3	0.2
IADL	8.0	0.0	7.8	0.6	7.8	0.5
BDI	16.2	7.1	9.4	6.9	11.4	7.5
SF-36 m	44.7	3.5	41.7	6.2	42.6	5.7
Sf-36 p	41.0	8.4	51.2	2.9	48.3	5.7
CRI-q	106.5	14.7	111.4	16.3	110.0	15.5
TS	2.5	1.0	2.2	1.3	2.3	1.3
MMSE	28.7	0.8	27.0	1.1	27.5	1.3
MoCA	22.0	1.4	21.1	3.3	21.4	2.9
DGS	4.7	0.5	4.5	0.9	4.6	0.8
CBTT	4.7	0.7	4.3	0.5	4.5	0.6
Verbal span	3.8	0.6	41.2	117.3	30.5	99.1
RAVLT-IR	3.2	0.9	1.2	0.9	1.8	1.3
RAVLT-DR	8.8	2.3	4.7	1.9	5.9	2.7
Logical memory	6.8	3.5	4.8	3.2	5.4	3.3
ROCF-delayed recall	19.1	4.8	11.9	5.2	13.9	5.9
RPM	29.8	5.8	30.1	4.6	30.0	4.7
FAB	15.5	1.5	14.6	3.0	14.8	2.6
TMTA	59.0	20.9	94.1	66.7	84.1	58.8
TMTB	65.0	35.5	224.6	198.3	179.0	181.9
Attentive matrices	44.2	8.3	45.3	6.4	45.0	6.6
FAS	31.3	8.6	32.7	10.1	32.3	9.4
SVF	33.0	2.7	34.0	6.1	33.7	5.3
ROCF-copy	34.2	2.0	31.3	4.5	32.1	4.1

SCD, subjective cognitive decline; mNCD, minor neurocognitive disorder; CDR, Clinical Dementia Rating scale; IADL, Instrumental Activities of Daily Living; BDI, Beck Depression Inventory; SF-36 m, Short Form 36 mental sub-dimension; SF-36 p, Short Form 36 physical sub-dimension; CRIq, Cognitive Reserve Index questionnaire; TS, Technological Skills; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; DGS, Digit Span; CBTT, Corsi's Block-Tapping Test; RAVLT-IR, Rey Auditory Verbal Learning Test immediate recall; RAVLT-DR, Rey Auditory Verbal Learning Test delayed recall; Logical Memory, logical memory immediate-delayed recall; ROCF, Rey-Osterrieth Complex Figure; RPM, Raven's Progressive Matrices; FAB, Frontal Assessment Battery; TMTA, Trail Making Test A; TMTB, Trail Making Test B; FAS, phonemic verbal fluency; SVF, semantic verbal fluency.

Assessment

See Table 2 for timing and the target user of each evaluation.

Clinical questionnaires and neuropsychological measures

- MMSE (44) and Montreal Cognitive Assessment (MoCA) (45) for cognitive screening
- Digit Span (DGS) (46), Corsi's Block-Tapping Test (CBTT) (46), Verbal Span (46), Rey Auditory Verbal Learning Test (RAVLT) Immediate and Delayed Recall (47), Logical Memory Immediate-Delayed Recall (48), Rey-Osterrieth Complex Figure (ROCF) (49), Raven's Progressive Matrices (RPM) (47), Frontal Assessment Battery (FAB) (50), Trail Making Test (TMT) part A and B (51), attentive matrices (46), and phonemic (FAS) (47) and semantic (SVF) verbal fluency (48) for neuropsychological evaluation
- Instrumental Activities of Daily Living (IADL) (52) for functional level
- Beck Depression Inventory (BDI) (53) for depressive symptoms
- 36-Item Short Form Health Survey questionnaire (SF-36) (54) for quality of life considering the mental and physical sub-dimensions
- Cognitive Reserve Index questionnaire (CRIq) (55) for cognitive reserve
- Self-reported evaluation of Technological Skills (TS) that participants think they had on a Likert scale with 0 (null), 1 (scarce), 2 (modest), 3 (good), and 4 (excellent) as possible answers.

Usability

- Percentage of completed sessions, completed tasks, and time spent to carry out the treatment as measures of adherence
- Overall "Weighted Score" (WS) (33), ranging from 0 to 100 (higher scores correspond to better performances), which is a unique value

TABLE 2 List of measures used in the study at baseline (T0; pre-treatment) and post-treatment (T1; final assessment at the end of the HomeCoRe rehabilitation program).

	T0	T1
Clinical questionnaires and neuropsychological measures		
Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA)	P	
Digit Span (DGS), Corsi's Block-Tapping Test (CBTT), Verbal Span, Rey Auditory Verbal Learning Test (RAVLT) Immediate and Delayed Recall, Logical Memory Immediate-Delayed Recall, Rey-Osterrieth Complex Figure (ROCF), Raven's Progressive Matrices (RPM), Frontal Assessment Battery (FAB), Trail Making Test (TMT) part A and B, attentive matrices, and phonemic (FAS) and semantic (SVF) verbal fluency	P	
Instrumental Activities of Daily Living (IADL)	P	
Beck Depression Inventory (BDI)	P, F	
36-Item Short Form Health Survey questionnaire (SF-36)	P	
Cognitive Reserve Index questionnaire (CRIq)	P	
Self-reported evaluation of Technological Skills (TS)	P,F	
Usability measures		
Total number of completed sessions		P
Total number of completed tasks		P
Total time spent for the whole treatment		P
Weighted score		P
User experience (UX) measures		
User Experience Questionnaire (UEQ)		P, F
System Usability Scale (SUS)		P, F
Patient Global Impression of Change (PGIC)		P
HomeCoRe User Experience questionnaire (HUXQ)		P, F
Descriptive session diary		P

P denotes measures administered to participants; F measures administered to family members.

summarizing participant's performance (see the "HomeCoRe intervention" section for more information).

User experience (UX)

- The User Experience Questionnaire (UEQ) (56) is a measure developed to investigate the subjective impression of users toward the UX of products. Several language versions were constructed and validated, including Italian[1]. It is a semantic differential questionnaire with 26 items consisting of a pair of terms with opposite meanings (e.g.: efficient/inefficient). Participants are asked to rate each item on a 7-point Likert scale from −3 (fully agree with negative term) to +3 (fully agree with positive term). The 26 items are arranged into six scales: Attractiveness (the product should look attractive, enjoyable, friendly, and pleasant, benchmark = 1.04 ± 0.64); Perspicuity (the product should be easy to understand, clear, simple, and easy to learn, benchmark = 0.97 ± 0.62); efficiency (I should perform my tasks with the product fast, efficient, and in a pragmatic way, benchmark = 1.06 ± 0.67); dependability (the interaction with the product should be predictable, secure, and meets my expectations, benchmark = 1.07 ± 0.52); stimulation (using the product should be interesting, exciting, and motivating, benchmark = 0.87 ± 0.62); novelty (the product should be innovative, inventive, and creatively designed, benchmark = 0.61 ± 0.72)
- The System Usability Scale (SUS) (57) is a tool used to quantify the satisfaction of a digital user experience. Scoring instructions of Brooke (57) were considered. The final score ranges from 10 to 100. A cut-off score of 68 indicates a satisfying level of technological system's usability
- The Patient Global Impression of Change (PGIC) (58) scale is a measure of perceived change in cognitive functioning, autonomy in daily activities, and quality of life after the rehabilitative treatment. Participants respond following the general stem "Compared to how you were before treatment" using the following symmetrical bipolar scale: (1) very much worse, (2) much worse, (3) minimally worse, (4) no change, (5) minimally improved, (6) much improved, and (7) very much improved
- The 8-item HomeCoRe User Experience Questionnaire (HUXQ) (Supplementary Table S1) is a measure created *ad-hoc* referring to other TR tools (23) to investigate specific issues experienced by participants and family members during the HomeCoRe program. Each item was scored on a 5-point Likert scale (0 = never, 4 = always). The questionnaire explores the following domains: Motivation (4 items, Cronbach's alpha = 0.73); Autonomy in the use of the device (2 items, Cronbach's alpha = 0.95); Inclusion in the routine (1 item); Technical problems (1 item). For each domain, the mean score is calculated. Given that negatively keyed items (item 3, 4, 5, 6, 7, and 8) have been reverted, higher scores reflect higher levels of user experience for that domain

1 www.ueq-online.org

TABLE 3 Description of HomeCoRe tasks.

Tasks	Description	Main involved skills
Learning of couples	Pairs of words are shown on the screen, the patient must rewrite the second word of the couple when it is shown in a different order.	Long-term memory abilities; learning and re-enactment strategies; visual imagery.
Word categorization	Words belonging to different categories are presented on the screen, the patient must rewrite them in any order but respecting the corresponding category.	Long-term memory abilities; learning and re-enactment strategies; visual imagery; categorical thinking.
Puzzle	The patient must recompose the tiles to form a figure, the whole figure in the simplest levels is shown at the beginning of the exercise.	Visuospatial long-term memory; visual imagery; mental representation and pianification.
Span backward	The patient must write the numbers in reverse order compared to how they were previously heard.	Verbal working memory; processing-speed.
Memory	Tiles that form pairs are shown on the screen, the tiles are turned and the patient has to choose two cards at a time to form all the pairs.	Long-term memory abilities; visuospatial abilities.
Visuospatial matrices	The patient has to store and represent in the correct order on the grid the spatial instructions received (for example up, down, left, right, etc.).	Working memory; visuospatial abilities; processing-speed.
Logical sequences	A sequence of images is shown, the patient must select, among several options, the one that completes the series.	Non-verbal reasoning; mental problem solving; decision making.
Image and sound	An image (small or big) is displayed and a sound (with low or high volume) is played; the patient must evaluate whether size and volume match.	Inhibitory control; processing-speed; working memory.
Unscramble the sentence	Scrambled words are displayed; the patient must select them in the right order to compose a sensible sentence.	Mental and verbal planning; conceptual abstraction abilities.
Unscramble the images	The patient must put the scrambled images in the right order to form a short story.	Planning of activities: problem solving; temporal sequencing; visual attention.
Find the elements	A matrix of random elements (letters or numbers) is displayed, the patient must identify and select all the requested ones.	Sustained and selective attention; visuospatial scanning; processing-speed.

- Participants were asked to fill in a descriptive session diary, to further gather the subjective impressions about HomeCoRe. In particular, they were stimulated to report any possible difficulty they experienced during each session.

HomeCoRe intervention

HomeCoRe is a research software tool developed within a long-lasting collaboration between clinicians and bioengineers. At the moment, the tool is limited to Italian speaking participants. The tool allows a patient-tailored intervention aimed to stimulate several cognitive abilities (e.g., logical-executive functions, attention/processing-speed, working memory, and episodic memory) through several sessions of cognitive exercises (see Table 3 for details). It is time-saving for the therapist, as it is ready to use and does not require a continuous manual setting of exercises for each training session. This is because once the therapist remotely set up the treatment plan according to the participant's cognitive profile (SCD or mNCD), the exercises are carried out in adaptive mode in all sessions. The treatment plan has a weekly structure, so it is repeated for 6 weeks. Each exercise could be carried out several times in each session, depending on the established plan and the level of difficulty achieved. Exercises are presented randomly and their duration could vary from 60 s to about 8 min, depending on the level of difficulty. In particular, during the dynamic generation of exercises, individual performance data are analyzed in order to set the appropriate difficulty level. Participant's performance data refer to the response accuracy normalized according to the number of aids that he/she has required to solve the task. For each exercise and each level, thresholds are defined to allow difficulty levels to progressively increase in order to stimulate neural plasticity (4, 59, 60). Hence, the system calculates an "overall weighted score" (WS), taking into account the correctness of the answers, the execution time, and the difficulty of the exercises. The score has a value ranging from 0 to 100 and is calculated with this formula: $WS = 25*P_{type}+25*P_{lev} + 25*P_{time}+25*P_{resp}$.

P_{type},P_{lev},P_{time}, and P_{resp} are specific scores (from 0 to 1) referring to:

- P_{type} = measures the complexity of the exercise calculated on the basis of the performance of healthy volunteers
- P_{lev} = DL/nDL
- P_{time} = (TT-TR)/TT
- P_{resp} = ACC.

Each of the variables reported in the formulas above has the following meaning:

- DL = difficulty level of the exercise
- nDL = maximum number of difficulty levels foreseen by the exercise
- TT = total time available to perform the exercise
- TR = response time
- ACC = accuracy ranging from 0 (wrong answer) to 1 (completely correct answer).

The WS informs the therapist about each participant's performance in a single value. Hence, WS represents a useful and advantageous index

that can be used to assess both the overall outcome of a training session and the global trend of the rehabilitation (see Figure 1).

HomeCoRe software architecture

HomeCoRe is installed on a touch-screen laptop (password protected and encrypted) that is supplied to the participant by the therapist. Before the beginning of HomeCoRe treatment, the participant and the family member have been trained together at the hospital on the use of the rehabilitation tool at home. This is in order to account for possible differences in baseline technological skills. Then, during the training sessions, participant (with the possible support of his/her family member) goes through each exercise of the treatment until he/she feels familiar with the use of the device. During the rehabilitative program, remote technical support is available when requested. To this aim, the participant is provided with the support team contacts as well as a specific text-messaging section is included in the interface. The treatment sessions can be paused in case of fatigue and resumed at a later time.

HomeCoRe architecture includes two main components, namely, therapist side and participant side, and a communication system (HomeCoRe Server). The therapist-side dashboard allows to remotely set and monitor all parameters of the treatment plan (e.g., frequency and duration of the plan, type of exercises, difficulty level). The interface of the participant is simple and it allows to view/execute the exercises of the day and to send the results to the therapist (see Figure 2).

The HomeCoRe system can be used online or offline, in the case that the Internet connection of the participant is not available. In the online mode, the communication between therapist side and participant side takes place automatically through a dedicated communication protocol managed by the HomeCoRe Server, while in the offline modality, some manual operations are required for loading the therapeutic plan and save results report on an external memory support (e.g., USB key or hard disk). The communication with the therapist is asynchronous.

Statistical analysis

Statistical analysis on quantitative outcome measures were conducted using SPSS software. Spearman's correlations were used for evaluating relationships between participant's technological skills and usability and UX measures. Wilcoxon signed-rank test was used for comparing WS scores across the intervention (session 18 vs. session 1). A $p \leq 0.05$, corrected for multiple comparisons if appropriate, was considered as significant.

We used a qualitative content analysis (61, 62) to evaluate subjective impressions recorded on session diary. Meaning units were identified and then condensed into themes (62). Revision of themes occurred until saturation was reached. A second coder reviewed coding and theme development for agreement.

Results

Participants' characteristics

Fourteen participants were enrolled in the study. They all successfully completed the 6-week intervention program. Eleven family

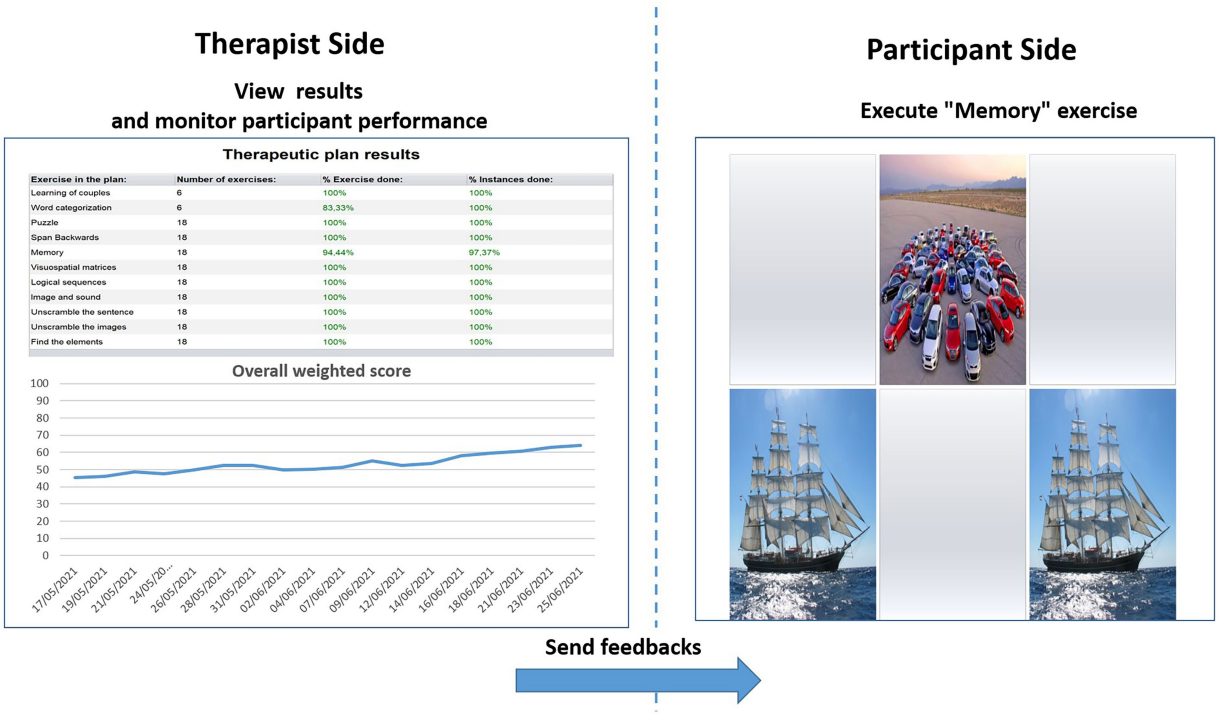

FIGURE 1
Therapist interface for monitoring performances in terms of weighted score (left) and interface of the participant for the execution of exercises (right). % Exercise done=the amount of exercises carried out until that moment; % Instance done=the number of times that a specific exercise has been performed as planned until that moment; the arrow with "send feedbacks" suggests that the difficulty level for the to-be-performed exercises (right) derives from the trend of treatment performance seen by the therapist (left).

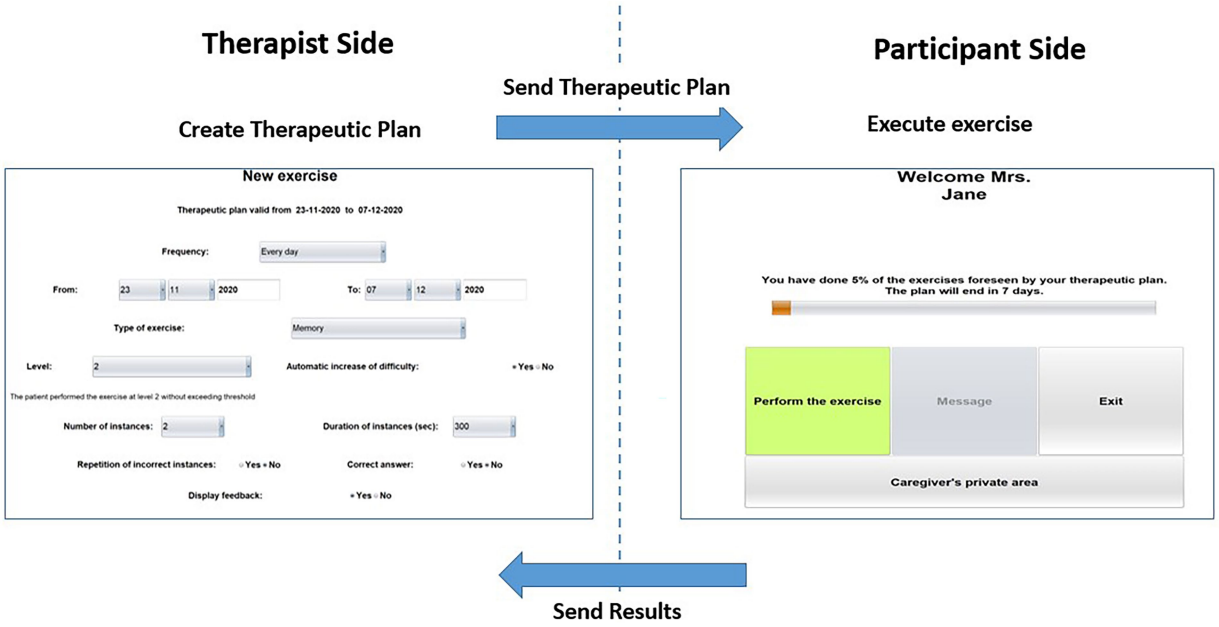

FIGURE 2
Home page of the therapist side of the interface for setting the requirements for the exercises plan (left) and home page of the participant side of the interface for HomeCoRe (right) in the offline and online modality.

TABLE 4 Means and standard deviations for usability indices (left panel) and correlations with participants' Technological Skills (right panel).

	Usability indices		Correlation with Technological Skills	
	Mean	SD	*r*	*p*
Treatment adherence				
Completed sessions (%)	96.1	7.3	0.27	0.34
Completed tasks (%)	94.5	5.5	0.44	0.12
Time spent for the treatment (hours)	14.2	3.7	−0.06	0.85
Weighted Scores				
Session 1	50.4	3.5	0.06	0.84
Session 18	59.2	6.0	0.25	0.38

members were involved in the study. Three individuals were without a family member because they did not need it, being very independent in the use of the device and software. The mean technological skills (range 0–4) was 2.1 ± 1.2 for participants and 2.4 ± 0.8 for family members.

Usability

Participants completed at least the 96.1 ± 7.3% of the scheduled sessions and the 94.5 ± 5.5% of the scheduled exercises (see Table 4). They spent 14.2 ± 3.7 h carrying out the 6-week treatment. Participants improved their overall WS performance at the HomeCoRe tasks at the end of the treatment (session 18 vs. session 1; $Z = -3.11$, $p = 0.002$) reporting an average WS of 50.4 ± 3.5 at session 1 and of 59.2 ± 6.0 in the last session of the treatment.

User experience

Participants

Participant' UX as resulted from self-reported questionnaires is reported in Table 5.

In all UEQ subscales, we obtained mean values corresponding to the benchmark interval for the excellent category. It means that participants had a good impression of both classical usability (efficiency = 3.6 ± 1.3; perspicuity = 3.1 ± 1.6; dependability = 2.8 ± 1.2) and user experience (attractiveness = 3.4 ± 1.1; novelty = 3.5 ± 1.4; stimulation = 3.6 ± 0.9) aspects.

As for the SUS (range 0–100), the mean total score was 86.1 ± 18.3, above the benchmark. Hence, participants perceived a good usability of HomeCoRe.

For the PGCI (range 1–7), participants' answers ranged between 3 and 6. The mean total score was 3.9 ± 1.0. Overall, individuals perceived an improvement in their cognitive status after the intervention with HomeCoRe.

For the HUXQ (range 0–4 for each domain), all domains obtained a mean score above 3, which means that participants reported to be highly motivated and autonomous in the use of HomeCoRe and in its inclusion in their daily routine, as well as they did not report particular technical problems.

For what concerns the treatment diary, we found 3 themes related to HomeCoRe criticisms: (1) study time for a specific task, i.e., time to process the stimuli presented by an exercise; (2) execution time, i.e., time for providing answers; and (3) task difficulty. Almost half of tasks did not present criticisms: *Word categorization*, *Memory, Logical sequences*, *Unscramble the sentence*, and *Find the elements*. By contrast, *Learning of*

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TABLE 5 User Experience assessed *via* self-reported questionnaires (means and standard deviations) for participants (left panel) and family members (right panel).

	Participants				Family members	
	Self-reported questionnaires		Correlation with Technological Skills		Self-reported questionnaires	
	Mean	SD	*r*	*p*	Mean	SD
UEQ						
Attractiveness	3.4	1.1	0.30	0.30	3.2	1.2
Perspicuity	3.1	1.6	0.07	0.80	3.0	1.2
Efficiency	3.6	1.3	0.06	0.84	3.1	1.7
Dependability	2.8	1.2	0.12	0.68	3.0	1.5
Stimulation	3.6	0.9	0.25	0.39	3.2	1.3
Novelty	3.5	1.4	0.36	0.20	3.3	1.7
SUS	86.1	18.3	0.54	0.051	88.2	12.3
PGIC	3.9	1.0	0.22	0.44		
HUXQ						
Motivation	3.1	0.6	0.41	0.15	2.6	0.7
Autonomy	3.1	1.4	0.71	0.004	2.8	1.5
Inclusion	4.0	0.0	-	-	2.5	0.8
Technical problems	3.5	0.6	−0.19	0.52	2.5	1.1

For participants is also reported the correlation with their Technological Skills. UEQ, User Experience Questionnaire; SUS, System Usability Scale; PGIC, Patient Global Impression of Change; HUXQ, HomeCoRe User Experience Questionnaire. *$p < 0.05$.

couples and *Span backward* resulted as particularly difficult for 64% ($n = 9$) of participants; whereas *Puzzle* and *Image and sound* were challenging for 29% ($n = 4$) of participants. Twenty-nine percent ($n = 4$) of participants reported concerns in terms of execution time for *Unscramble the images*, and of study time for *Span backward* and *Visuospatial matrices*.

Family members

For the UEQ, in all six scales we had mean values corresponding to the benchmark interval for the excellent category in both classical usability (efficiency = 3.1 ± 1.7; perspicuity = 3.0 ± 1.2; dependability = 3.0 ± 1.5) and user experience (attractiveness = 3.2 ± 1.2; novelty = 3.3 ± 1.7; stimulation = 3.2 ± 1.3) aspects.

As the SUS, all family members reported a final score 88.2 ± 12.3 which means that HomeCoRe usability was considered satisfactory.

For the HUXQ, all domains obtained a mean score above 2.5, which reflects that family members perceived a good level of motivation in their relatives in the use of HomeCoRe, as well as they did not report particular difficulties in including the treatment in their daily habits.

Correlation between technological skills and usability and UX measures

Technological skills correlated significantly only with HUXQ Autonomy domain ($p < 0.05$). We also found a tendency to significance for the correlation between technological skills and SUS scores ($p = 0.051$). No other significant correlations resulted between the score of technological skills and the indices of Usability and UX measures.

Discussion

TR represents a unique opportunity to guarantee constancy and continuity to cognitive rehabilitation at distance. Therefore, the proper development of TR programs and software in neurodegenerative diseases should result from an integrated view of their usability and UX. Unfortunately, in this field, these issues are poorly considered and rarely assessed (16–22). In the present pilot study, we aimed at measuring usability and UX of a cognitive TR intervention in individuals at risk of dementia. Preliminary assessment of their technological skills was performed in order to evaluate its correlation with usability and UX scores. This is because aging may be associated to difficulties in managing technological devices autonomously (28–30).

Interestingly, when considering the objective measurement of usability, including treatment adherence and WS values, we found a generalized good compliance to HomeCoRe coupled with a satisfactory efficiency of this system, which was not related to participants' level of technological skills. This result may stem from the fact that HomeCoRe was developed by clinicians based on the characteristics of individuals at risk of dementia (not healthy users) to provide a tool to be used in clinical practice. We also found that the total time for the treatment was about 14 h, which means that participants spent about 45 min per session. This result is in line with our previous experience with CoRe (35–37) in which we highlighted a very good adherence to the treatment when administered in hospital setting, where the dropouts were due to participants' medical conditions and not to the treatment itself. The adherence rate is a crucial issue for the home-based rehabilitation protocols (63). Individuals with neurodegenerative disorders that

could benefit from rehabilitation often do not adhere to a prescribed protocol once it is home-based due to the lack of familiarization with technology and computers (64–66) and to the loss of human interaction (67). The distinctiveness of TR systems such as HomeCoRe, by providing objective measures of the progress of the intervention and allowing remote monitoring and contact with the therapist, could be helpful in overcoming these limitations.

The UX was overall positive for both participants and family members. As regards participants, they expressed a good impression and satisfaction toward the product (data from the UEQ) and perceived usability of the HomeCoRe system (data from the SUS), which was also confirmed by their family members. In addition, feedbacks from the HUXQ suggested that participants considered HomeCoRe as particularly useful and enjoyable, were highly motivated, included the system in their routine, and were able to perform TR activities in autonomy without finding technical problems. From the family member side, some slight differences emerged at the HUXQ with respect to their relatives' answers. In particular, family members reported more technical problems while using HomeCoRe. However, they agreed in perceiving their relatives as motivated and autonomous and had no difficulty in including the treatment in their daily routines. Even if our UX data could be impacted by the risk of courtesy bias, we believe that the integration of these findings with those concerning the objective measurement of usability could support HomeCoRe as a satisfactory tool and then encourage its use for TR.

Correlation analysis highlighted a significant association between technological skills and the fact of being autonomous in performing HomeCoRe activities. This finding highlights the important role of the family member in supporting those individuals less skilled with technologies. In the future, it could be interesting to evaluate perceived technological skills across the intervention sessions in order to understand if they change while participants become more confident with the system.

Finally, we found that all participants reported a good perception of cognitive changes immediately after HomeCoRe intervention, as resulted from the PGIC, regardless of their technological skills. For what concerns the session diary, participants reported issues in performing some tasks and in the corresponding difficulty levels. Concerning this specific issue, it should be noticed that tasks duration and difficulty level were set as the same duration and level we generally used in the clinical setting (35–37). Consequently, it suggests that some little adjustments (e.g., extra time for training and performing some exercises) could be relevant in the TR session due to the lack of therapist feedbacks generally provided during in-person treatment. In addition, future studies exploring also the point of view of health care figures while using HomeCoRe may provide further insight into their experience. Despite the small sample size, the present results suggest that HomeCoRe could represent a useful and acceptable TR system for individuals at risk of dementia. This is important given the crucial role that technologies will play in future neurorehabilitation models. The availability of effective and feasible TR modalities is indeed critical to address the paucity of healthcare personnel dedicated to cognitive rehabilitation within the neuropsychology services, thus allowing to increase the offer to a wider number of participants. It should be noted that we enrolled participants aged above 50 years. This is because, in some cases, dementia-related impairment manifests prior to older adulthood and such a situation may underline different pathological processes (68, 69). The next step will consist in performing a RCT to explore the effectiveness of HomeCoRe in a broader context of neurocognitive disorders.

This study has some limitations. While the sample size is adequate for a usability study (41, 42), it is too small to draw definitive conclusions about the association of technological skills with outcome measures. Participants with poor familiarity with technological devices and without a compliant family member could be excluded by the use of TR, representing a selection bias for this kind of intervention (70). However, there is evidence about the possibility of using telemedicine devices in individuals with early cognitive impairment living alone, given that the compliance is strictly related to the level of monitoring remotely received (71). Our sample consisted of individuals with SCD and MCI who may have had memory problems that impaired their ability to provide a report about something that happened in the past (i.e., user experience indices). In this regard, it should be noted that we integrated UX measures with those provided directly by the system (i.e., usability indices) that could not suffer from this issue. Finally, our intervention lasted for 6 weeks. There are some evidences (66, 72, 73) showing that the level of adherence and compliance drop significantly after the first 3 months of TR. In any case, we believe that such a length of the intervention could be useful in order to avoid to stress participants and family members. In addition, it is important to consider the HomeCoRe architecture allows to customize and extend the treatment duration according to participants' characteristics.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: Zenodo; https://doi.org/10.5281/zenodo.7595576.

Ethics statement

The studies involving human participants were reviewed and approved by San Matteo Hospital, Pavia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SBe and SBo: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. SP and SQ: analysis and interpretation of data. AC, MP, and CC: participants' recruitment and data interpretation. SC, TV, and CT: critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1129914/full#supplementary-material

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Effects of the visual environment on object localization in posterior cortical atrophy and typical Alzheimer's disease

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Introduction: Visual processing deficits in Alzheimer's disease are associated with diminished functional independence. While environmental adaptations have been proposed to promote independence, recent guidance gives limited consideration to such deficits and offers conflicting recommendations for people with dementia. We evaluated the effects of clutter and color contrasts on performances of everyday actions in posterior cortical atrophy and memory-led typical Alzheimer's disease.

Methods: 15 patients with posterior cortical atrophy, 11 with typical Alzheimer's disease and 16 healthy controls were asked to pick up a visible target object as part of two pilot repeated-measures investigations from a standing or seated position. Participants picked up the target within a controlled real-world setting under varying environmental conditions: with/without clutter, with/without color contrast cue and far/near target position. Task completion time was recorded using a target-mounted inertial measurement unit.

Results: Across both experiments, difficulties locating a target object were apparent through patient groups taking an estimated 50–90% longer to pick up targets relative to controls. There was no evidence of effects of color contrast when locating objects from standing/seated positions and of any other environmental conditions from a standing position on completion time in any participant group. Locating objects, surrounded by five distractors rather than none, from a seated position was associated with a disproportionately greater effect on completion times in the posterior cortical atrophy group relative to the control or typical Alzheimer's disease groups. Smaller, not statistically significant but directionally consistent, ratios of relative effects were seen for two distractors compared with none.

Discussion: Findings are consistent with inefficient object localization in posterior cortical atrophy relative to typical Alzheimer's disease and control groups, particularly with targets presented within reaching distance among visual clutter. Findings may carry implications for considering the adverse effects of visual clutter in developing and implementing environmental modifications to promote functional independence in Alzheimer's disease.

KEYWORDS

posterior cortical atrophy, object localization, dementia, vision, clutter, reaching, environmental modifications, Alzheimer's disease

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is characterized by an insidious deterioration of multiple cognitive domains, including memory, language, executive function and visual processing. This deterioration is accompanied by a progressively diminishing capacity to carry out everyday activities independently (1, 2) which in turn is associated with institutionalization, increased carer burden and decreased quality of life for those living with the disease (3, 4). Visual processing deficits are common yet under-recognized consequences of AD and have been strongly associated with diminished autonomy, indeed more so than memory (5, 6).

Corticovisual dysfunction is a core feature of posterior cortical atrophy (PCA), a neurodegenerative syndrome most commonly associated with AD pathology (7, 8), which is characterized by a progressive decline in visuoperceptual and visuospatial abilities (9) and posterior parietal, occipital, and occipito-temporal atrophy (10, 11). In contrast to the predominantly memory-led presentation of typical AD (tAD), patients with PCA often demonstrate a variety of visual and posterior impairments while maintaining relatively spared episodic memory, language, executive functions and behavior (9, 12, 13); by comparison, patients with tAD exhibit deficits in visual function at later disease stages (14, 15). Examples of deficient visual processing in PCA and tAD include impairments in visual search behaviors (16–18), perceiving objects surrounded by visual clutter (2, 19, 20) and executing goal-directed reaching due to difficulties in localizing objects in relation to oneself (21, 22).

The physical environment may play an important role in managing the challenges that patients with PCA and tAD experience with everyday activities. For example, Dunne et al. (23) provided evidence that using high-contrast tableware increased liquid and food intake in patients with advanced tAD. Similarly, color and contrast adaptations are commonly cited as important approaches to supporting effective localization of signs, toilets and handrails in patients with tAD (24, 25), and we recently provided evidence of color contrast-based cues supporting navigation to destinations in a combined group of PCA and tAD patients (26). These findings invite the exploration of perceptual conditions that may support patients to carry out everyday actions such as localizing and reaching for objects. However, the evidence base for environmental guidance to support independence in dementia has been noted as weak or contentious (27–29). Of particular relevance to the current study are questions regarding whether the introduction of "landmarks" or objects intending to promote navigation, or to support reminiscence, in practice has adverse effects as "clutter." Notably, PCA patients commonly exhibit particular difficulties perceiving objects presented among visual clutter (19, 30), and Giovannetti et al. (1, 20) reported that patients with all-cause dementia made more object localization errors in the presence of clutter, especially when target and clutter were visually similar. This has prompted calls for more empirical research (27, 31).

The aim of the current study was to investigate the effects of visual clutter and color-contrast cues on object localization performance in patients with PCA and tAD, relative to healthy controls. Participants were asked to pick up a target object during two experiments (reaching from different standing positions; reaching from a seated position) conducted within a controlled real-world setting. The target was presented under varying conditions of clutter and position, with or without a color contrast cue. Our main hypotheses were that minimizing clutter and introducing a color contrast cue would reduce the time taken to pick up the target in both patient groups. A subsidiary hypothesis was that object localization deficits would be more apparent in PCA relative to tAD owing to the greater extent of corticovisual impairment.

2. Materials and methods

2.1. Participants

A total of 16 healthy controls, 15 PCA and 11 tAD patients took part in one or two experiments aimed at assessing the impact of visual clutter and color-contrast cues on object localization skills. PCA patients fulfilled consensus diagnostic criteria for PCA-pure (32) and tAD patients fulfilled research criteria for probable AD (33). Patients were recruited at the Dementia Research Centre and the National Hospital for Neurology and Neurosurgery London. Controls were recruited from a local database and did not have a history of neurological or psychiatric illness. Ethical approval for the study was provided by the National Research Ethics Service Committee London Queen Square and informed consent was obtained from all participants. Molecular pathology was available for 6/11 tAD patients and 7/15 PCA; all were consistent with AD pathology (positive amyloid scan on standard visual rating or CSF Aβ1-42 $\leq$ 450 and/or tau/Aβ ratio $>$ 1). Both patient groups underwent a battery of neuropsychological testing assessing general cognitive ability, early visual/visuoperceptual/visuospatial processing and verbal/non-verbal memory. See Tables 1, 2 for participant demographics and details of the neuropsychology assessments, respectively.

2.2. Experimental setting

The experimental setting was constructed at the Pedestrian Accessibility Movement and Environment Laboratory (PAMELA) at UCL. The setting consisted of an open room [4.8 m (D) $\times$ 4.8 m (W) $\times$ 2.0 m (H)] with an entry corridor and a table [60 cm (D) $\times$ 90 cm (W) $\times$ 74 cm (H)] on which both target object and distractor objects (clutter) were placed (Figure 1A). The target was a blue cup [94 mm (top outside diameter) $\times$ 56 mm (bottom outside diameter) $\times$ 155 mm (H)]; distractors were cups differing in size and color from the target (Figure 1B).

2.2.1. Experiment 1: Object localization from standing positions

2.2.1.1. Environmental conditions

Participants were standing in front of the table and asked to pick up the target object under the following environmental conditions:

1. Clutter: The target was presented among either 2 or 5 distractors (Figure 1Ci).
2. Cue: The target was presented either with or without a color contrast visual cue (21 cm $\times$ 30 cm yellow placemat) (Figure 1B).
3. Starting position: Participants were asked to pick up the target from one of four starting standing positions in front of the table: within reaching distance of the target (proximal—Figure 1Aiii),

TABLE 1 Demographic characteristics of participant groups.

	Control			PCA			tAD		
	#	M	± SD	#	M	± SD	#	M	± SD
Experiment 1									
N	16	–	–	15	–	–	11	–	–
Sex (F:M)	9:7	–	–	8:7	–	–	4:7	–	–
Age	–	67.0	± 6.4		68.7	± 6.3		68.9	± 6.5
MMSE (/30)	–	–	–	–	20.5	± 5.3	–	20.9	± 6.0
β-Amyloid PET/CSF consistent with AD*	–	–	–	7/7	–	–	6/6	–	–
Experiment 2									
N	14	–	–	7	–	–	6	–	–
Sex (F:M)	7:7	–	–	5:2	–	–	4:2	–	–
Age	–	67.0	± 6.3		69.0	± 9.3		66.0	± 2.7
MMSE (/30)	–	–	–	–	17.6	± 3.6	–	21.7	± 6.5
β-Amyloid PET/CSF consistent with AD*	–	–	–	4/4	–	–	3/3	–	–

Presented are number of participants (N), mean (M) and standard deviation (± SD) for experiment 1 and experiment 2. #: number or ratio; *positive amyloid imaging performed as part of another investigation or CSF Aβ1-42 $\leq$ 627 and/or tau/Aβ ratio $\geq$ 0.52. MMSE, Mini Mental State Examination (34) (maximum score shown in parenthesis); PCA, posterior cortical atrophy; tAD, typical Alzheimer's disease.

or approaching the target from a distance (from far left, right, or center of the setting; Figure 1Aiv).
4. Target position: The target was positioned on the near or far side of the table relative to starting standing positions (Figure 1Cii).

