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RESEARCH ARTICLE

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Brain pathology and cognitive scores prior to onset of late-life depression

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Abstract

Objectives: Understanding the biological changes that occur prior to onset of late-life depression (LLD) is key to its prevention. To investigate potential predictors of LLD, we assessed cognitive scores and neurodegenerative and vascular biomarkers in healthy older adults who later developed depression.

Methods: Longitudinal data from the Alzheimer's Disease Neuroimaging Initiative of 241 cognitively unimpaired and non-depressed older adults aged 56–90 at baseline with at least 4 years of follow-up were included. Participants were classified based on whether they developed an incident depression (n = 96) or not (n = 145). Cognitive measures of memory, executive functioning, and language, and biomarkers proposed to be related to LLD: hippocampal volume, white matter hyperintensity volume (WMH), and cortical and cerebrospinal fluid (CSF) amyloid beta levels, were compared between the incident depression and the never-depressed groups at four time points: at baseline, the visit prior to onset, at onset, and after the onset of depression.

Results: In the incident depression group, there was a mild decline in cognitive scores from baseline to the visit before depression onset compared with the never-depressed group. The cognitive differences between the groups became more marked after depression onset. Baseline cortical amyloid burden, CSF amyloid beta levels, and WMH were significant predictors of incident depression. Compared to the non-depressed group, hippocampal volume was not reduced before onset, but was reduced following depression.

Conclusions: Amyloid pathology and WMH can predict future development of LLD in cognitively unimpaired individuals and may be involved in precipitating vulnerability for depression in older adults.

KEYWORDS

aging, amyloid, cognition, hippocampus, late-life depression, white matter

Key points

- Subtle cognitive changes are observed before diagnosis of late-life depression

[#]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

- White matter hyperintensities are associated with incident but not established late-life depression
- Hippocampal volume loss is detected only after depression onset
- Amyloid brain pathology in healthy older adults can predict late-life depression

1 | INTRODUCTION

Depression is a leading cause of disability worldwide,[1,2] and with the rapid ageing of the world's population, late-life depression (LLD) constitutes a major and growing global challenge.[3,4] LLD is still believed to be under-recognised and undertreated[5–7] with detrimental effects on quality of life,[8] functional ability,[9] somatic health, and life expectancy.[10] To prevent LLD and its dire consequences, the changes preceding depression onset need to be understood.

Depression is commonly accompanied by deficits in several cognitive domains[11] and higher age is a risk factor.[12] Up to half of individuals with LLD have cognitive impairment significantly greater than their age- and education-matched peers.[13] Cognition may improve with antidepressant treatment, but in the majority of cases, the impairment persists even after adequate treatment of the mood disorder.[14] LLD has also been associated with subsequent cognitive decline. One-fourth of individuals with LLD who are cognitively unimpaired, when depressed, have cognitive impairment 1 year later,[15] and two meta-analyses have concluded that LLD results in two-fold increased risk of dementia.[16,17] Compared to the numerous studies assessing cognitive performance after or at the time of LLD diagnosis, there is a paucity of studies on cognition prior to LLD onset. From assessments in younger adults, there is some evidence suggesting that cognitive dysfunction can predate the affective symptoms.[18–21] In older adults, there have been few studies, but one found that mild cognitive impairment (MCI) is a risk factor for incident LLD[22] and that in a small cohort of normally ageing individuals aged ≥75 years, those with LLD 3 years later performed worse on the Mini-Mental State Examination (MMSE) at baseline than those without future depression.[23] The relationship between cognitive functions and incident LLD warrants further investigation.

Several scenarios could explain the association between LLD and concurrent or subsequent cognitive impairment. Cognitive dysfunction could be due to an underlying neurological disease (e.g., cerebrovascular, Alzheimer's, or Parkinson's disease), wherein depression occurs either because the disease disrupts the emotion control circuits and/or as a psychological reaction to the experience of functional deterioration. In this case, cognitive deficits could be detectable before the affective symptoms. Alternatively, or concomitantly, depression in itself could cause cognitive disturbance and trigger or worsen the process of cognitive decline, in which case the affective symptoms would be expected to precede cognitive impairment. The neuropathology most frequently implicated in the literature as the underlying disease in the first scenario is cerebrovascular changes, forming the basis for the vascular depression hypothesis.[24–30] Vascular lesions compromising fronto-striato-limbic circuits and evident on magnetic resonance imaging (MRI) by findings such as white matter hyperintensities (WMHs) are presumably involved in the development of vascular depression,[31] although the existence of a causal link remains controversial.[32] Disputed is also the hypothesis of amyloid-associated depression.[33,34] Among cross-sectional studies, several reported increased amyloid pathology in LLD or its association with late-life depressive symptoms,[35–39] others found no association,[40–43] while a recent study reported a reverse association.[44] In longitudinal studies on cognitively unimpaired older individuals, amyloid pathology assessed by positron emission tomography (PET) or in cerebrospinal fluid (CSF) has been linked to increased risk of incident depressive symptoms,[45–48] but not to incident screen-positive depression.[49] Dysregulation of the hypothalamic-pituitary-adrenal axis is common in depression, particularly in late-life, and depressed older adults have higher basal cortisol levels.[50] High cortisol levels have adverse effects on hippocampal neurogenesis[51] and can predict hippocampal atrophy and memory deficits in older adults.[52] Hippocampal atrophy is the most frequently reported volumetric finding in LLD[53] and appears to be related to higher cortisol levels[54] rather than to amyloid pathology.[41] As with cognitive impairment, it is still uncertain whether the loss of hippocampal volume occurs prior to or parallel with the affective symptoms. One longitudinal study found no association between baseline hippocampal volumes and incident depression,[55] while another reported that hippocampal atrophy is associated with subsequent depressive symptoms in older women.[56]

The objective of the current study was to use prospectively collected longitudinal data of cognitive performance and neuroimaging from older adults who were cognitively unimpaired and non-depressed at baseline and compare the individuals who later develop depression with those maintaining a stable mood. Assessing incident depression allows for the evaluation of whether cognitive impairment precedes clinical depression and for the examination of the temporal course of depression, cognitive impairment, and markers of the pathologies hypothesised to be involved in LLD, namely, (1) hippocampal atrophy, (2) WMH, and (3) amyloid proteins in the CSF and cortex, to elucidate whether they can predict LLD.

