

Depression Severity Predicts Accelerated Hypometabolism In Alzheimer’s Brain Regions Independent Of Insomnia

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Depression severity and chronicity were associated with accelerated hypometabolism in AD-vulnerable posterior cortical regions independent of insomnia. Chronic depression demonstrated the greatest metabolic decline. Effects persisted after stratification by diagnosis and education. Greater levels of depression exposure was associated with steeper MMSE decline after 24 months.

BACKGROUND

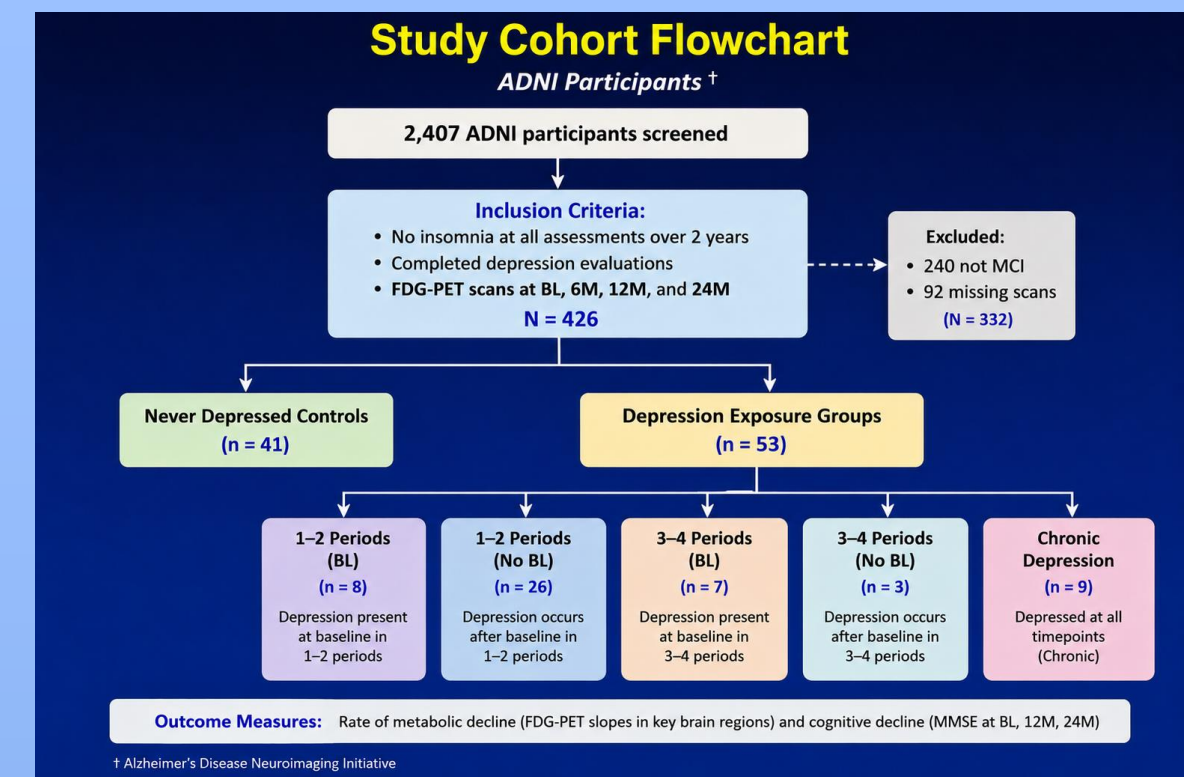
- Depression and Insomnia are associated with increased risk of developing cognitive dysfunction
- FDG-PET hypometabolism in posterior cortical regions is an early biomarker predictive of AD progression and functional decline
- Because depression and insomnia frequently co-occur, the independent contribution of depression to AD-related hypometabolism remains unclear
- Understanding whether depression alone contributes to accelerated cerebral hypometabolism may improve early risk stratification in vulnerable populations

STUDY QUESTION

When insomnia is removed as a confounding factor, does depression severity and timing still predict accelerated metabolic decline in AD-vulnerable brain regions?