2.2.1.2. Procedure

Participants underwent two practice trials during which their dominant hand preference was determined. An Arduino-based timing system fulfilled the following functions: playing an audio signal indicating the start of each trial and recording the start of each trial at 1,000 Hz. Between each trial, participants' view of the setting was obscured by an occluding screen and participants were instructed to keep their hands by their sides. Trials were administered through a repeated-measures design such that each participant performed 32 trials, one for each combination of clutter (2 or 5 distractor cups); cue (not present/present); target position (near/far) and starting position (proximal/left/right/center). To control for order effects cue and clutter variables were arranged in four counterbalanced variants of a Latin square design with variants randomly assigned to each participant.

2.2.2. Experiment 2: Object localization from a seated position

A subset of participants from Experiment 1 (7 PCAs; 6 tADs; 14 healthy controls) took part in Experiment 2 (Table 1). Experiment 2 was conducted in the same experimental setting as Experiment 1.

2.2.2.1. Environmental conditions

Participants were seated within reaching distance of the target and asked to pick up the target under the following environmental conditions:

1. Clutter: The target was presented in isolation (no distractors) or among 2 or 5 distractors (Figure 1Di).
2. Cue: The target was presented with or without the same visual color contrast cue reported in Experiment 1 (Figure 1B).
3. Target position: The target object was presented centrally (body midline) or laterally (left or right) in near or far-reachable space, for a total of six positions (Figure 1Dii).

2.2.2.2. Procedure

Between each trial, the participants' view of the setting was obscured by a blind and the participants were instructed to keep their dominant hand on their lap. Trials were administered through a repeated-measures design such that each participant performed 36 trials, one for each combination of clutter (0, 2 or 5 distractor cups); cue (not present/present) and target position (1, 2, 3, 4, 5, and 6). To control for order effects cue and clutter variables were arranged in six counterbalanced variants of a Latin square design with variants randomly assigned to each participant.

2.3. Data collection

Completion time was defined as the time interval between the start of each trial and when the participant's hand first came in contact with the target object. An inertial measurement unit (IMU) mounted within the base of the target object recorded its movement at 75 Hz (Figure 1E). IMU threshold acceleration values were used automatically to calculate trial time based on detected target movement (automatically calculated trials: Experiment 1: 1,312/1,344 (97.8%); Experiment 2: 957/972 (98.5%)); the remainder were manually determined. A total of 12 trials were missing from Experiment 1 owing to three participants picking up a distractor rather than target object: two PCA (missing either 2 or 3 trials) and one tAD participant (missing 7 trials).

TABLE 2 Medians, interquartile ranges of neuropsychological scores and estimated performance relative to normative datasets for patient groups.

		PCA		tAD		Below 5th %ile	
	Max	Mdn	Q1–Q3	Mdn	Q1–Q3	PCA	tAD
Background psychology							
SRMT[a] (words)	25	21.0	19.3–23.0	18.0	15.3–18.0	2/14	7/10
SRMT (faces)	25	18.0	17.0–21.0	20.5	18.3–21.8	4/15	2/10
Concrete synonyms[b]	25	20.0	18.5–23.5	20.0	18.0–23.5	4/15	3/11
Naming (verbal description)	20	14.0	10.5–19.0	17.0	13.0–18.0	10/15	5/11
Cognitive estimates[c]	0	10.5	7.0–14.8	9.0	6.5–15.5	11/14	8/11
Calculation (GDA)[d]	24	1.0	0.0–3.0	6.0	0.5–13.0	8/11	4/10
Spelling (GDST)[e]	20	7.5	3.8–13.5	14.0	6.5–19.0	4/14	1/11
Reading (CORVIST)[f]	16	16.0	14.0–16.0	16.0	16.0–16.0	–	–
Gesture production	15	13.0	11.0–14.0	15.0	12.5–15.0	–	–
Digit span—forwards	12	5.0	4.0–6.0	7.0	5.5–8.0	5/15	3/11
Digit span—max forwards	8	5.0	4.0–5.0	6.0	5.5–7.0	–	–
Digit span—backwards	12	3.5	3.0–5.0	4.0	3.0–5.0	2/14	2/11
Digit span—max backwards	7	3.0	3.0–3.6	3.0	4.0–1.0	–	–
Early visual processing							
Figure-ground discrimination[g]	20	17.0	13.3–19.0	19.0	18.5–20.0	8/12	3/11
Shape discrimination (B1)[h]	20	15.0	13.0–18.0	20.0	19.5–20.0	–	–
Hue discrimination (CORVIST)	4	2.5	1.0–3.0	4.0	3.0–4.0	–	–
Crowding[i]	10	9.0	6.0–10.0	10.0	10.0–10.0	–	–
Visual acuity (CORVIST)	6/9	6/9	–	6/9	–	–	–
Visuoperceptual processing							
Fragmented letters (VOSP)[g]	20	2.0	0.0–10.5	19.0	17.3–19.8	11/11	2/10
Object decision (VOSP)	20	11.0	8.0–16.0	17.0	16.5–18.5	8/13	1/11
Visuospatial processing							
Number location (VOSP)	10	4.5	0.8–6.8	9.0	2.5–9.0	7/10	5/11
Dot counting (VOSP)	10	6.0	4.3–8.5	10.0	8.5–10.0	9/12	3/11
A-Cancellation (time)[j]	90s	90s	70.0–90.0	39.0s	26.8–42.6	13/14	7/11
A-Cancellation (items)[k]	19	10.0	1.1–13.5	0.0	0.0–0.5	–	–

Mdn, median; Q1–Q3: interquartile ranges; PCA, posterior cortical atrophy; tAD, typical Alzheimer's disease. [a]Short recognition memory test—joint auditory/visual presentation (35). [b]Concrete and abstract word synonym test (36). [c]General knowledge-based questions (37). [d]Graded difficulty arithmetic test (38). [e]Graded difficulty spelling test—set B first 20 items (39). [f]Cortical visual screening test (40). [g]VOSP, Visual Object and Space Perception Battery (41). [h]Oblong edge ratio 1:1.20 (42). [i]10 alphanumeric strings. [j]Completion time (43). [k]Number of items missed (43).

2.4. Statistical methods

For experiment 1, the full data analysis model was a linear mixed effects model for the log-transformed completion times. Completion times were log-transformed so that normality assumptions were not materially violated. All results were back-transformed (exponentiated) to permit interpretation of results as geometric means, ratios of geometric means (or percentage differences), and ratios of these ratios when making comparisons between two patient groups. The model was as follows.

$$\log_e(t_{ijk}) = \beta_{0i} + \sum_{h=1}^{6} \beta_{hi} u_{hijk} + b_{0ij} + \sum_{h=1}^{6} b_{hij} u_{hijk} + \varepsilon_{ijk} \quad (1)$$

$$\textit{with } b_{hij} \sim N(0, \sigma^2_{hi}) \textit{ and } \varepsilon_{ijk} \sim N(0, \sigma^2_i), \textit{ all independently} \quad (2)$$

where: t_{ijk} = time for the kth repeated measure for the jth participant in the ith group and the $u_{hijk} (h = 1 \text{ to } 6)$ are indicator variables for the environmental conditions (number of distractors, cue, target position and starting position (the latter has four values so needs three indicators)). For example, u_{1ijk} is an indicator variable taking the values 0 and 1 according to whether the kth repeated measure for the jth participant in the ith group involves 2 or 5 distractors (where $h = 1$ represents the distractor variable).

The β_{1i} are the group-specific distractor effects; the β_{2i} are the group-specific cue effects; the β_{3i} are the group-specific target position effects; and the β_{4i}, β_{5i}, β_{6i} are the group-specific starting position effects.

The b_{0ij} are random effects that allow for associations between pairs of measurements from the same participant. The b_{hij} $(h = 1 \text{ to } 6)$ are random effects that allow these associations

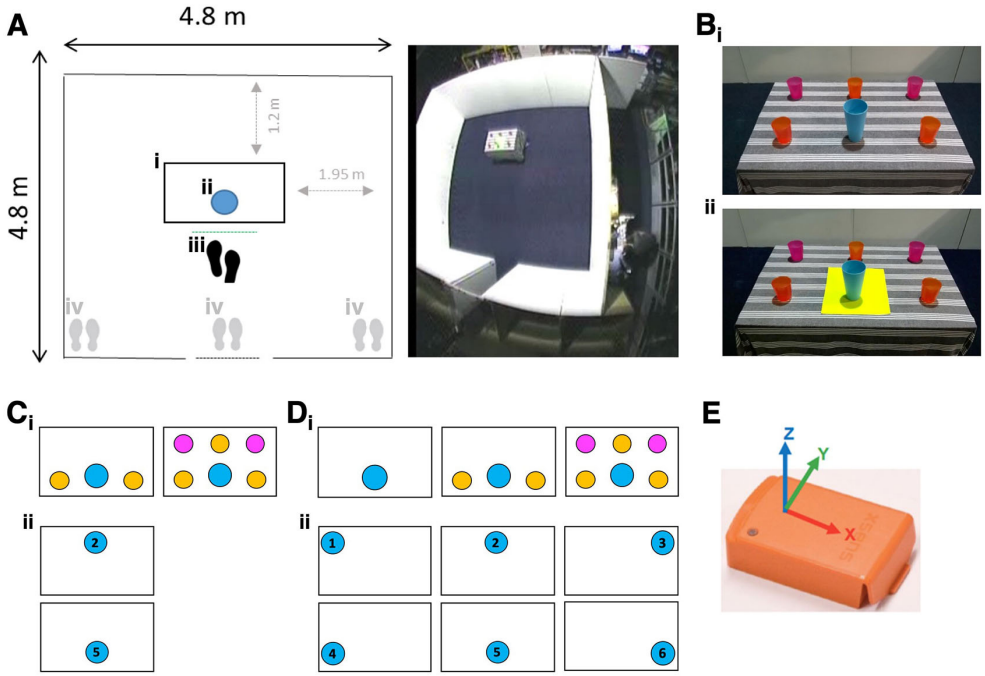

FIGURE 1
(Ai) Table position, **(Aii)** target position, **(Aiii)** starting position from reaching distance (proximal), **(Aiv)** starting position from far left, right, or center of the setting. **(Bi)** Blue target cup surrounded by clutter, **(Bii)** blue target cup with yellow color-contrast cue. **(Ci)** Clutter conditions (2 vs. 5 distractors) for Experiment 1, **(Cii)** Target positions for Experiment 1. **(Di)** Clutter conditions for Experiment 2 (2 vs. 0; 5 vs. 0 distractors), **(Dii)** target positions for Experiment 2. **(E)** Inertial measurement unit (IMU - Xsens MT, image courtesy of Xsens) mounted within the base of the target object.

to be greater when the pair involves shared environmental conditions (for example, a shared target position). If not statistically significant (using likelihood ratio tests) or the models did not converge these latter terms were omitted. The ε_{ijk} are individual level residuals.

An analogous model was used for experiment 2. In neither model was there evidence to include fixed effect interactions other than those between groups and each environmental condition. For each experiment, linear contrasts of parameter estimates were used to estimate (with 95% CI) each of the following:

1. Geometric mean completion times in each group (averaging over all environmental conditions);
2. Geometric mean completion times for each environmental condition in each group (averaging over all other environmental conditions);
3. Group-specific environment effects: defined as ratios of the environment-specific geometric means in 2) (e.g., for Experiment 1, cue vs. no cue; 5 vs. 2 distractors etc.); and
4. Pairwise between-group comparisons: ratios of the group-specific environment effects in 3) (i.e., ratios of ratios).

Wald tests were used to compare geometric mean completion times, first with a joint test across all three patient groups and then by estimating pairwise group comparisons (PCA vs. Control, tAD vs. Control, and tAD vs. PCA). Similarly, for each environmental condition, tests were performed to investigate whether the effect of the environmental condition differed between groups first using a joint test across all three groups and then separately for each individual pairwise between group comparison.

All analyses were carried out in Stata v.16.

3. Results

3.1. Experiment 1: Reaching from standing positions

Averaged over all conditions, completion times were longer ($p < 0.0001$, joint test) in PCA [estimated geometric mean completion time: 5.43 sec (95%CI: 4.36, 6.77)] and tAD [4.38 sec (3.97, 4.84), compared to the control group [2.85 sec (2.64, 3.08)]. Pairwise differences between each patient group and controls were formally statistically significant ($p < 0.001$, both tests) whilst that between the two patient groups was not ($p = 0.081$).

3.1.1. Environmental conditions

There was no formal statistical evidence of an effect of clutter or the color contrast cue on completion time within any of the three groups; as expected, completion time was shorter when the target was positioned nearer (Table 3A). There was no evidence that the effect of clutter or cue or target position differed between the three groups (clutter, $p = 0.25$; cue, $p = 0.98$; target position, $p = 0.25$).

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TABLE 3 Experiment 1: Estimated geometric mean completion time comparisons expressed as ratios (95% CI).

(A) Main effects of environmental conditions			
	Control	PCA	tAD
Cue			
Present vs. absent	0.99 (0.97, 1.02)	0.99 (0.94, 1.05)	1.00 (0.94, 1.07)
Clutter			
5 vs. 2 Distractors	1.02 (1.00, 1.04)	1.06 (0.98, 1.13)	0.98 (0.94, 1.04)
Target position			
Near vs. far	0.93 (0.91, 0.95)	0.97 (0.92, 1.02)	0.91 (0.86, 0.96)
Start position			
Left vs. proximal	2.91 (2.75, 3.08)	1.94 (1.76, 2.14)	2.37 (2.15, 2.61)
Central vs. proximal	2.53 (2.39, 2.67)	1.64 (1.48, 1.80)	1.97 (1.79, 2.17)
Right vs. proximal	2.91 (2.75, 3.08)	1.92 (1.74, 2.11)	2.30 (2.08, 2.53)
(B) Environmental conditions by group interactions			
	PCA vs. controls	tAD vs. controls	tAD vs. PCA
Cue			
Present vs. absent	1.00 (0.94, 1.06)	1.01 (0.94, 1.08)	1.01 (0.93, 1.10)
Clutter			
5 vs. 2 distractors	1.04 (0.96, 1.12)	0.97 (0.91, 1.02)	0.93 (0.85, 1.02)
Target position			
Near vs. far	1.04 (0.98, 1.10)	0.98 (0.92, 1.03)	0.94 (0.87, 1.01)
Start position			
Left vs. proximal	0.67 (0.60, 0.75)	0.82 (0.73, 0.91)	1.22 (1.07, 1.40)
Central vs. proximal	0.65 (0.58, 0.72)	0.78 (0.70, 0.87)	1.21 (1.05, 1.38)
Right vs. proximal	0.66 (0.59, 0.74)	0.79 (0.70, 0.88)	1.20 (1.04, 1.38)

Estimated geometric mean completion times expressed as (A) between condition ratios comparing cue, clutter, target and start position conditions within each participant group, and (B) ratios comparing cue, clutter, target, and start position ratios between participant groups. 95% CIs are in brackets; PCA, posterior cortical atrophy; tAD, typical Alzheimer's disease.

Expectedly, completion times in all groups were longer when reaching to the target object under distant relative to proximal (within reaching distance of the target) starting standing positions. However, distant vs. proximal ratios of completion times were greater in controls than in either patient group. For distant vs. proximal starting positions, estimated ratios of completion times were between 2.53 and 2.91 (i.e., between 153% and 191% increases) in the control group, but between 1.64 and 1.94 (64% to 94% increases) in the PCA group, with the corresponding ratios of these between route ratios for PCA vs. controls being 0.65 [1.64/2.53 = 0.65; 95%CI (0.58, 0.72)] and 0.67 [1.94/2.91 = 0.67; 95%CI (0.60, 0.75)] (Table 3B). Estimated ratios of completion times between distant vs. proximal starting positions in the tAD group were intermediate between those for the PCA and control groups.

Formal tests of differences between interaction terms provided evidence that the effect of starting position differed between controls and both patient groups (vs. PCA: $p < 0.0001$; vs. tAD: $p < 0.0001$) and between patient groups ($p = 0.012$). Relative to controls, PCA and to a lesser extent tAD groups were particularly inefficient at locating the target under proximal compared to distant starting standing positions.

3.2. Experiment 2: Reaching from a seated position

A subset of participants conducted the same task from a fixed seated position comparable to the proximal starting position under a greater number of clutter and target position conditions (Experiment 2). Averaged over all conditions, completion times were longer in PCA geometric mean completion time: 2.05 sec [95% CI 1.55, 2.70] and tAD [1.96 sec (1.63, 2.36)], compared to control groups [1.27 sec (1.15, 1.41)]. Pairwise differences between each patient group and controls were formally statistically significant ($p \leq 0.002$, both tests) whilst that between the two patient groups was not ($p = 0.804$).

3.2.1. Environmental conditions

See Figure 2 for observed completion times for each participant under different clutter conditions. An effect of clutter on completion time was observed within all three groups, with completion times being longer when reaching for the target object surrounded by distractors relative to being presented in isolation (Table 4A). However, having five distractors rather than none was associated with a disproportionately greater effect in PCA patients than in controls

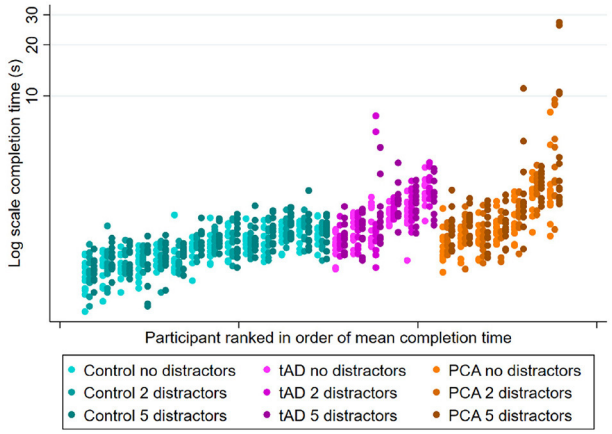

FIGURE 2
Experiment 2 scatter plots of observed completion time for each participant group under different clutter conditions (no, 2, and 5 distractors). Plots show individual completion times per participant per trial. Patients within each group are ranked left to right in order of mean completion time averaging over all conditions.

or tAD groups, with geometric mean completion times being 29% longer (ratio = 1.29) in PCA patients but only 9% longer (ratio = 1.09) in both controls and tAD. This represented an additional relative increase of 18% [1.29/1.09 = 1.18; 95%CI (1.06, 1.33)] for PCA vs. Control, and a relative decrease of 16% [1.09/1.29 = 0.84; 95%CI (0.74, 0.96)] for tAD vs PCA (Table 4B). Having two distractors rather than none produced smaller percentage increases in completion times for each group; and smaller, not statistically significant but directionally consistent, ratios of relative effects: a relative increase of 8% [1.12/1.04 = 1.08; 95%CI (0.96, 1.21)] for PCA vs. Control, and a relative decrease of 5% [1.06/1.12 = 0.94; 95%CI (0.83, 1.08)] for tAD vs. PCA.

Formal tests of interaction provided evidence that the effect of clutter differed between PCA and other participant groups (vs. Control: $p = 0.015$; vs tAD: $p = 0.031$), but not between tAD and control groups ($p = 0.84$). As in Experiment 1, there was no evidence of an effect of the color contrast cue on completion time within any of the three groups (Table 4A).

While estimated ratios of completion times were lower for targets under positions 4 and 6 in the control group (0.90 and 0.88, respectively), there was a non-statistically significant tendency toward corresponding ratios being higher for the PCA group (1.19 and 1.06). Overall tests of interaction found that the effect of target position was not formally statistically significantly different between PCA and other participant groups (vs. Control: $p = 0.081$; vs. tAD: $p = 0.15$).

4. Discussion

The current investigation evaluated effects of environmental conditions on object localization in PCA and tAD within a controlled setting. Overall, both patient groups took longer to locate a target object than healthy controls across two experiments. All participants completed the task from starting standing positions at varying distances from the target (Experiment 1), a subset subsequently completed the task from a fixed seated position (Experiment 2). In Experiment 1, there was no evidence of an effect of visual clutter or the presence of a color contrast cue on performance within any participant group. Similarly to Experiment 1, in Experiment 2 there was no evidence of an effect of the color contrast cue on performance within any participant group. However, not only did all three groups take longer to reach the target object when it was presented among visual clutter compared to being presented in isolation, there was also evidence that the effect of visual clutter on completion time was greater in PCA relative to both control and tAD groups. Effects of clutter on aspects of functional independence relating to clinical phenotype (visual-led more so than memory-led) may carry implications for tailoring environmental adaptations based on symptom profile.

The apparent inconsistency in effects of clutter across Experiments 1 and 2 may have related to differences in experimental conditions: Experiment 2 included trials where the object was presented in isolation, featured more target positions and was conducted at a fixed, proximal distance to targets from a seated position. Overall, findings are consistent with documented effects of clutter in neurodegenerative syndromes (1) and emphasize the impact of reducing surrounding visual clutter on reaching function in PCA (19, 44, 45).

The lack of the cue effect may have related to a number of visual deficits, such as excessive visual crowding in PCA resulting in difficulty perceiving the target when flanked by additional visual features introduced by the cue (19, 46). An anticipated benefit of the visual cue was to increase target visual saliency following documented effects of conspicuous, visually salient parts of scenes (for example, relating to variation in color, intensity and orientation) on visual search efficiency in PCA and to a lesser extent tAD (47). However, it is possible that introducing the color contrast cue did not materially increase visual saliency of the target relative to surroundings, given the target and distractors themselves differed in color (Figure 1).

In Experiment 1, while all three groups—as expected—performed more efficiently when standing in front of the table compared to approaching it from further away, overall healthy controls incurred a greater penalty in completion time when traveling a greater distance. In Experiment 2, all groups were faster at localizing the target object when it was presented centrally and in close proximity, as expected. There was an observed (non-statistically significant) tendency for the advantage in locating objects in close proximity to be diminished in PCA patients. This may reflect previously reported restrictions in the effective visual field in PCA, particularly limiting localization of objects which despite being in close proximity are also positioned in peripheral vision and the inferior visual field (48, 49). However, there was no evidence that effects of target position differed between groups. Moreover, it is possible that varying cues about self-motion from optic flow may contribute to aspects of performance, including particular difficulty locating the target from proximal vs. distant starting positions (Experiment 1). While case studies of PCA suggest better localization of moving relative to static objects (50, 51), PCA group studies have suggested impaired discrimination of optic flow (52) and/or have not provided evidence of visual motion cues on navigation (26). Future work might clarify the contribution of visual motion cues on object localization.

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TABLE 4 Experiment 2: Estimated geometric mean completion time comparisons expressed as ratios (95% CI).

(A) Main effects of environmental conditions			
	Control	PCA	tAD
Cue			
Present vs. absent	1.01 (0.99, 1.04)	1.03 (0.95, 1.11)	1.06 (0.97, 1.17)
Clutter			
2 vs. 0 distractors	1.04 (1.01, 1.07)	1.12 (1.00, 1.25)	1.06 (0.99, 1.13)
5 vs. 0 distractors	1.09 (1.06, 1.12)	1.29 (1.16, 1.44)	1.09 (1.01, 1.17)
Target position			
Position 1 vs. 2	1.09 (1.04, 1.13)	1.17 (0.96, 1.41)	1.10 (0.97, 1.26)
Position 3 vs. 2	1.06 (1.01, 1.10)	1.16 (0.96, 1.40)	1.08 (0.94, 1.23)
Position 4 vs. 2	0.90 (0.86, 0.94)	1.19 (0.98, 1.44)	0.92 (0.81, 1.05)
Position 5 vs. 2	0.80 (0.77, 0.84)	0.90 (0.74, 1.09)	0.83 (0.72, 0.94)
Position 6 vs. 2	0.88 (0.84, 0.92)	1.06 (0.88, 1.29)	0.83 (0.73, 0.94)
(B) Environmental conditions by group interactions			
	PCA vs. Control	tAD vs. Control	tAD vs. PCA
Cue			
Present vs. absent	1.02 (0.94, 1.10)	1.05 (0.95, 1.16)	1.03 (0.92, 1.16)
Clutter			
2 vs. 0 distractors	1.08 (0.96, 1.21)	1.02 (0.94, 1.10)	0.94 (0.83, 1.08)
5 vs. 0 distractors	1.18 (1.06, 1.33)	1.00 (0.92, 1.08)	0.84 (0.74, 0.96)
Target Position			
Position 1 vs. 2	1.07 (0.88, 1.31)	1.01 (0.88, 1.16)	0.94 (0.75, 1.19)
Position 3 vs. 2	1.09 (0.9, 1.33)	1.02 (0.89, 1.17)	0.93 (0.74, 1.17)
Position 4 vs. 2	1.33 (1.09, 1.62)	1.03 (0.90, 1.18)	0.78 (0.61, 0.98)
Position 5 vs. 2	1.12 (0.92, 1.36)	1.03 (0.90, 1.18)	0.92 (0.73, 1.16)
Position 6 vs. 2	1.21 (0.99, 1.47)	0.94 (0.82, 1.08)	0.78 (0.62, 0.98)

Estimated geometric mean completion times expressed as (A) between condition ratios comparing cue, clutter and target position conditions within each participant group, and (B) ratios comparing cue, clutter, and target position ratios between participant groups. 95% CIs are in brackets. PCA, posterior cortical atrophy; tAD, typical Alzheimer's disease.

The current investigations had a number of limitations. Firstly, while study strengths include the number of observations per participant, findings are from a small and heterogenous group of mostly young-onset patients and should be replicated and validated in larger samples. Secondly, conducting the tasks within a controlled experimental setting may limit how much the findings can be generalized to other settings. And thirdly, the study did not formally investigate the processes that may underly object localization behaviors in PCA and tAD. To further disentangle the mechanisms that give rise to the object localization deficits in PCA and tAD described in this study, future investigations may benefit from investigating eye and body motion tracking and assessing whether the impact of clutter depends on how similar/dissimilar it is in shape and color compared to the target.

The present study provides modest evidence of environmental conditions influencing efficiency in interacting with real-world objects. Findings underscore the impact of dementia-related visual loss on functional status, and highlight the importance of considering dementia diagnosis along with task and environmental conditions to inform approaches supporting patients to engage in everyday activities independently, including those involving object localization skills in PCA. Such interventions may include ensuring that target objects are presented with a limited number of distractors. Decreasing the proximity of target and distractors and the functional and visual similarity between the two may offer further benefits (19, 20).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Research Ethics Service Committee London

Queen Square. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DO took the lead in writing the manuscript with SP, TS, TP, IM, SC, CF, and KY providing critical feedback and helping to shape the manuscript and provided support for data analysis by TP and CF. KY recruited the study participants, carried out the experiments with the support of IM, TS, and SP, and provided support for data analysis by TP and CF and the writeup of the manuscript. SC conceived and planned the experiment with the support of NT and KY. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Poor insight and future thinking in early dementia limit patient projections of potential utility of technological innovations and advanced care planning

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Introduction: Cognitive psychology posits that thinking about the future relies on memory such that those with memory impairment may have trouble imaging their future technology and other needs.

Methods: We conducted a content analysis of qualitative data from interviews with six patients with MCI or early dementia regarding potential adaptations to a mobile telepresence robot. Using a matrix analysis approach, we explored perceptions of (1) what technology could help with day-to-day functioning in the present and future and (2) what technology may help people with memory problems or dementia stay home alone safely.

Results: Very few participants could identify any technology to assist themselves or other people with memory problems and could not provide suggestions on what technology may help them stay home alone safely. Most perceived that they would never need robotic assistance.

Discussion: These findings suggest individuals with MCI or early dementia have limited perspectives on their own functional abilities now and in the future. Consideration of the individuals' diminished understanding of their own future illness trajectory is crucial when engaging in research or considering novel technological management solutions and may have implications for other aspects of advanced care planning.

KEYWORDS

cognition, technology, geriatrics, qualitative, insight, patient-centered

1. Introduction

Alzheimer's disease and related dementias (ADRD) are neurodegenerative diseases that permanently alter neural processes impacting not only memory and other aspects of cognition but functional activities of daily living. Over 57 million people live with ADRD today and as many as 152 million may do so by 2050 (1). Brain imaging and other biomarker research demonstrate neurodegeneration is present long before individuals experience challenges in their everyday life (2). Memory loss, one of the hallmarks of ADRD, becomes more apparent

as the disease progresses. Individuals initially have trouble with new learning and remembering recent events, but as their dementia progresses, they become less able to call upon more remote past experiences (3).

Research into the cognitive and neural underpinnings of memory has shown that this process is an integral part of picturing future experiences. Memory is broadly categorized into semantic memory (facts, concepts) or episodic memory (experiences or life events). Episodic future thinking, as defined by Schacter et al. (4) refers to "the capacity to imagine or simulate experiences that might occur in one's personal future" (4 p. 41) and there is "a distinct role for episodic retrieval in imagining future experiences." (4 p. 44) Future thinking is understood to reflect the retrieval and recombination of past experiences, both internal details (what/when/where) and external details (semantic details and commentary), reimagined into a new, novel experience (4). That said, what if one's ability to accurately remember the past has been disrupted? Previous research has found that patients with Alzheimer's disease provided less details overall in their description of projected future events, suggesting a deficit in future thinking (5, 6). Further, when assessing future thinking as it relates to functional ability and completing instrumental activities of daily living independently (IADLs) (e.g., planning for travel, or managing medications or finances), researchers identified a significant connection between the ability to provide sufficient details in a future thinking task and independent completion of IADLs. It is suggested that future thinking may be a crucial element in the cognitive process that helps individuals conceptualize and sequence the steps necessary to successfully perform daily activities (7). Therefore, the challenges that mild cognitive impairment (MCI) and early ADRD pose on future thinking demonstrate the potential for negative clinical implications as the disease progresses.

Although those with MCI or early ADRD are still able to communicate and complete many functional tasks independently, a key question is, do they have the ability to accurately project into the future and imagine the supports they may need to maximize functional ability, safety, and independence as their dementia progresses? Policy planners and technology designers often assume that older adults are either not comfortable with technology or that technology will provide the majority of solutions for our growing number of older adults; however, the lived experiences of this population are more nuanced. Continued advances in and changes to technology coupled with memory decline may further limit the person with MCI or early ADRD's ability to imagine how technology could aid with functional independence. Per patient-centered care and user-centered design principles, it is important to involve target populations as study participants (8). Those with MCI or early ADRD are still able to communicate, and thus, should be asked about their thoughts and offer feedback on technology design. This poses challenges though when the population in question has cognitive decline and may demonstrate challenges in future thinking and imagining their future needs, especially related to technological assistance.

In this brief report, our goal is to offer insights into the key question posed above. To do this, we explore participants' perceptions of what technology could assist those with MCI or early ADRD in the future as their dementia progressed, as well as what technology may be needed in the future to help them stay home alone safely. Exploring these results on technological needs may help to provide additional perspectives into future thinking in dementia and inform clinical as well as technology research approaches.

2. Methods

For this brief report, we analyzed qualitative interview data collected in a previous study (July to August 2019) in which we obtained feedback on possible adaptations to a mobile telepresence robot and the robot's potential utility from stakeholder groups, including patients with MCI or early ADRD (9). Approval from the Institutional Review Board at the Veterans Affairs (VA) Bedford Healthcare System (approval number 110818) was received.

2.1. Recruitment and data collection

Recruitment was completed at the VA Bedford and inclusion criteria for the specific population of interest in this brief report included patients: (1) who were ages 50 and older with a diagnosis of MCI or early ADRD in their medical chart and living in the community (not a nursing home or assisted living facility); (2) who were routinely left home alone for periods of at least 4 h; and (3) who had no indication of incompetence in their medical record (9). Potential participants were identified as having either MCI or ADRD based on the terminology used in the most recent physician note of neurological function in their medical record from either the dementia clinic or outpatient primary care clinics at the Bedford VA. Researchers did not complete additional independent assessments of cognition for this study.

For those patients who chose to opt-in to the study, we obtained informed consent for participation as well as to audio record prior to beginning the interviews. Six patients participated in a 60–90 min semi-structured qualitative interview during which participants were shown a video of a remotely navigable mobile telepresence robot and we elicited opinions regarding their technology use and feedback about the robot. The specific robot depicted in the video participants viewed was a wheeled, upright robot approximately 120 cm tall with a top-mounted screen and was seen to be navigated through an elementary school under the remote guidance of a student who was homebound. We explained that mobile telepresence robots can be used in a wide variety of settings to facilitate communication between individuals who are not co-located. This allows for increase social connection and exchange and has potential implications for healthcare delivery and support. In addition, as part of the interview, we asked participants about: (1) What kind of technology do you think could help you with day to day functioning? and (2) What are the main things you think might prevent people with memory problems or dementia from staying home alone safely? Participants were compensated $50 for participating in the interview and an additional $30 stipend if they traveled to attend the interview in person. Additional details of the recruitment process, the mobile telepresence robot, the data collection process, and participant demographics are described in our previous study (9).

2.2. Data analysis

For this brief report, we conducted a content analysis using the reports that had been generated from the coding of the qualitative interview data in our previous study, which further describes our process (9). In this analysis, we focus on two specific areas of interest: participants' perceptions of technology to (1) help with day-to-day functioning and (2) help people with memory problems or dementia stay home alone safely. We used a matrix analysis approach to organize, review, and assess the data in the code reports for these

areas of interest (10). Our goal, when analyzing the content of the data in the matrix, was to explore any perceptions offered by participants that could provide insight into technology use and future thinking in patients with memory problems or dementia.

3. Results

3.1. Perceptions of what technology could help with day-to-day functioning

When asked about what potential technology could help with day-to-day functioning, only 2 out of 6 participants identified technology that would assist with memory problems commonly experienced by this population.

> "I do use my home Google for reminders all the time…I use that a lot…I'd be lost without it. I don't see how I functioned years [ago] because back then everything was paper and pencil." Participant D

> "I know a friend of mine had somebody on his phone that he asked questions to and they answered them. I don't have that on my phone." Participant F

Most participants discussed wanting technology to help address physical limitations of a task (e.g., assistance with IADLs like housework and picking up medication) vs. technology to address cognitive limitations (e.g., technology similar to Siri or Google Home for reminders).

> "Working around the house [and] getting things done.… Something to run around the house and clean." Participant A

> "I suppose if somebody is disabled and can't walk and can't do that if there are chores that [a robot] can do." Participant C

All participants perceived that the technology they had at the moment was sufficient both now and for the future.

We observed that participants had challenges in articulating their future technology needs. With further prompting from interviewers who provided a list of potential ways in which technology could assist with cognitive limitations (e.g., emergency help access, medication and schedule reminders, communication assistance with family and doctors, and social stimulation), 5 out of 6 participants were able to agree that, in general, some technology, especially if integrated into a mobile telepresence robot, may help with cognitive barriers experienced by individuals with MCI or early ADRD.

However, when interviewers asked participants about whether the mobile telepresence robot, in particular, could be helpful to them in the future, 4 out of the 6 participants responded that they, themselves, would not need robotic assistance at any time. Reasons included the lack of need for technology (e.g., a mobile telepresence robot) due to the presence of other family members as well as the lack of desire to learn how to use technology, such as a computer or the robot.

> "I don't think so. Not me personally because I won't be in a situation where it will be necessary to have [a mobile telepresence robot]… I'll be living with my children." Participant C

> "I don't think it would be helpful at all. Not for me. I wouldn't know how to use it. My wife would be fine, but me, no. It's just I'm computer illiterate and have no desire to even learn how to use a computer." Participant E

3.2. Perceptions of what technology may help people with memory problems or dementia stay home alone safely

When asked about what might prevent people with memory problems or dementia from staying home alone safely, participants mostly discussed physical issues that can prevent people from staying home alone safely (e.g., falling and tripping).

> "Tripping on carpets. I go upstairs – half the time when I go up the stairs I fall going up the stairs than the down. That's because my equilibrium gets off quite a bit and I forget." Participant A

> "Maybe for somebody that falls down or something like that and then can't get up. I would say either falling down or not being able to get hold of help would be the most important if something came up where you couldn't do it on your own." Participant D

Even with further prompting, participants had challenges in brainstorming safety issues and often noted that they would have their caregivers' help. In addition, they could not provide suggestions on what technology may help them stay home alone safely. Three out of six participants reported knowing someone close to them who had progressed through the stages of dementia; these participants were more likely to identify at least one potential technological solution for cognitive challenges.

> "[It would be helpful to have a mobile telepresence robot that reminded people with ADRD] to take your medicines that you need on time and when and how much. And time to eat – [a mobile telepresence robot could be helpful to] remember that. I think people with Alzheimer's and dementia forget to do those things. My dad had it and I remember seeing him and he forgot a lot so [a mobile telepresence robot] could help with that kind of a thing." Participant C

4. Discussion

While our previous study (9) showed that those with MCI or early ADRD were able to provide overall feedback regarding the proposed assistive technology, when asked to imagine the assistance they may require in the future, they lacked future thinking capability in predicting their own future cognitive and functional abilities. Participants had a limited ability to independently identify potential cognitive challenges and suggest technology that could be of assistance for their future cognitive and functional declines. These findings demonstrate both a decrease in insight and suggest potential deficits in future thinking cognitive abilities, specifically the ability to project in the future as the disease progresses. This is consistent with cognitive psychology research linking impaired memory to deficits in future thinking abilities (5, 6).

Even those participants who reported having witnessed someone progress through all the stages of dementia had challenges in

identifying potential technological solutions to address cognitive limitations. Findings presented in this report provide valuable insight into the mindset of persons with MCI or early ADRD and their limited perspectives on declines in function now and in the future. Results are consistent with previous research that identifies the clinical implications of individuals' (lack of) self-awareness or understanding of the likely progression of their own illness (also known as anosognosia). These include overall safety considerations as well as aspects of advanced care planning (e.g., creating a living will, end-of-life planning, etc.) (11). Our research supports these findings and also highlights the importance of understanding these deficits when considering novel technological dementia management solutions.

Similarly, most participants verbalized a discomfort with technology and more specifically, the idea of using a computer or a machine in the future to assist with tasks that could be impacted by functional or cognitive decline. As dementia is a neurodegenerative disease, people with dementia will eventually experience decline and require assistance to safely complete daily tasks. Technology and telehealth can help people with dementia age in place longer (12, 13). Previous research supports our findings that older adults are generally not as interested in adopting and utilizing technology in their daily life (14, 15). Coupled with our findings that reveal a decrease in future thinking for those with MCI and early ADRD, it demonstrates the need to identify a "sweet spot" in time to introduce older adults to technology as early on in the disease process as possible in an effort to maximize the potential for technology comfort and adoption as cognition declines.