2 | MATERIALS AND METHODS

2.1 | Materials

Data used for this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) after the approval of a data request application. ADNI is a longitudinal study encompassing 63 sites in the United States and Canada, launched in

2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. For up-to-date information on ADNI, visit www.adni-info.org. The current study comprised participants initially enrolled in ADNI1 or ADNI2, with some later rolled over to ADNIGO/2/3. In addition to the ADNI eligibility criteria,[57] all participants met the following criteria at baseline in this study: (1) Normal cognitive status, (2) No depression or other psychiatric disorders in medical history within the last 10 years, (3) No use of antidepressants, (4) Negative score on the screening question for depression in the Neuropsychiatric Inventory (NPI)[58] or the Neuropsychiatric Inventory Questionnaire (NPI-Q),[59] and (5) At least 4 years of subsequent follow-up to have an adequate observation period for the development of depression.

2.2 | Incident depression

Information about the presence of depression including medical history, NPI/NPI-Q scores, diagnostic summaries of visits, and concomitant medications was reviewed. Incident depression was defined by occurrence after baseline of either a depression diagnosis noted in the medical history or the diagnostic summaries, use of antidepressant(s) with supplemental information supporting that it was prescribed for depression, and/or the depression item of the NPI/NPI-Q scored as present. The corresponding criteria for the control group were no registered depression diagnosis, no antidepressants, and the depression item of the NPI/NPI-Q scored as absent on all visits where this was assessed. Participants with missing or ambiguous information were excluded. Figure 1 shows a flowchart of the inclusion.

2.3 | Included visits

The time intervals between the follow-up visits in ADNI vary, but the assessments were most commonly performed at 6- and 12-month intervals. The visit at which depression was first diagnosed (according to the above criteria) was noted as the 'onset visit'. For 15 participants, this was an interim phone visit, nine of whom had a subsequent in-clinic visit that was selected instead. The time of onset varied from the visit scheduled 6 months after baseline to that scheduled 156 months after baseline. The distribution of cases diagnosed at each visit is shown in Supplementary Table S1. To assess the controls at the comparable times, the same distribution was used and a computer randomly selected which controls should be assessed at each of the corresponding "onset visits". For evaluation prior to onset, the baseline visit and the in-clinic visit preceding the onset visit were included. For 10 participants in the incident depression group (and by design also for 14 controls), the onset visit was the first visit following baseline; thus, the visit prior to onset was the baseline visit. Finally, to assess participants in the long run after depression onset, the last visit with registered data (for cognitive scores/MRI/CSF/PET) was included in the study. In a minority, the onset visit was also the last visit with available data. Mean time from baseline to the last follow-up visit was 99.2 months (standard deviation [SD] 35.5) for the whole sample, 106.8 months (SD 34.7, range <49–171>) for the depression group, and 94.1 (SD 35.2, <49–172>) for the control group.

2.4 | Cognitive scores and cognitive diagnosis

Cognition was evaluated using the validated composite scores for executive functioning (CS-Executive), memory (CS-Memory), and language (CS-Language) derived from the ADNI neuropsychological battery with item response theory methods. These scores are robust and outperform individual domain-specific measures.[58,60,61] The MMSE[62] was included as a global cognitive measure. At baseline, all participants fulfilled the ADNI criteria for normal cognition (NC): Normal memory function with a score greater than education-adjusted cut-offs on delayed paragraph recall of the Logical Memory-II subscale from the Wechsler Memory Scale-Revised,[63] MMSE score 24–30, Clinical Dementia Rating 0, and absence of significant impairment in cognitive functions or activities of daily living. ADNI1 had the criteria of no memory complaints aside from those common to other normal subjects of that age. ADNI2 also included some participants with self-reported memory concern (SMC), but where the concern was not equated by the study partner. During follow-up, participants were classified as NC/MCI/dementia following published standards.[57,64]

2.5 | Magnetic resonance imaging and hippocampal volumes

MRI acquisition was performed as described previously.[65] The current study used hippocampal volumes and total intracranial volume (ICV) measurements from the University of California, San Francisco (UCSF) cross-sectional FreeSurfer datasets. These were extracted by cortical reconstruction and volumetric segmentation using the FreeSurfer image analysis suite[66–69] documented and freely available online (http://surfer.nmr.mgh.harvard.edu/). Only volumes from segmentations that passed quality control were included. As a meta-analysis found no lateralisation effect,[54] the right and left hippocampal volumes were summed. The ratio between total hippocampal volume and ICV was calculated to adjust for head size. In the UCSF dataset, 1.5 T scans were run with FreeSurfer version 4.3, 3T scans from ADNI1/2 with version 5.1, and 3T scans from ADNI3 with version 6. FreeSurfer-derived volumes generally have good reliability, but differences in field strength and FreeSurfer version can bias the results.[70,71] The pre-processed data from each version (at each time point) were, therefore, separately converted to *z*-scores, and the FreeSurfer version was also entered as a covariate.

