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Short Communication

Assessing the Role of Past Depression in Patients with Mild Cognitive Impairment, with and without Biomarkers for Alzheimer's Disease

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Abstract. Major depressive disorder (MDD) is a risk factor for Alzheimer's disease (AD). Cerebrovascular disease (CVD) is implicated in MDD and AD. Our study compared participants with AD positive and negative cerebrospinal fluid (CSF) biomarkers on neuropsychological performance, remitted MDD status, and CVD burden. Next, we compared AD-CSF biomarkers and white matter hyperintensities (WMH) burden among three groups: mild cognitive impairment (MCI) ($n = 12$), MCI with remitted MDD (MDD+MCI) ($n = 12$), and remitted MDD alone (MDD) ($n = 7$). Few participants (18%) with MCI+MDD exhibited AD(+) biomarkers. Nearly all participants had moderate-severe WMH. WMH may contribute to cognitive impairment or depression in MCI patients with AD(-) biomarkers.

Keywords: Alzheimer's disease, cerebrovascular disease, major depressive disorder, mild neurocognitive disorder

INTRODUCTION

A diagnosis of major depressive disorder (MDD) increases the risk of dementia by two-fold or greater [1]. Furthermore, depression has been shown to

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accelerate progression from mild cognitive impairment (MCI), referencing an intermediate stage of cognitive impairment between normal cognitive aging and dementia, to dementia [2]. This finding has been replicated consistently in late-onset depression (LOD), with mixed results in early-onset depression (EOD) [3–5]. It has been posited that EOD and LOD represent distinct phenotypes and pathological processes. Early adverse events and genetic predispositions are implicated in EOD, while accumulation of vascular burden and neuropathological substrates contribute to LOD [6–8].

Late-life depression (LLD), which includes EOD that reoccurs in late-life, is associated with deficits in verbal and visuo-spatial memory, executive function, and processing speed [9, 10]. Furthermore, these cognitive deficits commonly persist after remission of depressive symptoms and appear to increase the risk of dementia through poorly understood neuropathological processes [11–13]. Inflammation and increased glucocorticoid production, which can contribute to amyloid deposition, accelerated hippocampal atrophy, and cerebrovascular disease (CVD) are implicated in LLD [6, 14]. There is conflicting evidence to support a direct link between amyloid-β (Aβ) and tau, two of the pathological hallmarks of Alzheimer's disease (AD) and LLD [15–24]. Furthermore, many of these studies involve actively depressed individuals, with a paucity of research addressing the association of remitted depression and AD pathology [25].

CVD, as represented by white matter hyperintensities (WMH) on T2-weighted structural magnetic resonance imaging (MRI), is a common co-pathology of neurodegenerative diseases, particularly AD [26, 27]. White matter hyperintensities and AD pathology appear to have independent and additive effects on dementia risk [28, 29]. Among patients with normal cognition [30–32], MCI [30], and AD dementia [28–36], WMH are associated with lower levels of cerebrospinal fluid (CSF) $A\beta_{42}$ [28]. WMHs are also associated with depression [7, 36]. The link between depression and CVD appears to be bidirectional: depression increases the risk of CVD [37] and vascular damage disrupts frontal-subcortical-limbic neural pathways and connectivity in networks central to mood that predispose the development of depressive symptoms [38].

The interaction between AD, CVD, and depression is poorly understood. The aim of our study was to investigate the relationship between past depression and WMH burden in those with positive (AD+) and negative (AD-) CSF biomarker profiles for AD. We also aimed to better understand how CSF AD pathology and WMH burden relate to the clinical phenotypes of MCI and/or MDD. We compared AD CSF biomarker status (positive versus negative) and WMH burden among three groups: MCI, MCI with remitted MDD (MDD+MCI), and remitted MDD alone (MDD).

MATERIALS AND METHODS

Participants

Participants for this study were a subset of those enrolled in the Prevention of Alzheimer's dementia with Cognitive remediation plus Transcranial direct current stimulation in Mild cognitive impairment and Depression (PACt-MD) study (ClinicalTrials.gov Identifier: NCT02386670) with a diagnosis of MCI, remitted MDD, or both who completed a lumbar puncture [39]. This multi-site, interventional study assessed the efficacy of a combination of transcranial direct current stimulation and cognitive remediation in the prevention of dementia in two over-lapping high risk groups: older individuals with MCI, or a history of MDD. Extensive clinical and research assessments, including a comprehensive neuropsychological battery, characterized participants' cognitive performance. Participants were invited to provide biomarkers, including 3T MRI, CSF, peripheral blood biomarkers, genetics, PET, and EEG.