For technology developers, understanding how to best engage individuals with MCI or early ADRD in a participatory co-design process, such that the technology is patient-centered, is critical. Several recommendations have been made on what to do when using a participatory co-design process with people living with MCI or early ADRD regarding the utility of technological products, such as asking them how they would like to participate in the research, using supportive rather than offensive language, ensuring their emotional and physical safety, and being respectful, compassionate and tolerant when working with them (16). Technology developers as well as researchers should keep these recommendations in mind as they design and conduct their work as this can promote meaningful experiences across all who are involved. Our experiences in interviewing people living with MCI or early ADRD also support these suggestions. During the interviews, our study researchers utilized advanced interviewing techniques, such as rephrasing and clarifying questions as well as inquiring deeper about answers given, to increase engagement from participants. Given the challenges in their future thinking, this also required researchers to, for example, use supportive language use supportive language and remain respectful, compassionate, and tolerant of how participants were answering the questions. During each interview, observational notes were taken regarding the dynamics of the interview as well as overall thoughts, challenges, and successes. Researchers then met afterwards to debrief on what they were seeing or hearing (e.g., participant's body language or tone of voice when responding to questions) during the interview. This allowed researchers to more easily adjust their interviewing techniques with the next participant.

Medicolegally, it is important for healthcare teams to be aware of this deficit in future thinking ability as well as perspectives on technology adoption so they can educate their patients and families on cognitive and functional decline early in the disease process; this may include providing an introduction to healthcare technology and appropriate adaptations and modifications to ADL/IADL tasks. In addition, results suggest that people with MCI often cannot imagine the needs of their future self. As such, another important clinical consideration is for the healthcare team to introduce legal documentation that will most likely be required (e.g., healthcare proxy identification, physician orders for life sustaining treatment form [POLST]) at the earliest onset of cognitive decline, prior to the decrease of future thinking abilities. Introducing these early on may provide an opportunity for individuals to have difficult, yet important conversations about their health care goals, values, and preferences with their families, healthcare team, and legal advisors. In turn, these conversations may help individuals in their future thinking ability so that they can better identify and verbalize their wishes.

Continued research adapted for potential deficits in future thinking can inform technological needs for this population as well as interdisciplinary care plans to allow for maximized independence and quality of life for people with dementia and their family members as the disease progresses. By challenging the structure of care, we can meet individuals where they are at and offer a more person-focused intervention to support independence, functional participation, and safety at home. While patient-centered research approaches should continue to include persons with MCI or early ADRD when designing interventions or technology innovations targeting this population, limitations in future thinking ability also need to be taken into account.

5. Limitations

Regarding this study's limitations, we recognize the small sample size may limit the generalizability of the research, and replication of the study with a larger sample size would be beneficial to the current body of research in this area. The observation of impaired future thinking reported and discussed here emerged from the qualitative analysis of the interview results from the parent study; we did not set out to measure episodic future thinking in an experimental context. Therefore, results of formal assessment of specific cognitive domains (e.g., memory, executive function, or attention) and specific measures of episodic future thinking and formal evaluation of insight into the disease process are not available. Similarly, the parent study only included participants with MCI or early ADRD who had caregiver involvement, which may impact participant's episodic future thinking ability when it comes to imagining the need for assistive technology. Given these limitations, we suggest future studies explore this concept more formally by specifically identifying, separating, and assessing the impact of individual cognitive domains such as attention, memory, and executive function on episodic future thinking as well as the impact of having external support on perceptions of future need.

Data availability statement

The data analyzed in this study represents a secondary analysis of individually identifiable qualitative interview data that cannot easily be deidentified, and thus is subject to restrictions such that we have no permission to share. Requests to access these datasets cannot be entertained, but other inquiries can be directed to Jaye.McLaren@va.gov.

Ethics statement

The studies involving human participants were reviewed and approved by VA Bedford Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JM, MS, and LM made substantial contributions to the conception and design of the study and contributed equally to the interpretation of the data and preparation of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Stimulus material selection for the Dutch famous faces test for older adults

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Worldwide, approximately 22% of all individuals aged 50 years and older are currently estimated to fall somewhere on the Alzheimer's disease (AD) continuum, which can be roughly divided into preclinical AD, mild cognitive impairment (MCI), and AD dementia. While episodic memory loss (among other aspects) is typically required for a diagnosis of AD dementia, MCI is said to have occurred when cognitive impairment (including memory loss) is worse than expected for the person's age but not enough to be classified as dementia. On the other hand, preclinical AD can currently only be detected using biomarkers; clinical symptoms are not apparent using traditional neuropsychological tests. The main aim of the current paper was to explore the possibility of a test which could distinguish preclinical AD from normal aging. Recent scientific evidence suggests that the Famous Faces Test (FFT) could differentiate preclinical AD from normal aging up to 5 years before a clinical AD diagnosis. Problematic with existing FFTs is the selection of stimulus material. Faces famous in a specific country and a specific decade might not be equally famous for individuals in another country or indeed for people of different ages. The current article describes how famous faces were systematically selected and chosen for the Dutch older (60+) population using five steps. The goal was to design and develop short versions of the FFT for Dutch older adults of equivalent mean difficulty. In future work, these nine parallel versions will be necessary for (a) cross-sectional comparison as well as subsequent longitudinal assessment of cognitively normal and clinical groups and (b) creating personalized norms for the normal aged controls that could be used to compare performance within individuals with clinical diagnoses. The field needs a simple, cognitive test which can distinguish the earliest stages of the dementia continuum from normal aging.

KEYWORDS

aging, famous faces, famous names, memory, naming, preclinical AD, recollection

Introduction

Worldwide, 416 million older adults are currently estimated to fall somewhere on the Alzheimer's disease (AD) continuum, corresponding to approximately 22% of all individuals aged 50 years and older (1). This continuum can be roughly divided into three stages, namely: preclinical AD, mild cognitive impairment (MCI), and clinical AD dementia. Preclinical AD typically begins in midlife (2, 3) and is characterized by pathological processes in the brain

including, for example, abnormal levels of peptide amyloid-beta Aβ (Aβ+; 3, 4). At this stage cognitive impairment is usually not apparent and cognitive tests currently employed in clinical practice fail to detect it (5). As there are large between-person differences in cognitive abilities as well as within-person change over time, distinguishing cognitive impairment due to preclinical AD from that due to normal aging is difficult (6).

Currently, preclinical AD can only be detected via the assessments of biomarkers (3, 4), which are invasive, can be painful (e.g., cerebrospinal fluid needs to be tapped using a lumbar puncture), tend to be costly (e.g., PET/MRI scans) and are not widely available. In addition, noticeable biomarkers are also present in approximately 50% of healthy, cognitively normal (CN) older adults, many of whom never progress to clinical AD (7). Furthermore, many barriers exist toward (timely) AD diagnosis at the patient, caregiver, health care, and societal level, with many individuals being diagnosed too late or not at all (8–10). Research has also suggested that most (85–95%) CN older adults would still want to receive the AD diagnosis, either for themselves or for their partner, despite the fact that no cure for AD is available as yet (11, 12). One solution to these difficulties currently facing timely AD diagnosis could be an inexpensive, widely available cognitive screening test that could accurately distinguish preclinical AD from healthy aging while also taking individual differences into account.

Clinical AD dementia is typically determined according to established guidelines, for example, using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V; 13) with episodic memory loss a key symptom. Traditional episodic memory tests are not sensitive enough to detect preclinical AD (14, 15). "Normal" performance on standard episodic memory tests could lead to the erroneous conclusion that cognition is normal at the preclinical AD stage.

While some controversy exists, semantic memory performance is generally believed to remain preserved, at least until the later stages in the AD continuum (13, 16). However, in some studies, a steep decline in semantic memory performance was observed approximately 5 years prior to clinical AD diagnosis (15, 17). Furthermore, persons with preclinical AD often experience difficulty with verbal abilities, including category fluency for living things (e.g., animals), and the naming of famous people (18, 19). These findings suggest that a more detailed exploration of between-person differences in semantic memory performance could be fruitful when attempting to design a cognitive screening instrument sensitive enough to detect preclinical AD. This test, if it can distinguish normal aging from preclinical AD and/or MCI (between-person differences), could also be used to explore within-person change over time.

The Famous Face Test (FFT) could be the ideal screening tool to detect within-person change during the earliest stages of AD, while also considering between-person differences in level and change. In a standard FFT, participants are shown photographs of famous faces and then asked to name each face (20, 21). Different versions of the FFT exist that encompass a range of different photographs, all representing famous persons from different decades and categories (e.g., actors, athletes, musicians, media personalities, and/or politicians). Problematic with all existing FFTs is the selection of stimulus material. To our knowledge, this has never been systematically done for the population of interest (e.g., older adults), or indeed the country of origin (including, for example nationally and internationally famous faces). Most FFTs are not standardized in any way. Many of these tests use, for example, photographs with props/backgrounds which could make identification of the famous faces easier, and many do not report where their stimuli were sourced.

Previous research has investigated whether or not healthy younger and older adults recognized famous faces (e.g., 22–24). However, only four studies have explored FFTs in clinical samples of individuals diagnosed with either mild MCI or preclinical AD based on biomarker evidence or a clinical AD diagnosis at two-year follow up (25–28). In general, these studies found that these individuals performed more poorly on an FFT than CN older adults, despite seemingly normal performance on other tests of global cognition, memory, and fluency. This led these authors to conclude that the FFT can detect the earliest stages of AD. More specifically, individuals with mild MCI or preclinical AD perform more poorly on the naming of recent or current famous individuals, whereas naming of remote famous faces (individuals who were famous a long time ago) did not differ from CN older adults (26, 29). This implies a temporal gradient that may characterize the earliest signs of cognitive decline in AD, and that can be measured using the FFT.

There are many limitations however to these previous studies including: different items used across studies making comparison difficult, insufficient quality of photographs, and stimuli not standardized or selected for the population studied. Mostly, tasks included less than 50 famous faces that were not developed in a systematic manner (or not obviously so from the methodology described in the respective publications). Stimulus material often was not standardized, including props that indicate who the person was (e.g., a U.S. flag on the background of a U.S. president's photograph) In addition, while all were conducted in different countries and in specific populations (e.g., university students or older adults) previous FFT versions were not country-specific, nor tailored to the population of interest. Ideally, the FFT should also be suitable for longitudinal assessment in both cognitively normal and clinical groups, for example by means of different short FFT versions of equivalent mean difficulty. In the current study, the selection of stimulus material and development of nine short versions of the first Dutch FFT (D-FFT) is described that will be used at a later stage in this ongoing project for longitudinal assessment in both cognitively normal and clinical populations. By not only ensuring equivalent mean difficulty levels, but also that each version has an equal number of stimuli from each decade, the described temporal gradient can also be assessed in future steps as well.

Previous studies using an FFT furthermore included different tasks such as recall (recollection of the name of the famous person), identification [providing person-identity semantic knowledge (PISK) about the famous person], and recognition [indicating whether the person was famous, or choosing their name out of multiple options] (22–29). In a recall task, individuals can only rely on recollection, which involves the active recovery of information and is also referred to as remembering (30), which is more sensitive to the earliest stages of AD than familiarity, as the latter involves a feeling of knowing without remembering (30, 31). As floor effects are common on an FFT recall task in clinical populations, the D-FFT also includes a multiple-choice recognition task, where participants can rely on familiarity in addition to or instead of recollection. This recognition task, while not used to determine stimulus selection in this paper, may be especially informative in clinical populations in future steps of this project.

The aim of the current study was to develop different versions of the first Dutch FFT specifically for older adults aged 60 years and above, to be able in the future to conduct a (a) cross-sectional comparison as well as subsequent longitudinal assessment of cognitively normal and clinical groups and also be able to (b) create personalized norms for the normal aged controls that could be used to compare performance within individuals with clinical diagnoses. The development of this new test and its nine versions was conducted in five steps. These were as follows: (1) selecting famous names, (2) constructing a database containing one representative photograph per famous person, (3) selecting famous faces that Dutch older adults could indeed name, (4) developing different versions of the D-FFT, and (5) testing these D-FFT versions for equivalent mean difficulty. An overview of the five steps used to achieve these aims is presented in Figure 1.

General methods

Participants

Every step of the selection process included some form of data collection with different (partly overlapping) samples of Dutch older

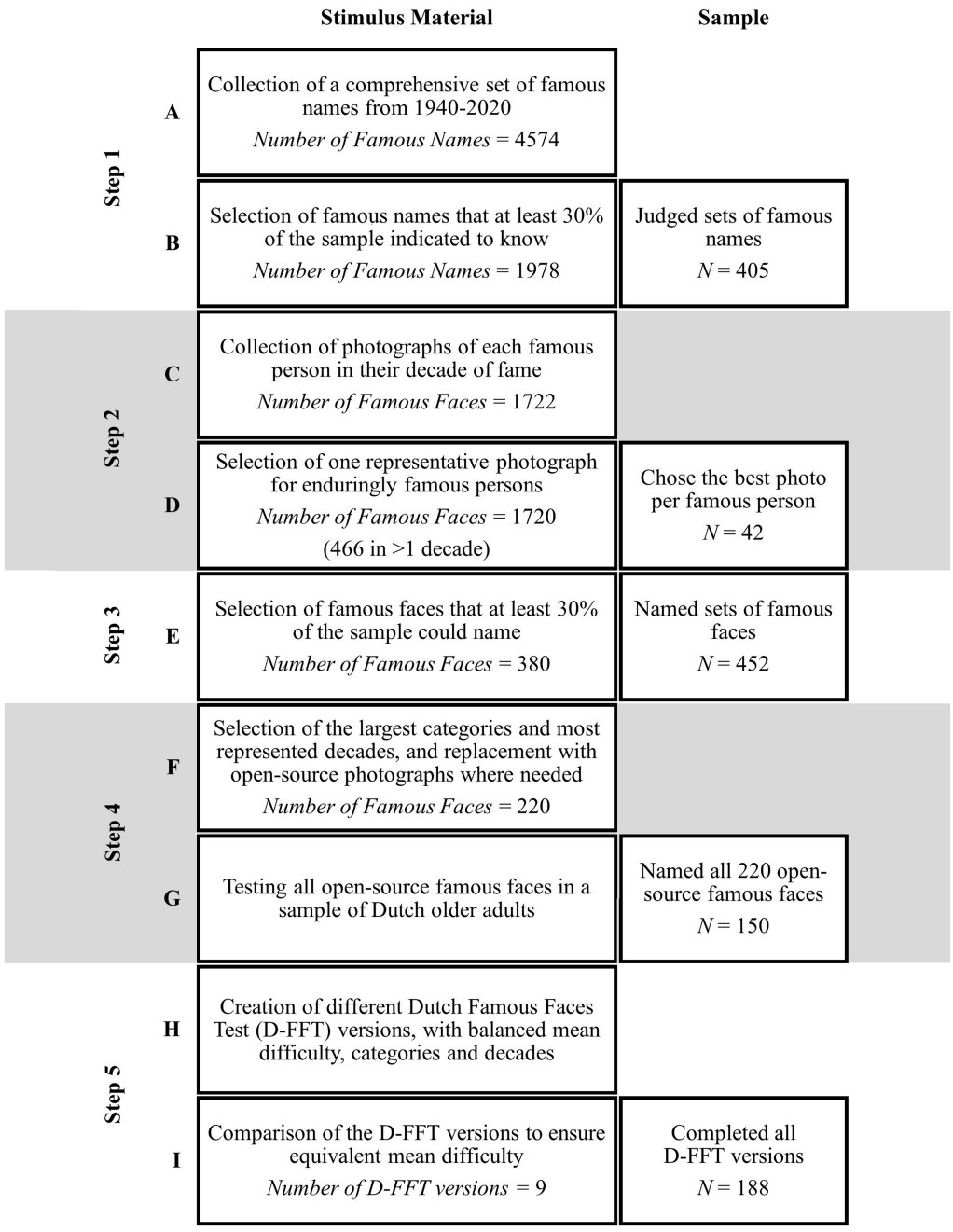

FIGURE 1
Flowchart of steps 1–5. Each step had one or more sub-steps, which are described together with the resulting number of famous names/faces. Each step included at least one sub-step that involved data collection, of which sample size and the main task are described. Further sample descriptive statistics are presented in Table 2.

adults. All Dutch-speaking older adults aged 60 and older could participate in this study if they had access to the internet on a computer, tablet, or smartphone. See Table 1 for the descriptive statistics for the samples assessed in each of the five steps.

Participants were recruited via the researchers' personal networks, social media, and different types of elderly associations that distributed the study invitation in their (online) newsletters. Such elderly associations included Higher Education for Elderly (Hoger Onderwijs voor Ouderen, HOVO) and local elderly organizations spread all over the Netherlands (e.g., Catholic Associations of Elderly/Katholieke Bond van Ouderen, KBO). This study was approved by the ethical review board of the Tilburg School of Social and Behavioral Sciences at Tilburg University (RP609) on 7 September 2021. All participants were informed about the study and gave written informed consent before participation.

Procedure

For all five steps, individuals indicated their interest to participate by filling in their email address, date of birth and (if they required more information) phone number using an online form. After registering, participants received an email with an information letter and personal link to the online task. They could complete all steps of this study on a PC (desktop or laptop), tablet, or smartphone, but were encouraged to use a PC due to the larger screen and keyboard.

Participants' registrations and subsequent data for all steps of this study were collected using Qualtrics Experience Management (EM) software (32). Participants answered all questions by pressing the button for the answer of their choice or, if applicable, typing their answers in a box and then pressing a button to continue. Although each step contained specific questions (e.g., questions about person-identity semantic knowledge, a recognition task, or confidence ratings), only the questions that were relevant for the selection of stimulus material will be reported here.

In each step, participants were presented with one famous name (steps 1 and 2) or famous face (steps 3 to 5) at a time. Famous names and faces were presented on a white background, in the middle of the screen of the participant's device of choice. Participants were always asked the first question of the task on the same page, right below the famous name or famous face. In case there were follow-up questions, the famous name or famous face would remain visible at the top of the screen. All calculations and analyses were performed using R version 4.2.1 (33) and RStudio version 2022.07.01 (34).

In steps 3 to 5, participants completed a multiple-choice recognition task directly after the recall task, in which they would see all famous faces again but now chose the correct name out of multiple options, respectively. However, recognition performance over the 1,720 items in step 3 was near-ceiling ($M_{recognition}$ = 83.37%, SD = 15.10%). Therefore, only the recall task was used for stimulus selection and the multiple-choice recognition task is not described in further detail in the current paper.

Statistical analysis

In steps 4 and 5, different versions were created and tested for equivalence of mean difficulty level. The sample of 338 persons was randomly split in two groups, stratified in terms of age, gender, and education, resulting in a sample of 150 for creating the D-FFT versions and 188 for testing equivalence of the mean difficulty level. First, to create the D-FFT versions, we used the following procedure in step 4: One hundred thousand sets of 10 versions were generated by randomly distributing the items over the (non-overlapping) D-FFT versions under the constraints set to obtain an equal number of items per decade and category in each version; the R software language for statistical computing was used for generating the versions. For each of the generated sets, the mean proportion of correct naming responses was obtained for each of the D-FFT versions in the set, using the data of the 150 participants. The set with the smallest difference between the largest and smallest mean proportion of correct naming responses was then retained to create the parallel versions. Second, the versions of this set were tested for equivalence on the remaining set of 188 participants in step 5. Each of the participants completed all items and versions, hence a repeated measures analysis applies in which we treated the version as a fixed factor and the participant as a random factor. The lme4 R package was used for the general linear mixed model analysis (35).

Step 1: Selecting famous names

Step 1's aim was (a) to collect a comprehensive set of famous peoples' names from 1940 to 2020 (decades of relevance for older adults) and (b) to test Dutch older adults on these famous names and then select the names which they recognized for the next steps of this study.

TABLE 1 Descriptive statistics of participants in steps 1–5.

Step	*N*	Age			Female (%)	Education level (%)			Overlap (%)[4]
		M	*SD*	Range		Low[1]	Middle[2]	High[3]	
1	405	69.84	5.98	60–91	62	5	17	78	
2	42	68.67	4.82	60–81	69	0	26	74	88
3	452	70.90	5.64	60–92	61	7	20	73	60
4	150	70.56	6.17	60–90	60	9	19	72	66
5	188	70.31	5.83	60–85	60	9	23	68	58

[1]Low education: Finished low-level secondary education or less. [2]Middle education: Finished average-level secondary education. [3]High education: Finished high-level secondary education or has a University degree. [4]The proportion of participants who had also participated in (a) previous step (s) is reported (Overlap %). Participants in step 5 could not have participated in step 4 as well.

A. Collection of a comprehensive set of famous names from 1940 to 2020

The systematic collection of famous names was based on the Pantheon 1.0 dataset of globally famous biographies that are categorized by occupation (36). Based on the Pantheon 1.0, 10 overarching categories were constructed, namely: Artists, Business & Law, Explorers, Film & Theater, Institutions, Literature & Science, Politicians, Public Figures, Singers & Musicians, and Sports. An overview of all categories and the number of Dutch and international famous names is presented in Table 2. After setting up the categories, famous names were searched for in two steps. First, the Dutch Wikipedia's yearly news overviews were searched for every year between 1940 and 2020. All famous names that appeared in these general Dutch news overviews were assigned to the correct category and decade(s) in which they occurred (1940–2020s). If famous names occurred in different categories or in multiple decades, they were assigned to several categories and decades. Second, the names in each category and decade were complemented by collecting the famous names from category-specific recurring events, both globally and specifically for the Netherlands. Extracting those names from Dutch Wikipedia pages led to a systematic collection of one or multiple names for each occurrence of the event. Examples include: winners of the FIFA world and Dutch premier league soccer player(s) of the year. A complete overview of all sources per category and the corresponding years can be found in the Supplementary material. This search led to a total of 4,574 unique famous names. The number of names per category, national and international, is presented in Table 2.

B. Selection of famous names that Dutch older adults indicated to know

In total, 405 older adults (see Table 1 for sample descriptive statistics) rated the 4,574 unique famous names that were collected indicating if they know this person ("Yes" or "No"). If they did not know the name (i.e., pressed "No") or did not answer within 10 s, they automatically proceeded to the next famous name.

As the total set of 4,574 famous names was too long for one participant to work through, each participant saw one set of 250 randomly selected names which they could complete in one 45-min session. Selection of names that were presented to each participant was achieved using Qualtrics software (32). Participants could decide to do more sets of 250 words each (up to a maximum of 4) in one session. Data collection ended when each of the 4,574 famous faces had been rated by at least 20 participants.

For each of the 4,574 famous names, the number of times a participant indicated to know the name was calculated, relative to the total number of responses provided for this famous name. To illustrate, if exactly 20 participants responded to a famous name and 10 of them indicated to know the name, the calculated percentage was 50%. For the distribution of know-responses per famous name, see Figure 2. In this and following steps, we used a 30% cut-off to ensure enough variation in difficulty of stimulus material in the D-FFT. This means that 30% of participants who responded to the name should have stated that they knew it in order for that name to make it into the next step. As a result, the initial pool of 4,574 famous names was reduced to 1,978.

TABLE 2 Overview of categories and the corresponding Dutch and international number of names in step 1.

	Number of names		
Category	Dutch	International	Total
Art	80	36	116
Business and law	23	45	68
Film and theater	256	408	664
Institutions (e.g., Royals)	43	147	190
Literature and science	180	127	307
Public figures	149	166	315
Politics	245	541	786
Singers and musicians	399	680	1,079
Sports	483	602	1,085

The total number of famous names adds up to over 4,574 famous names (i.e., 4,610), as several famous names were assigned to multiple categories.

Step 2: Selecting photographs of the famous names 30% of participants stated that they knew in step 1

For the 1,978 famous names which remained after step 1 we focused on constructing a database of representative photographs, one for each famous person. Importantly, the photographs needed to be taken in the decade when the person became/was famous, not a contemporary one. In addition, specifically Dutch older adults needed to find the photograph representative and recognizable. The aim of step 2 of this study was (c) to collect representative photographs of the 1,978 selected famous names from step 1, and (d) to select the most representative photograph of famous persons who were famous in more than one decade.

C. Collection of photograph(s) of each famous person in their decade of fame

For the 1,978 famous names which resulted from step 1 we focused on constructing a database of representative photographs, one for each famous person. Portrait photographs were collected for each of the 1,978 famous names in (each of) the decade(s) when they were famous. For famous persons who remained famous for more than one decade (hereafter labeled "enduring"), one photograph was collected for each decade they were famous in. For famous persons who were famous during only one decade (hereafter labeled "transient"), one photograph was collected that was taken in the specific decade they were famous in.

Photographs could be found anywhere on the internet, but they needed to meet the inclusion criteria listed in Table 3. Ideally, the photograph also had an open-source creative commons (CC) license, so that it could be adapted and shared in a later stage. As photographs were standardized and thereby adapted, all CC licenses were accepted except

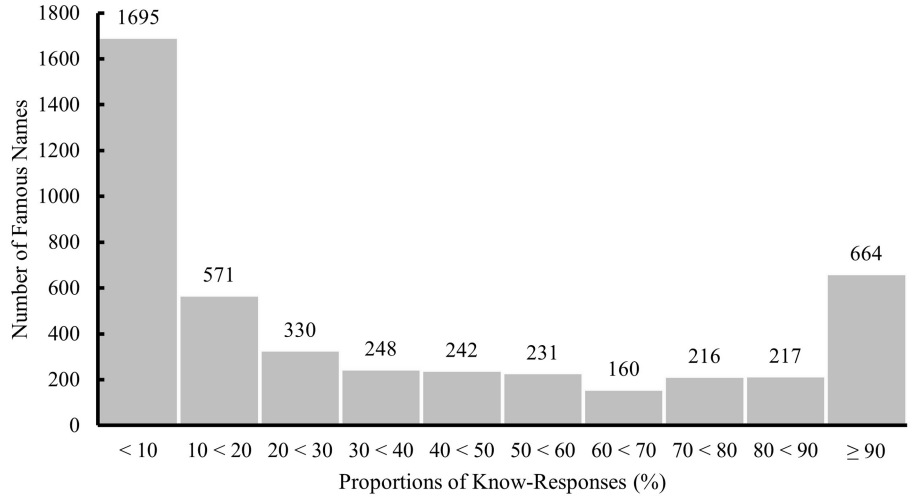

FIGURE 2
Distribution of proportions of know-responses to all 4,574 famous names evaluated in step 1. Labels on top of each bar indicate the number of famous names per interval.

TABLE 3 Inclusion criteria for photographs of famous faces.

Inclusion criteria
1. Sufficient size and quality, such that the face could be cut out and the remaining photograph would be of sufficient quality (i.e., at least 250 × 333 pixels).
2. Taken from the front (e.g., not side profile).
3. As few accessories as possible, but at least: no visible props (e.g., American flag, microphone, etc.) or accessories that could provide clues as to who the person was.
4. The photograph had to be dated and the photograph had to be taken within the decade that the person was famous.

for NoDerivatives (ND), as these may not be shared in adapted form. Hence, photographs with one of the following CC licenses could be included: Public domain or No Rights Reserved (CC0), Attribution (CC BY), Attribution Share Alike (CC BY-SA), Attribution-Non-Commercial (CC BY-NC), and Attribution-Non-Commercial-ShareAlike (CC BY-NC-SA). If multiple photographs were found of the same famous person in the same decade, the photograph that best matched the inclusion criteria was chosen. Of the 1,978 famous persons, 256 were excluded, because no photograph was found that met the inclusion criteria. Of the 1,722 remaining famous persons, 468 were enduringly famous and had multiple photographs from different decades. The other 1,254 transiently famous persons had one photograph. Using Photoshop, all famous faces were cut out and placed on a white background; the photograph was converted to black and white; and all photographs were resized to 250 by 333 pixels. In this way, all photographs were now in a standardized format. See Figure 3 for some example items.

D. Selection of the one representative photograph for enduringly famous persons

In total, 42 older adults participated in step 2 (see Table 1 for sample descriptive statistics). Stimulus material consisted of both the famous names that were selected in step 1 and the collected photographs of each famous face. For each famous name, participants saw the question: Do you know this person? ("Yes" or "No"). If they did not know the name (i.e., pressed "No") or did not answer within 10 s, they automatically proceeded to the next famous name. If they indicated to know the name, they saw the next question: Can you visualize this person's face? ("Yes" or "No"). If they indicated they could visualize the person's face, the different photographs of the famous person were presented on the screen at the same time. Participants selected the photograph(s) that they found most representative of the famous person, or they could indicate that they did not find any of the photographs representative.

As the total set of 468 enduringly famous persons was too long for one participant to work through, the total set was randomly split into two sets of 234 items. Subsequently, half of the participants saw one set of famous persons, and the other half of the participants saw the other set. The 234 famous names and the corresponding faces were presented in random order using Qualtrics EM software (32). Similar to step 1, data collection ended after each famous name/face had been evaluated by at least 20 older adults.

The photograph of each of the 468 famous persons was selected if participants judged them to be the most representative for that person. This selection was based on the number of times each photograph was judged as the most representative one. If different photographs of a famous person were chosen equally often, the photograph with an open-source CC license was chosen, as such photographs could be adapted, published, and shared. If none of the photographs had an open-source CC license, the photograph was selected that best matched the criteria in Table 3. Two famous persons were excluded after this step, as for them, most participants indicated that none of the photographs were representative. Consequently, a total of 1,720 photographs of famous faces remained, depicting 1,254 transiently and 466 enduringly famous persons.

FIGURE 3
Examples of test material of the D-FFT. The famous faces depicted here are part of the practice trial in steps 4 and 5 and are not included in the nine D-FFT versions. These photographs have a CC0 license (https://creativecommons.org/share-your-work/public-domain/cc0/) or are in the Public Domain and do therefore not require a consent statement.

Step 3: Selecting famous faces that Dutch older adults can actually name

Steps 1 and 2 of this study resulted in a collection of 1,720 representative photographs of famous persons. The aim of step 3 was (e) to examine which famous faces Dutch older adults could name when presented with the photographs remaining after step 2.

E. Selection of famous faces that older adults can actually name

In total, 452 older adults participated in step 3 (see Table 1 for sample descriptive statistics). Stimulus material in this step consisted of the photographs of 1,720 unique famous faces selected after steps 1 and 2. After a short practice session with five famous faces, participants completed the task. For each famous face, they saw the question: "Do you recognize this face?" ("Yes" or "No"). If they did not recognize the face (i.e., pressed "No") or did not answer within 10 s, they automatically proceeded to the next famous face. If they recognized the famous face, they saw the next question: "Do you know this person's name?" (responses could be: "Yes," "It is on the tip of my tongue," or "No, I do not know it"). If they did not answer within 15 s or answered anything other than "Yes," they automatically proceeded to the next famous face. If they answered "Yes," they were asked to enter the name of the person (without worrying about spelling).

As the total set of 1,720 famous faces was too much for one participant to work through in a single session, participants saw between 100 and 112 famous faces in one round. The 1,720 famous faces were divided into approximately similar sets with an equal number of faces per category. As some categories were bigger than others, this resulted in the different categories being unevenly represented in each set, e.g., one artist, 17 actors, 19 sportsmen, 9 public figures, 20 politicians, etc. Faces from each category were selected by pseudo random number generation in Excel (37). To be able to compare different sets that were completed by different participants, each set of 100–112 items had 24 overlapping items with only one other set. As an example, list 1 and list 2 had overlapping items and so did list 2 and list 3, but the overlap could not include the same items, such that list 1 and list 3 did not have overlapping items. After completing one set of famous faces, participants could choose to do another set. In that case, they would receive a new link via email. Participants could only see unique lists, that is, not do sets with overlapping famous faces. For each participant, the order of presenting the famous faces was randomized using Qualtrics EM software (32). Data collection ended when each of the 1,720 famous faces was evaluated by at least 35 older adults. The number of desired evaluations was higher for this step than for previous ones, because this step was the closest to a typical FFT and our eventual stimulus selection would be based on this.

Responses were defined as correct if the participant recalled the first and/or last name, or, if applicable, the correct artist's name (e.g., Madonna). Person-identity semantic knowledge (PISK) about the famous person was not taken as a correct response for the reason that specifically face-name associations appear sensitive to the earliest stages of AD (38, 39). In line with this, participants were not instructed to fill out semantic information if they did not know the proper name. In 76.23% of correct responses, the respondent filled out both parts of the name. In the remaining 23.77%, only the first or last name was filled out. In 3.90% of correct responses, a correct artist name was filled out instead of a first and/or last name. Responses that did not exactly match the correct name were checked and scored manually by two independent student assistants, after which the scoring forms were combined by a member of the research team. Spelling mistakes, phonological, and/or alternative spelling (e.g., Dutch spelling of an international name or vice versa) did not matter and happened in 26.51% of responses, which were then classified as correct. An incorrect response included when a person responded to the famous face but did not fill out the name, gave a wrong or incomplete name, or (in)correct PISK (e.g., former president of the U.S.). A response was missing if the participant did not respond to the famous face although it was presented to them for at least 10 s.

For each of the 1,720 famous faces, the number of correct responses was calculated relative to the total number of responses. To illustrate, if a famous face had 40 responses and 12 were the correct name, the relative performance for that face was 30%. In addition, the item-rest correlation (i.e., corrected item-total correlation) was calculated as the correlation between the score on each item and the rest score (total score minus the item score). The item-rest correlation served as an item-quality index, as higher item-rest correlations within a test are known to result in higher coefficient α (40). As the item score is binary, a point biserial item-rest correlation is obtained (41).

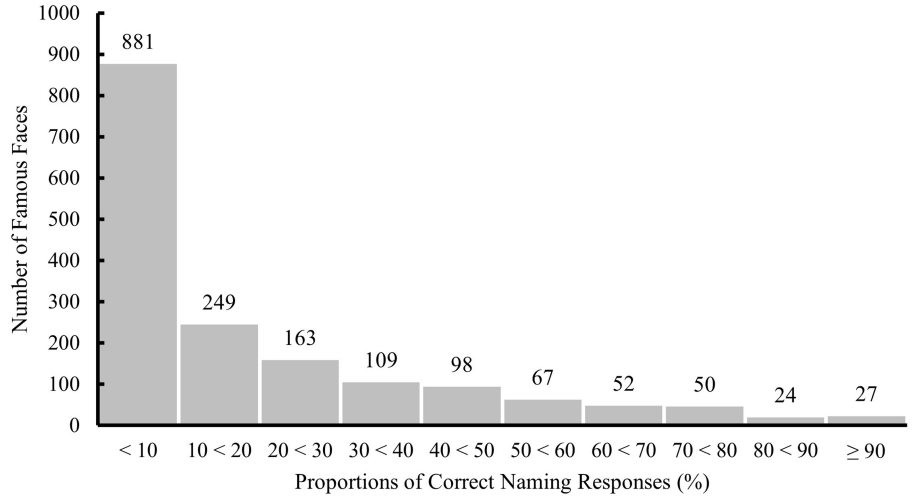

FIGURE 4
Distribution of proportions of correct naming responses to all 1,720 famous faces evaluated in step 3. Labels on top of each bar indicate the number of famous faces per interval.

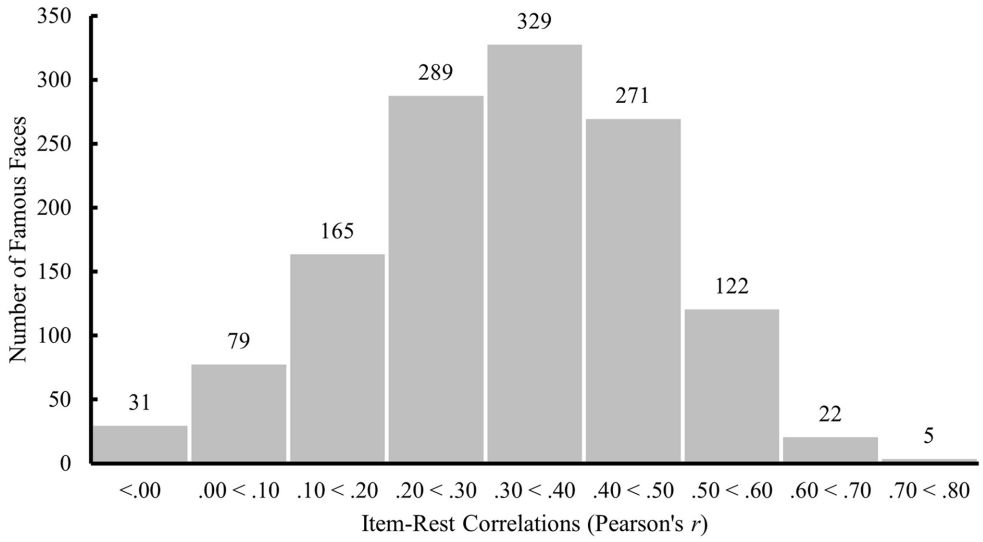

FIGURE 5
Distribution of item-rest correlations between participants' scores on a famous face and total scores for all other famous faces in step 3. Labels on top of each bar indicate the number of famous faces per interval [Item-rest correlations could not be computed for 407 famous faces which were either correctly (one face) or incorrectly (406 faces) named by all participants].

Over all 1,720 famous faces, the mean percentage of participants who gave a correct response was 19.01% ($SD = 23.51\%$, range: 0–100%, see Figure 4 for the distribution). The mean item-rest correlation was 0.32 ($SD = 0.15$, range: −0.19–0.78, see Figure 5 for the distribution). Relative performance of participants who had also completed steps 1 and/or 2 ($M = 55.03\%$, $SD = 21.99\%$) did not differ from that of individuals who had never seen the famous names before ($M = 53.04\%$, $SD = 20.72\%$), $t(450) = -0.97$, $p = 0.33$. There was no increase in performance for participants who did the task more than once, indicating that no learning effects occurred.

With the goal of only selecting famous faces that many participants could name while also avoiding ceiling effects, famous faces were selected for step 4 if at least 30% of the responses were correct. In addition, aiming for better item-quality, the point-biserial (item-rest) correlation had to be at least 0.20 (41). As a result, the 1,720 famous faces were reduced to 380.

Step 4: Selection of open-source Dutch-famous faces test items

Steps 1 to 3 of this study resulted in 380 photographs of famous faces. In step 4, we aimed for a final selection of items with an open-source CC license. In order to be able to share both the task

and stimulus material with other interested parties, an open-source CC license is required for each of the famous faces. The first aim of step 4 was (f) to replace famous faces with photographs with an open-source CC license if needed, that is, if they were not already open-source. This way, the stimulus material can be adapted, published, and shared in later stages. Subsequently, we aimed (g) to test all open-source famous faces in a sample of Dutch older adults, so that every participant saw each of the famous faces, of which some had been replaced by open-source photographs and were different from step 3.