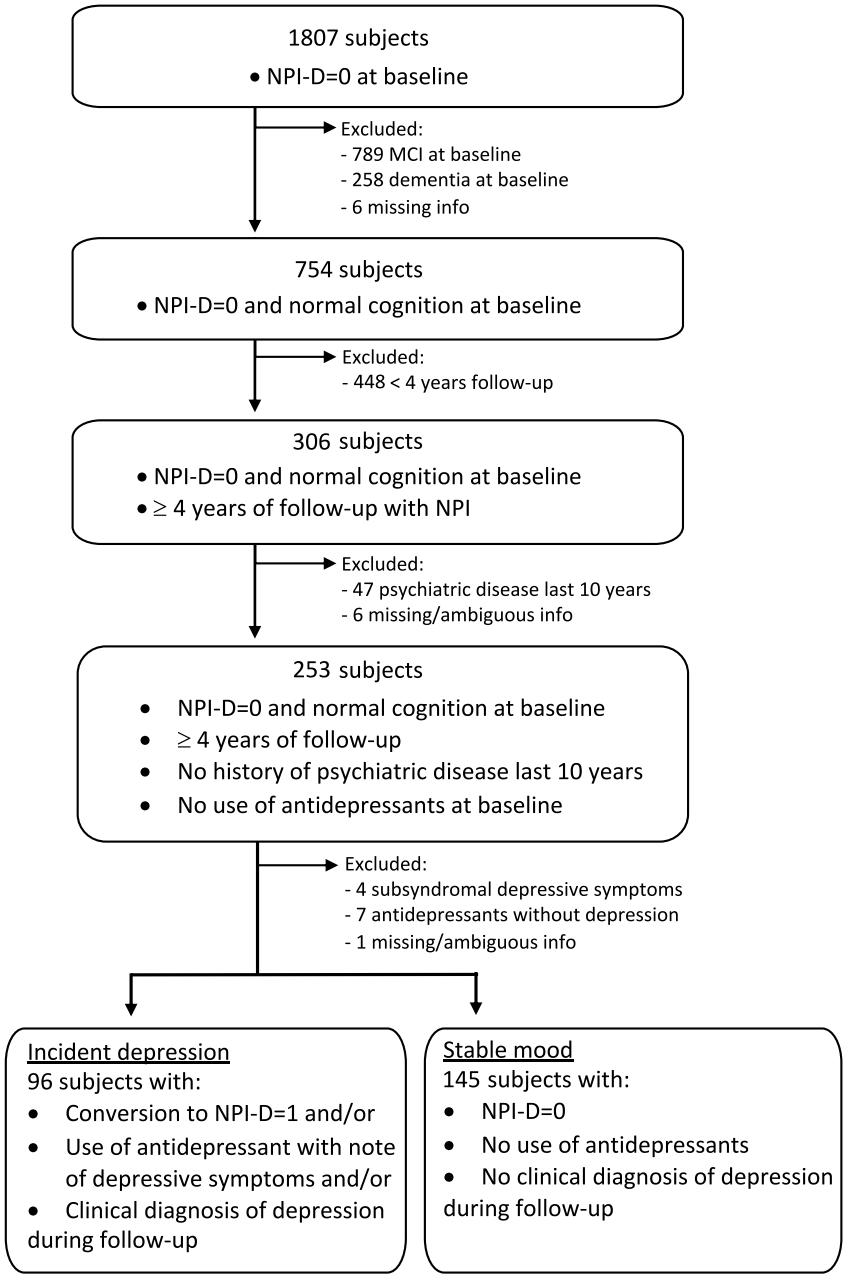

FIGURE 1 Flowchart over the inclusion process

2.6 | White matter hyperintensity

WMH volume estimates were included from the datasets released by the University of California (UC), Davis. In ADNI1, WMH detection was performed without the use of fluid attenuated inversion recovery (FLAIR) sequences, relying on proton density, T1- and T2-weighted MRI combined with prior anatomical knowledge of WMH occurrence in the brain. This method is robust, reliable, and performs well compared to FLAIR-based detection.[72] In ADNI2/3, WMH measures were obtained from T1 and FLAIR sequences, as described in the ADNI protocols.[73] The measures were adjusted for ICV and log-transformed before being converted to *z*-scores separately for the FLAIR and non-FLAIR methods. The detection method was included as a covariate.

2.7 | Amyloid biomarkers: CSF and PET

Protocols for lumbar puncture and CSF handling are explained in the ADNI manuals (http://adni.loni.usc.edu/methods/documents/). We included CSF amyloid beta 1–42 (Aβ42) analysed at the University of Pennsylvania using a fully automated electrochemiluminescence immunoassay (Roche Elecsys®).[74,75] The upper technical limit is 1700 pg/ml, but Roche Diagnostics has provided values above this based on extrapolation of the calibration curve for exploratory research purposes. Studies comparing Elecsys Aβ42 with amyloid PET have arrived at a cut-off of 1100 pg/ml,[76,77] which was adopted in the current study (Aβ42 ≤ 1100 pg/ml = positive; Aβ42 > 1100 pg/ml = negative amyloid biomarker). Florbetapir/^{18}F-AV-45 PET data analysed by UC Berkley were used for evaluating cortical amyloid. A

description of their processing methods can be found on the ADNI website. Following the recommendation of the UC Berkley group, we used standardised uptake value ratios (SUVRs) for a cortical summary region divided by the whole cerebellum, and the accompanying threshold 1.11 (SUVR > 1.11 = positive; SUVR ≤ 1.11 = negative amyloid biomarker).

2.8 | Telomere length

Cognitive performance, amyloid pathology, WMH, and hippocampal volume can be affected by normal ageing, and all analyses were performed with and without age adjustment. In addition to chronological age, advanced cellular ageing could be a separate factor as previous studies have found an association between depression and telomere shortening,[78] although for LLD, the results are conflicting.[79,80] Information about telomere lengths measured using a quantitative PCR assay[81,82] is available for some ADNI participants. Comparisons of telomere length between the groups before, at, and after onset were performed as supplementary analyses.

2.9 | Statistical analyses

For the descriptive data, *t*-test/Mann–Whitney *U*-test was used for continuous variables with normal/skewed distribution and χ^2-test for categorical variables. Binary logistic regression was used to assess the prediction of incident depression (coded 1, controls 0). Odds ratios were calculated with and without age, sex and time from baseline as covariates. Significant *p*-value <0.05. To address the cumulative risk of false positives due to multiple testing, false discovery rate (FDR) correction was performed following the Benjamini-Hochberg procedure for demographic and clinical scores at baseline, adjusted models with cognitive scores (three composite scores, MMSE, and cognitive classifications), and adjusted models with amyloid biomarkers (CSF, PET, and overall status) at each visit. Cohen's *d* was calculated using the Psychometrica calculators.[83] The main analyses were performed using SPSS version 26 (SPSS Statistics, IBM).