Diagnoses of MCI and MDD were made in accordance with the Diagnostic Statistical Manual of Mental Disorders, 5^{th} edition (DSM-5) [39]. The PACt-MD study required either a recent (defined as a history of a major depressive episode ((MDE) within ≤ 5 years) or remote history of MDD in current remission. Evidence of the need for medical attention to confirm clinical significance of a remote MDE was required, and to provide support that DSM-5 diagnostic criteria were met. A geriatric psychiatrist performed a comprehensive assessment, including clinical neuropsychological testing and a score of ≤ 10 on the Montgomery-Asberg Depression Rating Scale. The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4^{th} edition confirmed the MDD diagnosis and ruled out the presence of excluded psychiatric disorders [39]. A comprehensive medical review ruled out the presence of physical conditions contributing to MCI. Our sample consisted of exclusively those with

EOD that recurred (i.e., LLD). Patients with a clinical diagnosis of MCI (both amnestic and non-amnestic), remitted MDD, or both based on this clinical assessment were referred to the study and invited to sign the informed consent form approved by the CAMH Research Ethics Board.

Assessment of WMH Burden

All participants underwent MRI scanning on the same 3-T GE MR750 Echospeed (General Electric, Milwaukee, WI) research-dedicated scanner at CAMH [39]. The fluid-attenuated inversion recovery (FLAIR) sequence was optional and was only obtained in a subset of the participants. Therefore, a trained neurologist (MCT) classified WMH burden as none/mild, moderate, or severe based on visual inspection of T2-weighted images.

CSF collection and analysis

Approximately 15 mL of CSF was collected from each participant by allowing CSF to drip into a polypropylene collecting tube (gravity drip). The collecting tubes were then aliquoted and stored at –80°C within 30 min of collection. A sandwich ELISA was used to measure concentrations of $A\beta_{42}$ (Innotest β-amyloid (1–42), Fujirebio), phosphorylated-tau (Innotest phospho-tau (181p), Fujirebio), and total-tau (Innotest hTAU-Ag, Fujirebio) following the manufacturer's instruction [18, 19]. All samples were measured in duplicate and repeated if the difference between individual optic density values was greater than 20%. In addition to the ready-to-use calibrators (CAL) and Run Validation Controls (RVC) which were part of the Fujirebio Innotest assay kits, internal controls were also included in each run. After calculating the mean absorbance for the CAL, RVC, and unknown CSF samples, a sigmoidal 4-parameter curve fitting was used to determine the corresponding concentrations. CSF biomarkers were considered consistent with AD diagnosis (AD+) if phosphorylated tau > 68 pg/ml and $A\beta_{42}$ to total tau index (ATI) < 0.8 [18, 19].

Data analysis

Based on the results of the comprehensive neuropsychological assessments [39], composite scores were created for six cognitive domains: verbal memory, visuospatial memory, information processing speed, working memory, language, and executive function, in addition to an overall composite score [39]. First, AD+ and AD- participants were compared using *t*-tests for neuropsychological performance and Fisher's exact test for WMH burden. The MDD group was excluded for the analysis of neuropsychological performance. Next, we compared diagnostic categories (MCI, MDD, MDD+MCI) using one-way ANOVA for CSF AD biomarkers and WMH burden. An alpha level of 0.05 was set to determine statistical significance. Statistical analysis was conducted using SPSS software (IBM SPSS 28). Given that the analyses were exploratory, no corrections were made for multiple comparisons.

RESULTS

Participants

We obtained CSF from 31 participants of whom 27 completed an MRI. Table 1 provides demographic information. Caucasian individuals were over-represented and, overall, participants were well-educated. Age, sex, self-reported race/ethnicity, or education did not differ among the three diagnostic groups.

CSF AD biomarkers and cognitive performance

Table 2 summarizes the cognitive performance in AD+ and AD- participants: AD+ participants performed significantly worse than AD- participants in verbal memory ($p = 0.009$).

CSF AD biomarkers and diagnosis

None of the 7 participants (0%) with a diagnosis of remitted MDD were AD+; 7 of the 12 participants (58.3%) with MCI were AD+; and 2 of the 12 participants (16.7%) with MDD+MCI were AD+ ($p = 0.013$). Participants with MCI exhibited greater levels of phosphorylated tau (P tau) than participants with MDD ($p = 0.03$) (Table 3).

CSF AD biomarkers and WMH

Table 3 presents the WMH ratings in AD+ and AD- participants: 26 of 27 participants who completed an MRI (96%) had moderate or severe WMH; AD- participants had more severe WMH burden than AD+ ($p = 0.031$).