F. Selection of categories and decades and replacement with open-source photographs

Given the goal of creating multiple D-FFT versions for longitudinal assessment, only items in the four categories with the largest number of famous persons and six most represented decades were selected. These include Film & Theater, Politics, Singers & Musicians, and Sports, from the 1960s until the 2010s. In other decades and categories, there were not enough famous faces left to evenly distribute them over (approximately) 10 versions. This selection led to 284 remaining famous faces, of which 103 already had an open-source CC license, i.e., could be made both publicly available and also used in clinical practice during later steps of this project. At this point, the initial pool of famous persons was reduced from 4,574 famous names to 380 famous faces that older adults could actually name, and an attempt was made to find a new representative photograph of the 181 famous faces that did not yet have an open-source CC license. Replacement photographs needed to match the criteria in Table 3, taken in the same decade, and this time with an open-source CC license. This was successful for 117 items, resulting in 220 open-source famous faces. These 220 photographs were selected as the final stimulus material for the new D-FFT that is comprised of only open-source items. Note that ideally, only open-source items would have been selected from the beginning, but unfortunately, we did not come to this realization until step 4.

G. Testing all open-source photographs in a sample of Dutch older adults

In total, 338 older adults participated in steps 4 and 5, of which 150 older adults were selected for step 4 by means of a random split (see Table 1 for sample descriptive statistics). As completing the D-FFT was part of a larger set of tasks, participants in steps 4 and 5 received 15 Euros as a reward for their participation. They could choose to receive the money on their personal bank account or donate it to a good cause; 52 percent of participants chose to donate.

After a practice session with 10 famous faces, participants completed the naming task. The D-FFT procedure was highly similar to step 3, except that the first question participants saw was: "Do you know this person's name?" They could respond: "Yes," "Yes, but it is on the tip of my tongue," "No, but I recognize the face," or "No, and I do not recognize the face." If they did not answer within 15 s or answered anything other than "Yes," they automatically proceeded to the next famous face. If they answered "Yes," they were asked to enter the name of the person (without worrying about spelling). Participants were required to respond within 90 s after which the next famous face automatically appeared on the screen. In this way, participants were encouraged to give their first reaction to each face and not spend too much time deliberating on the answer. Subsequently, participants completed the recognition task, which was not used for stimulus selection due to near-ceiling effects and therefore is not described in further detail in the current paper.

Participants completed all 220 D-FFT items, divided over two sessions that were completed within 1 week. The definition of a correct response and the calculation of performance were identical to step 3. Over all 220 famous faces, performance ranged from 8.05 to 98.66 percent ($M = 52.25\%$, $SD = 19.76\%$, see Figure 6 for the distribution).

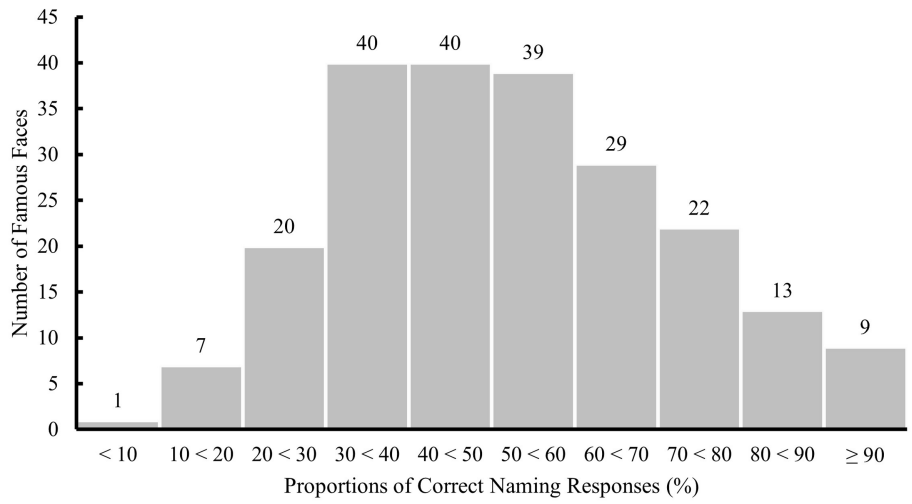

FIGURE 6
Distribution of proportions of correct naming responses to all 220 famous faces included in step 4. Labels on top of each bar indicate the number of famous faces per interval.

TABLE 4 Distribution of Dutch and international famous faces included in the 10 D-FFT versions in step 5 (excl. trial items).

		Category								
		Dutch				International				
		F&T	M	P	S	F&T	M	P	S	Total
Decade	1960s	3	0	12	5	5	9	13	1	48
	1970s	6	3	7	3	1	7	3	2	32
	1980s	8	9	9	4	2	5	2	1	40
	1990s	1	0	2	1	1	5	0	0	10
	2000s	1	6	2	4	2	7	3	1	26
	2010s	9	8	6	4	1	11	1	4	44
Total		28	26	38	21	12	44	22	9	200

F&T, film & theater; M, music; P, politics; and S, sports.

Step 5: Development of different Dutch famous faces test with equivalent mean difficulty levels

Step 4 of this study resulted in 220 open-source photographs of famous faces that had all been judged by 150 individuals (including 20 trial items). In step 5, we aimed to create short versions that were equivalent in terms of mean difficulty. Creation of short parallel versions is important in order to test individuals over time and also for use in clinical practice. The aims of step 5 were (h) to create parallel task versions of the D-FFT and (i) to test these versions in the remaining selection of 188 Dutch older adults in order to create tests with equivalent mean difficulty levels.

H. Creation of different D-FFT versions each with an equivalent mean difficulty

The 220 famous faces were divided into 10 D-FFT versions, each comprised of 20 famous faces, and 20 items that can be used for practice. The D-FFT versions were developed based on the following three criteria, in order of importance: (1) mean performance in step 3, (2) distribution of the four categories, and (3) distribution of the six decades. The distribution of Dutch and international famous faces included as stimulus material in the 10 D-FFT versions is presented in Table 4.

The items were divided over 10 D-FFT versions following the procedure described in the Statistical Analysis section. 200 items were divided over 10 D-FFT versions of 20 items each, with 20 trial items. Mean performance over all participants on each version ranged between 51.16 and 53.71 percent ($M = 52.42\%$, $SD = 0.97\%$), based on the 150 participants in step 4. All versions had four items in the category Film & Theater, seven items in Politics, six items in Singers & Musicians, and three items in Sports. All versions had eight items from the 1960 and 1970s, four items from the 1980s, one item from the 1990s, and seven items from the 2000 and 2010s.

I. Comparison of the D-FFT versions to ensure equivalent mean difficulty

The 10 D-FFT versions were tested in the remaining selection of 188 Dutch older adults (see Table 1 for sample descriptive statistics). As this selection resulted from splitting the total sample of 338 individuals who participated in steps 4 and 5, the D-FFT procedure was identical to step 4.

Equivalence of the 10 D-FFT versions was assessed by means of a repeated measure analysis as was described in the section Statistical Analysis. At the 0.05 level of significance, the omnibus F-test for testing the null hypothesis of equivalence of the proportion of correct naming responses was significant: $F(9, 1{,}683) = 2.82$, $p = 0.003$. Using Tukey's procedure for all pairwise comparisons, only the difference between the extremes was significant. Therefore, we removed the version with the highest mean and reassessed equivalence. For the remaining nine versions, the null hypothesis that all means are equal against the alternative that at least one pair has different means, could not be rejected at the 0.05 level of significance: $F(8, 1{,}496) = 1.89$, $p = 0.058$. Over the 180 famous faces that were included in the nine D-FFT versions (i.e., excluding the 20 trial items and the removed version), performance ranged from 12.97 to 98.94 percent ($M = 49.10\%$, $SD = 19.49\%$, see Figure 7 for the distribution).

Hence, nine of the D-FFT versions, all matched on the number of items per category and decade, were of equivalent mean difficulty. An overview of mean performance over the nine D-FFT versions is presented in Figure 8. The cumulative number of famous faces per proportion of correct naming responses to the 20 famous faces in each D-FFT version, including mean naming performance and standard deviations, is presented in the Supplementary material.

General discussion

The aim of the current study was to explore the possibility of developing a Famous Faces Test specifically for older adults living in the Netherlands. Previous FFTs have generally not been developed for specific populations so they tend to be unstandardized and not generalizable. In pilot work conducted in our lab, a generic FFT was indeed found to be unsuitable for our population of interest, mainly due to the stimulus material used in previous studies. A new test was required. We also wanted to develop enough, short versions which we could use to (a) compare mean performance between the normal-aged controls and a clinical population and (b) create personalized norms for the normal aged controls that could be used to compare performance within the clinical population. The current article outlines the five steps taken to select famous faces in order to design and develop nine short versions of the Dutch FFT for older adults (60+) that are equivalent in terms of mean difficulty.

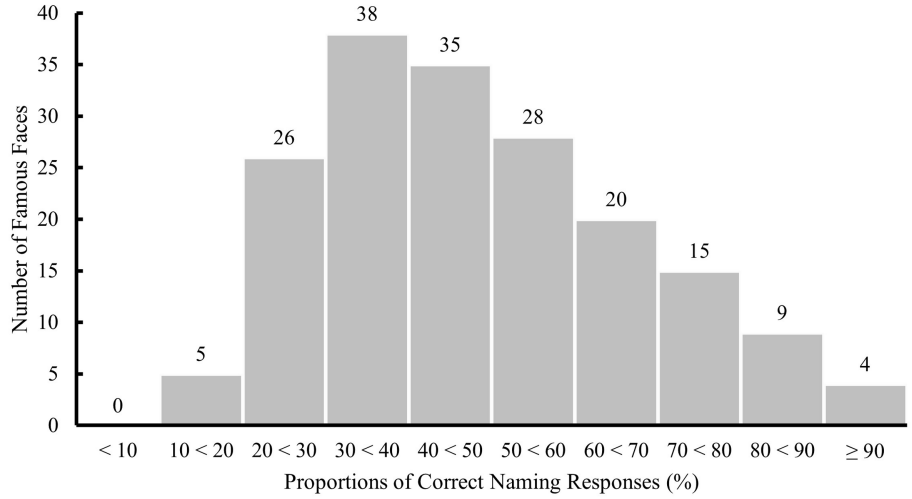

FIGURE 7
Distribution of proportions of correct naming responses to the 180 famous faces included in nine D-FFT versions in step 5 (excluding trial items and removed version). Labels on top of each bar indicate the number of famous faces per interval.

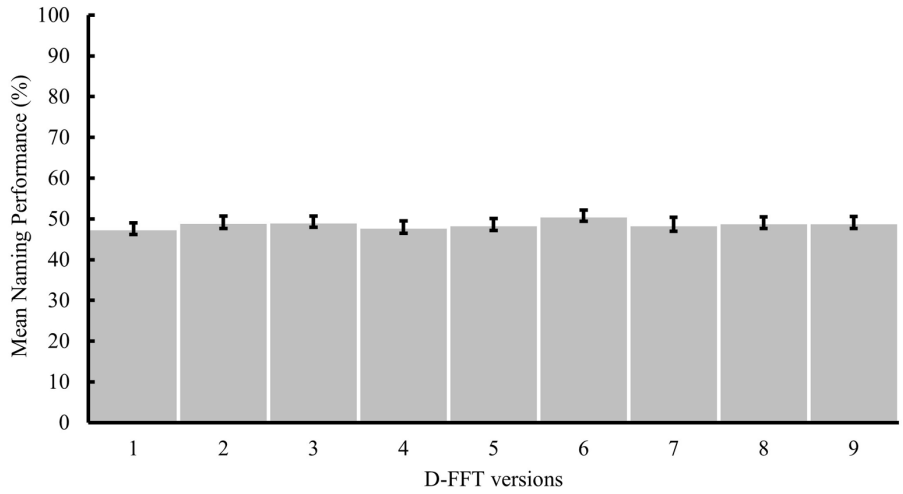

FIGURE 8
Mean naming performance on the nine D-FFT versions in step 5 with error bars representing the standard errors of the means.

The current study has several unique strengths. To the best of the authors' knowledge, this was the first time a Dutch FFT was developed specifically for older adults living in the Netherlands and also the first time an FFT was developed in a systematic, replicable manner. Starting with a collection of over 4,500 famous names in step 1, the current study produced nine short D-FFT versions of equivalent mean difficulty and balanced in terms of stimulus characteristics [i.e., the decade(s) in which the famous people were famous and the category they belong to] in step 5, that can be used for cross-sectional comparison as well as subsequent longitudinal assessment of cognitively normal and clinical groups. The selection of stimulus material was based on names that were known by at least a proportion (30%) of older adults, with photographs from the decade when the person was famous that were voted most representative by the current sample. Researchers interested in developing their own FFT-stimulus material could follow the steps outlined here for the specific country and/or population that they are interested in. They could also avoid some of the pitfalls possible in selecting material for such a task (including for example starting with open-source material if they want to make their task more widely available). The current study resulted in nine short D-FFT versions which we will use in the next part of this larger, ongoing project to explore both group differences (specifically do people with preclinical AD and/or MCI differ from normal, age-matched controls on this task) and individual differences (specifically which personal characteristics impact performance on this task).

A standard FFT was found in four previous studies to be sensitive to preclinical AD as indicated by biomarker assessment and/or clinical diagnoses several years after initial testing (25–28). Hence, detecting even the smallest impairment in FFT performance may be the key to timely AD diagnosis or at least indicate that comprehensive testing (i.e., standard clinical workup) should be considered. As every step in the development of the Dutch FFT is described in this article in detail,

the task can easily be updated for new generations, and it could feasibly be developed for other countries as well. Importantly, older adults enjoyed filling out the D-FFT, as indicated by their frequent positive informal feedback and by step 3 where some participants enjoyed doing the task so much, they completed up to 11 rounds. Attrition rates are high for older adults in most longitudinal studies, with up to 29% older adults lost per wave, even when those lost to death and illness are excluded (42, 43). Attrition rates in future studies designed to track within-person trajectories over populations of older adults could be reduced when participation enjoyment is high. We will continue to assess this important aspect in future studies using the D-FFT. Lastly, because all famous faces have an open-source CC license, they can be published and shared with other researchers and health care professionals, even in their adapted, standardized formats.

Some limitations are however also worth mentioning. A major limitation of this study and approach is of course that the entire process including the selection of new photographs of famous faces will need to be repeated at least every decade in order to remain up to date with what is current in the world of politics, film and theater, sports, and music. Highly educated people were overrepresented in all five steps in the current study, i.e., between 68 and 80% had either finished high-level secondary education or had even obtained a university degree. As highly educated people perform better than those with less education in the naming of famous faces (44), difficulty levels of the Dutch FFT may currently be underestimated. Future data collection should ideally focus on a more representative sample, to optimize understanding of how individual differences, including educational level, affect performance on the D-FFT. Furthermore, although the nine versions were of equivalent mean difficulty, individual differences that potentially impacted performance have not yet been examined. Although a 30% cut-off criterion was used in steps 1 and 3, this was not applied in the last steps, which resulted in a recall performance below 30% for 31 items in step 5. However, performance was not below 10% for any of the famous faces and the 31 items are distributed over the nine D-FFT versions. At the individual level, these more difficult famous faces may be helpful when testing people who perform at a high level in order to avoid ceiling effects. Furthermore, because there are so few of these items, it is not expected that they will cause floor effects.'

In the next step of this ongoing project, the comparability of the nine D-FFT versions will be further explored considering the effects of personal characteristics, such as demographics (i.e., age, gender, and education) and other background information, including overall cognition-related (e.g., cognitive reserve) and D-FFT-specific variables (e.g., participants' interests in the four different categories). Developing norms for our healthy older adults based on a range of such person-characteristics, as well as item-characteristics (e.g., the decades and categories in which celebrities occurred, their gender and nationality) will be useful to compare performance on the same FFT within clinical groups in a later phase of this project. In addition, we will examine in the next steps of this ongoing project whether a temporal gradient, as has been found in previous studies exploring preclinical AD (26, 29) is apparent or not in the D-FFT performance of CN older adults. As such, we aim to gain more insight into memory function in different stages of the AD continuum and specifically explore how to distinguish preclinical AD from normal aging. We will examine other response options, such as tip-of-the-tongue experiences (TOT), as well as the multiple-choice recognition task that was included in our D-FFT but not used for stimulus selection due to near-ceiling effects. We expect that this may be especially informative in individuals diagnosed with subjective cognitive complaints, MCI, and/or early AD (45). The D-FFT will also be compared to traditional neuropsychological tests within the same clinical population at a later stage in this ongoing project. Does our test perform as well as (or better) in classifying patients into the three clinical groups; namely preclinical AD or those who have subjective cognitive complaints (SCC), MCI and/or early AD? The nine versions of the D-FFT will also be used to explore group differences between normally aging and clinical populations. Standardizing the FFT, assessing background variables and testing these in both normally aging and clinical populations would be a major step forward in this field.

Conclusion

This article describes the steps taken to select stimulus material for the first Dutch FFT, specifically for older adults. The systematic collection and selection of famous faces through five steps led to nine short D-FFT versions of equivalent mean difficulty. These nine D-FFT versions allow for the comparison of cognitively normal older adults and clinical populations by means of a short, enjoyable task that can be performed at a time and location convenient for the participant. Given that the standard FFT appears to be sensitive to preclinical AD (25–28), the development of a standardized FFT specifically for Dutch older adults may be the next step toward timely AD diagnosis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the ethical review board of the Tilburg School of Social and Behavioral Sciences at Tilburg University. The participants provided their written informed consent to participate in this study.

Author contributions

EE, KD, RM, and YB contributed to the conception and design of the study. EE coordinated the data collection, organized the database, and wrote the first draft of the manuscript. EE and KD performed the statistical analysis. KD, RM, and YB critically revised the manuscript for important intellectual content. EE, RM and YB wrote the sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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A new multidimensional group intervention for cognitive and psychosocial functioning for older adults: Background, content, and process evaluation

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Introduction: An essential element of quality aging is the maintenance of cognitive and psychosocial functioning. The principal objective of the present paper was to present the theoretical framework, content and process evaluation of a newly developed multi-dimensional group intervention designed to strengthen/improve areas of cognitive and psychosocial functioning in adults over 65.

Methods: The intervention implements multiple methodologies aiming to facilitate contextual integration of learned concepts and strategies derived from clinical psychology and rehabilitation. It moves seamlessly on the cognition–emotion axes and consists of five active ingredients selected to address challenges associated with aging: Memory Compensatory Strategies, Problem-Solving, Emotion Regulation, Mindfulness, and Locus of Control. Thirty participants joined the intervention group aged 65–75 years (M=69.03; SD=3.04). All 30 participants who were included in the intervention group completed the program.

Results: Results from the Participant Satisfaction Scale indicate that the program was perceived very positively by participants, who also reported implementing their newly learned strategies in activities of daily life. Furthermore, there was high correlation between internal locus of control and the learned strategies.

Discussion: The outcomes of this analysis indicate that the intervention is feasible and well tolerated by our target group. This multidimensional intervention may offer a valuable contribution to public health care and dementia prevention for older adults.

Clinical Trial Registration: [https://clinicaltrials.gov/ct2/results?cond=NCT01481246], identifier [NCT01481246].

KEYWORDS

intervention, aging, cognitive aging, psychosocial functioning, cognitive functioning, emotion regulation, memory compensation strategies, locus of control

Introduction

The increase in life expectancy and health concerns associated with demographic aging is of global interest. An essential element of quality aging is the maintenance of brain health and actions to prevent dementia (1).

The literature supports a biopsychosocial perspective aiming at the development and implementation of interventions that target concepts such as successful aging, active aging and healthy cognitive aging (2, 3). Common to all concepts, is the need to develop and maintain functional capacity of older people, emphasizing in psychosocial and cognitive factors.

In line with the biopsychosocial approach, there has been a growing interest in interventions that adopt a multidimensional approach to cognitive aging (4). Some studies used a multidimensional approach for raising awareness of modifiable factors that contribute to cognitive decline such as physical activity, nutrition, interpersonal relations, and stress management, showing a significant increase in raising awareness after the intervention, indicating the effectiveness of such educational programs (5, 6). Another study used everyday memory and metacognitive intervention to improve everyday functioning (7) by focusing on improving older adults' ability to achieve cognitively challenging everyday life tasks. Results showed improvements in everyday memory functioning and extended functional independence. Hoogenhout et al. (8), focused on psychoeducation for cognitive health through the use of self-regulation over habitual behaviors that often interfere with daily functioning. Their findings indicated reductions in negative emotional reactions toward cognitive aging, which, they assert is a prerequisite for improved subjective cognitive functioning and well-being. Finally, Ruvalcaba and Merino (9) promoted quality of life, physical activity, improved nutrition and cognitive function, through the use of theoretical–practical intervention. Results showed improvements in self-efficacy for quality of life, physical activity, nutrition and cognitive function.

The present research is part of a systematic effort to design and implement interventions that promote healthy cognitive aging, targeting cognitive and psychosocial abilities. The new intervention extends previous research and integrates knowledge from clinical psychology and cognitive rehabilitation. It conceptualizes five active ingredients which are trained sequentially and in parallel and targets multiple outcomes. Furthermore, the intervention goes beyond the simple didactic mode of transmitting information, to the implementation of role-play and case scenarios from real life to provide opportunities for application of the new skills in the real-life context. At the same time, the intervention addresses a relatively stable component of personality, that of locus of control, whose modification is targeted through the intervention. The purpose of the present article, is to describe the intervention's theoretical background, content and methodology in order to enable application and replication by researchers in cognitive and psychosocial rehabilitation. In addition, it provides information on the intervention's feasibility and acceptability by the participants as recommended by the literature (8, 10, 11).

Integrating cognitive and psychosocial dimensions for the group intervention

The present novel multidimensional, non-pharmaceutical group intervention integrates key theoretical principles from clinical psychology and cognitive rehabilitation to improve cognitive and psychosocial functioning in adults over 65. The intervention moves seamlessly on the cognition–emotion axes and consists of five active ingredients selected to address challenges associated with aging: Memory Compensatory Strategies, Problem-Solving, Emotion Regulation, Mindfulness, and Locus of Control. These active ingredients were specifically selected as they are important for the cognitive and psychosocial well-being of older people and deficiencies in these areas may pose a threat to independent living and successful aging. The intervention integrated concepts of cognitive rehabilitation such as training in memory compensation strategies and problem-solving and from clinical psychology such as applied emotional regulation strategies, mindfulness, and locus of control, bringing to light the "hot" emotional aspects of executive functions (12). Hot executive functions include future-oriented cognitive processes relevant to environments or situations that can generate emotions and encompass motivation, decision making and social behaviors (13). Those connections between emotion and cognition help maximize functionality in daily life.

The above elements are important novel aspects of this intervention. As an example, previous interventions make reference to stress management through relaxation techniques (5) or the reduction of negative emotional reactions through positive thinking (14). The present intervention, in addition to relaxation to assist with stress management, incorporates concepts of mindfulness and emotion regulation in conjunction with problem-solving strategies, to build connections between emotion and cognition and to help maximize functionality in daily life.

Participants were trained on the interplay between cognition and emotion and the 10-week group intervention incorporated didactic (psychoeducational) methodologies, role-play, peer support, and take-home exercises for contextual integration of learned concepts and strategies. Figure 1 presents the multidimensional instruction methods used. Each session begins with direct instruction, which continues with interactive instruction and indirect instruction and concludes with independent study. In all methods, both cognitive and emotional processes are trained. During the program, the various teaching methods are aligned to positively reinforce each other. For example, during training in the use of Memory Compensation Strategies, interactive teaching methods such as role play and peer support, reinforce indirect teaching such as case studies, which in turn facilitate the participant's ability to complete homework and in turn reinforce indirect teaching methods such reflective discussions in the next session. Figure 2 presents the conceptual framework of the design of the intervention. The following sections provide a description of the key active ingredients and the primary outcome measures associated with each ingredient.

Memory compensation strategies

Since memory problems are the most obvious complaints in older people (15), most interventions have focused on strengthening the mnemonic function and the implementation of compensatory strategies. Memory Compensation Strategies (MCS) refer to a group of mechanisms through which individuals can continue to perform well in complex tasks despite having experienced deficits or reductions in memory capacity (16). MCS were incorporated as a key cognitive strategy aiming to train participants to develop effective strategies that support effective information coding (17). Participants were trained in the use of eight internal (e.g., semantic correlation and repetition) and external strategies (e.g., notes and placing reminders) derived from educational psychology (18), and cognitive rehabilitation (19, 20). Importantly, the new intervention encouraged participants through in-house and takes home exercises to learn and incorporate new MCS strategies in addition to their established ones. Improvement in this area was measured by "Scale of Implementation of Memory Compensation Strategies (21)."

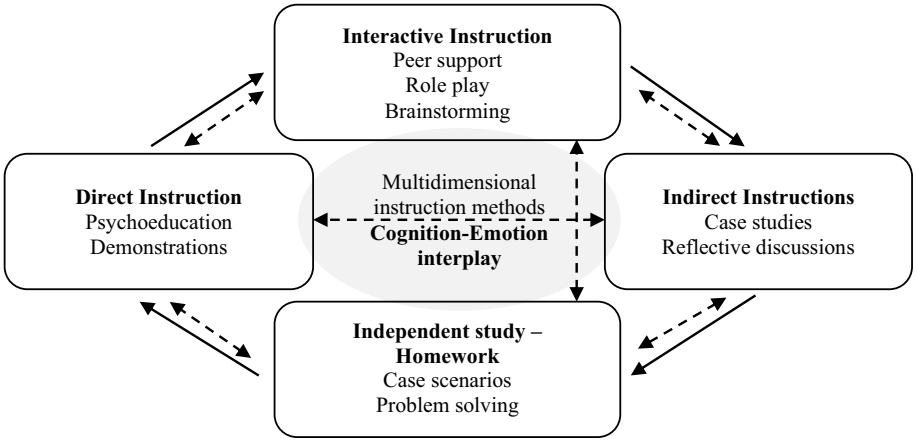

FIGURE 1
Multidimensional instruction methods.

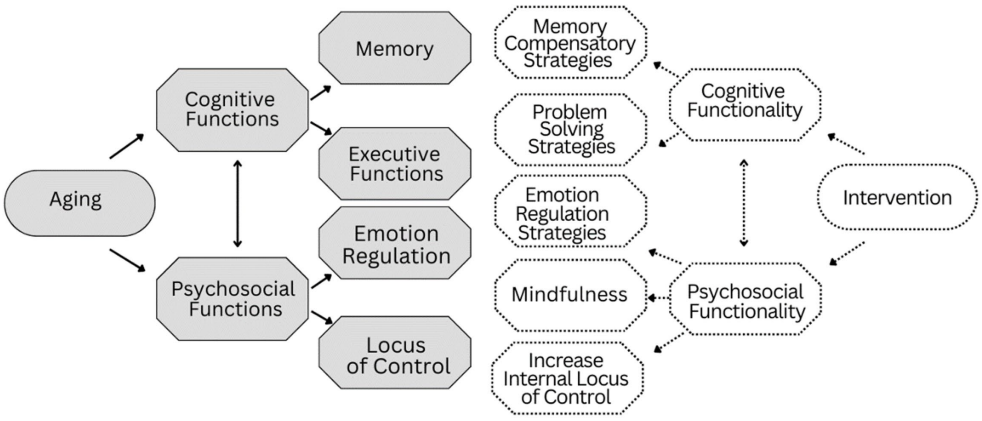

FIGURE 2
Conceptual framework of the intervention program.

Problem solving strategies

Along with MCS, Problem-solving (PS) training is an important aspect of cognitive interventions designed to enhance cognitive and psychosocial functioning (19, 22). PS is considered a component of executive functioning, a cognitive domain which, like memory, is also vulnerable to the effects of healthy aging (23–25). Older adults without neurodegenerative disease or mild cognitive decline, may demonstrate difficulties in problem solving and decision making (22, 26, 27).

The present study presented and trained participants in a five-step PS process as part of the "Think & Act" section. The PS training included four phases: (a) Brainstorming: participants were guided in generating possible and alternative solutions to solve a problem; (b) Planning and organization: individuals were guided in evaluating and comparing the solutions created and in defining the analytical implementation strategy for the selected solution; (c) Role play: practicing the strategies to scenarios presented by the researcher during the session; and (d) Generalization: applying their newly learned skills to a real-life problem at home as part of their homework assignment.

As part of the PS training, participants were guided in identifying areas of possible improvement for their overall health. Lifestyle factors such as nutrition and physical activities/movement were targeted as overall strategies promoting physical health and well-being. Specifically, deficiencies in those areas were identified individually for each participant and were approached with the PS process in order to implement positive changes to overall health. Improvement in this area was measured by "Problem-Solving Inventory" (28, 29).

Emotional regulation strategies

Emotional regulation (ER) is an important element of effective problem solving (30) and a key dimension of psychosocial functioning. ER is also considered an indicator of positive adaptation to the negative aspects of aging (31). ER was included in this study as a 'hot' area of executive functioning (32, 33) with the aim of

enhancing psychosocial and cognitive functionality. ER was addressed through the "Stop & Relax" process which incorporated key elements of regulating emotions as described by Gratz and Roemer (34). Participants were trained to recognize, name and accept emotions but also to use diaphragmatic breathing in order to relax, reduce physical arousal and implement effective PS strategies using the "Think & Act" techniques. They were asked to maintain a weekly diary of emotional clarity with the aim of identifying and accepting emotions as well as practicing diaphragmatic breathing weekly. Improvement in this area was measured by "Difficulties in Emotion Regulation Scale" (34, 35).

Mindfulness

Mindfulness refers to the present-oriented attention within the self (e.g., body sense, thoughts, feelings) and outside (environment) without criticism (36). Research on mindfulness indicates that it is a beneficial modality for ER, EF, and memory (37–40). However, research on mindfulness and aging is understudied. The present study incorporated mindfulness as part of ER and the "Stop & Relax" procedures to facilitate emotional functioning, problem-solving, executive functioning, and memory performance. The combination of ER and mindfulness is thought to have an additive effect as compared to using each of the two in isolation. The implementation of mindfulness and other strategies addressed in the program, aimed at improving locus of control. Improvement in this area was measured by "Mindful Attention Awareness Scale" (41, 42).

Internal locus of control

Locus of Control (LC) is a psychological construct that evaluates beliefs about one's ability to influence situations in their lives (internal LC) or whether these are left to external forces (external LC) (43). Research suggests that biological aging interferes with the sense of control in older people (44, 45). This decrease in perceptual control is clearly related to the increasing diffusion of age-related barriers and restrictions, such as biological and social changes (e.g., retirement, reduced incomes, cognitive changes, bereavement) (46).

LC may be modifiable in response to both life events and after training (46, 47). The present intervention integrates LC in all aspects of the program by empowering participants to gain knowledge the various aspects of aging, on implementing strategies for healthy physical and cognitive aging and applying methods to promote memory, PS and ER. Participants were encouraged to discuss personal obstacles and were guided to take systematic guidance actions in order to improve life outcomes and reduce beliefs that their lives depend on external factors (luck, strong others). The shift from external LC to internal LC could facilitate the implementation of cognitive and emotional strategies to promote healthy cognitive aging. Improvement in this area was measured by "Multidimensional Locus of Control" (29).

The aim of the present study was the implementation of a multi-dimensional group intervention designed to strengthen areas of cognitive and psychosocial functioning in adults over 65. The intervention implements multiple methodologies aiming to facilitate contextual integration of learned concepts and strategies derived from clinical psychology and rehabilitation. The intervention is novel as it moves seamlessly on the cognition–emotion axes and consists of five active ingredients selected to address challenges associated with aging: Memory Compensatory Strategies, Problem-Solving, Emotion Regulation, Mindfulness, and Locus of Control. It was hypothesized that participants would perceive the intervention as a useful approach to improve cognitive and emotional functioning and that those who demonstrated high levels of internal locus of control would report greater engagement in implementing their new knowledge in activities of daily living.

Methods

Participants

Sixty-nine community dwellers were initially recruited to participate in this study. Nine people were excluded due to non-compliance with the admission and exclusion criteria. This research was incorporated into the Neurocognitive Study of Aging (NEUROAGE) which is the first systematic and longitudinal study of cognitive aging in Cyprus (NCT01481246) (24, 48).

The remaining 60 participants were randomly assigned into the intervention and control groups. Thirty people joined the intervention group, of which 19 were women and 11 men aged 65–75 years ($M = 69.03$; SD = 3.04). The control group also consisted of 30 people, 21 of whom were women and nine men, aged 65–75 ($M = 70.12$; TA = 3.51). The level of education was quantified as the number of years of formal education achieved by each participant and ranged from 8 to 17 years ($M = 11.7$, SD = 2.11) for the intervention group, and for the control group ($M = 11.76$, TA = 2.02). The two groups were matched on key demographic variables as well as on the Mini-Mental State Examination performance ($M = 28.31$, SD = 1.80 for the intervention group and $M = 28.06$, SD = 1.95 for the control group). Figure 3 is the CONSORT diagram.

The inclusion criteria for all participants were the following: (1) Native Greek speakers; (2) males and females over the age of 60; (3) Good general health with no previous history of neurological disorder such as head trauma, stroke or neurodegenerative disorder; (4) No emotional or psychiatric disorder as defined by the Diagnostic-Statistical Manual of Mental Disorders, Fifth Edition (DSM-V); (5) Results on neurocognitive tasks falling within the normal range as derived from normative data of the NEUROAGE (within 1 and −1 z scores).

Measures

Participants were initially evaluated with the neurocognitive evaluation lasting about 2 hours, which examined the general mental function, memory, executive functions and language as described by our previous work (24, 48). This evaluation was conducted to ensure normal cognitive function for the study participations.

In addition to the neurocognitive evaluation, the study implemented the following primary outcome (dependent) measures relevant to the theoretical components of the intervention and were administered at baseline, posttest and follow-up:

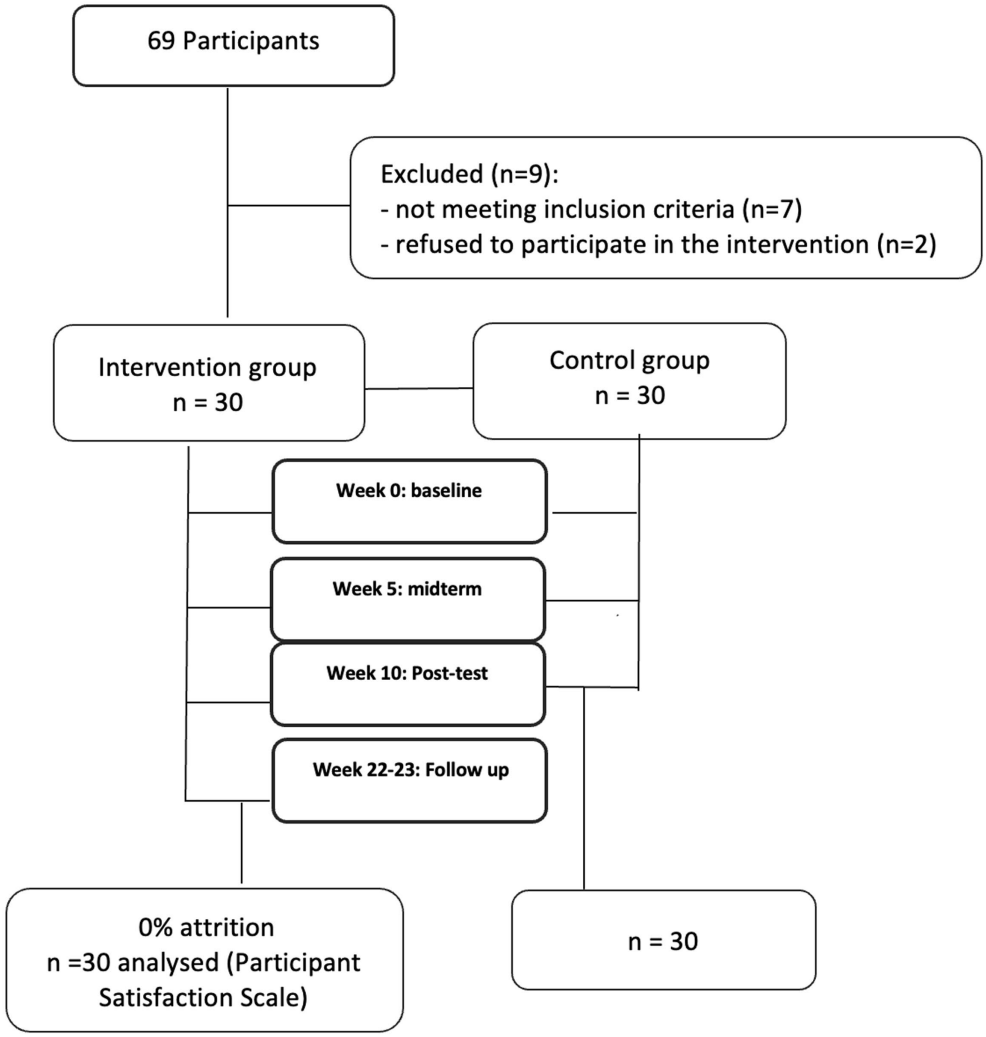

FIGURE 3
CONSORT flowchart.

1. Multidimensional Locus of Control Inventory (29, 49).
2. Problem-Solving Inventory (28, 29).
3. Difficulties in Emotion Regulation Scale (34, 35).
4. Scale of Implementation of Memory Compensation Strategies (21).
5. Mindful Attention Awareness Scale (41, 42).

Participant satisfaction scale

For the purpose of this intervention, a questionnaire consisting of 18 statements was created to investigate the satisfaction of participants in key areas of the intervention and their ability to apply the new knowledge and skills in their daily lives. The questionnaire consists of three parts. The first part consists of statements in which participants rate their satisfaction with general aspects of the intervention such as the topics addressed in the meetings, the organization and preparation of the instructor and satisfaction with the instructor. Questions could be answered on a 5-point scale (1 = very dissatisfied, 5 = very satisfied). The second part consists of statements assessing the degree of agreement on issues specific to the intervention such as gaining knowledge on healthy cognitive aging, on overall motivation to increase locus of control, and the effectiveness of the group format. Questions could be answered on a 5-point scale (1 = disagrees absolutely, 5 = agrees absolutely). The third part includes statements to evaluate their ability to apply strategies learned during the program in their daily lives (i.e., memory, problem-solving, and Emotion regulation strategies). Questions could be answered on a 5-point scale (1 = poor, 5 = very good). A high internal consistency of the questionnaire was identified in the sample, with Cronbach's a determined 0.91. Participant Satisfaction Scale was administered at the end of the intervention (10 week).

Multidimensional locus of control inventory

The Greek version of the Multidimensional Locus of Control was used (29). The scale consists of 24 items scored on a six-point Likert

scale, ranging from −3 (Strongly Disagree) to +3 (Strongly Agree). The scale yields three distinct factors: Internality, Powerful Others, and Chance. Each subscale produces a unique score by adding up the eight responses and adding to the sum a constant of +24 to eliminate negative sums. Therefore, each respondent received three scores (each one ranging from 0 to 48) indicative of his/her relative view on each of the three dimensions. An individual could score high or low on all three dimensions. Acceptable internal consistency of the questionnaire was identified in the present sample, with Cronbach's a determined 0.84 for Internality, 0.79 for Powerful Others, and 0.83 for Chance.

Study design

Participants were assigned into five groups of 6 people. The intervention was conducted weekly over ten, 90-min sessions, with a mid-point evaluation (at five weeks) and a post-treatment assessment at the end of the intervention. There was a follow-up assessment on the dependent measures 12 weeks after the end of the intervention. To reduce response bias error, all participants completed the questionnaire anonymously and privately; they placed the completed questionnaire in an envelope containing a unique code that was then used to manage the data.