3 | RESULTS

3.1 | Descriptives at baseline

As Table 1 shows, the average age at inclusion was higher in the incident depression group. There were no significant group differences in sex, education, frequency of self-reported memory concerns (ADNI2 SMC cohort), or presence of the Alzheimer's disease risk allele APOE-ε4. All participants had a Geriatric Depression Scale[84] score within the normal range, but fewer participants in the incident depression group had score 0 compared with controls (Table 1). The majority of cases in the study had late-onset depression, as only one

TABLE 1 Demographical and clinical characteristics at baseline

	Incident depression	Control group	*t*/MWU/χ^2	*p*	Cohen's *d*
N	96	145			
Age mean (SD) <range>	75.4 (5.1) <60–90>	73.7 (5.9) <56–89>	2.39	0.018*	0.31
Women (*n*, %)	47 (49)	65 (44.8)	0.40	0.598	0.08
Education, years median (IQR) <range>	16.0 (15–19) <8–20>	16.0 (15–18.5) <6–20>	6832.5	0.808	0.03
Married (*n*, %)	72 (75)	100 (69)	1.03	0.383	0.13
Widowed (*n*, %)	12 (12.5)	21 (14.5)	0.19	0.706	0.06
Not retired (*n*, %)	15 (15.6)	36 (24.8)	2.93	0.107	0.22
APOE-ε4 (*n*, %)	30 (31.3)	36 (24.8)	1.20	0.303	0.14
SMC (*n*, %)	11 (11.5)	20 (13.8)	0.28	0.696	0.07
Modified Hachinski score median (IQR) <range>	0 (0–1) <0–3>	0 (0–1) <0–3>	6721.5	0.609	0.06
Hypertension history (*n*, %)	43 (44.8)	62 (42.8)	0.10	0.792	0.04
GDS median (IQR) <range>	1 (0–1) <0–4>	0 (0–1) <0–4>	5581.5	0.003**	0.36
GDS score 0 (*n*, %)	44 (45.8)	95 (65.5)			
GDS score 1 (*n*, %)	32 (33.3)	30 (20.7)			
GDS score 2 (*n*, %)	14 (14.6)	17 (11.7)			
GDS score 3 (*n*, %)	3 (3.1)	1 (0.7)			
GDS score 4 (*n*, %)	3 (3.1)	2 (1.4)			

Note: Nominally significant group differences are asterisked (*) and significance also after false discovery rate correction for multiple comparisons are marked with a double asterisk (**).

Abbreviations: APOE-ε4, Apolipoprotein E ε4-allele carrier; GDS, Geriatric Depression Scale score; IQR, Interquartile range; MWU, Mann Whitney *U*-score; SMC, significant memory concern—self-report of memory concern cohort in ADNI 2; *t*, *t*-test; χ^2, Chi square.

TABLE 2 Neuropsychological scores and cognitive classification at each visit

		Months from baseline	CS-memory	CS-executive functioning	CS-language	MMSE	Classification[a]
Baseline	Incident depression	0	1.04 (0.55)	0.82 (0.68)	0.79 (0.62)	29.1 (1.1)	NC 100%
			[0.93–1.15]	[0.69–0.96]	[0.67–0.92]	[28.9–29.3]	
	Controls	0	1.07 (0.54)	0.95 (0.79)	0.89 (0.69)	29.0 (1.1)	NC 100%
			[0.98–1.16]	[0.82–1.08]	[0.78–1.00]	[28.9–29.2]	
	Cohen's *d*		0.06	0.17	0.15	0.03	
	OR		0.899, $p = 0.661$	0.794, $p = 0.196$	0.798, $p = 0.262$	1.028, $p = 0.814$	
	OR adjusted		0.925, $p = 0.765$	0.889, $p = 0.531$	0.842, $p = 0.401$	1.031, $p = 0.795$	
Visit prior to onset	Incident depression	41.1 (32.9)	0.92 (0.72)	0.74 (0.82)	0.68 (0.77)	28.8 (1.5)	NC 84 (87.5%)
		[34.4–47.7]	[0.78–1.07]	[0.57–0.90]	[0.52–0.84]	[28.5–29.1]	MCI 10 (10.4%)
				$N = 95$			Dementia 2 (2.1%)
	Controls	40.0 (32.7)	1.10 (0.62)	0.95 (0.82)	0.90 (0.68)	28.9 (1.2)	NC 133 (92.4%)
		[34.7–45.4]	[0.99–1.20]	[0.81–1.08]	[0.79–1.01]	[28.7–29.1]	MCI 9 (6.3%)
						$N = 144$	Dementia 2 (1.4%)
	Cohen's *d*		0.26	0.26	0.31	0.04	
	OR		0.67, $p = 0.051$	0.73, $p = 0.054$	0.65, $p = 0.022$	0.97, $p = 0.766$	1.50, $p = 0.254$
	OR adjusted		0.66, $p = 0.058$	0.79, $p = 0.169$	0.67, $p = 0.039$*	0.98, $p = 0.875$	1.57, $p = 0.224$
Onset visit	Depression	56.5 (36.7)	0.86 (0.74)	0.60 (0.97)	0.57 (0.81)	28.3 (2.5)	NC 66 (75%)
		[49.1–63.9]	[0.71–1.02]	[0.40–0.81]	[0.40–0.74]	[27.8–28.9]	MCI 16 (18.2%)
			$N = 89$	$N = 89$	$N = 89$	$N = 89$	Dementia 6 (6.8%)
	Controls	55.9 (36.3)	1.05 (0.58)	0.94 (0.85)	0.80 (0.71)	28.7 (1.6)	NC 127 (88.8%)
		[49.9–61.8]	[0.95–1.14]	[0.80–1.09]	[0.68–0.92]	[28.5–29.0]	MCI 13 (9.1%)
			$N = 142$	$N = 141$	$N = 142$	$N = 145$	Dementia 3 (2.1%)
	Cohen's *d*		0.29	0.38	0.31	0.22	
	OR		0.64, $p = 0.038$	0.66, $p = 0.007$	0.66, $p = 0.026$	0.90, $p = 0.119$	2.14, $p = 0.007$
	OR adjusted		0.62, $p = 0.035$*	0.67, $p = 0.014$**	0.69, $p = 0.049$*	0.89, $p = 0.091$	2.384, $p = 0.004$**
Last visit after onset with cognitive score and the last classification	Depression	104.0 (34.6)	0.43 (1.00)	0.23 (1.08)	0.16 (1.00)	27.0 (4.1)	NC 57 (59.4%)
		[96.8–111.3]	[0.22–0.65]	[0–0.46]	[−0.05–0.37]	[26.1–27.8]	MCI 23 (24.0%)
			$N = 90$	$N = 87$	$N = 90$	$N = 90$	Dementia 16 (16.7%)
	Controls	89.4 (34.8)	0.87 (0.72)	0.65 (0.87)	0.60 (0.83)	28.3 (2.7)	NC 118 (81.4%)
		[83.6–95.1]	[0.75–0.99]	[0.50–0.80]	[0.46–0.74]	[27.9–28.8]	MCI 21 (14.5%)