Table 1
Demographic Characteristics and Diagnosis of the Sample

	Sample $N=31$	MCI ($n=12$)	MDD ($n=7$)	MDD+MCI ($n=12$)	Statistical Test
Age, Mean (SD)	70.6 (4.40)	71.0 (4.6)	71.0 (4.9)	69.9 (4.2)	$F(2,28)=0.212$, $p=0.81$
Self-reported sex	20F:11M	7F:5M	5F:2M	8F:4M	Fisher's Exact $p=0.90$
Self-reported race (white/other)	23/8	8/4	7/0	8/4	Fisher's Exact $p=0.28$
Education (y)	15.3 (2.97)	15.3 (2.3)	16.4 (2.6)	15.3 (3.0)	$F(2,28)=0.697$, $p=0.51$
APOE $\varepsilon 4$ (%)	41.9	58.3	14.3	41.7	χ^2, $p=0.172$
Anti-depressant Use (%)	38.7	0	71.4	58.3	χ^2, $p=0.002^{\dagger}$

MCI, mild cognitive impairment; MDD, major depressive disorder; F, female; M, male. †statistical significance at the 0.05 level.

Table 2
Demographic Characteristics, CSF AD Biomarkers, Cognitive Performance, and Burden of WMH among Participants with and without CSF Biomarkers Consistent with Alzheimer's Disease Dementia (AD+ versus AD-*)

N	AD+ 9	AD– 15	Statistical Test	Cohen's d
Age	70.9 (3.44)	70.2 (4.95)	$t(22)=-0.368$, $p=0.716$	0.155
Self-reported sex	5F:4M	10F:5M	Fisher's Exact, $p=0.678$	–
Self-reported race (white/other)	6/3	17/5	χ^2, $p=0.582$	–
Education	14.6 (2.13)	15.3 (3.51)	$t(22)=0.547$, $p=0.590$	0.231
APOE $\varepsilon 4$ (%)	66.7	27.3	χ^2, $p=0.035^{\dagger}$	–
Aβ (pg/mL), Mean (SD)	1347.2 (694.1)	691.3 (126.8)	$t(22)=2.783$, $p=0.005$	1.174
Total tau (pg/mL), Mean (SD)	208.2 (91.4)	705.0 (256.3)	$t(22)=-6.894$, $p=<0.001$	2.907
P-tau (pg/mL), Mean (SD)	89.8 (19.1)	47.2 (12.3)	$t(22)=-6.523$, $p=<0.001$	2.750
ATI, Mean (SD)	0.690 (0.232)	2.78 (1.19)	$t(22)=5.168$, $p=<0.001$	2.179
Depression (Presence: Absence)	2 : 7	17 : 5	Fisher's Exact, $p=0.012^{\dagger}$	–
Overall Composite	–0.917 (0.698)	–0.330 (0.492)	$t(22)=1.782$, $p=0.088$	0.752
Verbal Memory	–1.82 (1.50)†	–0.391 (0.906) [$N=14$]†	$t(21)=2.862$, $p=0.009^{\dagger}$	1.223
Visuospatial Memory	–0.777 (1.54)	–0.293 (0.780)	$t(22)=1.024$, $p=0.317$	1.179
Processing Speed	–0.674 (1.16)	–1.13 (1.12)	$t(22)=-0.946$, $p=0.354$	0.399
Working Memory	–0.888 (0.763)	–0.447 (0.820)	$t(22)=1.306$, $p=0.205$	0.551
Language	–0.826 (1.02)	–0.248 (0.667)	$t(22)=0.739$, $p=0.468$	0.711
Executive	–0.514 (0.848)	–0.304 (0.553)	$t(22)=1.212$, $p=0.24$	0.312
No or Mild WMH	1 (12.5%)	0 (0)	Fisher's Exact $p=0.031^{\dagger}$	–
Moderate WMH	6 (75%)	8 (42.1%)		
Severe WMH	1 (12.5%)	11 (57.9%)		

ATI calculated as Aβ/(240 + 1.18×Tau). AD+ is defined as CSF phosphorylated tau > 68 pg/ml and $A\beta_{42}$ to total tau index (ATI) < 0.8. †Denotes statistical significance at the 0.05 level. CSF, cerebrospinal fluid

Table 3
CSF AD Biomarkers and Burden of WMH in participants with MCI, MDD, or MCI+MDD

N	MCI 12	MDD 7	MCI+MDD 12	Statistical Test
Aβ (pg/mL), Mean (SD)	963.1 (717.3)	1311.7 (275.6)	1239.4 (537.3)	$F(28,2)=1.052$, $p=0.363$
Total tau (pg/mL), Mean (SD)	473.0 (302.1)	173.8 (80.7)	315.9 (282.8)	$F(28,2)=3.001$, $p=0.066$
P-tau (pg/mL), Mean (SD)	71.1 (28.3) †	40.6 (10.2)†	55.3 (21.8)	$F(28,2)=4.077$, $p=0.028^{\dagger}$
ATI, Mean (SD)	1.61 (1.61)	2.99 (0.54)	2.37 (1.07)	$F(28,2)=2.876$, $p=0.073$
AD Status (Positive: Negative)	7 : 5	0 : 7	2 : 10	Chi-Square, $p=0.013^{\dagger}$
No or Mild WMH	1 [$N=11$] (12.5%)	0 [$N=5$] (0)	0 [$N=11$]	Fisher's Exact, $p=0.347$
Moderate WMH	6 [$N=11$] (75%)	1 [$N=5$] (42.1%)	7 [$N=11$]	
Severe WMH	4 [$N=11$] (12.5%)	4 [$N=5$] (57.9%)	4 [$N=11$]	