Intervention procedures

The intervention was designed as 90-min weekly group meetings lasting 10 weeks. The intervention was developed by a doctoral-level licensed and certified academic speech-language pathologist with expertise in cognitive-communication disorders (F.C.) and a doctoral student in Clinical Psychology (A.C.) also licensed in School Psychology, who facilitated all sessions. Another graduate-level researcher monitored the process in each session with the aim of confirming that all groups and meetings followed the same content and procedures. The meetings were originally planned to be conducted in person. However, due to the restrictions implemented to control the spread of COVID-19, the intervention was transformed into an online format. Study participants were trained in person in the use of the Rakuten Viber online platform. This specific platform was selected as participants were more familiar with it and several were using it already in their daily lives. It has numerous options; e.g. it has high-quality video call, better voice quality with less noise throughout all bandwidths, in comparison with other free platforms and provides group chat rooms (50). These elements make this platform suitable for teleconferencing purposes. Viber also provides official desktop version for the apps that can be used in laptops or personal computers. In addition, a family member familiar with the specific platform was available to offer technical support at home during the start of each session. Participants received printed packets of materials required for the program in advance of each group session.

Presentation format

Each session began with a presentation, followed by direct practice in the use of the proposed strategies through scenarios provided by the researchers as well as through scenarios derived from their personal experience. The content was organized hierarchically aiming to connect the theoretical principles for memory, problem-solving, emotion regulation, and locus of control through psychoeducation and contextual training *via* role play, repetition, and weekly homework with real-life scenarios. The intervention was adaptive in that, e.g., success in week 8 was partly dependent on mastering content from week 2. The intervention's content is listed in Table 1.

Statistical analyses

To investigate the satisfaction of participants in key areas of the intervention and their ability to apply the new knowledge and skills in their daily lives, standard descriptive statistics were utilized, including means, standard deviations and percentages. Pre and post-testing was conducted for all the primary outcome measures and mid-point assessment was conducted for the locus of control and memory strategies. For the purpose of the present study which was to explore potential associations between locus of control (LC) and the self-assessment of participants' ability to apply their newly trained strategies upon completion of the intervention (at post-test), the post test measures were analyzed. Pearson's correlations coefficients were performed to examine the relationships. All analyses were carried out with SPSS (version 27).

Results

Attrition rate

All 30 participants who were included in the intervention group completed the program. Most of them (94%) attended all 10 sessions. Three participants missed one session and one participant missed two sessions due to illness or family obligations.

Responses to the participant satisfaction scale

Participant responses regarding the general aspects of the intervention indicate that the majority of participants (90%) were extremely satisfied with the meeting topics ($M = 4.90$, SD = 0.30), with the organization and preparation of the instructor (97%, $M = 4.96$, SD = 0.30), and support provided by the instructor (96.7% $M = 4.96$, SD = 0.18). A high percentage of participants (86.7%) strongly agreed that the meetings were a positive experience ($M = 4.88$, SD = 0.34).

Participants reported high levels of satisfaction for gaining new knowledge and skills. Specifically, 87% indicated that the meetings met their expectations for receiving information related to cognitive health ($M = 4.50$, SD = 0.57) and 90% reported that the meetings met their expectations in developing new skills ($M = 4.90$, SD = 0.30). Specifically, 86.7% reported that they gained knowledge about risk factors for pathological aging ($M = 4.86$, SD = 0.34) and 86.7% that they learned applied strategies they can use in everyday life ($M = 4.83$, SD = 0.42). Most of the participants (76.3%) reported that the meetings motivated them to take control of their life and 76.7% felt motivated to take action for their cognitive health ($M = 4.76$, SD = 0.43). Finally, 63.3% indicated that they applied the general strategies they learned

TABLE 1 The main axes of the meetings of the intervention program.

Week 1	
Description	Introductions, group procedures, group rules and etiquette, setting goals and expectations
Homework	/
Week 2	
Description	Psychoeducation for cognitive aging, development of healthy lifestyle practices/protective factors (such as diet, physical exercise, socialization, involvement with activities that stimulate the brain). Discussion and sharing by group members about their experiences regarding cognitive difficulties/changes Introduction of locus of control and strategies to increase internal locus of control
Homework	Writing goals and monitoring progress in a diary in order to successfully implement actions (areas: diet, physical exercise)
Week 3	
Description	Psychoeducation on the memory system and the expected changes associated with increasing age. Training of external mnemonic compensatory strategies
Homework	Calendar of weekly recording of external strategies
Week 4	
Description	Training in the use of internal mnemonic strategies. Synthesis of external and internal strategies through everyday scenarios
Homework	Diary of recording external and internal mnemonic strategies. Solving two scenarios with everyday challenges that require the implementation of internal and external strategies.
Week 5	
Description	Psychoeducation about emotions and connection with cognitive functions. Discussion on the effects of stress and emotional difficulties on cognitive performance. Developing emotional adjustment skills using the STOP-RELAX approach.
Homework	Logbook of recording external and internal mnemonic strategies. Weekly calendar of recording emotional clarity
Week 6	
Description	Further development of emotional regulation skills (diaphragmatic breathing and mindfulness) and gaining knowledge on their effect on the cognitive system. Mindfulness breathing session (5 min)
Homework	Recording of mindfulness goals in the diary. Daily mindfulness breathing and relaxation session. Daily journaling on personal emotional clarity state
Week 7	
Description	Psychoeducation on executive functions and association with problem solving. Role of emotions and emotion regulation in problem solving. Five-step technique for problem solving – THINK-ACT, + emotional regulation strategies – STOP – RELAX,
Homework	Solving two scenarios with everyday challenges that requires the implementation of the problem-solving model provided by the instructor. Also, each participant is requested to identify a personal problem and implement the problem-solving model. Continuing the mindfulness training using the audio exercise of mindfulness and diaphragmatic breathing. Daily journaling on personal emotional awareness and clarity state.
Week 8	
Description	Deepening in problem solving, the role of emotions and the overall effect on cognitive function. Four strategies of emotional regulation – STOP-RELAX, Five-step technique for problem solving-THINK-ACT,
Homework	The aim this week is to make connections between the newly learned skills with the protective factors for healthy cognitive aging (meeting 2). Participants identified a personal challenge and developed a solution based on the problem-solving strategy. Participants kept a log of external and internal mnemonic compensatory strategies they implemented during daily activities. Daily journaling on personal emotional awareness and clarity state.
Week 9	
Description	Synthesis of all previous meetings focusing on problem solving: Protective factors for aging (meeting 2), mnemonic compensatory strategies (meeting 3 and 4), emotional regulation strategies (meeting 5 and 6), problem-solving strategies (meeting 7 and 8)
Homework	In relation to the protective factors for healthy cognitive aging (meeting 2) identification of a different personal goal and its approach based on the problem-solving steps. Diary of recording external and internal mnemonic strategies during activities of daily life. Recording of mindfulness goals and their implementation in the diary. Continuing with the audio exercise on mindfulness and diaphragmatic breathing.
Week 10	
Description	Summary, debriefing, feedback by participants, recommendations, closure and planning of reassessment at four weeks and 12 weeks post training.
Homework	Completion of post-testing questionnaires

during the intervention for good cognitive health (e.g., healthy diet and exercise) ($M = 4.56$, SD = 0.42).

Regarding the group format of the intervention, 83.3% of participants strongly agreed that this format was optimal ($M = 4.80$, SD = 0.48) and the majority (66.7%) felt a strong connection with their group peers ($MM = 4.66$, SD = 0.59), and 63.7% felt supported by them ($M = 4.30$, SD = 0.66). In Table 2, the means, standard deviations, and percentages for all questions are presented in detail.

Applying trained skills

The majority (60–90%) of participants rated their ability to apply their newly learned strategies very highly. Specifically, their ability to apply Memory Compensation Strategies in their daily life was on average 4.73 (SD = 0.52) on a 5-point scale. Their ability to apply Emotion Regulation and Problem-Solving strategies in daily life was evaluated as 4.86 (SD = 0.43) and 4.55(SD = 0.50) respectively. Lastly, their ability to apply general life-style modification strategies to promote overall health (physical exercise and diet) was also rated highly 4.33 (SD = 0.54) on a 5-point scale.

Association between locus of control and application of trained skills

The internal LC subscale showed a positive correlation with the Memory Compensation Strategies, $r(28) = 0.48$, $p < 0.001$, Problem-Solving, $r(28) = 0.74$, $p < 0.001$, Emotion Regulation, $r(28) = 0.64$, $p < 0.001$ and general modification strategies for brain and cognitive health such as physical exercise and diet, $r(28) = 0.58$, $p < 0.05$. These findings indicate that individuals who reported an internal LC also reported greater engagement in using strategies trained by the program.

Discussion

The present novel multidimensional group intervention integrates key theoretical principles from cognitive rehabilitation and clinical psychology. This is one of the first multidimensional, non-pharmaceutical, theory driven interventions focusing on healthy adults over 65 with the purpose to strengthen/improve areas of cognitive and psychosocial functioning. The principal objective of the present paper was to present the theoretical framework of this intervention, the process of the program and results from the evaluation that was carried out to investigate participant satisfaction and implementation of their newly learned strategies in their daily lives. The outcomes of this analysis indicate that the intervention is feasible and well tolerated by our target group. Participants were committed to this intervention, as shown by zero dropout.

The intervention incorporated multiple methodologies for contextual integration of learned concepts and strategies: The current intervention adds to existing multidimensional psychoeducational interventions on cognitive aging which were mostly educational (5, 6, 8) through the implementation of multiple methodologies for contextual integration of active components. Specifically, direct instruction through psychoeducation, indirect instruction such as case studies, reflective discussions, interactive instruction such as role-play, peer support, online chatting, and independent study *via* take-home exercises, journals, and case scenarios were integrated during the 10-week period. Results indicate that participants were satisfied with the implementation strategy of the present intervention and with their ability to gain knowledge and apply their newly learned skills.

The intervention incorporated five key active ingredients: Memory Compensation Strategies (MCS), Problem-Solving (PS), Emotion Regulation (ER), Mindfulness, and Locus of Control (LC), in order to address challenges associated with healthy aging. The present findings suggest that, upon completion of the program, participants were able to apply their new knowledge and skills in activities of their daily life, upon completion of the program.

Internal LC, a key ingredient of the present intervention, was associated with participant engagement and their ability to use skills and strategies trained during the program in everyday life. Key aspects of internal locus of control were incorporated in all meetings through active engagement and investment in the learning process. Participants were systematically guided to take action during the group sessions and in their daily lives and to improve their cognitive and psychosocial functioning. Results from the satisfaction questionnaire indicate that most participants reported motivation to take control and action to improve their life. In fact, higher levels of internal LC increased the likelihood of engagement in using strategies trained by the program. This finding has important implications for interventions targeting healthy older adults, since internal LC may maximize the likelihood of active participation in the rehabilitation process by applying compensatory strategies to improve cognition and emotional functioning such as problem-solving and emotion regulation (51).

Another important element of the study was the group format as the delivery modality of the intervention. The group format encouraged the interaction of the participants, elements that potentially contributed to the commitment of the group. The overwhelming majority of participants reported satisfaction with the group format and a connection with their teammates. These results are consistent with a recent meta-analysis showing that interventions produce maximum benefits when participants train in groups (52). The present intervention is conducive to a group format as it offers an opportunity for participants to support each other, increase motivation and allow people to share their emotions and concerns about their cognitive and everyday problems.

Another component of the group intervention in this study was the online delivery method. As mentioned, the online platform was selected as the delivery method in response to the pandemic and the requirement for physical distancing during COVID-19. The present online intervention promoted social interaction during the meetings and the opportunity for online chatting between weekly sessions, creating rapport among the group participants. Findings indicate that the creation of online chats for the group members should be an important consideration when organizing and designing such programs, even if the delivery of the intervention is in the conventional in person format.

In summary, the present study indicates that this theory driven group intervention is feasible and well tolerated by the study participants. Based on the process evaluation and satisfaction results, participants were satisfied with the implementation strategy of the intervention and their ability to gain knowledge and most importantly apply their newly learned

TABLE 2 Means, standard deviations, and percentages for the participant satisfaction scale.

	Mean	SD	A and B %	C %	D %	E %
Topics covered during the meetings	4.90	0.34			10%	90%
Organization and preparation of the instructor	4.96	0.19			3%	97%
I felt supported by the instructor	4.96	0.18			3.3%	96.7%
The meetings were a positive experience	4.88	0.34			13.3%	86.7%
The meetings met my expectations for receiving information related to cognitive health	4.50	0.57			3%	87%
The meetings met my expectations for developing new skills	4.90	0.30			10%	90%
Through the meetings I learned about key risk factors for pathological cognitive aging	4.86	0.34			13.3%	86.7%
I apply the general strategies for good cognitive health (healthy diet, exercise, etc.), I learned during the program	4.56	0.62		6.7	30%	63.3%
I learned practical strategies that I can use in my everyday life	4.83	0.42			13.3%	86.7%
The meetings motivated me to take control of my life	4.73	0.44			23.7%	76.3%
The meetings motivated me to take action for my cognitive health	4.76	0.43			23.3%	76.7%
The group format of the intervention was useful	4.80	0.48		3.3%	13.3%	83.3%
I felt supported by the members of my group	4.66	0.59		6.7%	26.7%	66.7%
I felt connected with the members of my group	4.30	0.66		10%	26.3%	63.7%
I routinely apply the memory strategies (e.g., use memory aids, associations, repetition) I learned in the program	4.73	0.52			13.3%	86.7%
I routinely apply the problem-solving steps, I learned in the program (e.g., problem definition, alternative solutions etc)	4.55	0.50		3.3%	20%	76.6%
I routinely apply the emotion regulation strategies (e.g. self-control, diaphragmatic breathing, mindfulness), I learned in the program.	4.86	0.43		3.3%	6.7%	90%
I routinely apply the lifestyle strategies for brain and cognitive health (e.g., physical exercise, diet), I learned in the program	4.33	0.54		3.3%	36.7%	60%

A = very dissatisfied/absolutely disagree/bad, B = dissatisfied/disagree/low, C = neither dissatisfied nor satisfied/neither agree or disagree/moderate, D = satisfied/agree/good, E = very satisfied/strongly agree/very good.

skills in their daily life. The current study described the background and content of the intervention program in detail to enable application and replication by other clinicians and researchers. We are currently collecting follow-up data from our study participants and we will be disseminating the outcomes of the intervention to the research community in future publications. In conclusion, the intervention program that was described in the current paper may offer a valuable contribution to the design of a multidimensional intervention and contribution to public health care for older adults, especially in the face of our rapidly aging Western society.

Data availability statement

The datasets presented in this article are not readily available because the dataset used in this study belongs to an ongoing research project. Therefore, no data can be shared. Requests to access the datasets should be directed to AC, dr.chadjikyprianou@gmail.com and FC, fofic@ucy.ac.cy.

Ethics statement

The studies involving human participants were reviewed and approved by Cyprus National Bioethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AC conceptualized and designed the project, coordinated the data collection, analyzed data, and wrote the manuscript. FC conceptualized and designed the project, supervised the data collection, analysis, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Assessment of adjunct cognitive functioning through intake interviews integrated with natural language processing models

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In this article, we developed an interview framework and natural language processing model for estimating cognitive function, based on an intake interview with psychologists in a hospital setting. The questionnaire consisted of 30 questions in five categories. To evaluate the developed interview items and the accuracy of the natural language processing model, we recruited participants with the approval of the University of Tokyo Hospital and obtained the cooperation of 29 participants (7 men and 22 women) aged 72–91 years. Based on the MMSE results, a multilevel classification model was created to classify the three groups, and a binary classification model to sort the two groups. For each of these models, we tested whether the accuracy would improve when text augmentation was performed. The accuracy in the multi-level classification results for the test data was 0.405 without augmentation and 0.991 with augmentation. The accuracy of the test data in the results of the binary classification without augmentation was 0.488 for the moderate dementia and mild dementia groups, 0.767 for the moderate dementia and MCI groups, and 0.700 for the mild dementia and MCI groups. In contrast, the accuracy of the test data in the augmented binary classification results was 0.972 for moderate dementia and mild dementia groups, 0.996 for moderate dementia and MCI groups, and 0.985 for mild dementia and MCI groups.

KEYWORDS

gerontology, intake interview, natural language processing, data augmentation, cognitive function

1. Introduction

Dementia is defined as "a chronic decline or loss of various cognitive functions, resulting in the inability to lead a normal daily or social life," and is an acquired cognitive disorder (1). Cognitive functions are essential for planning and carrying out daily activities such as cleaning, washing clothes, eating, and going out (2). Therefore, people with dementia are unable to make plans and perform routine activities, which can seriously interfere with their daily lives (3). Approximately 10% of the total population will develop this disorder at some point in their lives, and it is generally considered to be a consequence of aging (4). One person develops dementia every 3 s worldwide, and this number almost doubles every 20 years, with the total number of persons with dementia estimated to reach 152 million by 2050 (5).

However, as medical science is yet to find a cure for dementia, it is imperative to detect the trend of cognitive decline as early as possible and intervene at an early stage, as in the case of cancer (6, 7). Positron emission tomography (PET) and magnetic resonance imaging (MRI) are commonly used to test for dementia, but they are not only time-consuming but also require expensive testing equipment (8). Other methods, such as the Mini-Mental State Examination (MMSE) and Hasegawa Dementia Scale (HDS-R), are quick and easy assessment methods; however, because the questions on the test form are fixed, they can be memorized by the examinee, making the tests unsuitable for periodic monitoring (9, 10). In addition, the knowledge that their cognitive function is being tested places a mental burden on those being tested. Many older people refuse to be tested for dementia, and it has been reported that 16% of people with Alzheimer's disease show distress-fueled reactions such as anxiety, anger, and refusal during testing (11).

Therefore, assessment for dementia based on the verbal abilities of older people has recently attracted attention. Such assessment is not physically invasive and does not require spending long durations of time in a medical facility. In addition, because cognitive function can be monitored periodically, this technique may make it possible to detect changes in cognitive function over time, attracting attention in the medical and research communities.

2. Related studies

In general, patients with dementia have reduced language ability compared to healthy controls. Several studies have screened for dementia based on language ability. Studies focusing on language began with the Nun Study in 1996 (12), and the number of studies using machine learning to discriminate patients with dementia from healthy controls has been gradually increasing. According to previous systematic reviews, machine learning-based assessments of cognitive function can be broadly classified into four categories according to the types of features employed: (i) linguistic, (ii) acoustic, (iii) images/movie, and (iv) other types of features such as expressive features or features that depict specific shapes (13, 14). This study focuses on linguistic features that can deal with fillers and feature words in classification tasks.

2.1. Classification of cognitive functions by linguistic features

There are mainly three types of analyses for extracting linguistic features: (1) primary lexical-level analysis, (2) semantic analysis, and (3) sentence-level syntactic analysis.

Automated primary lexical analysis (i.e., lexical or word-level analysis) can produce objective linguistic indices and provide valuable insights into cognitive functions. In its most basic form, the text body is treated as a bag of words. That is, the order of words in the text is not considered.

Jarrold et al. used speech data from healthy participants ($n = 23$) and patients with dementia ($n = 22$) to extract part-of-speech counts, semantic density, and word industry classification [using the Linguistic Inquiry and Word Count (LIWC) tool], which were used as features for machine learning (15). Asgari et al. reported that speech data (daily conversation) obtained from people with mild cognitive impairment ($n = 14$) and normal participants ($n = 21$) could be classified as healthy control and mild cognitive impairment (MCI) with up to 73% accuracy using LIWC (16), and LIWC could discriminate HC and MCI with up to 84% accuracy (17).

Fraser et al. (18) used several key lexical features in their analysis of patients with Alzheimer's disease (AD), wherein the authors used the type-token ratio (TTR) as measures of lexical diversity and richness to discriminate between healthy older controls ($n = 16$) and a small sample of patients with AD ($n = 8$). In addition, they examined the use of other parts of speech (nouns, pronouns, adjectives, and verbs). In particular, the TTR, BI, oscillation, and adjective rates all showed strong group differences between patients with AD and healthy controls, and group classification was achieved with 87.5% cross-validation accuracy.

For semantic analysis, the semantic similarity of natural languages is usually measured computationally by embedding text into a high-dimensional vector space representing its semantic content. The notion of the distance between vectors can then be used to quantify the semantic similarity or difference between words or sentences represented by the vector embedding.

Snowdon et al. calculated semantic density (the number of propositions in a sentence divided by the number of words) and grammatical complexity from autobiographies written by 93 nuns in their 20s (12). They showed that lower semantic density and grammatical complexity in adolescence were associated with lower cognitive function later in life and reported a certain relationship between these values and cognitive function. Kemper et al. also reported that grammatical complexity decreased with age, regardless of the presence of dementia, but semantic density decreased only in the dementia group (19).

Sentence-level parsing can also provide important insights into the cognitive function of the word order in sentences and sentences in paragraphs. For free speech, we need to determine not only which words best convey ideas but also the order in which words form sentences. The complexity of the sentences we produced provides clues to cognitive linguistic health. This section outlines various methods used to measure syntactic complexity as a proxy for cognitive health. Many common structural measures of language are easy to compute, such as average clause length, average sentence length, and the ratio of the number of clauses to the number of sentences.

Orimayre et al. extracted several syntactic and lexical features from a corpus consisting of patients with dementia ($n = 314$) and healthy participants ($n = 242$) provided by the Dementia Bank and classified them using machine learning to achieve an F-measure of 0.74 (20).

Fraser et al. performed an image description task on mildly cognitively impaired ($n = 37$) and normal ($n = 37$) participants. Linguistic features were extracted from the obtained speech data and discriminated, resulting in an area under the curve (AUC) value of up to 0.87 (21).

Recently, methods using deep learning have also been proposed, and Klekar et al. used the Dementia Bank to classify people with dementia and healthy people and reported that they achieved 91% accuracy (22). In a review article, we surveyed studies that experimented with image description tasks on corpora (23). As GPU performance has improved, it has become easier to construct computationally expensive models, and high accuracy can be expected for sentence-level parsing.

2.2. Tasks contributing to classification accuracy and the feasibility of their application

Shihata et al. (24) created a corpus of 60 (30 men and 30 women) older adults (GSK2018-A) with a control group, linking their speech data to a stimulus task and the results of a cognitive function test on the MMSE. Three types of stimulus tasks were included: an episodic task in which participants talked about personal events, an explanatory task for a Cookie Theft Picture, and a task in which participants watched and described a NAIST DOGS animation (produced by Nara Institute of Science and Technology). The episodic task included "1a. recent sad event," "1b. when it occurred," "2. recent events that made you feel anxious," "3. recent events that made you angry," "4. recent event that made you feel disgusted," "5. A recent surprising event," "6a. a recent pleasant event," "6b. when did it happen?," "7. what are you passionate about?" and "8. Who do you admire and respect?," and one image and animation for a total of 12 tasks. Participants were instructed to speak freely for 1–2 min in response to each task question, and their utterances were recorded as audio accompanied by manually transcribed text data.

In a previous study by Igarashi et al. (25) using a corpus created by Shihata et al., the binary classification of a healthy older group and an MCI older group by natural language processing showed high accuracy in the picture description task, the animation description task, and some episodic tasks.

However, the picture description and animation description tasks require a display during the conversation, thus, it is difficult to consider these tasks as natural conversations. On the other hand, in psychiatry and geriatrics, intake interviews are conducted with patients to obtain relevant information in order to provide comprehensive support in treatment. Intake interviews are the most common type of interview in clinical psychology, occurring when a client first comes to a clinician for help (26). The interviews are often conversational in nature and considered beneficial to both parties, as the inclusion of personal conversation topics can lead to a mutual understanding of the interviewer's and patient's communication styles (27).

In practice, interviews are conducted by nurses, psychologists, and social workers about the patient's life history and current living situation, and this information is shared with the physicians and medical teams for smooth treatment and discharge planning. In some cases, the examiner's findings on the patient's cognitive function are also included, but these are findings based on experience and are often difficult to extract for nurses and psychologists who have just been assigned to the patient's care.

If the cognitive function could be estimated mechanically from conversations conducted with patients in practice, it would reduce the burden on hospital staff and patients. However, when considering their constant and widespread use in hospitals, it is necessary to develop question items that can be used universally for any patient. Therefore, this study aims to develop interview items that can be used in hospital practice.

In addition, we will verify the degree of classification accuracy that can be expected from the data collected through interviews. Although previous studies have shown that it is possible to distinguish between an older group and an MCI older group based on MMSE results with an accuracy of 89% or higher, it is not yet known whether the same level of accuracy can be achieved when cognitive decline has progressed beyond MCI. Therefore, we will also develop and validate the accuracy of a natural language processing model capable of multilevel classification of three types of dementia: moderate dementia with an MMSE score of 20 or less, mild dementia with an MMSE score of 21–23, and MCI with an MMSE score of 24 or more and 27 or less.

3. Materials and methods

3.1. Creation of life history interview items for the intake interview

3.1.1. Experimental environment

The experiment was conducted in a laboratory at the University of Tokyo Hospital. The participant and interviewer sat face-to-face at a desk in the examination room, and questions were asked. Audio and time-lapse images were recorded using a recorder and a small camera [Gopro hero10 (28)].

To prevent COVID-19 infection, as the interviews were conducted in the period when the pandemic was abating, the interviewer and the questioner wore a face guard and the participants' hands were disinfected when they entered the room. The room was ventilated with a circulator, and an acrylic board was used as a partition between the participant and interviewer. In addition, the desks and chairs used were disinfected with alcohol spray and paper napkins after the participants left the room. Figure 1 shows a psychological testing room in a hospital.

3.1.2. Method of creating life history interview items for intake interviews

The life history interview items required content that could be used in actual hospital practice. Therefore, interview items were developed according to the following protocol:

a. The author attended an intake interview with a psychologist at the University of Tokyo Hospital and surveyed the questionnaire items.
b. Items deemed unimportant or duplicated from the questionnaire items were deleted to develop a preliminary draft.
c. The draft was checked by five licensed psychologists working at the University of Tokyo Hospital, who made additions and revisions, and changed the order of the questions as required.
d. After confirmation by the authors and supervisors, a final version was prepared.

The questionnaire consisted of 30 questions in five categories. The categories were: (1) process before coming to the hospital, (2) life history, (3) ordinary life, (4) interests and concerns, and (5) plans for the rest of the day, with questions related to each category included in the lower tiers. Table 1 shows the questions included in each category.

3.1.3. Interviewer attitude, reactions, and additional questions

The interviewer was a licensed psychologist; however, he is not a hospital staff member. Therefore, there was no prior relationship between the questioner and the study participants, as they were completely new to each other. As for the interviewer's attitude, the

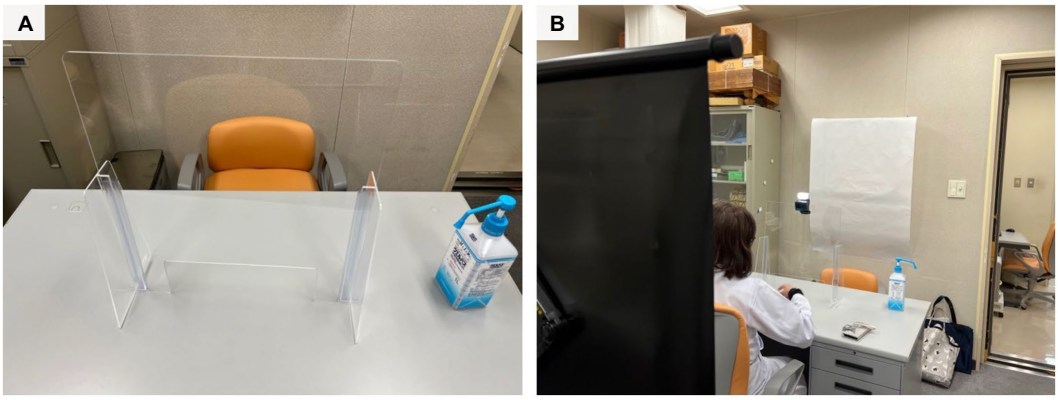

FIGURE 1
(A) A table is partitioned by an acrylic board. **(B)** The questioner sits on the far side and the participant sits on the front side.

interviewer was masked, but nonverbal expressions such as nodding and eyes smiling were used to establish a comfortable situation for speaking.

To ensure that the conversation did not end with a short response after asking a question, the interviewer implemented two types of reactions: one was to repeat the information given by the participant as mirroring, to encourage the participant to continue talking after their initial response. The second was a reaffirmation of the participant's response of "nothing in particular," followed by the question, "If you had to give a strong answer, what would it be?"

3.2. Evaluation

3.2.1. Participants

Participants were recruited from August to September 2022, on the inclusion conditions that they were older people aged 65 years or above, had been diagnosed with dementia by a physician and were able to provide their consent after explaining the outline of the study. As a result, 32 people (9 men and 23 women) between the ages of 72 and 91 years participated in the experiment. A consent form was obtained from the patient if they came to the hospital alone or from a relative accompanying the patient. This study was approved by the Ethical Review Committee of the University of Tokyo Hospital.

3.2.2. Assessment tests

The test content was divided into (a) MMSE, (b) GDS, and (c) life history interview as part of the intake interview. The MMSE is one of the most common assessment methods for detecting dementia. It is a 30-point cognitive function test consisting of 11 items: time and place perception, immediate and delayed wordplay, calculation, object calling and sentence recitation, 3-step verbal command, written command, and graphic imitation. In the MMSE, 23 points or less indicates potential dementia (sensitivity of 81%; specificity of 89%), and 27 points or less indicates potential MCI (sensitivity of 45–60%; specificity of 65–90%) (29–32).

Since sequelae of cerebrovascular disease, lacunar infarction, moderate white matter lesions, parkinsonism, and hypothyroidism can affect speech fluency, we always conduct a set of medical examinations by dementia specialists as well as psychological testing. The dementia specialist has confirmed that the participants selected for this study have cognitive decline and the selected participants did not show any language impairment in other factors. However, it has been reported that the results of cognitive function tests show no significant changes within 3 months. Therefore, if the patient had undergone a cognitive function test at the same hospital within 3 months, the test was omitted, and the most recent test result was referred to in order to reduce the patient's burden.

The GDS is a screening test used to assess depression in older adults. It was administered to ascertain which participants were above the threshold, as it is known that the amount of conversation is reduced when a person is depressed.

The MMSE results showed that 12 participants had moderate dementia with scores of 20 or less, eight participants had mild dementia with MMSE scores between 21 and 23, and nine participants had mild cognitive impairment (MCI) with MMSE scores between 24 and 27. The GDS results also showed that 27 patients scored below the GDS cutoff of 7 points, while two patients scored higher than the cutoff. However, given that the diagnosis of depression was not made by a specialist's examination immediately after the test, these two patients were not excluded from the study.

3.2.3. Classification methods

Generalized language models pre-trained on large corpora achieve excellent performance in natural language tasks. Although many pre-trained transformers for English have been published, there are not many model options available, especially for Japanese texts. In this study, we used Bidirectional Encoder Representations from Transformers (BERT), a pre-trained Japanese language model that is considered a ubiquitous baseline for NLP experiments. BERT is a type of neural network based on an architecture called Transformer (33) and provides powerful encoding for sentences and text using word embedding. The representation of a word as a vector of fixed length is called word embedding and it is now possible to obtain multiple distributed representations from a single word by using BERT. Speech data was transcribed manually due to the possibility of transcription errors when using ASR; before loading into BERT, the data were shuffled and split into training data, validation data, and test data.

The model used in this study is a pretrained Japanese BERT model published by the Inui/Suzuki Laboratory of Tohoku University. The

TABLE 1 Intake interview questions created.

(1) *Process before coming to the hospital*
Q1. Where is your home?
Q2. How long did it take you to get here today?
Q3. After you left your home, how did you come here?
Q4. What time did you leave home to come to the hospital today?
(2) *Life history*
Q5. Where were you born?
Q6. Do you have any siblings (if so, how many?)
Q7. Which elementary school did you attend?
Q8. What did you do after elementary school? (Which junior high school did you attend?)
Q9. What did you do after graduating junior high school? (Which high school did you attend?).
Q10. What do you do for work? (Do you have any memorable stories?)
Q11. Are you married? (When was your wedding?)
Q12. Do you have any children? (Where do your children live?)
(3) *Normal life*
Q13. How do you usually spend your time? (Please tell us your approximate weekly schedule.)
Q14. What time do you get up in the morning and go to bed?
Q15. How often do you go out? (Where do you go most often?)
Q16. Do you bathe every day? (Do you bathe in a bathtub?)
Q17. How do you prepare your meals? (Do you eat three meals a day?) / What did you eat last night?
Q18. How do you clean your house? (How often do you clean your house?)
Q19. How do you do your laundry? (How often do you do it?)
(4) *Interests*
Q20: What news have you been interested in on TV or the Internet recently?
Q21: Please tell me about a sad event that happened to you recently.
Q22: Please tell me about a recent unsettling event.
Q23: Tell me about a recent event that made you angry.
Q24: Tell me about a recent event that made you feel bad.
Q25: Tell me about a recent event that surprised you.
Q26: Tell me about a recent happy event that happened to you. When did it happen?
Q27: Tell me about someone you admire.
Q28: What are you passionate about these days?
(5) *Plans for the rest of the day*
Q29: What are your plans for the rest of the day? (How will you get home?)
Q30: When was the date of your last visit?

models consist of 12 layers, 768 dimensions of hidden states, and 12 attention heads. As the parameters for fine-tuning in this study, we set the batch size as 1, the learning rate as 2e-5, and the number of epochs as 5 based on previous studies using similar methods. In addition, because there were several sentences in the dataset that exceeded 256 characters, sentences longer than 256 were truncated.

Training data, validation data, and test data are split at a ratio of 8:1:1. The splitting is performed using scikit-learn. The classification methods used for multi-level and binary classification are essentially the same. As the target genre, [moderate][mild][MCI] is given as teacher data, and the training data portion is trained. The language processing model called BERT is trained while masking (replacing with expressions such as ****) the original teacher data, which improves generalization performance for various applications.

3.2.4. Dealing with unbalanced data

Obtaining data from patients with dementia is difficult owing to issues of research ethics surrounding obtaining their consent, and collecting a large number and variety of cases is not always possible. In this study, the data were unbalanced: 12 patients had moderate dementia with MMSE scores of 20 or less, eight patients had mild dementia with MMSE scores between 21 and 23, and nine patients had mild cognitive impairment (MCI) with MMSE scores between 24 and 27. The sample sizes should be comparable because different sample sizes make it difficult to analyze the methods and tasks that may have contributed to the classification results.

Undersampling is the simplest method for dealing with unbalanced data, but it leaves the issue of the total amount of data being small (34). One oversampling method that adjusts minority data to the majority is data balancing through data augmentation (35). This method has been particularly successful in the field of imaging, where similar data are augmented by inverting, scaling, and various other methods. It has the advantage of enabling improved classification accuracy on small datasets. Therefore, we augmented the dataset using a technique called easy data augmentation (EDA), which has been shown to be effective in natural language processing (36).

Easy data augmentation consisted of four algorithms. Synonym replacement randomly selects a word in a sentence and replaces it with one of a list of synonyms for that word (excluding stop words). Random Insertion randomly selects a word in a sentence and randomly inserts it at a different position in the sentence (excluding stop words). Random swap randomly selects two words in a sentence and swaps their positions. Random deletion deletes a word in a sentence with probability p (Table 2).

For the list of synonyms that needed to be replaced, we used the Japanese WordNet proposed by Isahara et al. (37). The percentage of EDA in each algorithm is represented by the parameter α. The value of α was set to 0.05, which was recommended for this amount of data in the original article because a large value would reduce accuracy (Table 2).

A list of stopwords is necessary for augmentation. Some sentences may contain words that do not make sense when the terms are augmented, and these words can be excluded from text augmentation. Slothlib provided by Oshima et al. cannot be used as it is (38). Slothlib is a Japanese word list proposed by Oshima et al. of Kyoto University. Originally, it was an exclusion item to effectively retrieve information on the web and its associated character code identification, existing clustering algorithms, and web search API services (what words are searched); however, in the field of Japanese natural language processing, it is now often set as a stop word when performing data augmentation. According to previous studies, people with dementia are known to use pronouns more frequently, and pronoun use should not be excluded from augmentation (24). Therefore, as suggested by Igarashi et al. (25), 288 unnecessary words for text augmentation in Japanese, excluding pronouns, were set as stop words.

4. Results

From the 12 participants with moderate dementia, 334 responses were obtained. The total number of words was 36,734, with an average

TABLE 2 List of easy data augmentation algorithm.

Synonym replacement:	A word in a sentence is randomly selected and replaced with one of the synonyms for that word. The stop words were excluded from the analysis.
Random insertion:	Randomly select a word in a sentence and randomly insert it into another position in the sentence. The stop words were excluded from the analysis.
Random swap:	Randomly select two words in a sentence and swap their positions.
Random deletion:	Randomly Deletes a word in a sentence with probability p.

of 109.98 words per response. The average duration of silence was 6.15 s.

From the eight participants in the mild dementia group, 234 responses were obtained. The total number of words was 25,647, and the average number of words per response was 109.60. The average duration of silence was 2.02 s.

From the nine participants in the MCI group, 256 responses were obtained. The total number of words was 28,423, with an average of 107.26 words per response. The average duration of silence was 1.93 s.

4.1. Multi-level classification results

A total of 660 training data, 82 validation data, and 82 test data are included when multi-level classification is used. The results of the validation with the model of multi-level classification which assigns the three groups showed that the correct answer rate in the training data was 0.919, the correct answer rate in the validation data was 0.530, and the correct answer rate in the test data was 0.405.

4.2. Binary classification results

For moderate and mild binary classification, 456 training data, 56 validation data, and 56 test data are included. The results of the validation with the binary classification model, which allocates the group with moderate dementia and the group with mild dementia, showed that the correct answer rate in the training data was 0.821, the correct answer rate in the validation data was 0.482, and the correct answer rate in the test data was 0.488.

For the binary classification of moderate and MCI, 472 training data, 59 validation data, and 59 test data are included. The results of the validation with the binary classification model to sort moderate dementia and MCI groups were as follows: the correct answer rate in the training data was 0.956, the correct answer rate in the validation data was 0.633, and the correct answer rate in the test data was 0.767.

For the binary classification of mild and MCI, 392 training data, 49 validation data, and 49 test data are included. The results of the validation with the model of binary classification to separate the mild dementia group and the MCI group were as follows: the correct answer rate in the training data was 0.965, the correct answer rate in the validation data was 0.660, and the correct answer rate in the test data was 0.700.

4.3. Multi-valued classification results (with augmentation)

In the case of augmentation, the number of data for each group is increased until it reaches 5,000. This means that when multi-level classification is used, 12,000 training data, 1,500 validation data, and 1,500 test data are included. The results of the validation with the model of multi-level classification, which assigns three groups, showed that the correct answer rate was 0.994 for the training data, 0.992 for the validation data, and 0.991 for the test data. Figure 2 shows a comparison of accuracy results with and without augmentation.