TABLE 2 (Continued)

	Months from baseline	CS-memory	CS-executive functioning	CS-language	MMSE	Classification[a]
		$N = 142$	$N = 140$	$N = 142$	$N = 141$	Dementia 6 (4.1%)
Cohen's *d*		0.52	0.44	0.49	0.41	
OR		0.54, $p < 0.001$	0.63, $p = 0.002$	0.58, $p = 0.001$	0.88, $p = 0.007$	2.32, $p < 0.001$
OR adjusted		0.58, $p = 0.002$**	0.71, $p = 0.033$**	0.64, $p = 0.007$**	0.91, $p = 0.037$**	2.09, $p = 0.001$**

Note: Descriptives reported as mean (standard deviation) [95% confidence interval]. *N* listed only when less than full sample (96 incident depression and 145 controls). Depression/Control groups coded 1/0. NC/MCI/Dementia coded 1/2/3. Reported are the odds ratios for each cognitive score in unadjusted models (OR) and models adjusted for age, sex, and time from baseline (OR adjusted). Nominally significant adjusted models are asterisked (*). Significance also after false discovery rate correction for the adjusted models at each visit (five comparisons) is marked with double asterisk (**).

Abbreviations: CS, Composite score; *d*, Cohen's *d*; MCI, mild cognitive impairment; NC, Cognitively normal.

[a]Cognitive classification was missing for one control at the visit before onset, and for two controls and eight in the depression group (six because this was a phone visit) at the onset visit.

participant in the incident depression group and two controls had depression more than 10 years prior to baseline in their medical history. Telomere length was equivalent between the two groups (Supplementary Table S2).

3.2 | Neuropsychological scores

There were no significant group differences in cognitive scores at baseline (Table 2, Figure 2). At the time of depression, the depressed group performed worse on CS-Executive, CS-Memory, and CS-Language with small effect sizes, the largest being for CS-Executive. At the last visit prior to onset only lower score on CS-Language was a nominally significant predictor of subsequent depression, but did not survive FDR correction. In terms of the longitudinal change in scores between baseline and the visit prior to depression (Table 3), decline in memory and MMSE scores were nominally significant predictors of later depression with small effect sizes, but these were not significant after FDR correction for multiple tests. The cognitive differences increased after onset and were of moderate size at the end of follow-up.

3.3 | Hippocampal volumes

Hippocampal volumes were significantly reduced in the depression group, but only after onset (Table 4). Hippocampal volume was not correlated with cognitive scores at baseline, but after onset, there were significant correlations, specially in the depressed group (Supplementary Table S3).

3.4 | White matter hyperintensity

Higher WMH burden at baseline was a significant predictor of later depression (Table 4). The effect size was also at the same level at the visit prior to onset but with *p*-value only close to being significant. At the later visits, the effect sizes were lower and there were no significant differences. WMH did not correlate significantly with cognitive scores before onset, and there were only weak, negative correlations at the later stages of follow-up (Supplementary Table S4).

3.5 | Amyloid markers

Cortical amyloid burden was a significant predictor of incident depression both at baseline and at the visit prior to onset, with moderate to large effect sizes (Table 4). It remained significant after correction for dementia or MCI during follow-up. The depression group had a higher cortical amyloid load at onset and at the last amyloid PET assessment. Low CSF Aβ42 levels at baseline were a significant predictor of later depression but without significant group differences after baseline. The only significant correlations between