ATI calculated as Aβ/(240 + 1.18×Tau). AD+ is defined as CSF phosphorylated tau > 68 pg/ml and $A\beta_{42}$ to total tau index (ATI) < 0.8. †Denotes statistical significance at the 0.05 level. Post-hoc Bonferroni. CSF, cerebrospinal fluid

DISCUSSION

Our study examined the relationship between AD CSF biomarkers (AD+ versus AD-), diagnosis (MCI, MDD, or MDD+MCI), WMH burden and neuropsychological performance. Among the MCI participants in our sample, more than half (7/12) were AD+, while only 2/12 of those with MDD+MCI

were AD+. As expected, all participants with AD+ CSF were cognitively impaired and performed worse than the AD- participants in verbal memory. In AD- participants, we did not observe a distinct cognitive profile. Finally, nearly all participants had moderate or severe WMH burden, irrespective of their diagnosis or AD biomarker status; however, AD- participants had more severe WMH burden.

Depression has been identified as one of twelve modifiable risk factors for dementia [1], and there is evidence to support a direct link to AD pathogenesis [15–23]. The neuropathological processes associated with MDD and increased dementia risk are highly variable [39, 40]. Age of onset of first episode and severity and duration of depressive episodes serve as important mediators for dementia and AD risk [42–44]. As discussed above, older patients with MCI or a history of recent or remote MDD which has recurred (i.e., LLD) are considered to be at high risk for cognitive decline. There is evidence that LLD is a prodromal state of neurodegenerative disease [45–47]. The PACt-MD sample attempts to capture those with remitted EOD and LOD. Among the 19 LLD participants in our sample, all had EOD; 12 had MCI, with CSF AD pathology evident in only two participants. These results suggest that the etiology of cognitive impairment among participants with a history of MDD may be distinct from participants with MCI alone [6]. This may also differ between patients with remitted versus non-remitted LLD; since our study excluded patients with current MDE, we cannot comment on this group.

The role of WMH in cognitive decline and the etiology of dementia is well established [48, 49]. Nearly all participants in our sample (26/27) exhibited moderate or severe WMH, however a sizeable number ($n = 7$) of participants were cognitively intact despite significant CVD burden. Participants with AD+ CSF performed worse in verbal memory than AD- participants, consistent with the neurocognitive profile of AD [50, 51]. All participants with MCI exhibited slowed processing speed, which is typical of vascular cognitive impairment in the context of moderate to high WMH burden [52]. Variations in the spatial distribution of WMH are known to contribute to a range of clinical phenotypes [53]. Although our study did not assess WMH localization, periventricular WMH are more closely related to cognitive impairment than deep WMH [28–30]; frontal [31–34] and temporal [35] WMH are associated with depression. We hypothesize that vascular lesions in clinically meaningful loci may account for those exhibiting MCI, given that only 38% of those with MCI had positive CSF AD biomarkers ($n = 9$). The sizeable WMH burden in our sample suggest that protective processes such as cognitive reserve [62] may be contributing to intact cognition in the MDD group. Participants in our sample were highly educated, with a mean of 15.3 years of education, lending support to this hypothesis.

The $\varepsilon 4$ allele of the apolipoprotein E (APOE4) is a well-established risk factor for AD [63]. In our sample, the frequency of APOE4 was as expected significantly higher among AD+ participants. The relationship between APOE and AD is poorly understood. One theory suggests that APOE4 may impair the clearance of Aβ, contributing to its accumulation [63]. There is mixed evidence that APOE4 carrier status may increase the risk of depression [64] and influence the association between WMH and cognitive decline in AD [65]. In our sample, the MDD+MCI group has a greater proportion of APOE4 carriers compared to the MDD group (41.7% versus 14.3%, respectively), however, our small sample size precludes any analysis of the relationship between APOE4 status, depression, WMH, and AD.