4.4. Binary classification results (with augmentation)

For binary classification, 8,000 training data, 1,000 validation data, and 1,000 test data are included for each group's classification. The results of the validation with the binary classification model that assigns the group with moderate dementia and the group with mild dementia showed that the correct answer rate in the training data was 0.984, the correct answer rate in the validation data was 0.971, and the correct answer rate in the test data was 0.972.

The results of the validation with the binary classification model to sort the moderate dementia and MCI groups were as follows: the correct answer rate in the training data was 0.999, the correct answer rate in the validation data was 0.997, and the correct answer rate in the test data was 0.996.

The results of the validation with the binary classification model, which allocates mild dementia and MCI groups, showed that the correct answer rate in the training data was 0.991, the correct answer rate in the validation data was 0.987, and the correct answer rate in the test data was 0.985.

4.5. Differences in the text data of each group

The number of words per response in the three groups was 109.98, 109.60, and 107.26 for moderate dementia, mild dementia, and MCI groups, respectively. The number of words per response to the same question in the three groups indicated a tendency to become more verbose as cognitive function declined, but the differences between the groups were small. The results of a t-test with no correspondence among the three groups showed no significant differences.

On the other hand, the average number of seconds of silence per response in the three groups was 6.15 s for the moderate dementia group, 2.02 s for the mild dementia group, and 1.93 s for the MCI group. The average number of silent seconds per response to the same question for the three groups tended to increase as cognitive function declined. In addition, the results of the *t*-test without correspondence among the three groups showed significant differences.

This suggests that at least for the results of the intake interview-based open queries used in this study, the previous study's finding that conversations become more verbose as cognitive function declines is related to an increase in the number of silent seconds in the conversation rather than the number of words in the response.

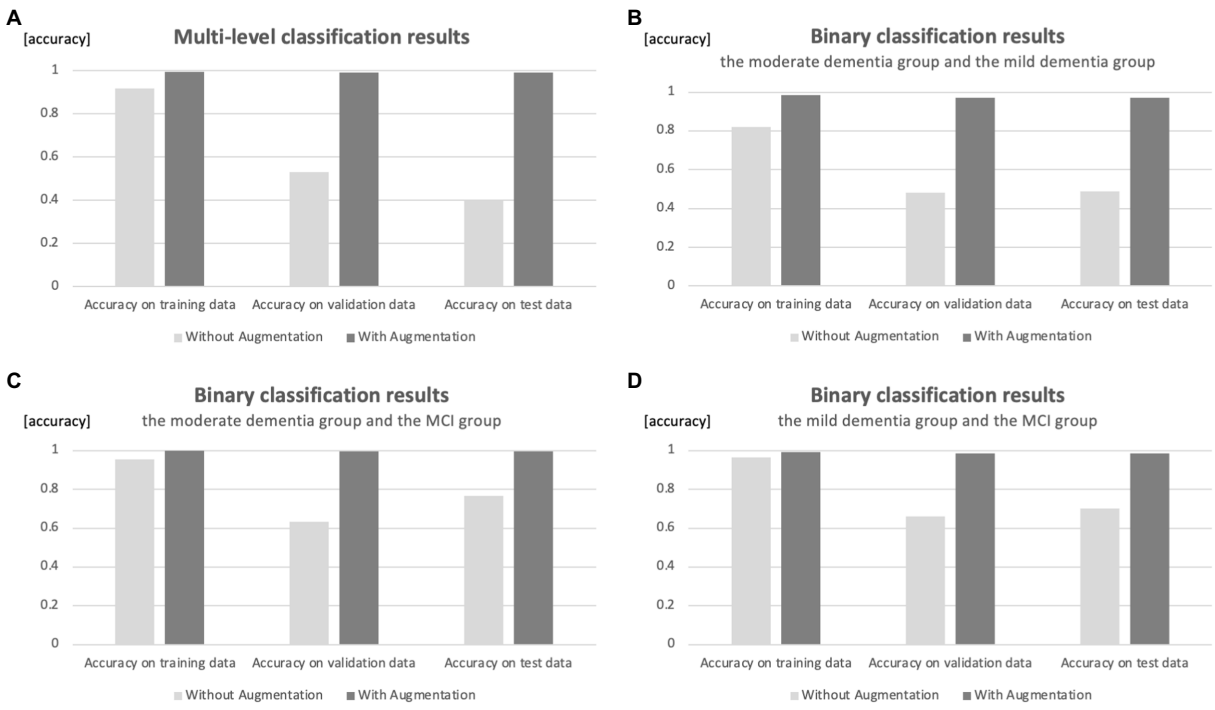

FIGURE 2
Comparison of accuracy results with and without augmentation. **(A)** Classification of three groups. **(B)** Binary classification of moderate and mild dementia groups. **(C)** Binary classification of moderate dementia and MCI groups. **(D)** Binary classification of mild dementia and MCI groups.

5. Discussion

5.1. Relationship between classification accuracy and augmentation

The accuracy of the test data in the multi-value classification results was 0.405 without augmentation and 0.991 with augmentation.

The accuracy of the test data in the results of the binary classification without augmentation was 0.488 for moderate dementia and mild dementia groups, 0.767 for moderate dementia and MCI groups, and 0.700 for mild dementia and MCI groups. This suggests that without augmentation, it was possible to classify moderate dementia (or mild dementia) and MCI groups with an accuracy of over 70%; however, it was difficult to classify moderate dementia and mild dementia groups.

On the other hand, the accuracy of the test data in the binary classification with augmentation was 0.972 for moderate dementia and mild dementia groups, 0.996 for moderate dementia and MCI groups, and 0.985 for mild dementia and MCI groups.

In the case of no augmentation, the correct response rate for both the multi-level and binary classification cases was high for the training data but low for the validation and test data. This is thought to be due to overlearning, which results in excessive adaptation to the training data.

In both multi-level and binary classification cases, the accuracy of the case with augmentation was significantly higher than that without. The accuracy of both multilevel and binary classification cases with augmentation exceeded 97%, suggesting that augmentation may be useful as reference information in cases where the MMSE or other tests cannot be performed.

5.2. Future study

There is a possibility of overfitting due to the small data size. For the reliability of the language processing model, it would be desirable to revalidate the model with an increased sample size. We plan to recruit community-dwelling older adults to test a similar questionnaire and MMSE in future. We believe that a study of the four-value classification of MCI, mild dementia, and moderate dementia, including healthy older adults, could provide additional information on reliability. However, we are using a model that has been fully trained in Japanese by BERT in a fine-tuned form. In the study by Marius et al., the accuracy remained almost unchanged in the range of training loss from 10^{-5} to 10^{-1}, indicating that overfitting (overfitting to the training data) did not occur during fine-tuning. Nevertheless, more data is important to reduce the effect of overtraining.

As mentioned in related studies, using existing publicly available datasets in Japanese, the classification performance of healthy older adults and MCI was higher when using the picture description task, the animation description task, and some episodic tasks. There were 30 questions in total in the questionnaire we developed, all of which were used for this classification. However, there are five categories of questions, and it is believed that some of the categories and individual questions significantly enhance the accuracy of the classification, while others, on the contrary, reduce it.

Although the average interview with participants in our study lasted about 1 h, it is necessary to conduct interviews for a shorter duration of time to reduce the burden on hospital staff and patients, especially in hospital settings. Therefore, a detailed analysis of each question item in order to create a more refined questionnaire will be a future task.

Regarding the classification of silence time, we believe that image data drawn with MFCC or Mel spectrogram of the original acoustic features will leave better results than features extracted with text. Since those analyses are different from the accuracy verification by augmentation in this study, we hope to be able to verify them in future studies.

5.3. Use case

As described in related studies, intake interviews are conducted in many psychiatry departments. As a use case, when conducting an intake interview with a new patient, a pin microphone or similar device is provided to record data. After the intake interview, the voice data are converted to a text file on a PC, and this model can be used to check the classification results in a few 10 of seconds. If the intake interview is conducted prior to the physician's visit, the physician can review the results at that time for additional consultation.

On the other hand, in terms of rigor, the proposed system, like MMSE, is not a screening system. MRI is needed to pinpoint phenomena in the brain more precisely. Therefore, rather than considering this system as a comparative system that aims to completely replace MRI, it may be better to consider it as a system that can be applied to outreach activities in remote medical areas and home visits where expensive medical equipment resources are scarce.

6. Limitation

In this study, the transcription of statements was performed manually to prevent errors in the transcription process. However, hand transcription is unrealistic for clinical use. Therefore, if this is to be fully automated, automatic speech recognition (ASR) should be utilized; however, it is not known whether the same accuracy can be achieved if transcription errors that occur in such cases are included. In addition, the use of ASR may be affected by noise and in-building broadcasts. However, these problems may be resolved using a pin microphone that picks up the volume only around the patient's mouth.

The small size of the data and its split method for training and validation is also a limitation of this study. With the contribution of this study, future research collaboration is encouraged to expand the sample size. As explained in the Methods section, there were 29 participants in this study, 12 people had moderate dementia, 8 people had mild dementia, and 9 people had MCI. Therefore, it is clear that our data cannot be split 8:1:1 when divided by the number of participants.

Since data within the same group are considered to have the same sentence feature, it is natural that the response data from the same participant could be in either the training or validation dataset. However, there is no doubt that it would be best if the sample size could be increased. Validation of only one data from each group with the large dataset should be clarified in future studies.

7. Conclusion

In this study, we developed an interview framework and natural language processing model for estimating cognitive function, based on an intake interview with psychologists in a hospital setting. The interview items were prepared by the author, who witnessed the psychologist's intake interview and deleted unimportant or duplicated items from the questionnaire.

The questionnaire consisted of 30 questions in five categories. The categories were as follows: (1) process before coming to the hospital, (2) life history, (3) ordinary life, (4) interests and concerns, and (5) plans for the rest of the day, with questions related to each category included in the tier below it.

The Japanese version of BERT, pre-trained on a large corpus, was used as the natural language processing model for estimating cognitive functions. However, because of the small number of study participants, it was difficult to achieve accuracy simply by using the raw data without modification for training; therefore, EDA was conducted to increase the text data using four different methods. During EDA, augmentation was performed by excluding terms that were thought not to be characterized by a cognitive decline as stop words.

To evaluate the feasibility of the developed interview items and the accuracy of the natural language processing model, we recruited participants with the approval of the University of Tokyo Hospital and obtained the cooperation of 29 participants (7 men and 22 women) aged 72–91 years. Three types of tests, MMSE, GDS, and a life history interview, were conducted at the laboratory of the University of Tokyo Hospital. The examinations were recorded using a recorder and a small camera (Gopro hero10) for audio and time-lapse images.

The results of the MMSE showed that 12 patients had moderate dementia with an MMSE score of 20 or less, eight patients had mild dementia with an MMSE score between 21 and 23, and nine patients had mild cognitive impairment (MCI) with an MMSE score of 24 or more and 27 or less. Therefore, based on the MMSE results, a multilevel classification model was created to classify the three groups, and a binary classification model was used to sort the two groups. For each of these models, we tested whether the accuracy would improve when text augmentation was performed.

The accuracy in the multi-level classification results for the test data was 0.405 without augmentation and 0.991 with augmentation. The accuracy of the test data in the results of the binary classification without augmentation was 0.488 for moderate dementia and mild dementia groups, 0.767 for moderate dementia and MCI groups, and 0.700 for mild dementia and MCI groups. This suggests that without augmentation, it was possible to classify moderate dementia (or mild dementia) and MCI groups with an accuracy of over 70%; however, it was difficult to classify moderate dementia and mild dementia groups.

In contrast, the accuracy of the test data in the augmented binary classification results was 0.972 for moderate dementia and mild dementia groups, 0.996 for moderate dementia and MCI groups, and 0.985 for mild dementia and the MCI groups.

Comparing the accuracy with and without augmentation for both multilevel and binary classification, the accuracy increased significantly with augmentation. The accuracy of both multilevel and binary classification cases with augmentation exceeded 97%, suggesting that augmentation may be useful as reference information in cases where the MMSE or other tests cannot be administered.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Committee, The University of Tokyo Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TI, YU-K, TK, MA, and MN contributed to the conception and design of the study. TI organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Machine learning approach for early onset dementia neurobiomarker using EEG network topology features

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Introduction: Modern neurotechnology research employing state-of-the-art machine learning algorithms within the so-called "AI for social good" domain contributes to improving the well-being of individuals with a disability. Using digital health technologies, home-based self-diagnostics, or cognitive decline managing approaches with neuro-biomarker feedback may be helpful for older adults to remain independent and improve their wellbeing. We report research results on early-onset dementia neuro-biomarkers to scrutinize cognitive-behavioral intervention management and digital non-pharmacological therapies.

Methods: We present an empirical task in the EEG-based passive brain-computer interface application framework to assess working memory decline for forecasting a mild cognitive impairment. The EEG responses are analyzed in a framework of a network neuroscience technique applied to EEG time series for evaluation and to confirm the initial hypothesis of possible ML application modeling mild cognitive impairment prediction.

Results: We report findings from a pilot study group in Poland for a cognitive decline prediction. We utilize two emotional working memory tasks by analyzing EEG responses to facial emotions reproduced in short videos. A reminiscent interior image oddball task is also employed to validate the proposed methodology further.

Discussion: The proposed three experimental tasks in the current pilot study showcase the critical utilization of artificial intelligence for early-onset dementia prognosis in older adults.

KEYWORDS

EEG, dementia, biomarker, mild cognitive impairment, machine learning, artificial intelligence, prevention, network neuroscience

1. Introduction

Late-age cognitive decline, beginning with mild cognitive impairment (MCI) and often leading to dementia, caused mainly by Alzheimer's syndrome (AS) (Herrup, 2021) or vascular dementia spectrum of neurodegenerative diseases, is an actual healthcare emergency exemplified by evolved mental impairment in older adults with a span of psychological or behavioral symptoms (Livingston et al., 2020). Until now, there is no viable non-invasive biomarker helping to predict a possible early onset of MCI or even dementia, nor a pharmacological intervention stopping the disease progress, and only a postmortem autopsy is the conclusive determination (Herrup, 2021). Still, modern late-age dementia decline diagnostics comprises paper and pencil examinations such as a Montreal Cognitive

Assessment (MoCA) (Fujiwara et al., 2010). MoCA scores 25 and below (MoCA≤ 25) define MCI onset. There are several trials to develop an objective examination brain monitoring techniques focusing on non-invasive EEG (Rutkowski et al., 2020b, 2021a,b, 2022a,b) concurrently with behavioral evaluations (Rutkowski et al., 2020a). Such timely research for a neurodegenerative decline, particularly MCI, prediction is an essential scientific topic but still in the emerging research stages (WHO, 2019; Myszczynska et al., 2020; Shi et al., 2022).

Aging-societies-related dementia case increases represent a substantial and rapidly rising load on the healthcare ecosystem (WHO, 2019; Livingston et al., 2020). Contemporary societies expect the feasible attention of AI research to focus on possible diagnostics and non-pharmacological-therapeutic (NPT) approaches (Zucchella et al., 2018) in order to aid the wellbeing of aging communities. Our present report illustrates an application of a wearable headset Unicorn EEG by g.tec medical engineering GmbH, Austria. We focus our research on retail wearable headsets to capture EEG shortly in home-based environments, considering substantial environmental electromagnetic noise and no clinical experimental experience of the target older adult users. The wearable EEG headbands have already been proven satisfactory in academic research (Barachant et al., 2019; Rutkowski et al., 2022b).

Contemporary neurotechnology applications such as brain-computer interfaces (BCI) and efficient machine learning (ML) algorithms improve the daily lives of individuals with limited mobility or communication skills (Guger et al., 2015). An extension of the neurotechnology applications to a field of neuro-biomarkers of age-related cognitive decline and early onset dementia opens new opportunities to monitor cognitive-behavioral interventions (Otake-Matsuura et al., 2021) and digital non-pharmacological therapies (NPT; Sikkes et al., 2020). We discuss a unique experimental task in an EEG-based passive BCI application framework to evaluate working memory, which estimates MCI prediction. We report findings from two older adult volunteer groups in Poland of the proposed cognitive decline prediction task by analyzing EEG responses to short facial emotion-displaying videos. The EEG responses are analyzed in a framework of network neuroscience using an ordinal partition network (OPN) approach (Varley et al., 2021; Varley and Sporns, 2022).

A positive result of increased lifespan globally is associated with chronic late-age-related illnesses such as cognitive decline (Livingston et al., 2020). Fortunately, a possible application of digital health technologies, home-based self-management, and the development of novel screening tests for assessing cognitive dysfunction in older adults might help minimize the negative impact of healthcare systems (WHO, 2019). An introduction of home-based self-assessment and self-management approaches for older adults with cognitive dysfunction is of critical importance. Our research project aims to develop simple EEG wearable-based neurotechnology for easy self-evaluation and possible cognitive or lifestyle intervention monitoring.

Behavioral studies have shown that recognizing facial expressions may be impaired in patients with AS. There is already literature reporting studies on electrophysiological indicators of face recognition disorders in patients with AS (Güntekin et al., 2019), which provides the basis for future research to elucidate the behavioral and neural basis of facial emotional processing in AS (Fide et al., 2019). These non-linear methods, especially the calculation of permutation entropy values, offer opportunities for discrimination leading to the identification of AS. MCI and AS result in less variability and complexity in brain dynamics. Moreover, these advanced analysis methods can already apply to existing EEG data for future research. Thus, reducing EEG complexity could be considered a marker for detecting AS. The development of such a classification will give a chance to use this classification as a clinical tool (Şeker et al., 2021). The studies cited above may be the basis for research on emotional processing in patients with various types of dementia. The goal here will be to discover electrophysiological indices helpful in clinical practice as correlates of emerging behavioral problems.

Lately, there has been a flurry of research inspiration in modeling the brain as a network, with nodes indicating brain regions or single neurons and edges resembling structural or statistical dependencies (Bullmore and Sporns, 2009). Morabito et al. (2015) suggested a complex network technique integrated with time dynamics to perform a time-space investigation to illustrate the progression of AS in longitudinal studies. However, a recently rising discipline of network neuroscience focusing on the so-called network analysis of time series (Varley et al., 2021; Varley and Sporns, 2022) has permitted researchers to leverage the substantial force of graph theory and network science to analyze neural manifolds for temporal brain microstate number elucidation. Varley and Sporns (2022) in a recent review on network analysis of brainwave time series such as ECoG, LFP, or EEG, have shown that a complementary branch of network neuroscience, which focuses on an analysis of temporal data structures instead of functional or structural connectivity networks, could be a novel tool in computational neuroscience. Such a novel approach to network analysis of time series allows for collapsing at a given instant signal into a single state vector with edges corresponding to movement via state space. The edges could be directed or undirected, weighted, or not.

We propose three unique experimental tasks allowing for EEG recordings that consider the evaluation of working/short-term during facial emotion assessment learning, evaluation, and reminiscent interior oddball tasks. We next apply network analysis of EEG time series to elucidate differences between healthy aging cognition and MCI in older adult participants. We acknowledge the limitation of the current study concerning a restricted number of older adult participants in the reported pilot study. The presented encouraging results in the leave-one-out-subject cross-validation setting shall possibly be soon reproduced with a larger older adult participants cohort. The motivation and details of the proposed experimental procedure are explained in subsequent sections. We also develop novel EEG processing and machine learning classification procedures, which we describe in methods focusing sections. The results presentation and future application discussion conclude the paper.

1.1. Working/short-term memory in healthy and MCI-concerned older adults

Among late and middle-aged adults, self-reported short-term memory problems often signify intermediate and long-term risk factors of vascular and all-cause dementia (Möllers et al., 2022).

Working-memory impairments often occur in MCI patients and a further decline in dementia-diagnosed individuals, indicating that working memory evaluation is a good candidate for assessment as part of neuropsychological diagnostics of age-related cognitive decline possibly leading to dementia (Kessels et al., 2011).

As mentioned earlier, the reports indicate impaired working memory in age-related cognitive decline with a gradient between MCI and dementia (Gagnon and Belleville, 2011) are feasible candidates for behavioral and neurotechnological experimental tasks leading to digital neuro-biomarker development. We propose including working memory learning of a new skill in the proposed emotion assessment learning and evaluation task as introduced in Sections 2.1.1 and 2.1.2.

1.2. Reminiscent image interventions for the older adults

Reminiscence is a non-pharmacological intervention technique employed to manage the behavioral and psychological symptoms of dementia (Khait et al., 2021). Park et al. (2019) reported depression symptom reduction and increased quality of life in older adults after applying reminiscence intervention. A reminiscence is an act of recalling one's past experiences and affairs. Personal memories define one's identity by connecting past events with the future (Buzsáki et al., 2022). Reminiscence intervention or stimulation is an interaction that involves communicating past life events utilizing tangible audiovisual aids such as photos, music, or videos (Thomas and Sezgin, 2021). In the current study, we employ a previously developed by our research group (Rutkowski et al., 2021a, 2022b) reminiscent interior photography/images oddball task to assess the working memory of older adult subjects and subsequent development of EEG neuro-biomarker as explained in Section 2.1.3.

1.3. Facial emotion recognition and visuospatial learning in healthy and MCI-concerned older adults

Facial emotion recognition and emotional intelligence improve with age (Gutchess, 2019). Blessing et al. (2010) reported that even in subjects with severely impaired explicit memory, implicit learning of affective responses (e.g., valence and arousal ratings) is still possible in patients with dementia. The above report suggests that a facial emotion assessment task is feasible for evaluating short-term memory learning skills of affective responses in MCI-declining and dementia-diagnosed older adult individuals since emotion recognition is a stable trait even in dementia, but the short-term memory declines (Gutchess, 2019). Therefore we propose to include facial emotion evaluation assessment learning and testing tasks to utilize implicit learning and short-term memory characteristics in healthy cognitive aging vs. MCI participants (see Sections 2.1.1 and 2.1.2 for details).

Alescio-Lautier et al. (2007) reported that visual recognition memory and specific attentional mechanisms are impaired in early dementia of AS type. The authors concluded that a combination of attentional and visuospatial evaluation should be a viable direction for discovering predictive neuro-biomarkers distinguishing MCI individuals from those converting to dementia. A report by Seo et al. (2018) further suggested that including visuospatial reproduction and working memory would also facilitate early detection of MCI. The two above studies inspired our research team to include a visuospatial task in the experimental task, a skill-learning task to evaluate facial emotions with an emoji-grid first proposed by Toet et al. (2018), as explained in Sections 2.1.1 and 2.1.2.

2. Methods

EEG experimental data collection with the older adult volunteering participants was accomplished at the Nicolaus Copernicus University in Torun, Poland, in the summer of 2022. The Institute of Psychology UNC Ethical Committee for Experiments with Human Subjects has endorsed the investigation. The experimental procedure and information collection adhered to The Declaration of Helsinki, regulating ethical principles for research concerning human subjects, including the investigation of identifiable human material and data. In the study, 27 older adult participants took part with a mean age of 70.76 $\pm$ 5.34 years old (for detailed age distribution, see Supplementary Figure 1), single male and remaining female participants. In the initial group of 27 participants, 18 older adults were MCI and the remaining nine of healthy cognitive aging (see Supplementary Figures 2–4 for detailed MoCA score distribution in each experimental task). All participants volunteered for the study and signed informed consent forms.

2.1. Stimulus presentation

Taking into account previous research findings related to working memory, facial emotion recognition, visuospatial learning, and reminiscence, as summarized in Sections 1.1–1.3 we create three simple cognitive tasks for the older adult subjects.

2.1.1. Emotion evaluation learning task

The stimulus presentation protocol is the same as in the previously published by our research group employing Japanese participants (Rutkowski et al., 2020a, 2021b). This time, each Polish older adult sitting in front of a display presenting short facial emotion videos from a Mind Reading database (Baron-Cohen, 2004) is instructed to also observe a two-dimensional grid of valence and arousal (Toet et al., 2018; Rutkowski et al., 2020a, 2021b) and later, after the end of each video, to input similar score on the same design grid on a touchpad. This task involves facial emotion assessment evaluation learning and visuospatial memory elements. In the reported project, we record continuous EEG with triggers marking all stimulus presentation and participant response stages from 27 older adults. We present 24 videos (5 s each on average), from the Mind Reading database (Baron-Cohen, 2004), for each participant covering valence and arousal for positive and negative scores (six in each quadrant of a two-dimensional grid;

Toet et al., 2018). An experimental session consists of 24 emotional video clip presentations resulting in 24 responses contributed by each subject (212 from healthy and 432 from MCI participants in total after rejecting responses with missing markers due to stimulus system or network errors, as explained with $n_{healthy}$ and n_{MCI} variables in the top panels of Figures 1, 2).

2.1.2. Emotion evaluation assessment task

In the subsequent task, we instruct the participants to test how they learned to evaluate the short facial emotion display videos. This time they are instructed to input their valence and arousal evaluation on the same touchpad grid without a preceding suggestion prompt (Toet et al., 2018; Rutkowski et al., 2020a, 2021b). In this case, we also record continuous EEG with triggers marking all stimulus presentation and participant response stages from 24 older adults in the reported project. Similarly, as we have done in an emotion assessment evaluation learning task, we also present 24 videos (5 s each on average), from the Mind Reading database (Baron-Cohen, 2004), for each participant covering valence and arousal for positive and negative scores (six in each quadrant of a two-dimensional grid; Toet et al., 2018). An experimental session consists of 24 emotional video clip presentations resulting in 24 responses contributed by each subject (191 from healthy and 367 from MCI participants in total after rejecting responses with missing markers due to stimulus system or network errors, as explained with $n_{healthy}$ and n_{MCI} variables in the middle panels of Figures 1, 2).

2.1.3. Reminiscent interior images oddball task

In order to evaluate working memory in older adults, for dementia neuro-biomarker development purposes, we modify a standard oddball task to include childhood reminiscent interior images (Rutkowski et al., 2022b). Each short experimental trial presents eight types of modern and participants' childhood-time interior photographs. As in the classical oddball task, each stimulus from the series of eight became a target once, and participants are instructed to remember it before each trial. Here too, we record continuous EEG with triggers marking all experimental stages from 23 older adults in the reported project. Each participant session contains a presentation of eight oddball sessions containing eight randomly ordered interior images (four reminiscent and four modern rooms). An experimental session consists of 8 oddball sessions consisting of a single interior image (a target) presentation followed by eight presentations with a randomly positioned target photograph, thus, resulting in 72 responses contributed by each subject (503 from healthy and 1,141 from MCI participants in total after rejecting responses with missing markers due to stimulus system or network errors, as explained with $n_{healthy}$ and n_{MCI} variables in the bottom panels of Figures 1, 2).

2.2. EEG capture

We collect EEG data in the current study using a Unicorn EEG headset by g.tec Medical Engineering, Austria. The Unicorn EEG headset has already been proven a reliable experimental device, compared to other available wearables, in our previously published studies (Rutkowski et al., 2022c). For the initial investigation, we use eight EEG channels uniformly covering the human scalp at the standard locations of (*Fz*, *C*3, *Cz*, *C*4, *Pz*, *PO*7, *Cz*, and *PO*8). The eight EEG streams initially digitized with a sampling frequency of 250 Hz are bandpass filtered in the first preprocessing step to remove signal baseline shifts and high-frequency noise within a frequency band of 1–40 Hz. We next segment ("epoch") the EEG signals using video and image stimulus onset recorded triggers in emotion assessment and reminiscent interior tasks for five- and two-second epochs, respectively. We implement the filtering and segmentation procedures using the MNE package ver. 1.3.0 (Gramfort et al., 2014) in Python ver. 3.10.9. In the next step, to remove eye-blink and muscle movement-related artifacts in the collected EEGs, we employ a previously developed methodology by the members of the current research team (Rutkowski et al., 2008; Rutkowski and Mori, 2015). EEG channels are decomposed into intrinsic mode functions (IMF) using an empirical mode decomposition (EMD) method, and all the components that exceed the 100 μV threshold we reject before the final signal reconstruction from sub-threshold IMFs. We implement the above EEG cleaning procedures in PyEMD ver.1.4.0 (Laszuk, 2017). We next rectify the resulting filtered EEG traces to extract amplitude envelope traces using a Hilbert transform (SciPy ver. 1.10.0; Virtanen et al., 2020 implementation) and pass them to the network neuroscience application to time series, as explained in the next section.

2.3. Network science approach to EEG time-series

Permutation sequences in a time series are sensitive characteristics of the dynamic state of an observed system (Bandt and Pompe, 2002). They can be efficiently computed even for long time-series EEG. One crucial advantage of the permutation analysis approach is the possibility of mapping a continuous EEG recording to a little cluster of discrete permutations. Subsequently, it is possible to apply principled information-theoretic approaches, such as permutation entropy (Bandt and Pompe, 2002).

Varley et al. (2021) proposed an exploration of temporal dynamics of an observed system to derive ordinal partition network (OPN) representations of recorded neuropsychological data (EEG in our case). We also apply a similar procedure, and to avoid problems with multivariate OPNs, we analyze each EEG channel separately, and afterward, we combine the obtained network characteristics as input to final classifiers. Such a methodology allows for limitations of possible remaining EEG artifacts (eye-blinks, etc.) impact on the analysis, and each electrode cortical-region-related network features separate examination with limitations related to the spatial EEG resolution.

To create an OPN model characterizing EEG time series from a single channel c, we assemble a vector $\mathbf{X}_c = x_{c,1}, x_{c,2}, \ldots, x_{c,n}$, for limited time points $t = 1, \ldots, n$ in a single experimental

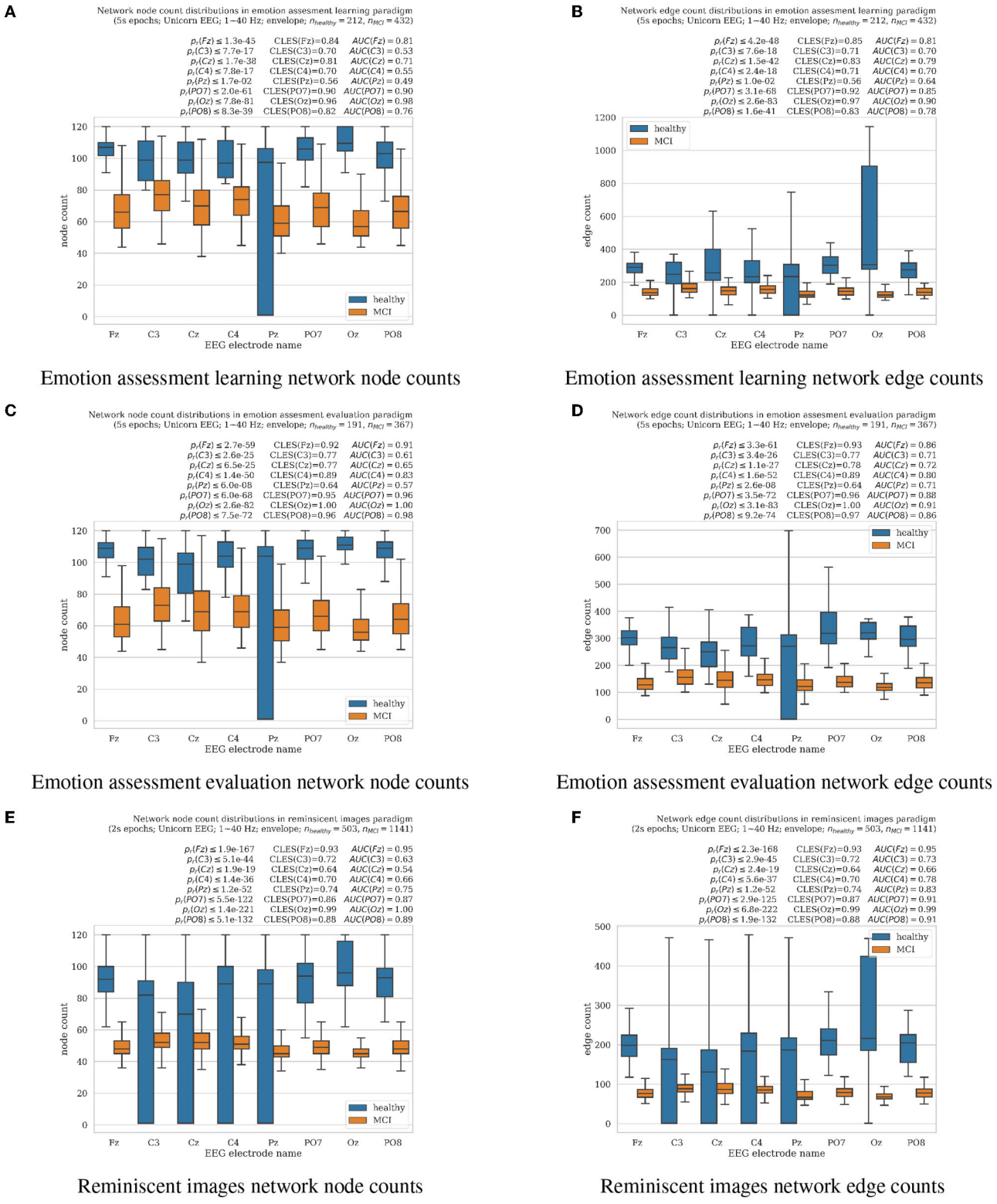

FIGURE 1
Boxplots with marked median, quartile ranges, and whiskers extending to show the rest of the distributions (all non-normal) of the network signal analysis resulting in node and edge counts for MCI vs. healthy aging cognition subjects for all EEG electrodes analyzed separately (Unicorn EEG headset with eight *Fz*, *C3*, *Cz*, *C4*, *Pz*, *PO7*, *Oz*, and *PO8* scalp locations). **(A, B)** represent results from emotion assessment learning, **(C, D)** from emotion assessment evaluation, and **(E, F)** reminiscent interior images oddball tasks, respectively. Wilcoxon rank-sum test for significantly differing distributions resulting p_r-values together with the common language effect size (CLES) (McGraw and Wong, 1992) and area under the ROC curve (AUC) (Hanley and McNeil, 1982) scores are summarized for each electrode over each panel, respectively.

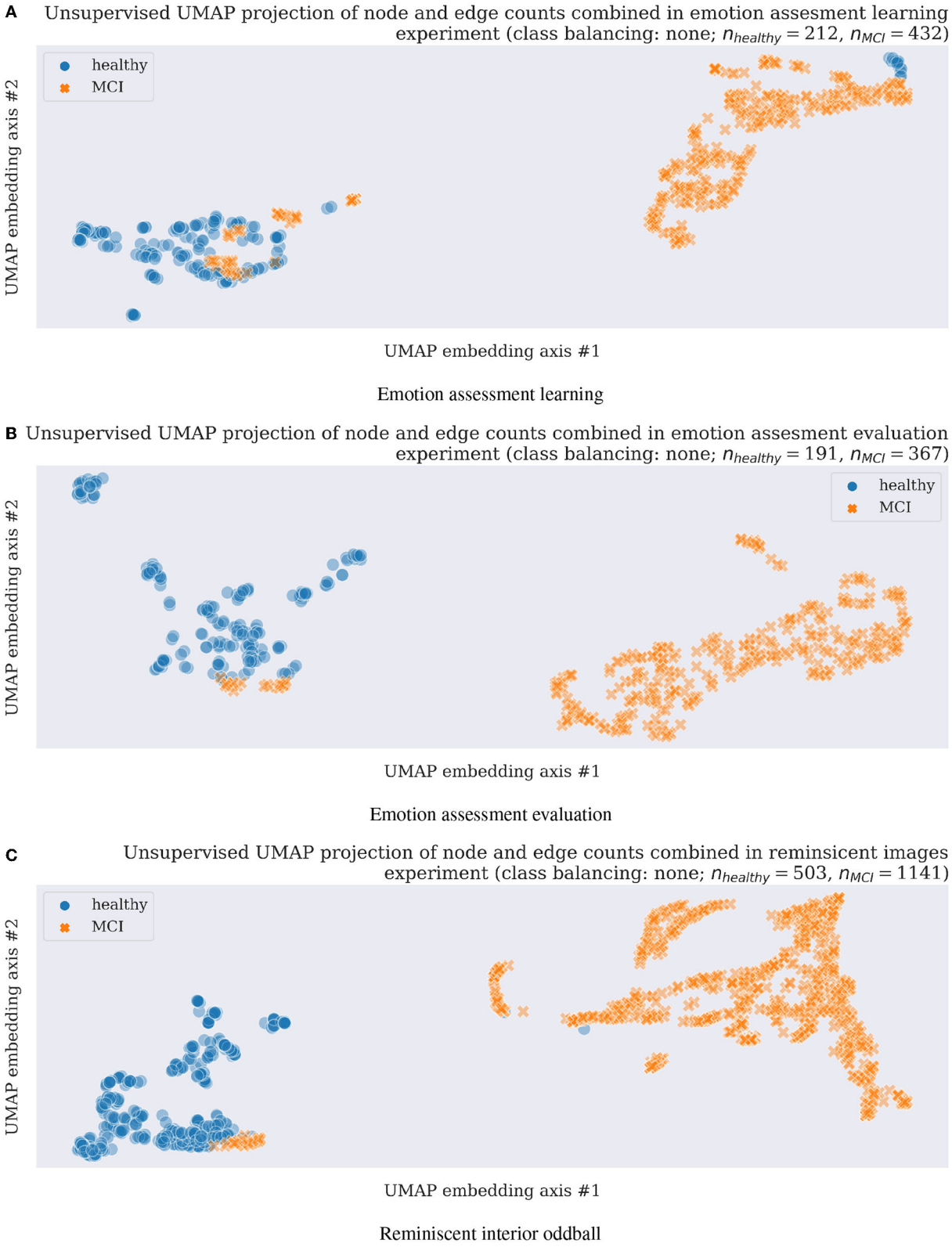

FIGURE 2
Unsupervised clustering (a machine learning training without class labels) scatter plots using UMAP in three experimental tasks and original data without any data augmentation, thus with unbalanced classes as shown with $n_{healthy}$ vs. n_{MCI} feature numbers above each scatterplot. **(A)** Emotion assessment learning. **(B)** Emotion assessment evaluation. **(C)** Reminiscent interior oddball.

trial to be analyzed next. The so obtained data vector is next embedded in $d-$dimensional space, utilizing τ time-lag. We select τ using the first zero crossing of the autocorrelation for each EEG channel time series representing an experimental trial. We limit a search for optimal τ in a range of 0–80 ms for computational and research reproducibility reasons. For the same reasons, we also specify the embedding dimension to $d = 5$ (similarly as in examples published by Varley et al., 2021), for results visualization purposes as shown in Figures 1, 2, as well as in the final supervised learning classification results reported in Figure 3. The resulting temporally ordered d-length vectors $\upsilon_{c,i} = \left[x_{c,i}, x_{c,i+\tau}, \ldots, x_{c,i+(d-1)\tau}\right]$ are next mapped to the permutation π to sort, in increasing order, their coefficients. The positions of the coefficients are next replaced in ordering π, and the resulting new vector $n_{c,i} = [\pi(x_{c,i}), \pi(x_{c,i+\tau}), \ldots, \pi(x_{c,i+(d-1)\tau})]$ represents a permutation of the numbers $1, 2, \ldots, d$. These permutations we consider as nodes in a directed network graph. The nodes we connect with directed edges and create from consecutive points. The so-created transition network results with fewer nodes than the initially analyzed EEG channel time series since there might be many i for which the delay vectors υ_i result in the same permutation π. The final OPN receives weights to each node representing a count of time points i representing the same permutation. At our project's current stage, we characterize each EEG channel c with a number of nodes and edges modeling each experimental trial (the so-called EEG epoch). The open-source package OPyN (Varley et al., 2021) has been used in our project to compute network neuroscience applications to EEG time series.