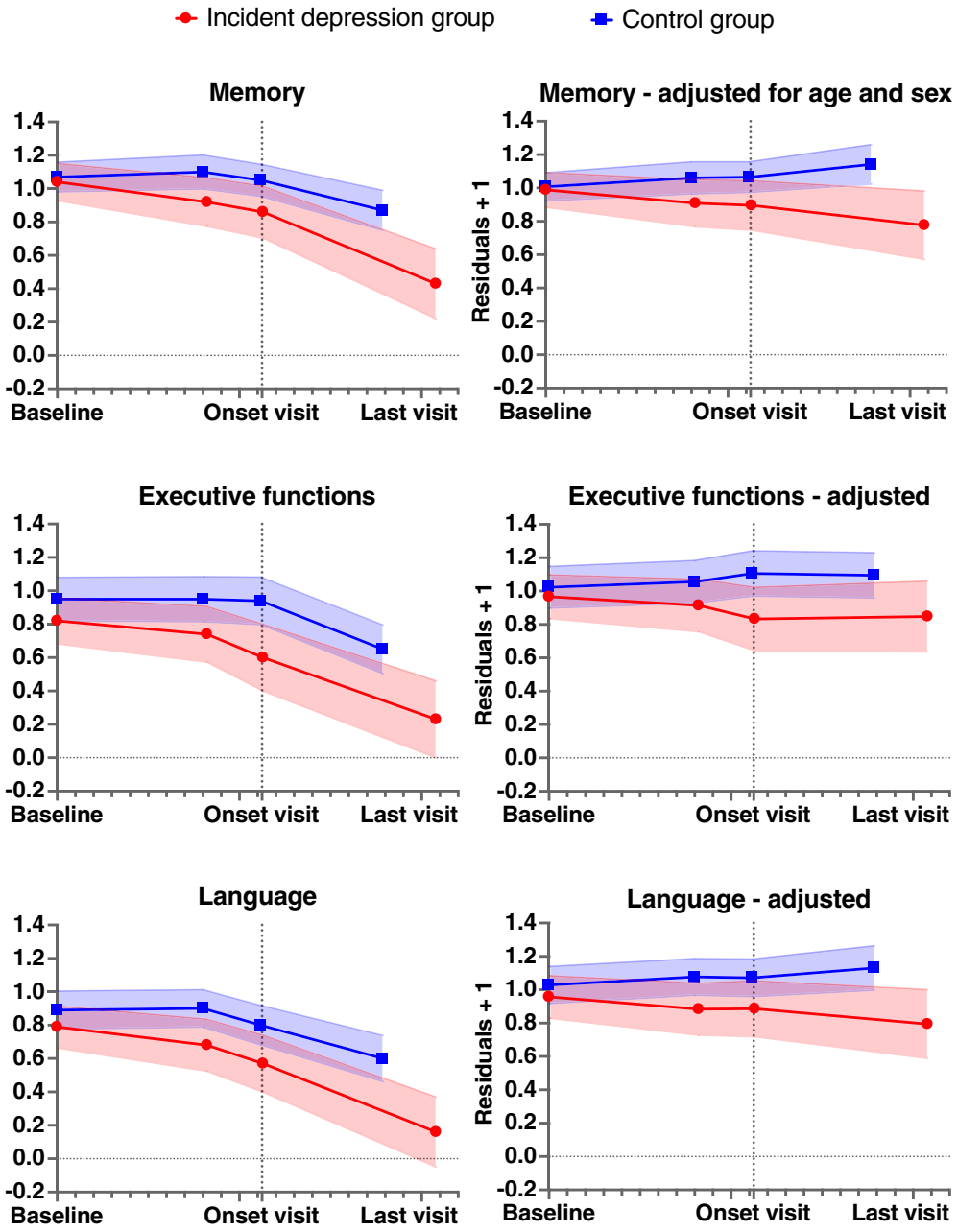

FIGURE 2 Composite cognitive scores at the four assessed visits for the incident depression group and control group presented as means with 95%-confidence intervals for raw scores and age- and sex-adjusted residuals

amyloid biomarkers and cognitive performance, after FDR correction were at the last visit (Supplementary Tables S5 and S6). Changes in cognitive scores between baseline and the visit prior to onset (Table 3) were no longer significant predictors of incident depression when amyloid biomarkers were added as covariates.

4 | DISCUSSION

As expected, we observed worse cognitive performance in the depressed group. The first question we asked was whether cognitive impairment was present before depression. On average 15 months prior to depression, there were indications that memory and language functions had subtly declined in the incident depression group. This is in line with the observation in younger adults that poor cognition can be a premorbid marker of depression.[18,20,21] The next question concerned the underlying mechanisms of pre-depression cognitive impairment. In studies involving young individuals, cognitive deficits predating depression could be explained by shared neurodevelopmental and/or genetic factors mediating both lower cognitive abilities and vulnerability to depression.[19,85–87] This explanation does not fit with the current results for LLD as there were no cognitive group differences at baseline. Cognitive impairment initially became apparent during the years/months leading

TABLE 3 Changes in neuropsychological scores from baseline to the visit before onset

	Incident depression	Control group	Cohen's *d*	Regression coefficients	Regression model Adj2 with additional correction for each of the biomarkers
Change	−0.13 (0.57)	0.03 (0.42)	0.32	OR = 0.51, $p = 0.023$	OR (Adj2 + Hippocampal volume) = 0.49, $p = 0.023$*
CS-memory	[−0.25 – −0.01]	[−0.04–0.10]		OR Adj1 = 0.50, $p = 0.022$	OR (Adj2 + WMH) = 0.48, $p = 0.027$*
	$N = 86$	$N = 131$		OR Adj2 = 0.48, $p = 0.018$*	OR (Adj2 + CSF Aβ42) = 0.66, $p = 0.273$
					OR (Adj2 + Florbetapir SUVR) = 0.88, $p = 0.812$
Change	−0.11 (0.69)	−0.01 (0.65)	0.15	OR = 0.80, $p = 0.280$	OR (Adj2 + Hippocampal volume) = 0.75, $p = 0.218$
CS-executive functioning	[−0.26–0.04]	[−0.12–0.11]		OR Adj1 = 0.81, $p = 0.320$	OR (Adj2 + WMH) = 0.87, $p = 0.563$
	$N = 85$	$N = 131$		OR Adj2 = 0.78, $p = 0.281$	OR (Adj2 + CSF Aβ42) = 0.92, $p = 0.773$
					OR (Adj2 + Florbetapir SUVR) = 1.95, $p = 0.104$
Change	−0.13 (0.57)	0.01 (0.54)	0.25	OR = 0.64, $p = 0.078$	OR (Adj2 + Hippocampal volume) = 0.54, $p = 0.029$*
CS-language	[−0.25–0]	[−0.08–0.10]		OR Adj1 = 0.63, $p = 0.075$	OR (Adj2 + WMH) = 0.58, $p = 0.055$
	$N = 86$	$N = 131$		OR Adj2 = 0.57, $p = 0.042$*	OR (Adj2 + CSF Aβ42) = 0.53, $p = 0.054$
					OR (Adj2 + Florbetapir SUVR) = 0.95, $p = 0.901$
Change	−0.13 (0.57)	0.03 (0.42)	0.32	OR = 0.51, $p = 0.023$	OR (Adj2 + Hippocampal volume) = 0.53, $p = 0.041$*
MMSE	[−0.25 – −0.01]	[−0.04–0.10]		OR Adj1 = 0.50, $p = 0.022$	OR (Adj2 + WMH) = 0.52, $p = 0.045$*
	$N = 86$	$N = 131$		OR Adj2 = 0.51, $p = 0.029$*	OR (Adj2 + CSF Aβ42) = 0.76, $p = 0.455$
					OR (Adj2 + Florbetapir SUVR) = 0.94, $p = 0.902$

Note: The incident depression group is coded 1 and the control group coded 0. The first adjusted model (Adj1) includes age at baseline, sex, and time from baseline as covariates. The second adjusted model (Adj2) also includes the cognitive score at baseline as a covariate. The nominally significant group differences in the adjusted models are asterisked (*). None survived false discovery rate correction for multiple comparisons. The 24 participants for whom the onset visit was the first visit after baseline, are not included.

Abbreviations: CS, composite score; CSF, cerebrospinal fluid; OR, odds ratio; SUVR, standardised uptake value ratio; WMH, volume of white matter hyperintensities.

toward depression onset, which is a course more suggestive of neurodegenerative mechanisms.