Study limitations include the limited generalizability of our results arising from the small sample size, and a predominantly White and highly educated demographic. We did not capture potentially salient details of prior MDEs, such as episode frequency, which could have potential correlations to WMH burden and an evolving vascular neurocognitive disorder. Anti-depressant use also appears to mediate improved cognitive performance among individuals with depression [66]. Anti-depressant use appeared to be more common in the MDD group compared to the MDD+MCI group (71.3% versus 58.3%, respectively); however, we were unable to perform statistical analyses to control for anti-depressant use due to our small sample size. We may also have underestimated WMH burden using non-fluid attenuated T2 images rather than FLAIR images, which is the gold standard for WMH quantification. Finally, despite the use of well-validated diagnostic criteria of the DSM-5, diagnosing a remote MDE remains unreliable [39, 67].

Further research with larger samples sizes are needed to examine the potential contribution of WMH in patients with a remitted MDD and MCI in conjunction with pathological biomarkers for AD and CVD. A causal link between WMH burden and depression with associated persistent cognitive impairment would provide a rationale for primary

prevention of depression with control of vascular risk factors.

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CONFLICT OF INTEREST

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Dr. Fischer is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review.

DATA AVAILABILITY

The data supporting the findings of this study are available on reasonable request from the corresponding author.

REFERENCES

[1] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* **396**, 413-446.

[2] Chung JK, Plitman E, Nakajima S, Mallar Chakravarty M, Caravaggio F, Takeuchi H, Gerretsen P, Iwata Y, Patel R, Mulsant BH, Graff-Guerrero A (2016) Depressive symptoms and small hippocampal volume accelerate the progression to dementia from mild cognitive impairment. *J Alzheimers Dis* **49**, 743-754.

[3] Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L (2017) Depression as a modifiable factor to decrease the risk of dementia. *Transl Psychiatry* **7**, e1117.

[4] Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, Sabia S (2017) Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. *JAMA Psychiatry* **74**, 712-718.

[5] Prince M, Albanese E, Guerchet M, Prina M (2014) *World Alzheimer Report 2014: Dementia and risk reduction: An analysis of protective and modifiable risk factors*. Alzheimer's Disease International, London.

[6] Ly M, Karim HT, Becker JT, Lopez OL, Anderson SJ, Aizenstein HJ, Reynolds CF, Zmuda MD, Butters MA (2021) Late-life depression and increased risk of dementia: A longitudinal cohort study. *Transl Psychiatry* **11**, 147.

[7] Taylor WD, Aizenstein HJ, Alexopoulos GS (2013) The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Mol Psychiatry* **18**, 963-974.

[8] Aizenstein HJ, Baskys A, Boldrini M, Butters MA, Diniz BS, Jaiswal MK, Jellinger KA, Kruglov LS, Meshandin IA, Mijajlovic MD, Niklewski G, Pospos S, Raju K, Richter K, Steffens DC, Taylor WD, Tene O (2016) Vascular depression consensus report – a critical update. *BMC Med* **14**, 161.

[9] Lockwood KA, Alexopoulos GS, Kakuma T, van Gorp WG (2000) Subtypes of cognitive impairment in depressed older adults. *Am J Geriatr Psychiatry* **8**, 201-208.

[10] Butters MA, Bhalla RK, Mulsant BH, Mazumdar S, Houck PR, Begley AE, Dew MA, Pollock BG, Nebes RD, Becker JT, Reynolds CF 3rd (2004) Executive functioning, illness course, and relapse/recurrence in continuation and maintenance treatment of late-life depression: Is there a relationship? *Am J Geriatr Psychiatry* **12**, 387-394.

[11] Bhalla RK, Butters MA, Mulsant BH, Begley AE, Zmuda MD, Schoderbek B, Pollock BG, Reynolds CF, Becker JT (2006) Persistence of neuropsychologic deficits in the remitted state of late-life depression. *Am J Geriatr Psychiatry* **14**, 419-427.

[12] Alexopoulos GS, Meyers BS, Young RC, Mattis S, Kakuma T (1993) The course of geriatric depression with "reversible dementia": A controlled study. *Am J Psychiatry* **150**, 1693-1699.

[13] Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF, DeKosky ST, Becker JT (2008) Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues Clin Neurosci* **10**, 345-357.

[14] Byers AL, Yaffe K (2011) Depression and risk of developing dementia. *Nat Rev Neurol* **7**, 323-331.

[15] Gatchel JR, Rabin JS, Buckley RF, Locascio JJ, Quiroz YT, Yang HS, Vannini P, Amariglio RE, Rentz DM, Properzi M, Donovan NJ, Blacker D, Johnson KA, Sperling RA, Marshall GA (2019) longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. *JAMA Netw Open* **2**, e198964.

[16] Gatchel JR, Donovan NJ, Locascio JJ, Schultz AP, Becker JA, Chhatwal J, Papp KV, Amariglio RE, Rentz DM, Blacker D, Sperling RA, Johnson KA, Marshall GA (2017) Depressive symptoms and tau accumulation in the inferior temporal lobe and entorhinal cortex in cognitively normal older adults: A pilot study. *J Alzheimers Dis* **59**, 975-985.