Ranges of timing includes never depressed, intermittent depression, and chronically depressed

METHODS



Inclusion Criteria

- No insomnia during entire 2-year study period
- Complete FDG-PET scans at BL, M6, M12, M24
- Completed depression assessments at all timepoints

Exclusion Criteria

- Missing scans
- Insomnia present at any assessment
- Incomplete depression data

Demographics:

Group	n	Mean Age ± SD	Education >12 (%)
Control	41	73.45 ± 4.03	78%
Chronic Depression	9	76.75 ± 7.07	88.9%
1 – 2 BL	8	77.15 ± 6.55	100%
3 – 4 BL	7	76.21 ± 9.42	85.8%
1 – 2 no BL	26	80.33 ± 1.53	80.8%
3 – 4 no BL	3	71.33 ± 5.75	33%
Any Depression Exposure	53	76.2 ± 7.0	83%

Depression Exposure Groups

Control: never depressed

1–2 BL: depression present at baseline in 1–2 periods

3–4 BL: depression present at baseline in 3–4 periods

1–2 no BL: depression occurs after baseline in 1–2 periods

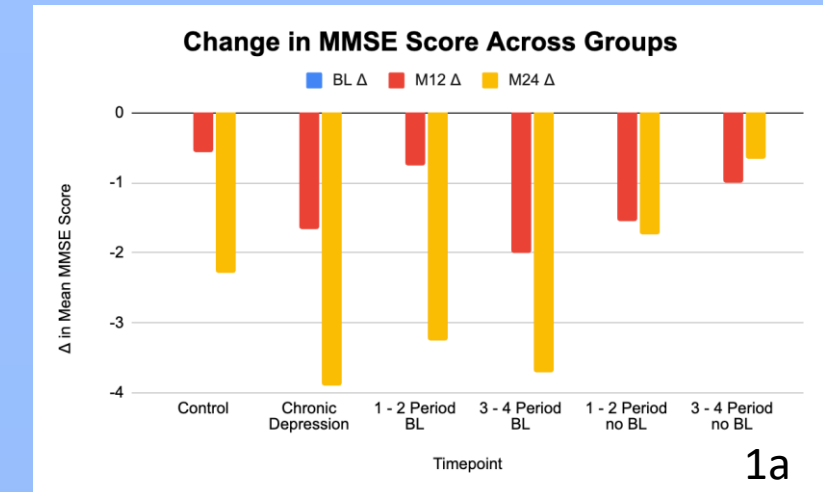
3–4 no BL: depression occurs after baseline in 3–4 periods

Chronic Depression: depressed at all timepoints

Measurements:

Regional cerebral glucose metabolism was assessed using FDG-PET and quantified as standardized uptake value ratios (SUVr) normalized to the pons across 47 predefined cortical and subcortical regions.

RESULTS



N = 94
MMSE: overall cognitive function over time (Patient completed MMSE test under Physician supervision)

Figure 1a. Longitudinal cognitive decline by depression exposure group

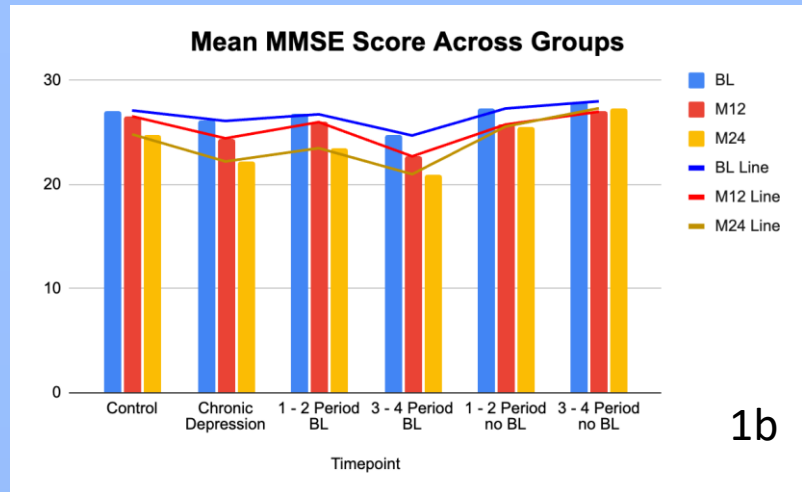


Figure 1b. Longitudinal cognitive decline organized to show change over time from baseline