2.4. Unsupervised machine learning for network features visualization and dimensionality reduction

Unsupervised machine learning methods allowing for a datasets dimensionality reduction and visualization such as a uniform manifold approximation and projection (UMAP; McInnes et al., 2018) assume the available features (in the current project case, those are network node and edge counts from analyzed EEG electrode time-series separately as explained in Section 2.3; thus the final inputs to unsupervised model contain eight-node and edge counts obtained from each EEG responses and concatenated together, resulting in 16-dimensional feature vectors) are uniformly distributed across a topological manifold. The manifold could be approximated from these finite network features and projected to a lower-dimensional space. In the presented study, we apply the UMAP technique first in unsupervised learning mode to visualize EEG-derived network neuroscience features (Varley et al., 2021; Varley and Sporns, 2022) separability with results presented in Section 3.2. Next, a supervised learning mode of UMAP (McInnes et al., 2018) is applied for the network neuroscience features' dimensionality reduction in a leave-one-out-subject cross-validation classification to prove further the proposed methodology validation for future healthy cognitive aging vs. MCI early diagnostics with results discussed in Section 3.2.

2.5. Supervised machine learning models for leave-one-out-subject cross-validation of healthy aging vs. MCI EEG classification

In order to finally evaluate the usability of the proposed network neuroscience application to EEG time series for the early onset dementia (MCI with MoCA $\leq$ 25) elucidation, we employ several machine learning models in the leave-one-out-subject cross-validation (LOOS) setting. Similarly, as in the case of the unsupervised model discussed in Section 2.4 here, initial supervised machine learning input features are likewise composed of the network node and edge counts concatenated for all analyzed EEG electrode time-series separately as explained in Section 2.3 creating 16-dimensional integer-value-features, which are next reduced to eight dimensions using a supervised version of UMAP methodology explained in Section 2.4. The LOOS approach allows for keeping in each cross-validation step all data of a single subject and training a model using all the remaining subjects; thus, the procedure could be repeated for all the available subjects and final accuracies are concatenated and averaged, with a standard deviation calculation as discussed in Section 3.3.

In the reported study, we first applied UMAP supervised dimensionality reduction (McInnes et al., 2018) and next the following machine learning models (see Table 1 for details), available in the scikit-learn ver. 1.2.0 (Pedregosa et al., 2011) for classification: logistic regression (LR), linear discriminant analysis (LDA), linear kernel support vector machine (linearSVM), random forest classifier (RFC), deep fully connected neural network (DFNN).

3. Results

The results of the present study could be summarized three-fold. Firstly, we have shown that the network neuroscience approach to EEG time series resulted in statistically significantly differing node and edge counts. Secondly, applying the unsupervised machine learning clustering UMAP technique visualized a clear separation of network neuroscience application to EEG time series features from healthy cognitive aging and MCI participants in three simple cognitive experimental tasks. Finally, the leave-one-out-subject cross-validation evaluation of supervised machine learning classifiers resulted in mean classification outcomes that were significantly above chance levels.

3.1. Network neuroscience node and edge distribution results

Results of EEG time-series analysis with the OPN technique described in Section 2.3 were summarized in the form of the network node and edge count distributions as shown in Figure 1. For all introduced in this paper, experimental cognitive tasks of facial emotion assessment learning (Section 2.1.1) and evaluation (Section 2.1.2), as well as reminiscent interior images (Section 2.1.3), healthy cognitive aging participants resulted in significantly higher results comparing to MCI cases as evaluated in

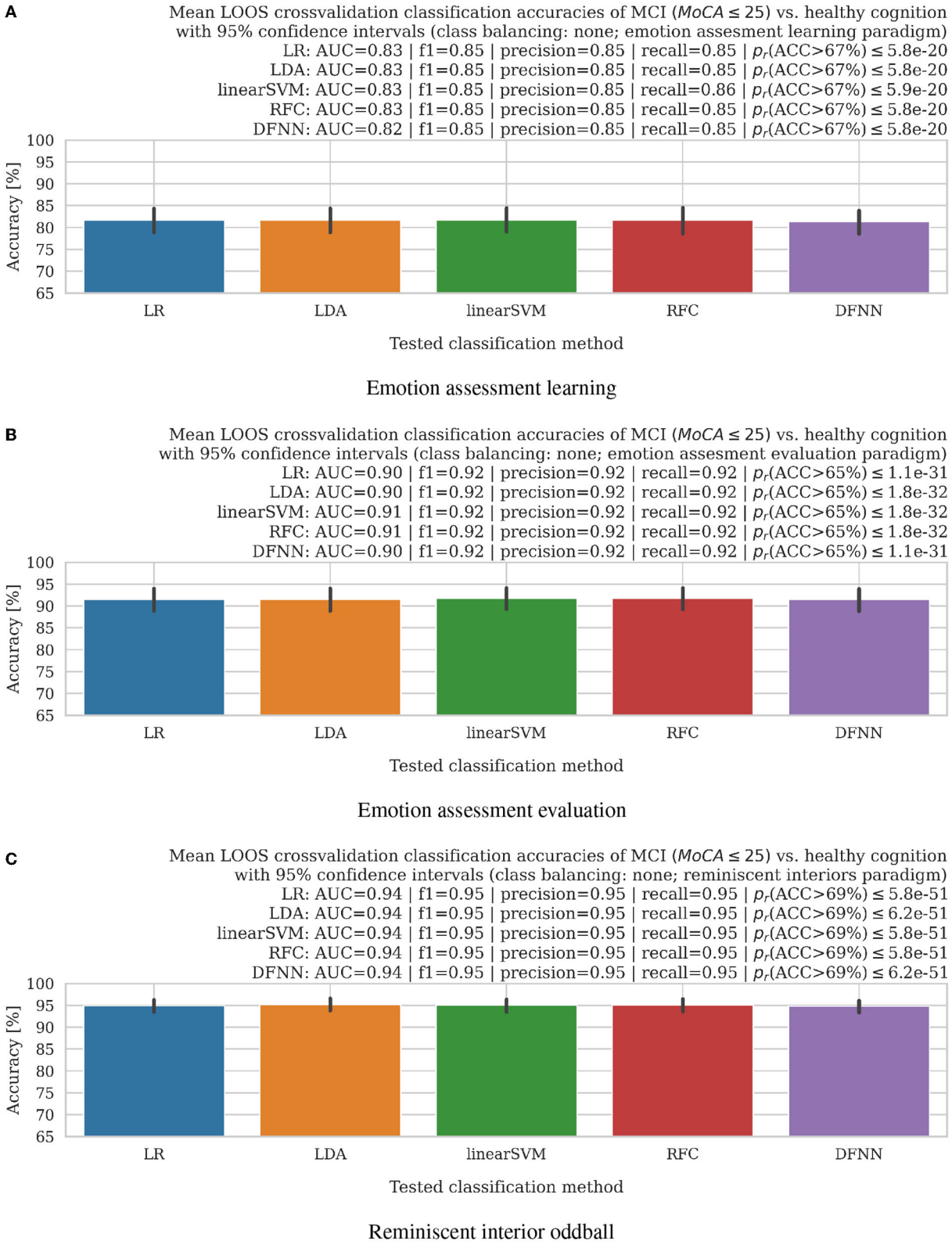

FIGURE 3
Bar plots with 95% confidence intervals of mean accuracies in leave-one-subject-out (LOOS) cross-validation setting of MCI vs. healthy aging cognition subjects using logistic regression (LR), a linear discriminant analysis (LDA), linear support vector machine (linearSVM), random forest (RFC), and deep fully-connected neural network (DFNN) classifiers. AUC, f1-scores, precision, recall, and Wilcoxon rank-sum test for significance p_r-values (all non-normal distributions) of the accuracy distributions above training set chance levels (denoted in parentheses for all experimental settings separately), which we listed above the bar plots, further supported good results of the proposed methodology. **(A)** Emotion assessment learning. **(B)** Emotion assessment evaluation. **(C)** Reminiscent interior oddball.

TABLE 1 Supervised machine learning models employed in the study for binary classification of healthy aging cognition vs. early onset dementia (MCI) (Pedregosa et al., 2011).

Machine learning (ML) model name	Parameters
LR—logistic regression	Liblinear solver
LDA—linear discriminant analysis	Solver using least-squares
linearSVM—linear support vector machine	Squared hinge loss; *l*2—penalty
RFC—random forest classifier	Maximum depth of 15
DFNN—deep fully connected neural network	Six layers of 8, 256, 245, 128, 32, 16 ReLU units (RU);
	two softmax units; early stopping; ADAM optimizer

non-parametric Wilcoxon rank-sum tests at $p_r \ll 0.01$, except for *Pz* electrode for which $p_r < 0.05$ for nodes in emotion assessment tasks. All results did not follow normal distributions (normality tests failed with $p_n < 0.05$ for all); thus, non-parametric statistical significance outcomes we supported by reliable common-language-effect-size (CLES) (McGraw and Wong, 1992) and area under the ROC curve (AUC) (Hanley and McNeil, 1982) evaluations indicated above all panels in Figure 1. The *Pz* electrode location has been known for difficulties in clear EEG recording due to larger hair volumes, especially in female subjects, who were a majority in the reported experiments. Limiting the number of EEG electrodes shall also contribute to a more comfortable experimental setup for the older adult participants. The significantly higher node and edge network counts refer to higher consciousness levels as previously reported by Varley et al. (2021) in anesthetized vs. awake animals. In the current study, the MCI subject EEG analysis resulted in significantly lower node and edge numbers than the healthy cognition participants, as shown in Figure 1. In previous animal study (Varley et al., 2021), results reported in anesthesia-modulated consciousness also resulted in lower network node and edge counts of analyzed brainwaves in lower awareness. Therefore, we hypothesize that the MCI group's EEG in our study might suggest lower stages of participant awareness than the healthy aging cognition group. The results also illustrated a less predictable EEG signal structure in healthy cognitive aging participants or more flexible than in MCI cases.

3.2. Unsupervised UMAP clustering results

A subsequent application of unsupervised UMAP clustering technique resulted in the majority of cases separation as visualized in Figure 2 for all three experimental tasks described in Sections 2.1.1–2.1.3. The very encouraging results on a still limited participant group of 27 in emotion assessment learning (Section 2.1.1), 24 emotion assessment evaluation (Section 2.1.2), and 23 in the final reminiscent interior oddball (Section 2.1.3) supported the project hypothesis of network neuroscience methodology feasibility as a strong candidate for early onset dementia neuro-biomarker development. In order to address the problem of imbalanced datasets (almost double of MCI cases compared to healthy participants), we resembled results with data augmentation steps using majority under- and minority class over-sampling steps as implemented using a synthetic minority over-sampling technique (SMOTE; Chawla et al., 2002; Lemaître et al., 2017). We summarized the still easily separable clustering results in Supplementary Figures 5, 6. Future research steps shall confirm the preliminary findings with a more extensive and preferably multicultural research group focusing on dementia level regression or multi-class or -cluster approaches.

3.3. Supervised leave-one-out-subject cross-validation classification of MCI vs. healthy aging cognition cases

The very encouraging results in the LOOS setting modeled a future real-world neuro-biomarker application, in which a machine learning model would be trained on a known, limited dataset and next applied to an unknown brainwave dataset for diagnostic purposes. The LOOS supervised machine learning accuracy results applied to four shallow- and one deep-learning models, as explained in Section 2.5, were summarized in Figure 3. Here again, to address the problem of imbalanced datasets (almost double of MCI cases compared to healthy participants), we resembled results with data augmentation steps using majority under- and minority class over-sampling steps as implemented using a synthetic minority over-sampling technique (SMOTE; Chawla et al., 2002; Lemaître et al., 2017). The data augmentation-based class balancing results did not vary significantly, as summarized in Supplementary Figures 7, 8. For the case of the facial emotion assessment learning (Section 2.1.1), mean accuracies were safely above chance levels of 67% as imposed by training data imbalance and summarized in the top panel of Figure 3 with following results: $ACC_{LR} = 81.63\%$ (83.24% for class-balance over-sampling and 83.31% for under-sampling), $ACC_{LDA} = 81.63\%$ (83.24% for class-balance over-sampling and 83.08% for under-sampling), $ACC_{linearSVM} = 81.69\%$ (83.24% for class-balance over-sampling and 83.08% for under-sampling), $ACC_{RFC} = 81.64\%$ (83.24% for class-balance over-sampling and 83.08% for under-sampling), $ACC_{DFNN} = 81.34\%$ (83.24% for class-balance over-sampling and 83.08% for under-sampling); for all the cases median accuracies were at 100% level for LR, LDA, linearSVM, RFC, and DFNN (see Section 2.5 for details), respectively. Similarly, mean accuracy results in the facial emotion assessment evaluation task (see Section 2.1.2 for details) were safely above chance levels of 65% as imposed by training data imbalance and summarized in the middle panel of Figure 3 with following results: $ACC_{LR} = 91.53\%$ (92.56% for class-balance over-sampling and 92.82% for under-sampling), $ACC_{LDA} = 91.57\%$ (92.56% for class-balance over-sampling and 92.61% for under-sampling), $ACC_{linearSVM} = 91.78\%$ (92.56% for class-balance over-sampling and 92.61% for under-sampling), $ACC_{RFC} = 91.78\%$ (92.56% for class-balance over-sampling and 92.82% for under-sampling), $ACC_{DFNN} = 91.53\%$ (92.56% for class-balance over-sampling and 92.61% for under-sampling); for all the cases median accuracies were at 100% level for LR, LDA, linearSVM, RFC, and DFNN (see Section 2.5 for details),

respectively. Finally, mean accuracy results in the reminiscent interior oddball task (see Section 2.1.3 for details) were safely above chance levels of 69% as imposed by training data imbalance and summarized in the bottom panel of Figure 3 with following results: $ACC_{LR} = 94.94\%$ (95.81% for class-balance over-sampling and 95.48% for under-sampling), $ACC_{LDA} = 95.20\%$ (93.74% for class-balance over-sampling and 95.48% for under-sampling), $ACC_{linearSVM} = 95.02\%$ (95.81% for class-balance over-sampling and 95.48% for under-sampling), $ACC_{RFC} = 95.09\%$ (95.72% for class-balance over-sampling and 95.48% for under-sampling), $ACC_{DFNN} = 94.84\%$ (95.53% for class-balance over-sampling and 95.48% for under-sampling); for all the cases median accuracies were at 100% level for LR, LDA, linearSVM, RFC, and DFNN (see Section 2.5 for details), respectively. The excellent supervised learning and LOOS cross-validated accuracy results with median accuracies reaching 100% levels for all the proposed cognitive tasks further supported a choice of network neuroscience approaches as the very reliable dementia neuro-biomarker prospects.

4. Discussion

Previous application of network neuroscience analysis to brainwave time series resulted in consciousness level association with network edge and node numbers (Varley et al., 2021) in anesthetized animals. Higher consciousness levels were associated with the larger node and edge numbers modeling brainwave time series, pointing to higher complexity and more brain microstates associated with those cognitive states (Varley et al., 2021). Consciousness is closely related to awareness (Ehret and Romand, 2022); thus, results presented in the current study with conscious (awake) subjects clearly show significantly lower network node and edge counts in MCI participants, indicating lower awareness levels compared to healthy cognitive aging older adults. In the presented study, more significant numbers of node and edge numbers in networks modeling EEG in healthy cognitive aging participants elucidated those brains characterized by more affluent microstates during cognitive tasks designed for the current study. Three different experimental tasks introduced in the study resulted in a larger number of modeling network nodes and edges for healthy cognitive aging vs. MCI older adults, further confirming a stable neuro-biomarker candidate, as summarized in Section 3.1.

The reproduced results in three cognitive tasks also elucidate potentially sound characteristics of the network neuroscience neuro-biomarker prospect. The statistical significance of network node and edge distribution differences was also confirmed with the unsupervised machine learning clustering UMAP approach as presented in Section 3.2.

The resulting unsupervised clusters formed easily separable quantities for most analyses used in the study. The final LOOS cross-validation experiment presented in Section 3.3 indicated a possible subsequent candidate for the following study with a more significant number of participants to infer all MoCA or other cognitive scores and not only binary healthy vs. MCI stages, as in the currently reported project.

The inherent study limitation has been a still low number of subjects (27, 24, and 23 in the three evaluated tasks) and unbalanced class membership (double the number of MCI compared to healthy cognitive aging). A single male participant also limited the study from the gender impact evaluation perspective. A near-future project with better gender-balanced subjects and possibly in cross-cultural settings shall be conducted to reproduce and validate the results. Another limitation of the current study, due to a low number of participants, has been a binary class membership (MCI vs. healthy cognitive aging). A subsequent study with more participants shall aim at continuous cognitive state estimation by predicting (regressing) exact MoCA or other cognitive state evaluations. A final limitation of the current study was a lack of relation of the predicted MCI stages based on only MoCA scores. The proposed neuro-biomarker shall be further validated with PET and cerebrospinal fluid (CSF) biomarkers for AS or structural MRI for vascular dementia evaluation.

5. Conclusions

This work discusses how network neuroscience methods' application to EEG time series can elucidate the separation between two distinct states of age-related healthy cognition and MCI. To assess each EEG channel's temporal dynamics, we assemble discrete state-transition graphs employing the ordinal partition networks approach, demonstrating how the brain evolves through state space in time. We discover that the healthy cognitive aging condition is characterized by a high degree of within each EEG channels interactions. Additionally, a less predictable EEG signal structure, or more flexible, is observed in healthy cognitive aging participants compared to MCI. Finally, unsupervised and supervised machine learning approaches allow us to separate and classify network neuroscience features for possible subsequent diagnostics of early onset dementia (MCI with MoCA $\leq$ 25) onset. The work is a step forward in developing a low-cost, home-based neuro-biomarker to monitor cognitive interventions and dementia care management.

Data availability statement

The datasets presented in this article are not readily available because, the raw EEG data generated and analyzed for this study cannot be shared due to participant privacy protection purposes. Requests to access the datasets should be directed to tomasz.rutkowski@riken.jp.

Ethics statement

The studies involving human participants were reviewed and approved by the Institute of Psychology UNC Ethical Committee for Experiments with Human Subjects. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TR conceived the concept of the working memory emotional learning and assessment, as well as reminiscent interior images oddball tasks, designed and programmed experimental stimulus presentation, EEG acquisition, analysis, and wrote the manuscript. TR and MA proposed network neuroscience to EEG time-series

application for subsequent classification using unsupervised and supervised machine learning methods. TK, SN, and TR recruited and managed the subjects, as well as conducted the experiments. TR, MA, SN, TK, and HS interpreted the results. TR, MA, HS, SN, TK, and MO-M examined outcomes. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1155194/full#supplementary-material

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The association between regional adiposity, cognitive function, and dementia-related brain changes: a systematic review

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Background: Adiposity has been previously associated with cognitive impairment and Alzheimer's disease and related disorders (ADRD). Body mass index (BMI) is the most common measure of global adiposity, but inconsistent results were found since it is a global measurement. BMI does not represent regional fat distribution which differs between sexes, race, and age. Regional fat distribution may contribute differently to cognitive decline and Alzheimer's disease (AD)-related brain changes. Fat-specific targeted therapies could lead to personalized improvement of cognition. The goal of this systematic review is to explore whether regional fat depots, rather than central obesity, should be used to understand the mechanism underlying the association between adiposity and brain.

Methods: This systematic review included 33 studies in the English language, conducted in humans aged 18years and over with assessment of regional adiposity, cognitive function, dementia, and brain measures. We included only studies that have assessed regional adiposity using imaging technics and excluded studies that were review articles, abstract only or letters to editor. Studies on children and adolescents, animal studies, and studies of patients with gastrointestinal diseases were excluded. PubMed, PsychInfo and web of science were used as electronic databases for literature search until November 2022.

Results: Based on the currently available literature, the findings suggest that different regional fat depots are likely associated with increased risk of cognitive impairment, brain changes and dementia, especially AD. However, different regional fat depots can have different cognitive outcomes and affect the brain differently. Visceral adipose tissue (VAT) was the most studied regional fat, along with liver fat through non-alcoholic fatty liver disease (NAFLD). Pancreatic fat was the least studied regional fat.

Conclusion: Regional adiposity, which is modifiable, may explain discrepancies in associations of global adiposity, brain, and cognition. Specific regional fat depots lead to abnormal secretion of adipose factors which in turn may penetrate the blood brain barrier leading to brain damage and to cognitive decline.

KEYWORDS

regional adiposity, fat distribution, visceral, liver, cognition, brain, dementia, Alzheimer's disease

Background

Adiposity refers to the state of being excessively overweight or obese, which is typically caused by an excessive accumulation of body fat and is strongly associated with type II diabetes (T2D), cardiovascular disease, hypertension, and hyperlipidemia (1). Adiposity has been previously associated with cognitive impairment and Alzheimer's disease and related disorders (ADRD) (2, 3). Characterization of how adiposity impacts ADRD is necessary because adiposity prevention and treatment could be a safe, efficacious approach to prevent ADRD. Body mass index (BMI) is the most common measure of global adiposity. BMI is calculated as weight (kg) divided by the square of height (m^2). Obesity is defined as BMI ≥30 kg/m2. Higher BMI in midlife has been associated with poor cognitive outcomes in late life (4, 5). Poorer performance in executive function (6) as well as working memory (7) and verbal fluency (8) have been consistently associated with higher BMI. We have shown that greater weight variability in midlife is associated with an increased risk of dementia three decades later (4). We have also found evidence for associations of greater variability in BMI over time with faster cognitive decline in late life (9). However, inconsistent results were found in old-age where high BMI has been associated with both higher risk (10, 11) but also lower risk (5, 12–14) for dementia. This non-linear association is often attributed to the fact that weight-loss can precede the development of AD (15–17) along with sarcopenia, the loss of skeletal muscle mass and function (18–21).

One explanation for these discrepancies is that BMI may not be a good measure of adiposity (22) since it represents global, rather than regional fat distribution (23, 24) especially in old age (25, 26). While BMI can assess excessive body fat, it does not account for different regional fat depots and muscle mass. Regional fat depots can be at the origin of different metabolic risks (27) since different fat depots have specific metabolic and hormonal characteristics. Previous data suggest that some obese individuals are metabolically healthy, free from high cardiovascular disease and with a normal metabolic risk profile. Contrariwise, metabolically unhealthy individuals with normal weight can be at high risk of cardiovascular disease (27, 28). Investigation of regional fat in these unique populations may shed light into these discrepancies. For them, little is known about the association of regional fat, brain, and cognition and such research is warranted.

Previous studies have shown that visceral adipose tissue (VAT) rather than obesity calculated by BMI, was associated with cardiovascular disease risk and metabolic syndrome (29, 30) while lower amounts of lower-body fat mass (gluteo-femoral) were also found to be a determinant of cardiometabolic diseases (27, 31). Ectopic fat, which refers to the accumulation of fat in areas where it is not normally found, such as the liver, and pancreas, is strongly associated with obesity and insulin resistance (32, 33). However, previous research has shown that nonalcoholic fatty liver disease (NAFLD) was associated with the metabolic syndrome regardless of central obesity assessed by BMI and insulin resistance (34). These findings suggest that some adipose tissues are deleterious while others have a protective role, indicating that although BMI is a widely used tool to assess central obesity, different regional fat depots may have different roles in cardiovascular risk factors and disease, themselves associated with ADRD (35, 36).

Furthermore, the appropriateness of BMI as a phenotypic marker of adiposity across populations differing in race and ethnicity is now questioned (37). Additionally, BMI does not account for sex differences in excessive fat. Women tend to have more fat than man, but the fat distribution is different between the sexes (38). This leaves critical gaps in knowledge about specific adiposity phenotypes that may differentially affect ADRD risk and neuropathology in old age. Body fat distribution has been linked to cognitive function in old age. Specific anatomical location of stored excess fat, including VAT, subcutaneous adipose tissue (SAT), or fat stored within the organs has been linked to cognition (39–41). Greater VAT was associated with lower delayed memory and language scores suggesting that regional adiposity may be linked to specific cognitive domains (39). There is evidence that the development of cognitive decline seems more strongly related to specific body fat distribution than to BMI (40). Exploring regional adiposity might contribute to the understanding of the mechanisms underlying the relationship of adiposity, cognitive function, and associated brain changes. Indeed, increased fat mass in different abdominal regions contributes to the dysregulation of adipokine secretion, increase of inflammation and release of fatty acids into the circulation (42), different human fat pools could lead to different interventions. Therefore, it is important to use additional measurements and assessments to obtain a more accurate picture of an individual's overall health and body composition.

Thus, the aim of this review is to explore the association between regional adiposity, different fat depots, cognitive function, and associated brain changes.

Method

Eligibility criteria

The present systematic review included studies of all designs if they were in the English language, conducted in humans aged 18 years and over with assessment of regional adiposity, cognitive function, dementia, and brain changes.

We included studies that have assessed regional adiposity using imaging techniques. There are several methods for measuring regional adipose tissues (43). Bioelectrical impedance analysis has been widely used to assess different fat tissues including VAT (44) but was shown to be less accurate in differentiating between the abdominal fat tissues compared to imaging techniques such as computed tomography (CT) (45), magnetic resonance imaging (MRI) (46) and dual energy x-ray absorptiometry (DEXA) (43, 47). Abdominal Ultrasound (US) is an accurate imaging technique for the detection of fatty liver (48). Therefore, we kept studies that used only imaging techniques to assess regional fat depots. Those include abdominal CT, DEXA, abdominal MRI, and abdominal US.

Studies were excluded if they were review articles, abstract only or letters to editor. Studies on children and adolescents and animal studies were excluded. Studies on patients with severe gastrointestinal diseases were excluded because significant inflammatory changes in the intestine can affect body composition (49, 50).

Search strategy

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (51). PubMed, PsychInfo, and web of science were used as electronic databases for literature search until November 2022. The search terms were: ("Cognitive decline" OR "cognition" OR "memory" OR "executive function" OR "cognitive" OR "Alzheimer's disease" OR "Dementia" AND "regional adiposity") further research was done replacing the term "regional adiposity" with "visceral adiposity," "subcutaneous adipose tissue," "hepatic fat," "fatty liver," "pancreatic fat," "pancreatic steatosis," "fat distribution."

Study selection

Title and abstract screening were carried out by one researcher (EB), duplicates and articles which did not meet the eligibility criteria were excluded. Articles which did not investigate regional adiposity and cognition or brain changes, were conducted on children or which used adiposity assessment that did not include imaging techniques were excluded. Full text screening was conducted independently by two researchers. Articles that fulfilled the selection criteria after the full text was read, were included in this systematic review. The study selection is shown in the flowchart in Figure 1.

The search strategy resulted in 2621 articles. From these, 2,520 articles were deemed ineligible after title and abstract screening. A hundred and one studies were eligible for full-text screening and 69 were excluded for the following reasons: measure of adiposity not with imaging technique ($n = 32$), meta-analysis or review ($n = 16$), no cognitive or brain outcomes ($n = 15$), not available online ($n = 2$), participants with inflammatory bowel disease ($n = 1$), animal study ($n = 1$), and studies on children or adolescents ($n = 2$). One study was found after independent research. Hence, 33 observational studies were included in this systematic review.

Data extraction and grouping

Data was extracted from 40 studies by one researcher and then re-checked by a second researcher. Both researchers agreed on

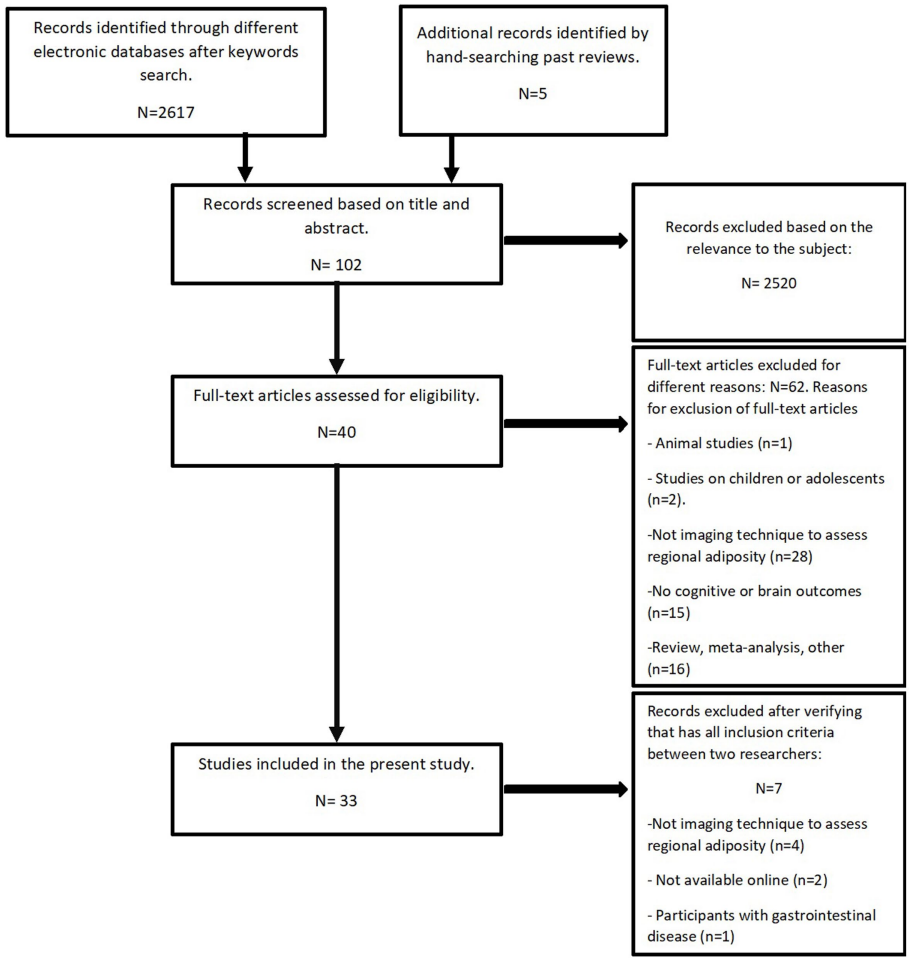

FIGURE 1
Flow chart.

including 33 studies in the present study based on inclusion criteria previously stated. Data extraction included the following: author, year published, country of the study, population characteristics including number of participants, number of women, mean age, which regions of adiposity were assessed, the technique of assessment, the measurement methods for cognitive function or brain measures. These findings are shown in Tables 1, 2.

Study characteristics

The data extracted from the 33 studies included in this review (36, 41, 52–82) are presented in Tables 1, 2. All studies had an observational design and were cross-sectional studies except for three longitudinal cognition studies (56, 60, 68). The articles were published between 2009 and 2022. The studies were conducted in the United States, Korea, Canada, Poland, Germany, Singapore, Serbia, Sweden, Turkey, Italy, Iceland and Spain, and included a total of 44,327 participants aged between 18 and 89 years (mean 54.11 years).

Statistical analysis

Results including the association of different regional fat depots with cognition and brain changes are presented narratively. For qualitative analysis, differences in measures between higher regional fat depots and control groups or the appropriate results were reported for individual studies. Data is considered statistically significant if the results reported have a value of p smaller than 0.05.

Results

Visceral adiposity and cognition

According to our search, we have grouped 13 studies assessing VAT and cognitive outcomes, nine (52, 54–59, 61, 62) of them using global cognition measurement such as Mini-mental state examination (MMSE) (83), modified MMSE (3MS) (84) and the Montreal Cognitive Assessment, (MoCA) (85). All studies were cross-sectional (52–55, 57–63) except for two longitudinal (36, 56). Among them, six studies have also assessed SAT and cognitive outcomes (36, 54, 56, 57, 59, 60). While in some studies, absence of significant associations of VAT (36, 55, 56, 58, 59, 62) and SAT (57, 59) with cognitive functioning have been shown, in most of our search, higher VAT was found to be associated with lower cognitive scores (52–54, 57, 60, 61, 63). In studies including both VAT and SAT measures, variable results were found. SAT and VAT were associated with lower verbal memory; VAT was independently associated with lower cognition when accounting for SAT but not the other way around (54). In another study, higher VAT but not higher SAT was associated with poor cognitive functioning (57). Interestingly, sex had opposite effects in these associations. Higher SAT (but not VAT) was associated with worsening cognitive functioning after 7 years in men (56). In contrast, in women higher levels of SAT and VAT were associated with less cognitive decline over the years (56). In another study, higher SAT and subcutaneous thigh fat were associated with a decreased likelihood of dementia in women (36). The impact of regional fat depots on cognitive functions can be found in Table 3.

Visceral adiposity and brain changes

Twelve articles reported on the association between VAT and SAT and different brain changes (41, 52–54, 59, 62, 73–78). The association between different brain compartments and regional fat depots can be found in Table 4. All the papers have used structural brain measures via brain MRI (41, 52–54, 59, 62, 73–78), while only one study used also functional measures via functional MRI (fMRI) to assess degree of connectivity (eigenvector centrality, EC) (73). This study showed that high VAT was associated with lower cerebellar structure (gray matter density) as well as lower degree of connectivity of the cerebellum with other brain regions in younger subjects; no associations were found in older individuals (73). These results suggest that the relationship of increased VAT with reduced gray matter density and reduced connectivity in the cerebellum, which is involved in cognitive function, are age-dependent (73). Structural measures have shown that higher VAT and SAT were associated with smaller total brain volume (78). Moreover, elevated VAT was correlated with cortical thinning especially with lower hippocampal volume (54) but not with gray matter and white matter volumes (54, 59). Similarly, higher VAT was linked to smaller temporal lobe and the volume of several other sub-compartments of the brain (76). Six studies (52, 54, 59, 62, 77, 78) have assessed the associations between VAT and White Matter Hyperintensities (WMH) which has been recognized as a risk factor for cognitive impairment and dementia (86). Among them, two have found a significant positive association, namely, associations of high VAT with greater volumes of WMH (62, 77). Similar associations were observed for higher VAT and greater vascular brain injury (52), or lower brain connectivity (fractional anisotropy [FA]), a measure of white matter integrity (74). Higher VAT was associated with higher damage in a brain network implicated in cognitive decline (53), suggesting that VAT is associated with accelerated brain aging (53). In contrast to this relatively broad evidence linking VAT with lower brain volumes and pathologies, two studies found associations of higher VAT with thicker cortex in the posterior cingulate gyrus (75), and with greater left cuneus volume (76).

Visceral adiposity and AD-related pathology

The relationship of VAT with dementia pathology has been examined in two studies (55, 58). Individuals with higher VAT metabolism, a marker of higher VAT dysfunction assessed through PET-CT, compared with individuals with low VAT metabolism, exhibited significantly higher cerebral Aβ burden (55). Those findings suggest that VAT dysfunction could contribute to AD development. In a second study, using brain ^{18}F-fluorodeoxyglucose (FDG) PET as a neurodegenerative biomarker for AD, computing the PALZ score a global index of AD-related hypometabolism, no significant correlation between VAT and the risk of AD pathology was found (58).

Fatty liver and cognition

In the present study, we have identified seven studies examining the relationships of cognition and fatty liver or NAFLD (60, 67–72). In the past literature, we have identified three previous systematic review and meta-analyses (87–89) of observational studies, providing

a comprehensive evaluation of the relationship between NAFLD and the risk of dementia or cognitive impairment. However, the studies included in our review include only the ones that have assessed liver fat and NAFLD with imaging technique. In most of the studies, higher severity of NAFLD was associated with increased risk of cognitive impairment (60, 67–71); in some cases, cardiovascular disease attenuated this relationship (60). Strong associations between NAFLD and worsening of cognition in patients meeting the criteria for vascular dementia was found (72). The impact of regional fat depots on cognitive functions can be found in Table 3.

Fatty liver and brain changes

Five studies have reported the association between structural brain changes and fatty liver (41, 67, 79, 80, 82). Among them only one used a noninvasive functional measure, pseudo-Continuous Arterial Spin Labeling (pCASL) measuring cerebral blood flow (CBF) (79). The results are reported in Table 4. Hepatic fat depots were significantly associated with smaller total cerebral brain volume (79) as well as smaller cingulate gyri and hippocampal volumes (41). NAFLD was associated with a smaller total cerebral volume even after adjustment for VAT, pointing to a relationship between NAFLD and brain aging (80). In this study, no significant associations were observed between NAFLD and hippocampal and WMH volumes, nor with covert brain infarcts (small ischemic cerebral lesions here assessed by abnormal signal intensity) (80). Conversely, NAFLD was significantly associated with the presence of WMHs, even after adjusting for cardiometabolic risk factors (82) in another study. In NAFLD patients with lower cognitive score, the volumes of brain gray and white matter were significantly reduced compared to NAFLD patients with higher cognitive score (67). However, no comparison between the NAFLD patients and the control group without NAFLD volumes was done (67). Finally, higher liver fat shown by lower liver attenuation on abdominal CT was associated with decreased total-CBF and gray matter-CBF and this association remained after adjustment for cardiovascular risk factors (79).

Fatty liver, AD-related pathology, and dementia

One study assessed NAFLD and AD-related neuropathology via PET-CT (81). Prevalent NAFLD was not associated with Aβ or tau PET, the main two pathologies characterizing AD (81). We found only one study investigating associations of NAFLD and dementia risk (66). Moderate-to-severe NAFLD was found to be associated with dementia and AD risk, especially with vascular dementia (66). Moreover, participants with vascular dementia and NAFLD had worse neuropsychological outcomes than participants without NAFLD (66).

Other fat depots

Higher epicardial adipose tissue (EAT) has been associated with poorer cognitive functioning in two studies (64, 65). Pericardial adipose tissue (PAT) has been associated with lower hippocampal white matter but not hippocampal gray matter (59). One study examined associations of pancreatic fat with regional brain volume. Albeit in all analyses higher pancreatic fat was associated with lower hippocampal, cingulate gyri and temporal lobe volumes, none of these associations reached statistical significance (41). To our knowledge, no studies examining relationships of kidney fat depots with cognition or brain changes have been done.

Factors potentially linking fat depots, brain changes and cognition

A few studies have explored inflammatory markers as possible factors linking fat depots, brain changes and cognition. Cannavale et al. (63), hypothesized that inflammatory markers would mediate the negative effect of VAT on selective attention. Indeed, plasma C-reactive protein (CRP) and Interleukin-6 (IL-6) concentrations mediated the relationship between higher VAT and lower attentional inhibitory control, suggesting that systemic inflammation could play a role in the deleterious effects of VAT on cognition (63). Higher levels of SAT and VAT were associated with worsening cognitive function in men even after controlling for metabolic disorders, adipocytokines (adiponectin, IL-6, tumor necrosis factor α [TNF-α], and plasminogen activator inhibitor-1[PAI-1]), and sex hormone levels (estradiol and testosterone) (56). Conversely, there was no association between adiposity and cognitive change in women (56). However, in another study where higher VAT was associated with lower cognitive functioning, estradiol level attenuated the negative consequences of VAT on cognition in women (53). Similar results were found for moderate-to- severe NAFLD, which was associated with increased serum levels of multiple cytokines, i.e., higher IL-6 concentrations partially mediated the association of moderate-to-severe NAFLD with vascular dementia (66).