[17] Lavretsky H, Siddarth P, Kepe V, Ercoli LM, Miller KJ, Burggren AC, Bookheimer SY, Huang SC, Barrio JR, Small GW (2009) Depression and anxiety symptoms are associated with cerebral FDDNP-PET binding in middle-aged and older nondemented adults. *Am J Geriatr Psychiatry* **17**, 493-502.

[18] Smith GS, Kuwabara H, Nandi A, Gould NF, Nassery N, Savonenko A, Joo JH, Kraut M, Brasic J, Holt DP, Hall AW, Mathews WB, Dannals RF, Avramopoulos D, Workman CI (2021) Molecular imaging of beta-amyloid deposition in late-life depression. *Neurobiol Aging* **101**, 85.

[19] Kumar A, Kepe V, Barrio JR, Siddarth P, Manoukian V, Elderkin-Thompson V, Small GW (2011) Protein binding in patients with late-life depression. *Arch Gen Psychiatry* **68**, 1143-1150.

[20] Wu KY, Hsiao IT, Chen CS, Chen CH, Hsieh CJ, Wai YY, Chang CJ, Tseng HJ, Yen TC, Liu CY, Lin KJ (2014) Increased brain amyloid deposition in patients with a lifetime history of major depression: Evidenced on 18F-florbetapir (AV-45/Amyvid) positron emission tomography. *Eur J Nucl Med Mol Imaging* **41**, 714-722.

[21] Madsen K, Hasselbalch BJ, Frederiksen KS, Haahr ME, Gade A, Law I, Price JC, Knudsen GM, Kessing LV, Hasselbalch SG (2012) Lack of association between prior depressive episodes and cerebral [11C]PiB binding. *Neurobiol Aging* **33**, 2334-2342.

[22] Mackin RS, Insel PS, Landau S, Bickford D, Morin R, Rhodes E, Tosun D, Rosen HJ, Butters M, Aisen P, Raman R, Saykin A, Toga A, Jack C, Koeppe R, Weiner MW, Nelson C (2021) Late-life depression is associated with reduced cortical amyloid burden: Findings from the Alzheimer's Disease Neuroimaging Initiative Depression Project. *Biol Psychiatry* **89**, 757-765.

[23] Babulal GM, Roe CM, Stout SH, Rajasekar G, Wisch JK, Benzinger TLS, Morris JC, Ances BM (2020) Depression is associated with tau and not amyloid positron emission tomography in cognitively normal adults. *J Alzheimers Dis* **74**, 1045-1055.

[24] de Oliveira FF, Miraldo MC, de Castro-Neto EF, de Almeida SS, Matas SLDA, Bertolucci PHF, Naffah-Mazzacoratti MDG (2021) Associations of neuropsychiatric features with cerebrospinal fluid biomarkers of amyloidogenesis and neurodegeneration in dementia with Lewy bodies compared with Alzheimer's disease and cognitively healthy people. *J Alzheimers Dis* **81**, 1295-1309.

[25] Loureiro JC, Stella F, Pais MV, Radanovic M, Canineu PR, Joaquim HPG, Talib LL, Forlenza OV (2020) Cognitive impairment in remitted late-life depression is not associated with Alzheimer's disease-related CSF biomarkers. *J Affect Disord* **272**, 409-416.

[26] Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, Monsell SE, Kukull WA, Trojanowski

JQ (2013) Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain* **136**, 2697-2706.

[27] Attems J, Jellinger KA (2014) The overlap between vascular disease and Alzheimer's disease–lessons from pathology. *BMC Med* **12**, 206.

[28] Soldan A, Pettigrew C, Zhu Y, Wang MC, Moghekar A, Gottesman RF, Singh B, Martinez O, Fletcher E, Decarli C, Albert M (2020) White matter hyperintensities and CSF Alzheimer disease biomarkers in preclinical Alzheimer disease. *Neurology* **94**, e950-e960.

[29] Roseborough A, Ramirez J, Black SE, Edwards JD (2017) Associations between amyloid β and white matter hyperintensities: A systematic review. *Alzheimers Dement* **13**, 1154-1167.

[30] Marnane M, Al-Jawadi OO, Mortazavi S, Pogorzelec KJ, Wang BW, Feldman HH, Hsiung GYR (2016) Periventricular hyperintensities are associated with elevated cerebral amyloid. *Neurology* **86**, 535-543.

[31] Kester MI, Goos JDC, Teunissen CE, Benedictus MR, Bouwman FH, Wattjes MP, Barkhof F, Scheltens P, van der Flier WM (2014) Associations between cerebral small-vessel disease and Alzheimer disease pathology as measured by cerebrospinal fluid biomarkers. *JAMA Neurol* **71**, 855-862.