Overall MMSE scores decreased across the 24-month period in nearly all subject groups, especially the subjects who had depression at baseline

Table 1. Standardized Volume of Interest Analysis (pons-normalized means)

sVOI	Control	Chronic	1 – 2 BL	3 – 4 BL	1 – 2 no BL	3 – 4 no BL
Right Posterior Cingulate Cortex (rPCC)	-0.0453	-0.0468 **	0.00719	-0.00561	-0.0498 **	-0.0794
Left Posterior Cingulate Cortex (lPCC)	-0.0428	-0.0428 *	0.0107	-0.00484	-0.0511 **	-0.0736
Right Parietotemporal Cortex (rPTC)	-0.0511	-0.0590 **	-0.0299	-0.0200	-0.0490 **	-0.0917
Left Parietotemporal Cortex (lPTC)	-0.0301	-0.0512 *	-0.0654 *	0.0096	-0.0581 **	-0.0624
Left Superior Parietal Lobule (lsPL)	-0.000056	-0.03351 **	0.0131	0.0694	-0.0160 **	-0.0161
Left Inferior Lateral Posterior Temporal Cortex (llLPT)	-0.0369	-0.0182 *	-0.0279 *	-0.0182 **	-0.0281 **	-0.0570 *

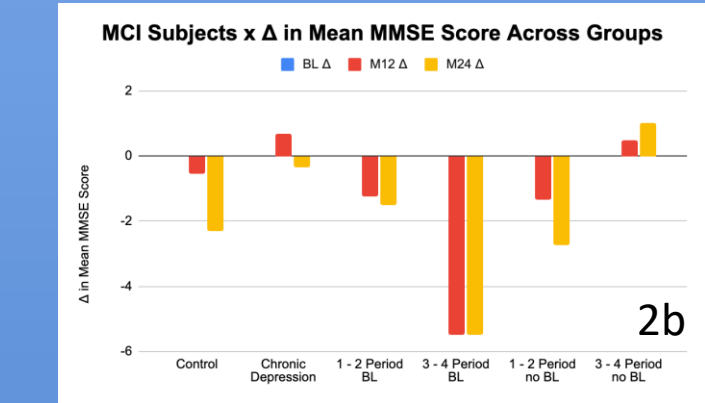
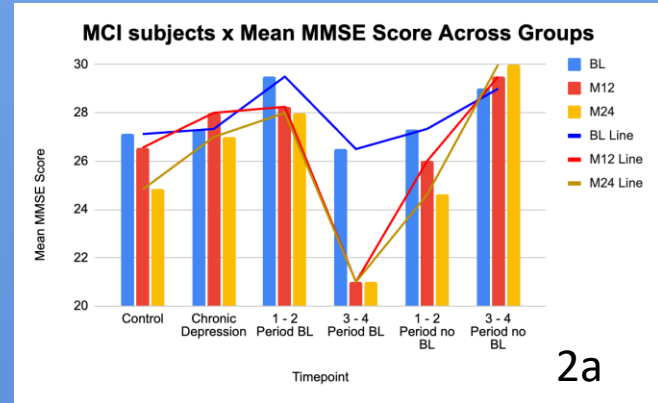
Table 2. Between-Group Statistical Comparisons (pons-normalized)

sVOI	Controls vs Chronic (p-value)	Controls vs 3 – 4 Period BL (p-value)	Chronic vs 3 – 4 Period BL (p-value)	Control vs 1 – 2 Period BL (p-value)
Inferior Lateral Posterior Temporal Cortex (lLPT)	Right: 0.357 Left: 0.439	Right: 0.153 Left: 0.915	Right: 0.595 Left: 0.559	Right: 0.586 Left: 0.771
Superior Parietal Lobule (sPL)	Right: 0.227 Left: 0.138	Right: 0.011	Right: 0.014 Left: 0.017	Right: 0.372 Left: 0.856
Left Inferior Parietal Lobule (llPL)	0.775	0.033	0.0914	0.635
Left Posterior Cingulate Cortex (lPCC)	0.998	0.183	0.306	0.037