Higher VAT and hepatic fat remained significantly associated with WMH (62, 82), decreased total-CBF and GM-CBF (79) and smaller brain volumes (41, 80) after adjustment for cardiovascular risk factors. Similarly, VAT was found to be significantly associated with reduced cognitive scores, after adjustment for cardiovascular risk factors, and for MRI-detected vascular brain injury (52). In several studies (60, 68, 69, 71) the association between NAFLD and cognitive impairment varied across the cognitive tests when adjusting for cardiovascular risk factors and diseases. Indeed, the NAFLD-cognitive function association was either attenuated (60, 71) or disappeared (68, 69, 71) when adjusting for these factors.

Discussion

Regional adiposity is associated with brain changes and higher risk of cognitive decline

Based on the current available literature, the findings indicate that different regional fat depots are likely associated with increased risk of cognitive impairment and dementia (36, 41, 52–82). Specifically, VAT (52, 54, 57, 61, 63), EAT (64, 65) and liver fat through NAFLD (60, 67–71, 79) were associated with cognitive impairment. Moreover, regional fat was linked to different brain changes (41, 52–63, 73–78), with a relatively consistent association

TABLE 1 Characteristics of the included studies about regional adiposity and cognition.

Ref.	Article	Origin of population	Nb of participants	Women %	Age Mean years (SD)	Regional Adiposity	Method of acquisition	Measures of Cognition	Cognitive tests	Brain MRI	Brain parts
(52)	Anand et al. (2022)	Canada Poland	*N* = 6,773	56.4%	57.8 (8.8)	VAT	Abdominal MRI	Global cognitive function	DSST MoCA	Brain MRI	WMH BI
(53)	Zsido et al. (2019)	Germany	*N* = 974	48.6%	50.7 (15.6)	VAT	Abdominal MRI	Memory performance	CERAD	MPRAGE	Brain network covariance
(54)	Isaac et al. (2011)	Singapore	*N* = 184	52.2%	67.9 (6.4)	VAT SAT	Abdominal MRI	Six cognitive domains: attention, verbal memory, visuo-spatial memory, executive functioning, speed of processing, language	MMSE DSST Spatial span task RAVLT WMS-III Verbal fluency test Design fluency test, TMT A TMT B SDMT Object and action naming battery	Brain MRI	Total brain volume, Hippocampal volume, Ventricular volume, and Cortical thickness.
(55)	Kim et al. (2022)	Korea	*N* = 54	63%	66.4 (8.4)	VAT metabolism	PET-CT FDG	Global cognitive function	MMSE	PET-CT Brain MRI	Amyloid burden by PET-CT WMH
(56)	Kanaya et al. (2009)	USA	N = 3,054	51.2%	73.6 (2.8)	VAT SAT	Abdominal CT	Global cognitive function	3MS		
(57)	Yoon et al. (2012)	Korea	*N* = 250	54%	66.4 (2.8)	VAT SAT	Abdominal CT	Global cognitive function	MMSE		
(58)	Kim et al. (2019)	Korea	*N* = 110	41%	63.0 (6.4)	VAT	Abdominal CT	Global cognitive function	MMSE	Brain FDG PET/CT scan	PALZ score
(59)	Hsu et al. (2016)	USA	*N* = 604	59.9%	57.7 (9.3)	VAT SAT PAT	Abdominal CT	Global cognitive function Executive function	3MS DSST RAVLT Stroop Task COWA	Brain MRI	WMV GMV WM lesions hippocampal GMV, hippocampal WMV,

(Continued)

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TABLE 1 (Continued)

Ref.	Article	Origin of population	Nb of participants	Women %	Age Mean years (SD)	Regional Adiposity	Method of acquisition	Measures of Cognition	Cognitive tests	Brain MRI	Brain parts
(60)	Gerber et al. (2021)	USA	*N* = 2,809	57%	50.1 (3.6)	VAT SAT LA	Abdominal CT	Attention, working memory, psychomotor speed, executive function, Verbal memory.	DSST RAVLT Stroop Task		
(21)	Spauwen et al. (2017)	Iceland	*N* = 5,169	57.1%	76.4(5.5)	VAT SAT Thigh SAT	Abdominal and thigh CT	Dementia	DSM-IV		
(61)	Meng et al. (2020)	USA	*N* = 30	50%	69.9 (7.1)	VAT	DEXA	Global cognitive function N-back cognitive function	MoCA		
(62)	Pasha et al. (2017)	USA	*N* = 126	54.8%	49.1 (6.6)	VAT	DEXA	Global cognitive function Memory Executive function	MMSE WASI-II FSIQ CVLT-II TMT A TMT B WASI-III DSST Stroop task	Brain MRI	WM lesion
(63)	Cannavale et al. (2021)	USA	*N* = 115	66.1%	33.8 (6.1)	VAT	DEXA	Attentional inhibitory control	Eriksen Flanker task		
(64)	Mazzoccoli et al. (2014)	Italy	*N* = 71	50.7%	72.7 (7.1)	EAT	Transthoracic echocardiography	Global cognitive function	MMSE		
(65)	Verrusio et al. (2019)	Italy	*N* = 65	52.3%	72.1 (8.9)	EAT	Transthoracic echocardiography	Global cognitive function	MMSE		
(66)	Wang et al. (2022)	China	*N* = 5,129	61.79%	71.06 (5.97)	NAFLD	Transabdominal US	Dementia	DSM IV		

(Continued)

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TABLE 1 (Continued)

Ref.	Article	Origin of population	Nb of participants	Women %	Age Mean years (SD)	Regional Adiposity	Method of acquisition	Measures of Cognition	Cognitive tests	Brain MRI	Brain parts
(67)	Filipovic et al. (2018)	Serbia	*N* = 76	42.1%	47.5 (6.5)	Hepatic fat	Abdominal US	Global cognitive function	MoCA	Brain MRI	TCBV, lateral ventricle volume, GMV WMV
(68)	Liu et al. (2022)	China	*N* = 1,651	51.2%	53.4 (8.4)	NAFLD	Abdominal US	Global cognitive function	MMSE		
(69)	Yu et al. (2022)	USA	*N* = 4,973	50.3%	37.2 (11.1)	NAFLD	Abdominal US	Global cognitive function	SDLT, SRTT, DSST		
(70)	Celikbilek et al. (2018)	Turkey	*N* = 143	62.9%	45.3 (9.7)	NAFLD	Abdominal US	Global cognitive function	MoCA		
(71)	Seo et al. (2016)	USA	*N* = 4,472	52.5%	37.3(0.3)	NAFLD	Abdominal US	Global cognitive function	SRTT, DSST, SDLT		
(72)	Moretti et al. (2022)	Italy	*N* = 285	48.1%	76 (1)	NAFLD	Abdominal US	Frontal dementia Anxiety Apathy Global behavioral symptoms Quality of life in dementia scale	FAB, HAM-A, AES-C, NPI,QUALID		

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; PAT, pericardial adipose tissue; NAFLD, non-alcoholic fatty liver disease; LA, liver attenuation; EAT, epicardial adipose tissue; MRI, magnetic resonance imaging; MPRAGE, magnetization prepared – rapid gradient echo; DEXA, dual- energy X- ray absorptiometry; CT, computed tomography; PET-CT FDG, positron emission tomography – CT F-fluorodeoxyglucose; US, ultrasound; Fmri, functional MRI; WMH, white matter hyperintensities; BI, brain infarctions; WMV, white matter volume; GMV, gray matter volume; CSF, cerebrospinal fluid; FA, fractional anisotropy; LI, lacunar infarct; TCBV, total cranial brain volume; WMHV, WMH volume; GM, gray matter; WM, white matter; CBF, cerebral blood flow; MBs, microbleeds; DSST, digit symbol substitution test; MoCA, the Montreal cognitive assessment; MMSE- the mini-mental state examination; 3MS, the modified mini-mental state test; SDMT, the symbol digit modalities test; RAVLT, the Rey auditory verbal learning test; COWA, controlled oral word association test; CERAD, the consortium to establish a registry for Alzheimer's disease; FAB, frontal assessment battery; BDI, beck depression inventory test; HAM-A, Hamilton anxiety rating scale; AES-C, the apathy evaluation scale; SDLT, serial digit learning test; SRTT, the simple reaction time task; NPI, the neuropsychiatric inventory questionnaire; QUALID, quality of life in late stage dementia; DSM IV, diagnostic and statistical manual of mental disorders IV.

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TABLE 2 Characteristics of the included studies about regional adiposity and brain.

Ref	Article	Origin of population	Nb of participants	Women %	Age Mean years (SD)	Regional adiposity	Method of acquisition	Measures of cognition	Cognitive tests	Brain MRI	Brain regions
(53)	Zsido et al. (2019)	Germany	*N* = 974	48.6%	50.68 (15.6)	VAT	Abdominal MRI	Memory performance	CERAD	MPRAGE MRI	Brain network covariance
(41)	Beller et al. (2019)	Germany	*N* = 351	43.3%	56.2 (± 9.0)	VAT SAT Hepatic fat pancreatic fat	Abdominal MRI			Brain MRI	Cingulate gyri, hippocampus, temporal lobe
52	Anand et al. (2022)	Canada Poland	*N* = 6,773	56.4%	57.8 (8.8)	VAT	Abdominal MRI	Global cognitive function	DSST MoCA	Brain MRI	WMH BI
(54)	Isaac et al. (2011)	Singapore	*N* = 184	52.2%	67.9 (6.4)	VAT SAT	Abdominal MRI	Six cognitive domains: attention, verbal memory, visuo-spatial memory, executive functioning, speed of processing, and language was used.	MMSE, digit span, spatial span task (echsler), RAVLT, WMS-III, verbal fluency test, design fluency test, trail making test B and A, SDMT, object and action naming battery	Brain MRI	Total brain volume, hippocampal volume, ventricular volume, and cortical thickness.
(73)	Raschpichler et al. (2016)	Germany	*N* = 100	42%	51.7 (16.4)	VAT SAT	Abdominal MRI			Brain MRI Fmri	Gray matter density
(74)	Cardenas et al. (2020)	Spain	*N* = 23	0%	36.79 (8)	VAT	DEXA			Brain MRI	WM FA
(62)	Pasha et al. (2017)	USA	*N* = 126	54.8%	49.1 (6.6)	VAT	DEXA	Global cognitive function Memory Executive function	MMSE WASI-II FSIQ subtest, California Verbal Learning Test-II (CVLT-II), Trail Making Tests A and B, Wechsler Adult Intelligence Scale III (WASI-III) Digit Span subtest -Stroop color-word subtest.	Brain MRI	WM lesion
(75)	Kaur et al. (2015)	USA	*N* = 103	52.4%	49.63 (6.47)	VAT	DEXA			Brain MRI	Cortical thickness

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TABLE 2 (Continued)

Ref	Article	Origin of population	Nb of participants	Women %	Age Mean years (SD)	Regional adiposity	Method of acquisition	Measures of cognition	Cognitive tests	Brain MRI	Brain regions
(55)	Kim et al. (2022)	Korea	*N* = 54	63%	66.4 (8.4)	VAT	PET-CT FDG	Global cognitive function	MMSE	PET-CT Brain MRI	Amyloid burden by PET-CT WMH
(59)	Hsu et al. (2016)	USA	*N* = 604	59.9%	57.7(9.3)	VAT SAT PAT	Abdominal CT	Global cognitive function Executive function	3MS Digit Symbol Coding, the RAVLT-delayed recall, the Stroop Task COWA	Brain MRI	WMV GMV WM lesions hippocampal GMV, hippocampal WMV,
(58)	Kim et al. (2019)	Korea	*N* = 110	41%	63.0 (6.4)	VAT	Abdominal CT	Global cognitive function	MMSE	Brain FDG PET/CT scan	PALZ score
(76)	Lee et. al. (2021)	Korea	*N* = 1,209	52.5%	63.6 (6.9)	VAT	Abdominal CT			Brain MRI	CSF,frontal, parietal,temporal,occipital, subcortical and cerebellum
(77)	Kim et al. (2017)	Korea	*N* = 1991	37.4%	50.3 (5.2)	VAT SAT	Abdominal CT			Brain MRI	WMH LI
(78)	Debette et al. (2010)	USA	*N* = 733	53%	64 (9)	VAT SAT	Abdominal CT			Brain MRI	TCBV, temporal horn volume, WMHV BI
(79)	VanWagner et al. (2017)	USA	*N* = 505	55.8%	50.1(3.6)	VAT SAT LA	Abdominal CT			Brain MRI pCASL	Total brain tissue volume GM WM CSF CBF
(80)	Weinstein et al. (2018)	USA	*N* = 766	53.5%	67 (9)	Hepatic fat	Abdominal CT			Brain MRI	TCBV, hippocampal volume WMHV BI
(81)	Weinstein et al. (2022)	USA	*N* = 169;	43%	52 (9)	NAFLD	Abdominal CT			PET-CT	Regional Amyloid-β and Tau Pathology
(67)	Filipovic et al. (2018)	Serbia	*N* = 76	42.1%	47.5 (6.5)	Hepatic fat	Abdominal US	Global cognitive function	MoCA	Brain MRI	TCBV, lateral ventricle volume, GMV WMV

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TABLE 2 (Continued)

Ref	Article	Origin of population	Nb of participants	Women %	Age Mean years (SD)	Regional adiposity	Method of acquisition	Measures of cognition	Cognitive tests	Brain MRI	Brain regions
(82)	Jang et al. (2019)	Korea	$N = 1,260$	49.2%	63.7(6.8)	NAFLD	Abdominal US	Global cognitive function	MMSE	Brain MRI	CSVD WMH Lacunes Microbleeds (MBs)

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; PAT, pericardial adipose tissue; NAFLD, non-alcoholic fatty liver disease; LA, liver attenuation; EAT, epicardial adipose tissue; MRI, magnetic resonance imaging; MPRAGE, magnetization prepared – rapid gradient echo; DEXA, dual- energy X- ray absorptiometry; CT, computed tomography; PET-CT FDG, positron emission tomography – CT F-fluorodeoxyglucose; US, ultrasound; Fmri, functional MRI; Pcasl, pseudo-continuous arterial spin labeling; WMH, white matter hyperintensities; BI, brain infarctions; WMV, white matter volume; GMV, gray matter volume; CSF, cerebrospinal fluid; FA, fractional anisotropy; LI, lacunar infarct; TCBV, total cranial brain volume; WMHV, WMH volume; GM, gray matter; WM, white matter; CBF, cerebral blood flow; MBs, microbleeds; DSST, digit symbol substitution test; MoCA, the Montreal cognitive assessment; MMSE, the mini-mental state examination; 3MS, the modified mini-mental state test; SDMT, the symbol digit modalities test; RAVLT, the Rey auditory verbal learning test; COWA, Controlled Oral Word Association Test; CERAD, the consortium to establish a registry for Alzheimer's disease; FAB, frontal assessment battery; BDI, beck depression inventory test; HAM-A, Hamilton anxiety rating scale; AES-C, the apathy evaluation scale; SDLT, serial digit learning test; SRTT, the simple reaction time task; NPI, the neuropsychiatric inventory questionnaire; QUALID, quality of life in late stage dementia; DSM IV- diagnostic and statistical manual of mental disorders IV.

of different fat depots with cortical volume (41, 54, 59, 73, 76, 78–80), and with white matter disease (62, 74, 77). Both lower cortical volume and white matter disease have been linked to cognitive decline, AD and dementia (90, 91). Interestingly, higher VAT, but not the other regional fat depots, was associated with amyloid β, a core neuropathological feature of AD (55, 81). This could be explained by the excessive secretion of leptin by high VAT, which in turn could inhibit the transport of Amyloid-β precursor protein and promote the fabrication of amyloid β (92). Finally, one of the studies has shown that greater severity of NAFLD was associated with higher risk of dementia (66), while among women higher SAT and thigh fat with lower likelihood of dementia (36). Overall, results from this systematic review suggest that different regional fat depots may lead to different neurobiological alterations and ultimately to different cognitive-related outcomes and dementia. Exploring potential mechanisms underlying the inter-relationships of regional adiposity- brain changes - cognition could lead to targeted and personalized treatments for cognitive-related outcomes.

Metabolic syndrome and insulin resistance may link regional adiposity, brain changes, and cognition

The findings of associations of different regional fat depots with lower cognitive scores are concordant with previous research indicating that adiposity (assessed by BMI) is associated with cognitive impairment and risk of dementia (93). Central adiposity is a core feature of the metabolic syndrome (94) and has been associated with cognitive decline, dementia and neuropathology (94, 95), especially in old age (96). Yet, the metabolic syndrome has been associated with NAFLD and pancreatic fat independently of central obesity and insulin resistance (34, 97). Also, accumulation of VAT was found to be the best predictor for metabolic syndrome in women while it was a poor predictor for men compared to SAT (98). One possibility is that the impaired vascular function resulting from the different conditions of the metabolic syndrome could lead to brain changes that could then lead to cognitive impairment (95).

Another core feature of the metabolic syndrome is insulin resistance which also has been linked to cognitive decline and dementia (99). VAT rather than SAT is more strongly associated with insulin resistance (100) and NAFLD has also been closely linked to insulin resistance (101), showing that different fat compartments may be associated with differential metabolic risk. Although both VAT and fatty liver have been shown to be related to impaired cognition and both are determinants of insulin resistance, their impact is different due to the different roles played by adipokines and hepatokines, respectively (101). Those results imply the importance of assessing regional adiposity rather than central adiposity to understand the specific contribution of excess adiposity to cognition. Therefore, further studies should be done on regional fat depots to better understand the mechanism underlying the association between adiposity, metabolic syndrome, cognition, and brain changes. Investigation of regional fat in metabolically healthy obese population may shed light into these discrepancies (27, 28).

TABLE 3 Cognition and regional adiposity in studies included in the systematic review: the table is ordered by fat depots from the newest to the oldest publication.

Regional adiposity	Cognitive variables	Results	References
Visceral adipose tissue (VAT)	DSST MoCA	Higher VAT was associated with significantly lower DSST scores but not with MoCA scores.	Anand et al. (52)
	Attentional inhibitory control [Eriksen Flanker task]	High VAT was associated with poorer selective attention.	Cannavale et al. (63)
	DSST RAVLT STROOP TASK	VAT was associated with lower cognitive function at baseline and follow-up.	Gerber et al. (60)
	MoCA N-back (Reaction time and accuracy.)	Higher VAT associated with higher MoCA score. Higher VAT is significantly associated with longer reaction time. No association found between VAT and response accuracy.	Meng et al. (61)
	Memory network covariance	Higher VAT was associated with lower memory network covariance in men. This association was not found in women.	Zsido et al. (53)
	Dementia	No significant association of VAT with dementia.	Spauwen et al. (36)
	MMSE Memory Executive function [WASI-II FSIQ CVLT-II TMT-A TMT-B DIGIT SPAN subtest STROOP TASK]	No significant associations were found between VAT and cognitive function in any of the tests or the cognitive domains.	Pasha et al. (62)
	3MS DSST RAVLT STROOP TASK COWA	No significant associations were found between VAT and any of the cognitive tests.	Hsu et al. (59)
	MMSE	Higher VAT was associated with poorer cognitive performance among subjects younger than 70 years old. No significant associations were found for older subject.	Yoon et al. (57)
	Attention Verbal Memory Visuo-spatial Memory Executive functioning Speed of processing Language	Higher VAT was significantly associated with lower attention and verbal memory scores. There were no significant associations with the other cognitive domains.	Isaac et al. (54)
	Modified MMSE (3MS)	Higher level of VAT was significantly associated with worse cognitive function in men but not in women.	Kanaya et al. (56)
VAT metabolism	MMSE K-BNT score	Higher VAT metabolism was significantly associated with lower K-BNT score. No significant associations were found with MMSE.	Kim et al. (55)

(Continued)

Regional adiposity affects brain volumes and vasculature via systemic inflammation

In the present review, we have gathered data showing that regional fat depots are associated with deleterious brain changes. Regional fat depots including VAT, SAT and fatty liver were associated with smaller cerebral volumes (78–80). Fatty liver and VAT but not SAT were significantly associated with smaller hippocampal volume (41, 54, 59) which is one of the first regions affected by AD (90). Those results are concordant with recent evidence from our group showing associations of higher BMI with thinning of the middle temporal gyrus (102). Overall, the present review indicates that different fat depots can affect

TABLE 3 (Continued)

Regional adiposity	Cognitive variables	Results	References
Subcutaneous adipose tissue (SAT)	DSST RAVLT STROOP TASK	SAT was associated with lower cognitive function at baseline and follow-up	Gerber et al. (60)
	Dementia	Higher amounts of SAT and subcutaneous thigh fat were associated with a decreased likelihood of dementia in women.	Spauwen et al. (41)
	3MS DSST RAVLT STROOP TASK COWA	SAT was not associated with any of the cognitive tests.	Hsu et al. (59)
	MMSE	SAT was not related to poorer cognitive performance among younger and older adults.	Yoon et al. (57)
	Attention Verbal Memory Visuo-spatial Memory Executive functioning Speed of processing Language	Higher SAT was significantly associated with lower attention and verbal memory scores.	Isaac et al. (54)
	Modified MMSE (3MS)	Higher level of SAT was significantly associated with worse cognitive function in men but not in women.	Kanaya et al. (56)
Hepatic fat	MMSE	Older adults with NAFLD had higher 4-year incidence of cognitive impairment than those without NAFLD.	Liu et al. (68)
	SDLT SRTT DSST	NAFLD was significantly associated with high risk of low SDLT, SRTT and DSST scores. The fully adjusted model remained significant only for SRTT.	Yu et al. (69)
	FAB HAM-A NPI QUALID	NAFLD was strongly associated with vascular dementia.	Moretti et al. (72)
	Dementia	Moderate to severe NAFLD was associated with increased likelihood of all cause dementia.	Wang et al. (66)
	DSST RAVLT STROOP TASK	NAFLD was associated with lower cognitive function	Gerber et al. (60)
	MoCA	NAFLD patients had lower MoCA scores.	Filipovic et al. (67)
	MoCA	MoCA scores were significantly lower in participants with NAFLD than in healthy controls	Celikbilek et al. (70)
	SDLT SRTT DSST	Compared to healthy participants, NAFLD was significantly associated with high risk of low SDLT, SRTT and DSST scores. In a fully adjusted model only the associations with SDTL remained significant.	Seo et al. (71)
Pericardial adipose tissue (PAT)	3MS DSST RAVLT STROOP TASK COWA	No significant association were found between pericardial adipose tissue and cognitive functions.	Hsu et al. (59)

(Continued)

TABLE 3 (Continued)

Regional adiposity	Cognitive variables	Results	References
Epicardial adipose tissue (EAT)	MMSE	High epicardial adipose tissue thickness was associated with lower cognitive function.	Verrusio et al. (65)
	MMSE	High epicardial adipose tissue thickness was associated with lower cognitive function.	Mazzoccoli et al. (64)

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; PAT, pericardial adipose tissue; NAFLD, non-alcoholic fatty liver disease; EAT, epicardial adipose tissue; DSST, digit symbol substitution test; MoCA, the Montreal cognitive assessment; MMSE, the mini-mental state examination; 3MS, the modified mini-mental state test; SDMT, the symbol digit modalities test; RAVLT, the Rey auditory verbal learning test; COWA, controlled oral word association test; CERAD, the consortium to establish a registry for Alzheimer's disease; FAB, frontal assessment battery; BDI, beck depression inventory test; HAM-A, Hamilton Anxiety rating scale; AES-C, the apathy evaluation scale; SDLT, serial digit learning Test; SRTT, the simple reaction time task; NPI, the neuropsychiatric inventory questionnaire; QUALID, quality of life in late stage dementia; WASI-II, Wechsler abbreviated intelligence scale; FSIQ, full scale intelligence quotient; CVLT-II, California verbal learning test; TMT, trail making test.

different parts of the brain suggesting a potential role of different regional fat depots in brain atrophy and pathology, targeting those fats could then prevent deleterious impact on the brain.

Brain small vessel disease which includes higher WMHs, and lacunar infarcts may lead to cognitive impairment and dementia (91). In the present review, different regional fat depots have also been associated with higher WMHs (62, 77, 82). In addition to its associations with cognitive impairment and AD (86), WMH is prevalent in individuals with insulin resistance, metabolic syndrome and T2D (103), all conditions accompanied by high adiposity (103). Furthermore, adiposity is associated with chronic low-grade systemic inflammation, which increases proinflammatory cytokine secretion (104). Pro-inflammatory cytokines have been linked to greater volumes of WMHs (104) which in turn are linked to cognitive impairment. As suggested by one of the studies reviewed, mechanisms by which VAT exerts a negative influence on cognitive function includes systemic inflammation (63). Therefore, disentangling factors secreted by different fat depots affecting systemic inflammation may shed light into their role in cognitive decline and dementia.

Indeed, different fat depots release different secreted factors, some of which cross readily the blood brain barrier (BBB) and may cause damage, ultimately leading to cognitive decline (56, 63, 66). For example, pro-inflammatory factors such as leptin, IL-6, TNF-α (105, 106) which are secreted by adipocytes can cross the BBB and lead to neuroinflammation, which plays a role in cognitive impairment and AD (107). Conversely, anti-inflammatory adipocytokines such as Adiponectin (108), Interleukin 10 (IL-10) (109, 110), and Apelin (111), are associated with less adiposity and are related to cognition and AD. Neuroinflammation likely causes synaptic remodeling and neurodegeneration resulting in disruption of cognitive functioning possibly resulting from damage brain regions subserving cognition such as the hippocampus (112). Targeting these factors could be an efficacious way to prevent or delay later cognitive decline and AD.

Associations of adipose-secreted factors with neuropathology and impaired cognitive functioning

Other factors, such as proteins are secreted from different fat depots, and may explain the role of peripheral fats in the brain. For example, Amylin, a hormone synthesized and co-secreted with insulin by pancreatic β-cells, is elevated in obesity and may share similar pathophysiology with Amyloid-β, characteristic of AD neuropathology (113). Also, Glucagon-like peptide-1 (GLP-1), a gut released hormone, which can protect pancreatic β-cells from apoptosis and induce insulin secretion, is attracting attention as a possible link between metabolic syndrome and brain impairment (114, 115). Additional factors, secreted by hepatocytes, the most common cells in the liver, are found to be related to cognition such as plasminogen activator inhibitor 1 (PAI-1) (116), and fetuin (117, 118). Indeed, in the presence of elevated fatty acids (119), circulating fetuin-A can induce insulin resistance (119) and inflammatory signaling (120) which may cause damage to the brain leading to cognitive impairment (117, 118). Therefore, identifying novel factors altered due to excess fat in different abdominal regions and associated with cerebrovascular pathology, neuropathology, and impaired cognitive functioning is crucial for developing fat-specific interventions. Potential mechanisms underlying the inter-relationships of adiposity- brain changes – cognition and therapeutic modalities, is presented in Figure 2.

Sex differences in regional adiposity, brain changes, and cognition

Finally, sex differences should be taken into consideration as they may also contribute to the fat-brain-cognition axis. Women have overall more fat mass than men. Specifically, women have more SAT, which explains the "pear shape" (38), while they are characterized by lower VAT compared to men (121). Those differences in regional fat depots may lead to different consequences on cognition. Higher levels of VAT were associated with worsening cognitive function in men after adjustment for metabolic disorders, adipocytokines, and sex hormone levels (56). Conversely, there was no association between adiposity and cognitive changes in women (56). Furthermore, while VAT exacerbates the association between aging and poorer brain network covariance in both men and women, estradiol reduces the negative association in women (53). These findings highlight the need to account for sex differences in the investigation of relationships of regional adiposity with brain and cognition.

Limitations

This review provides evidence for the association of different regional fat depots, cognition, and brain changes. However, this study had several limitations. First, the initial intention of our group was to conduct a meta-analysis on regional adiposity and cognition. But, due

TABLE 4 Brain changes and regional adiposity in studies included in the systematic review.

Brain changes	Brain parts	Studies	Regional fat depots	Association with regional fat depot	Difference
Volumetrics	Total brain volume	Isaac et al. (54)	VAT	–	NS
			SAT	+	NS
		Debette et al. (78)	SAT	–	$p < 0.001$
			VAT	–	$P < 0.001$
		Weinstein et al. (80)	NAFLD	–	$P < 0.001$
		VanWagner et al. (79)	LA	–	$p < 0.05$
	Frontal	Lee et al. (76)	VAT	+	NS
	Parietal	Lee et al. (76)	VAT	+	NS
	Temporal	Lee et al. (76)	VAT	–	$p < 0.05$
		Beller et al. (41)	VAT	+	NS
			Hepatic	–	NS
			Pancreatic	–	NS
	Occipital	Lee et al. (76)	VAT	+	NS
	Subcortical	Lee et al. (76)	VAT	–	NS
	Cerebellum	Lee et al. (76)	VAT	–	NS
	Gray Matter	Lee et al. (76)	VAT	–	NS
		Hsu et al. (59)	VAT	–	NS
			SAT	+	NS
			PAT	+	NS
		Raschpichler et al. (73)	VAT	–	$P < 0.05$
	White matter	Lee et al. (76)	VAT	+	NS
		Hsu et al. (59)	PAT	+	NS
			VAT	+	NS
			SAT	–	NS
	CSF	Lee et al. (76)	VAT	+	NS
	Hippocampal	Isaac et al. (54)	VAT	–	$P < 0.05$
			SAT	–	NS
		Hsu et al. (59)	PAT	–	NS
			VAT	–	$P < 0.05$
			SAT	–	NS
		Hsu et al. (59)	PAT	–	$P < 0.05$
			VAT	–	NS
			SAT	–	NS
		Weinstein et al. (80)	NAFLD	+	NS
		Beller et al. (41)	VAT	–	NS
			Hepatic	–	$P < 0.05$
			Pancreatic	–	NS
	Ventricular	Isaac et al. (54)	VAT	+	$P < 0.05$
			SAT	+	$P < 0.05$
	Cortical thickness	Isaac et al. (54)	VAT	–	$p < 0.01$
		Kaur et al. (75)	VAT	+	$P < 0.05$
	Temporal horn volume	Debette et al. (78)	SAT	+	NS

(Continued)

TABLE 4 (Continued)

Brain changes	Brain parts	Studies	Regional fat depots	Association with regional fat depot	Difference
			VAT	+	NS
	Cingulate gyri	Beller et al. (41)	VAT	–	NS
			Hepatic	–	$P < 0.05$
			Pancreatic	–	NS
Wmhs	HWMHS	Anand et al. (52)	VAT	+	NS
		Isaac et al. (54)	VAT	+	NS
			SAT	–	NS
		Hsu et al. (59)	PAT	–	NS
			VAT	+	NS
			SAT	–	NS
		Pasha et al. (62)	VAT	+	$P < 0.05$
		Kim et al. (77)	VAT	+	$P < 0.01$
			SAT	+	NS
		Debette et al. (78)	SAT	–	NS
			VAT	–	NS
		Weinstein et al. (80)	NAFLD	–	NS
		Jang et al. (82)	NAFLD	+	$P < 0.01$
Brain infarcts	Vascular brain injury	Anand et al. (52)	VAT	+	$P < 0.05$
	Silent brain infarctions	Anand et al. (52)	VAT	+	NS
	Brain network covariance	Zsido et al. (53)	VAT	–	$P < 0.01$
	Fractional anisotropy	Cardenas et al. (74)	VAT	–	$P < 0.05$
	Lacunar infarct	Anand et al. (52)	VAT	+	NS
		Kim et al. (77)	VAT	+	$P < 0.05$
			SAT	+	NS
	Lacunes	Jang et al. (82)	NAFLD	+	NS
	Brain infarcts (BI)	Debette et al. (78)	SAT	–	NS
			VAT	–	NS
		Weinstein et al. (80)	NAFLD	+	NS
	Microbleeds	Jang et al. (82)	NAFLD	+	NS
Functional changes	Eigenvector centrality	Raschpichler et al. (73)	VAT	–	$P < 0.01$
	Cerebral blood flow	VanWagner et al. (79)	LA	–	$P < 0.05$
Ad-neuropathology	Tau pathology	Weinstein et al. (81)	NAFLD	+	NS
	Amyloid burden	Kim et al. (55)	VAT	+	$P < 0.05$
		Weinstein et al. (81)	NAFLD	+	NS

The table is ordered by brain changes. Significant findings are emphasized in bold.

to the limited number of studies and the variability in methodologies the meta-analysis could not be conclusive as it carried high heterogeneity. The studies have different designs, sample sizes, and cognitive tests as well as different ways of assessing regional fat depots to quantify adiposity, adding complexity to the interpretation of results. Indeed, quantification of the degree of adipose tissues is different in each of the studies, as some quantify by fat volume and others by surface or percentage of fat in the different regions, making it difficult to directly compare the studies. Further prospective studies are needed to establish the relationship between regional fat depots with brain changes and cognition with similar methodologies. Only three studies in this review had longitudinal cognitive decline (56, 60, 68). Considering that the duration of exposure to adiposity may affect the onset and the severity of cognitive impairment, the lack of longitudinal data for regional adiposity is a significant limitation in the field. All studies were observational studies and not clinical trials

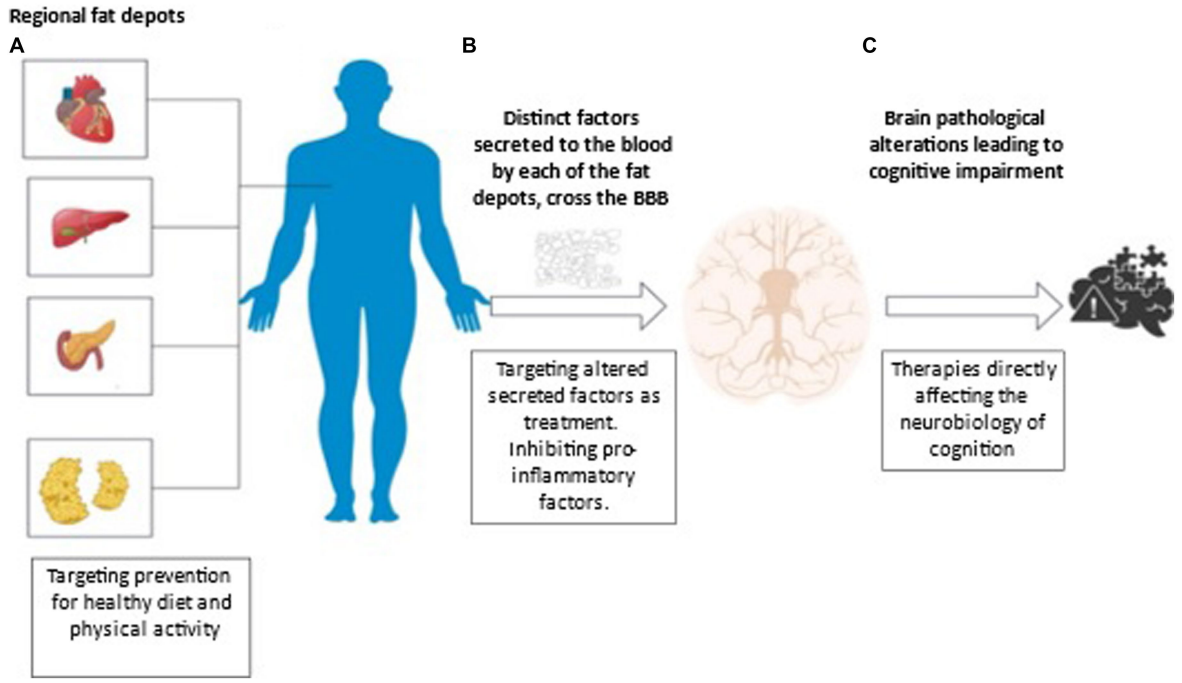

FIGURE 2
Potential mechanisms underlying the adiposity- brain changes - cognition inter-relationships and therapeutic modalities. **(A)** Adiposity is commonly used to describe excess body fat or obesity. Different fat depots can be found in the body independently of central obesity. Subcutaneous adiposity refers to the accumulation of fat underneath the skin, in the adipose tissue layer. Visceral adiposity refers to the accumulation of fat in the abdominal cavity, specifically around the organs such as the liver, pancreas, and intestines. Ectopic fat refers to the accumulation of fat in areas where it is not normally found, such as the liver, muscle, and pancreas. Both types of fat are associated with increased risk of metabolic disorders such as insulin resistance, type 2 diabetes, and cardiovascular disease. Understanding the association of adiposity, brain changes and cognitive abilities would provide key insights into the mechanisms by which adiposity impacts cognitive health and to possible treatments. Lifestyle interventions, such as specific diets and physical activity may diminish accumulation of fat depots. **(B)** Adiposity is associated with chronic low-grade systemic inflammation. Different fat depots can release different proinflammatory cytokines, hormones and enzymes some of which cross readily the blood brain barrier (BBB) and may cause damage ultimately leading to cognitive decline. For example, pro-inflammatory factors such as leptin, secreted by adipocytes, can cross the BBB and lead to neuroinflammation, which plays a major role in cognitive impairment and AD. Conversely, anti-inflammatory adipocytokines such as adiponectin, are associated with less adiposity and are related to better cognitive functioning and lower AD risk. Treatment targeting enhancing protective factors released from adipocytes and diminishing inflammatory factors secreted from fats could be an efficacious way to prevent brain damage and ultimately support healthy cognition. **(C)** Initial evidence suggests that different fat depots affect a plethora of brain pathologies including cortical volume, the cerebral vasculature, primarily white matter hyperintensities, and neuroinflammation. These pathologies contribute to cognitive impairment and as treatments addressing the neurobiology of cognition evolve, cognitive health may be maintained in spite of accumulation of fat deposits and their respective secreted factors.

therefore no causation can be inferred. In some studies, there were no associations between regional fat and cognition. However, many of these studies included relatively young individuals (e.g., 54.11 years, age at baseline for longitudinal studies). In such young ages the range of cognitive functioning is relatively narrow, possibly contributing to the lack of associations. It is important to note that the literature on fat and cognition may suffer from selection bias since older adults with cognitive impairment are less likely to participate in research. Finally, this review focuses specifically on body fat composition, rather than on general body composition, and does not discuss muscle mass and function which are strongly associated with cognitive decline and dementia risk (18–21).

Conclusion

This review of 33 studies indicates that different regional fat depots may affect cognition and different regions of the brain. Regional fat depots, especially VAT and hepatic fat, have been associated with cognitive decline, cortical thinning and WMHs. Regional fat depots, rather than central obesity, may better explicate the association between adiposity and brain and may open horizons for new personalized fat-reducing treatments for prevention of cognitive decline.

Author contributions

EB, SG, and MB conceived the presented idea and have made a substantial contribution to the concept and design of the manuscript. EB carried out the literature search from electronic databases, drafted the manuscript, and provided the tables. SG participated with EB to the full-text screening of the articles from the literature search, read and approved the manuscript. MB revised critically the manuscript and approved the version to

be published. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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