[32] Scott JA, Braskie MN, Tosun D, Maillard P, Thompson PM, Weiner M, DeCarli C, Carmichael OT (2016) Cerebral amyloid is associated with greater white-matter hyperintensity accrual in cognitively normal older adults. *Neurobiol Aging* **48**, 48-52.

[33] Pietroboni AM, Scarioni M, Carandini T, Basilico P, Cadioli M, Giulietti G, Arighi A, Caprioli M, Serra L, Sina C, Fenoglio C, Ghezzi L, Fumagalli GG, de Riz MA, Calvi A, Triulzi F, Bozzali M, Scarpini E, Galimberti D (2018) CSF β-amyloid and white matter damage: A new perspective on Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **89**, 352-357.

[34] van Westen D, Lindqvist D, Blennow K, Minthon L, Nägga K, Stomrud E, Zetterberg H, Hansson O (2016) Cerebral white matter lesions - associations with Aβ isoforms and amyloid PET. *Sci Rep* **6**, 20709.

[35] Shams S, Granberg T, Martola J, Li X, Shams M, Fereshtehnejad SM, Cavallin L, Aspelin P, Kristoffersen-Wiberg M, Wahlund LO (2016) Cerebrospinal fluid profiles with increasing number of cerebral microbleeds in a continuum of cognitive impairment. *J Cereb Blood Flow Metab* **36**, 621-628.

[36] Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M (1997) 'Vascular depression' hypothesis. *Arch Gen Psychiatry*, **54**, 915-922.

[37] Hare DL, Toukhsati SR, Johansson P, Jaarsma T (2014) Depression and cardiovascular disease: A clinical review. *Eur Heart J* **35**, 1365-1372.

[38] Linnemann C, Lang UE (2020) Pathways connecting late-life depression and dementia. *Front Pharmacol* **11**, 279.

[39] Rajji TK, Bowie CR, Herrmann N, Pollock BG, Bikson M, Blumberger DM, Butters MA, Daskalakis ZJ, Fischer CE, Flint AJ, Golas AC, Graff-Guerrero A, Kumar S, Lourenco L, Mah L, Ovaysikia S, Thorpe KE, Voineskos AN, Mulsant BH (2020) Design and rationale of the PACt-MD randomized clinical trial: Prevention of Alzheimer's dementia with cognitive remediation plus transcranial direct current stimulation in mild cognitive impairment and depression. *J Alzheimers Dis* **76**, 733-751.

[40] Hulstaert F, Blennow K, Ivanoiu A, Schoonderwaldt HC, Riemenschneider M, De Deyn PP, Bancher C, Cras P, Wiltfang J, Mehta PD, Iqbal K, Pottel H, Vanmechelen E, Vanderstichele H (1999) Improved discrimination of AD patients using beta-amyloid(1-42) and tau levels in CSF. *Neurology* **52**, 1555-1562.

[41] Maddalena A, Papassotiropoulos A, Müller-Tillmanns B, Jung HH, Hegi T, Nitsch RM, Hock C (2003) Biochemical diagnosis of Alzheimer disease by measuring the cerebrospinal fluid ratio of phosphorylated tau protein to beta-amyloid peptide42. *Arch Neurol* **60**, 1202-1206.

[42] Cherbuin N, Kim S, Anstey KJ (2015) Dementia risk estimates associated with measures of depression: A systematic review and meta-analysis. *BMJ Open* **5**, e008853.

[43] Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF (2013) Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry* **202**, 329-335.

[44] Gatz JL, Tyas SL, John PS, Montgomery P (2005) Do depressive symptoms predict Alzheimer's disease and dementia? *J Gerontology* **60**, 744-747.

[45] Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, Cedarbaum J, Brashear R, Miller DS (2011) Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement* **7**, 532-539.

[46] Bennett S, Thomas AJ (2014) Depression and dementia: Cause, consequence or coincidence? *Maturitas* **79**, 184-190.

[47] Schweitzer I, Tuckwell V, O'Brien J, Ames D (2002) Is late onset depression a prodrome to dementia? *Int J Geriatr Psychiatry* **17**, 997-1005.

[48] Brickman AM, Zahodne LB, Guzman VA, Narkhede A, Meier IB, Griffith EY, Provenzano FA, Schupf N, Manly JJ, Stern Y, Luchsinger JA, Mayeux R (2015) Reconsidering harbingers of dementia: Progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiol Aging* **36**, 27-32.