Significant between-group differences were most prominent within the superior parietal lobule (sPL) and posterior association cortices

- PCC/PTC are early AD-vulnerable association cortices
- sPL and lLPT demonstrated significant metabolic decline
- Greatest decline occurred with chronic depression exposure
- Posterior cortical hypometabolism is an AD-relevant metabolic pattern. The persistence of decline after excluding insomnia suggests that depression exposure may contribute independently to metabolic vulnerability in AD-sensitive regions

Follow up Question: Does depression-associated decline persist when stratified by brain status, education, and age?



N = 70
MCI = Mild Cognitive Impairment

Figure 2a and 2b. Depression-associated cognitive decline persists in participants with MCI. When analyses was restricted to individuals with MCI, greater depression exposure remained associated with lower MMSE scores over time, suggesting that the relationship is not solely attributable to diagnostic differences

Table 3. Metabolic Decline in AD-Vulnerable Regions (after >12 years Education stratification) (N = 70)

sVOI	Control	Chronic	1 – 2 BL	3 – 4 BL	1 – 2 no BL
Right Posterior Cingulate Cortex (rPCC)	-0.0464	-0.06530	-0.01980	0.07110	-0.04623 **
Left Posterior Cingulate Cortex (lPCC)	-0.0410	-0.06370	-0.00145	0.04960	-0.04911 **
Right Parietotemporal Cortex (rPTC)	-0.04913	-0.09630	-0.05873 *	0.09330	-0.04721 **
Left Parietotemporal Cortex (lPTC)	-0.0336	-0.07730	-0.08858	0.04760	-0.06981 **
Left Superior Parietal Lobule (lsPL)	0.0061	-0.02495 *	0.00508	0.06130	-0.03416 **
Left Inferior Lateral Parietotemporal Cortex (llLPT)	-0.0322	-0.05380	-0.02285	0.00740	-0.02119 *

- Depression-associated metabolic decline persists within posterior association cortices

Table 4. Metabolic Decline in AD-Vulnerable Regions (70s stratification) (N = 49)

sVOI	Control	Chronic	1 – 2 BL	1 – 2 no BL
Right Posterior Cingulate Cortex (rPCC)	0.01507	-0.0468 **	-0.00164	-0.03859 **
Left Posterior Cingulate Cortex (lPCC)	0.02545	-0.04281 *	-0.0009	-0.03367 *
Right Parietotemporal Cortex (rPTC)	0.01057	-0.05904 **	-0.02564	-0.05112 **
Left Parietotemporal Cortex (lPTC)	0.0276	-0.05122 *	-0.07082	-0.05074 **
Left Superior Parietal Lobule (lsPL)	0.05252	-0.0337 **	0.0029	-0.008033
Left Inferior Lateral Posterior Temporal Cortex (llLPT)	0.02076	-0.01697 *	-0.04914 *	-0.0216 *

Differences observed between the chronic and 1–2 BL analyses should be interpreted with caution, as the stratified analyses included fewer participants than the primary analysis. Nevertheless, the 1–2 BL subgroup demonstrated a consistent association with brain volume decline, supporting the robustness of the primary findings.

CONCLUSIONS

Greater severity and longer duration of depression were linked to accelerated hypometabolism, independent of insomnia, with the most pronounced effects observed in chronically depressed participants and those with prolonged exposure. These findings suggest a robust association between cumulative depression burden and early Alzheimer’s disease–related brain changes.

FUTURE DIRECTIONS / LIMITATIONS

- Small sample sizes within depression subgroups may limit statistical power and reduce generalizability of findings
- Follow up with the 1 – 2 no BL depression group to understand what other underlining factors affected their dramatic decline
- Antidepressant treatment status and medication effects were not evaluated and may influence cerebral metabolic trajectories, but are not present for dataset
- Validate these findings in larger and diverse cohorts with longer follow-up periods
- Investigate other mechanisms linking depression to AD-related neurodegeneration

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