The authors of the studies reporting memory deficits preceding depression in younger adults[18,20] suggested that this impairment could be linked to hippocampal dysfunction and atrophy. We only observed significantly lower hippocampal volumes in the depressed group late in the disease course. Cognitive performance did not appear to be greatly influenced by hippocampal volumes before onset, but after onset, cognitive scores were correlated with hippocampal volumes, suggesting that reduced hippocampal volume occurs in conjunction with symptomatic LLD rather than as a predisposing event. Our findings corroborate those of den Heijer et al.[55] who found no association between baseline hippocampal volumes and incident depression but observed steeper decline in hippocampal volumes following depression. Elbejjani et al.[56] reported that the rate of hippocampal atrophy was associated with more and worsening depressive symptoms, but only in older women, not in men. Their observation of a sex difference is interesting as women more frequently report depressive symptoms also in late life[88] and hippocampal structures could be impacted by the postmenopausal oestrogen drop because hippocampal progenitor cells express sex hormone receptors involved in proliferation control.[89] We reassessed our data for each sex separately and indeed, the hippocampal volume differences between the incident depression group and controls were greater for women, but the differences before onset remained non-significant. Atrophy is a late finding, and functional and cellular aberrations may be present long before detectable MRI volume changes ensue. Our results do not exclude hippocampal changes preceding LLD, but cross-sectional hippocampal volumes remained comparable to controls before depression.

TABLE 4 Hippocampal volume *z*-scores, WMH *z*-scores, CSF Aβ42, Florbetapir SUVRs, and overall amyloid biomarker status at each visit

		Hippocampal volume	WMH volume	CSF Aβ42	Florbetapir SUVRs	Overall amyloid biomarker status
Baseline	Incident depression	−0.02 (1.06)	0.24 (1.01)	1224 (741–1706)	1.12 (1.04–1.35)	Positive 29 (40.3%)
		[−0.24–0.20]	[0.02–0.45]			Negative 30 (41.7%)
		N = 93	*N* = 89	*N* = 68	*N* = 47	Mixed 13 (18.1%)
	Controls	0.19 (0.96)	−0.15 (0.96)	1467 (1025–1794)	1.03 (0.98–1.09)	Positive 19 (17.3%)
		[0.03–0.35]	[−0.32–0.01]			Negative 76 (69.1%)
		N = 141	*N* = 137	*N* = 101	*N* = 79	Mixed 15 (13.6%)
	Cohen's *d*	0.21	0.40	0.33	0.86	
	OR	0.81, $p = 0.117$	1.52, $p = 0.005$	0.9995, $p = 0.054$	146, $p < 0.001$	3.9, $p < 0.001$
	OR adjusted	0.83, $p = 0.238$	1.44, $p = 0.019$*	0.9995, $p = 0.048$**	125, $p < 0.001$**	3.7, $p < 0.001$**
Visit prior to onset	Incident depression	−0.15 (1.03)	0.26 (0.83)	1052 (734–1682)	1.14 (1.04–1.37)	Positive 24 (53.3%)
		[−0.40–0.11]	[0.05–0.47]			Negative 16 (35.6%)
		N = 64	*N* = 62	*N* = 27	*N* = 39	Mixed 5 (11.1%)
	Controls	0.08 (0.97)	−0.16 (1.06)	1449 (920–1820)	1.03 (0.98–1.17)	Positive 22 (30.1%)
		[−0.10–0.26]	[−0.37–0.05]			Negative 41 (56.2%)
		N = 113	*N* = 101	*N* = 47	*N* = 64	Mixed 10 (13.7%)
	Cohen's *d*	0.23	0.44	0.24	0.67	
	OR	0.79, $p = 0.143$	1.61, $p = 0.009$	0.9995, $p = 0.274$	46, $p = 0.002$	2.8, $p = 0.014$
	OR adjusted	0.79, $p = 0.203$	1.45, $p = 0.056$	0.9996, $p = 0.337$	40, $p = 0.003$**	2.7, $p = 0.023$**
Onset visit	Depression	−0.19 (1.10)	0.14 (0.98)	1013 (710–1625)	1.13 (1.04–1.32)	Positive 22 (50%)
		[−0.44–0.07]	[−0.11–0.39]			Negative 20 (45.5%)
		N = 71	*N* = 62	*N* = 21	*N* = 38	Mixed 2 (4.5%)
	Controls	0.13 (0.90)	−0.09 (1.00)	1421 (1034–1739)	1.03 (0.96–1.11)	Positive 15 (22.1%)
		[−0.05–0.31]	[−0.31–0.12]			Negative 48 (70.6%)
		N = 98	*N* = 89	*N* = 27	*N* = 62	Mixed 5 (7.4%)
	Cohen's *d*	0.32	0.23	0.33	0.72	
	OR	0.72, $p = 0.041$	1.27, $p = 0.163$	0.9994, $p = 0.250$	38, $p = 0.004$	3.5, $p = 0.004$
	OR adjusted	0.73, $p = 0.087$	1.15, $p = 0.448$	0.9995, $p = 0.341$	32, $p = 0.005$**	3.3, $p = 0.007$**
Last visit after onset with biomarker available	Depression	−0.25 (1.10)	0.18 (0.95)	959 (719–1823)	1.20 (1.05–1.39)	Positive 43 (57.3%)
		[−0.50–(−)0.01]	[−0.03–0.40]			Negative 28 (37.3%)
		N = 80	*N* = 77	*N* = 34	*N* = 74	Mixed 4 (5.3%)

TABLE 4 (Continued)

		Hippocampal volume	WMH volume	CSF Aβ42	Florbetapir SUVRs	Overall amyloid biomarker status
	Controls	0.17 (0.88)	−0.13 (1.01)	1266 (832–1775)	1.03 (0.97–1.17)	Positive 36 (32.4%)
		[0.01–0.33]	[−0.31–0.06]			Negative 70 (63.1%)
		$N = 119$	$N = 112$	$N = 55$	$N = 106$	Mixed 5 (4.5%)
	Cohen's *d*	0.43	0.31	0.15	0.61	
	OR	0.64, $p = 0.004$	1.38, $p = 0.039$	1.00003, $p = 0.924$	14, $p < 0.001$	3.0, $p = 0.001$
	OR adjusted	0.67, $p = 0.019$*	1.25, $p = 0.201$	1.0002, $p = 0.618$	13, $p = 0.001$**	2.9, $p = 0.001$**

Note: Descriptives reported as mean (standard deviation) [95% confidence interval] for hippocampal and WMH volumes and as median (interquartile range) for the amyloid biomarkers. Depression/Control groups coded 1/0. All adjusted models include age, sex, and time from baseline as covariates. Hippocampal volumes were also adjusted for FreeSurfer version, and WMH volumes adjusted for WMH detection method (FLAIR and non-FLAIR). Nominally significant adjusted models are asterisked (*). Due to multiple comparisons at each visit for the amyloid biomarkers (three tests; CSF, PET, and overall status) false discovery rate correction was applied and significance for the adjusted models of amyloid markers after false discovery rate correction is marked with double asterisk (**). Mixed biomarker status denotes the cases were results of CSF and PET were divergent. Positive biomarker status coded 1, negative 0, mixed 0.5.