[49] Debette S, Markus HS (2010) The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. *BMJ* **341**, c3666

[50] Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, Bakardjian H, Benali H, Bertram L, Blennow K, Broich K, Cavedo E, Crutch S, Dartigues JF, Duyckaerts C, Epelbaum S, Frisoni GB, Gauthier S, Genthon R, Gouw AA, Habert MO, Holtzman DM, Kivipelto M, Lista S, Molinuevo JL, O'Bryant SE, Rabinovici GD, Rowe C, Salloway S, Schneider LS, Sperling R, Teichmann M, Carrillo MC, Cummings J, Jack CR Jr; Proceedings of the Meeting of the International Working Group (IWG) and the American Alzheimer's Association on "The Preclinical State of AD"; July 23, 2015; Washington DC, USA (2016) Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement* **12**, 292-323.

[51] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.

[52] Hotz I, Deschwanden PF, Mérillat S, Liem F, Kollias S, Jäncke L (2021) Associations of subclinical cerebral small

vessel disease and processing speed in non-demented subjects: A 7-year study. *Neuroimage Clin* **32**, 102884.

[53] Yoshita M, Fletcher E, Harvey D, Ortega M, Martinez O, Mungas DM, Reed BR, DeCarli CS (2006) Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology* **67**, 2192.

[54] van den Heuvel DMJ, ten Dam VH, de Craen AJM, Admiraal-Behloul F, Olofsen H, Bollen ELEM, Jolles J, Murray HM, Blauw GJ, Westendorp RGJ, van Buchem MA (2006) Increase in periventricular white matter hyperintensities parallels decline in mental processing speed in a non-demented elderly population. *J Neurol Neurosurg Psychiatry* **77**, 149.

[55] Debette S, Bombois S, Bruandet A, Delbeuck X, Lepoittevin S, Delmaire C, Leys D, Pasquier F (2007) Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment. *Stroke* **38**, 2924-2930.

[56] de Groot JC, de Leeuw FE, Oudkerk M, van Gijn J, Hofman A, Jolles J, Breteler MMB (2002) Periventricular cerebral white matter lesions predict rate of cognitive decline. *Ann Neurol* **52**, 335-341.

[57] Firbank MJ, Lloyd AJ, Ferrier N, O'Brien JT (2004) A volumetric study of MRI signal hyperintensities in late-life depression. *Am J Geriatr Psychiatry* **12**, 606-612.

[58] MacFall JR, Payne ME, Provenzale JE, Krishnan KRR (2001) Medial orbital frontal lesions in late-onset depression. *Biol Psychiatry* **49**, 803-806.

[59] MacFall JR, Taylor WD, Rex DE, Pieper S, Payne ME, McQuoid DR, Steffens DC, Kikinis R, Toga AW, Krishnan KRR (2005) Lobar distribution of lesion volumes in late-life depression: The Biomedical Informatics Research Network (BIRN). *Neuropsychopharmacology* **31**, 1500-1507.

[60] Taylor WD, MacFall JR, Steffens DC, Payne ME, Provenzale JM, Krishnan KRR (2003) Localization of age-associated white matter hyperintensities in late-life depression. *Prog Neuropsychopharmacol Biol Psychiatry* **27**, 539-544.

[61] O'Brien JT, Firbank MJ, Krishnan MS, van Straaten ECW, van der Flier WM, Petrovic K, Pantoni L, Simoni M, Erkinjuntti T, Wallin A, Wahlund LO, Inzitari D (2006) White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: The LADIS Study. *Am J Geriatr Psychiatry* **14**, 834-841.

[62] Stern Y (2009) Cognitive reserve. *Neuropsychologia* **47**, 2015-2028.

[63] Uddin MS, Kabir MT, Al Mamun A, Abdel-Daim MM, Barreto GE, Ashraf GM (2019) APOE and Alzheimer's disease: Evidence mounts that targeting APOE4 may combat Alzheimer's pathogenesis. *Mol Neurobiol* **56**, 2450-2465.

[64] Delano-Wood L, Houston WS, Emond JA, Marchant NL, Salmon DP, Jeste DV, Thal LJ, Bondi MW (2008) APOE genotype predicts depression in women with Alzheimer's disease: A retrospective study. *Int J Geriatr Psychiatry* **23**, 632-636.

[65] Mirza SS, Saeed U, Knight J, Ramirez J, Stuss DT, Keith J, Nestor SM, Yu D, Swardfager W, Rogaeva E, St George Hyslop P, Black SE, Masellis M (2019) APOE ε4, white matter hyperintensities, and cognition in Alzheimer and Lewy body dementia. *Neurology* **93**, e1807-e1819.

[66] Prado CE, Watt S, Crowe SF (2018) A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. *Neuropsychol Rev* **28**, 32-72.

[67] Lieblich SM, Castle DJ, Pantelis C, Hopwood M, Young AH, Everall IP (2015) High heterogeneity and low reliability in the diagnosis of major depression will impair the development of new drugs. *BJPsych Open* **1**, e5.