Abbreviations: CSF, cerebrospinal fluid; *d*, Cohen's d; OR, odds ratio; SUVR, standardised uptake value ratio; WMH, white matter hyperintensities.

Hippocampal volume is associated with both chronological age and cellular age measured by telomere length.[90] Telomere shortening has been frequently observed in studies on depressed younger adults[78] and in a recent, small study of LLD.[79] Our supplementary analyses of telomere length revealed no evidence of more advanced cellular ageing in the LLD group at any time point. Our sample size was small, but the results are in line with those of a larger LLD study[80] and other studies of depressive symptoms in older adults[91,92] that have failed to find an association with telomere length. Older adults' high cumulative exposure to factors that can shorten telomeres has been suggested to make a depression-related effect difficult to detect.[80]

Unlike hippocampal volume, WMH volume at baseline predicted later LLD. Previous longitudinal studies have reported that WMH at baseline are associated with incident LLD or incident depressive symptoms,[93–97] albeit not consistently.[98,99] WMH are believed to be a marker of vascular changes. Periventricular WMH correlate with histological severity of arteriosclerosis and breakdown of the ventricular lining, and deep WMH correlate with cortical microinfarcts and demyelination.[100] Histopathological correlates of WMH are, however, heterogeneous and can be as minimal as slight matrix disentanglement.[101] Divergence in reports of WMH in LLD may thus derive both from variations in WMH location[102,103] and from WMH with similar MRI appearance harbouring dissimilar cellular pathology.[101] The timing of WMH-related increase in depression risk may also depend on WMH location. Bae et al. found an association between severe periventricular WMH and depression 2 weeks after stroke, while severe deep WMH at this time point were associated with depression occurring 1 year post-stroke.[102] Demyelination and axonal loss underlying WMH in fronto-limbic circuits could impact the emotional control networks and predispose individuals to depression. This 'vascular depression' hypothesis[24,31] has, however, been challenged by autopsy studies failing to find more vascular lesions in established LLD compared to controls.[104,105] Congruously, we found that WMH load was not significantly higher at depression onset. WMH might thus be important primarily in early stages of depression development, relating to initiating events increasing the vulnerability to depression, while later in the disease, there might be no direct stimulus-response function between WMH/vascular lesions and depression.

The strongest predictor of incident depression was cortical amyloid. Although the sample size was reduced because Florbetapir PET was not available for all participants, our results corroborate those found in previous studies of incident depression/depressive symptoms in cognitively normal older adults[45–48,106] with one exception.[49] The overall evidence from longitudinal studies thus converges on amyloid pathology being a risk factor for LLD/depressive symptoms. The effect sizes for CSF Aβ42 levels in our study were lower than those for cortical amyloid. Unlike amyloid PET, CSF Aβ42 is only an indirect measure of brain Aβ accumulation. Incongruity between Aβ CSF and Aβ PET is quite common and individuals with positive PET and negative CSF reportedly have higher GDS scores.[107] In our study baseline cortical amyloid was also a

significant predictor when correcting for later dementia or MCI. This makes it less likely that amyloid-associated incident depression was solely caused by a psychological reaction to the awareness of dementia development. Amyloid plaques accumulate in the brain several years, even decades, before the emergence of cognitive signs.[108] The earliest amyloid depositions occur within the core nodes of the default mode network, accompanied by disruption of the internal functional connectivity of this network and its connections with the frontoparietal network.[109] Functional connectivity changes within and between these networks are also observed in depression.[110–112] Therefore, amyloid accumulation in the brain may directly impact the pathophysiology of LLD. Resting-state functional MRI before depression onset was only available for a minority of the participants and deferred us from assessing network connectivity changes in relation to amyloid pathology and incident depression. Nevertheless, this should be addressed in future studies.

The main strength of our study is the assessment at several time points: twice before, at, and after depression onset, probing both cognitive functions and neuroimaging biomarkers. The method of detecting depression was based on review of all available information. This makes it more difficult to reproduce compared with, for example, using a threshold on a single depression scale, but it represents an inclusive approach with lower likelihood of depression cases being overlooked. NC ADNI participants are volunteers recruited to research and are probably not representative of the general older population,[57] limiting generalisability. The study was restricted by its sample size and the fact that not all data types (e.g. CSF and PET) were available at all visits. Another limitation is the choice to evaluate neuroimaging cross-sectionally at each visit, rather than conducting a longitudinal analysis based on a base image for each participant. Furthermore, LLD is a clinically heterogeneous condition probably comprising several subtypes with diverse aetiologies; however, in this study, we did not attempt to differentiate between clinical subtypes.

In conclusion, cerebral amyloid pathology and WMH can predict future LLD. Subtle cognitive changes occur prior to LLD onset and can partly be explained by the underlying amyloid pathology. These results support the hypothesis that amyloid plaque formation and emerging ischaemic lesions disrupt networks involved in cognitive and emotional processing, thus predisposing older adults to depression.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The ADNI clinical protocol states that the study is conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, US Code of Federal Regulations Title 21 Part 50 -Protection of Human Subjects, and Part 56 - Institutional Review Boards, and pursuant to state and federal Health Insurance Portability and Accountability Act regulations. The study was unconditionally approved by the Institutional Review Boards and Research Ethics Boards of all the participating institutions. Written informed consent was obtained from all participants and study partners before study procedures were carried out.

AUTHOR CONTRIBUTIONS

Ina S. Almdahl designed the study, performed the data analysis, interpreted the results, and wrote the article. Ingrid Agartz, Kenneth Hugdahl, and Maria S. Korsnes critically revised the article and approved the final version.

DATA AVAILABILITY STATEMENT

The data used in this study belong to the Alzheimer's Disease Neuroimaging Initiative (ADNI), a neuroscience consortium of universities and research institutes, and are available through the ADNI database (adni.loni.usc.edu) after approval of a data request application. For more information about how to access ADNI data see http://adni.loni.usc.edu/data-samples/access-data/.

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SUPPORTING INFORMATION

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