

Key Finding: Co-occurring AD plus LATE has a greater neuropsychiatric symptom burden compared to AD or LATE alone

Background

- Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a neurodegenerative condition that contributes to memory impairment in older adults and commonly co-occurs with Alzheimer's disease (AD)^{1,2}
- LATE neuropathic change (LATE-NC) primarily affects structures of the limbic system, such as the amygdala, hippocampus, and entorhinal cortex (ERC), which are commonly implicated in behavioral and neuropsychiatric symptoms (BNPS)³
- Significant clinical overlap between LATE and AD and a lack of *in vivo* biomarkers for LATE has confounded previous work characterizing BNPS features of AD, and even less is known about the BNPS profile of LATE without co-occurring AD
- Previous work has validated a novel method of identifying individuals who may harbor LATE-NC along the AD continuum *in vivo* using MRI-based hippocampal volumes and Amyloid PET¹
- We assessed BNPS burden in suspected LATE with (AD+sLATE+) and without (AD-sLATE+) AD, AD without suspected LATE (AD+sLATE-), and amyloid negative cognitively unimpaired (Aβ-CU)

Aims & Hypotheses:

- Characterize BNPS reported on the Neuropsychiatric Inventory (NPI) in an imaging-defined sample of suspected LATE, AD, and co-occurring AD+sLATE+
Hypothesis 1: AD+sLATE+ will show a greater burden of BNPS relative to AD-sLATE+ and AD+sLATE-
Hypothesis 2: AD-sLATE+ will show elevated rates of depression relative to AD+sLATE- and AD+sLATE+
- Characterize depression symptoms reported on the Geriatric Depression Scale (GDS) in an imaging-defined sample of suspected LATE, AD, and co-occurring AD+sLATE+
Hypothesis 2: AD-sLATE+ will show elevated rates of depression relative to AD+sLATE- and AD+sLATE+

Methods

Participants

- We included 386 participants from ADNI (Alzheimer's Disease Neuroimaging Initiative) who were identified as AD+sLATE+, AD-sLATE+, AD+sLATE- or Aβ-CU based on hippocampal volumes and Amyloid PET¹
- Quartile-based cutoffs applied to age and ICV-adjusted hippocampal volumes for MCI and dementia
- Segmentations were performed on each participant's T1-MRI scan closest in time to their tau-PET scan⁴

Measures

- BNPS were assessed using the Neuropsychiatric Inventory (NPI)⁵ and Geriatric Depression Scale (GDS)⁶
- NPI domains were summarized using frequency x severity scores

Statistical Analyses

- Aim 1:** Assessed for group differences in NPI total and domain scores using ANCOVAs covarying for age, sex, education, and Global Tau-Max followed by pairwise posthoc comparisons with Tukey's HSD correction
- Aim 2:** Assessed for group differences in GDS total and item endorsement using ANCOVAs covarying for age, sex, education, and Global Tau-Max followed by pairwise posthoc comparisons with Tukey's HSD correction

Figure 1. Imaging-based classification of AD+sLATE+, AD-sLATE+, and AD+sLATE- groups using Amyloid PET status and quartile-based cutoffs for age and ICV-adjusted hippocampal volumes for MCI (light grey bars) and dementia (dark grey bars)

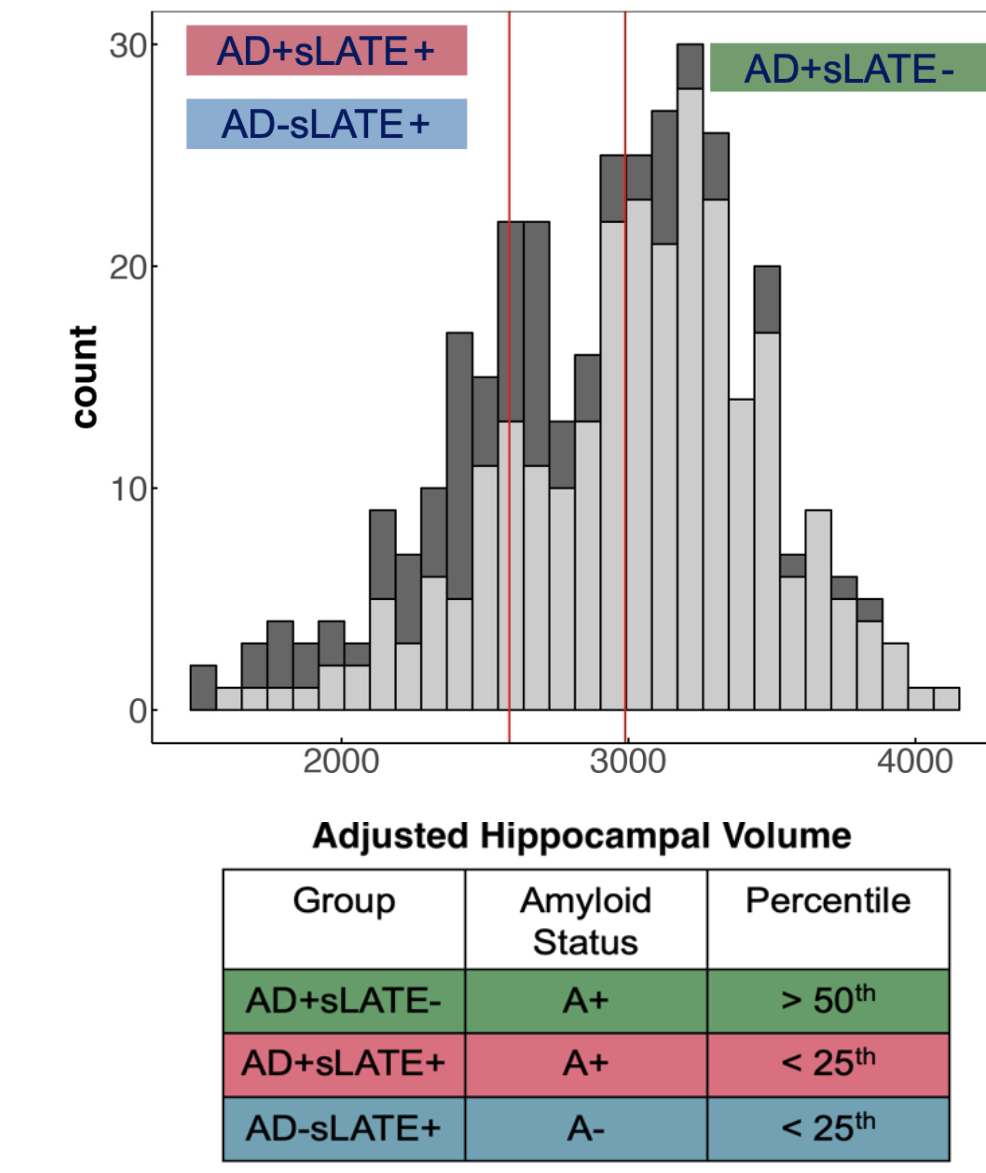


Table 1. Sample characteristics

	AD-sLATE+ (n = 20)	AD+sLATE- (n = 115)	AD+sLATE+ (n = 58)	Aβ-CU (n = 193)
	M (SD)	M (SD)	M (SD)	M (SD)
Age	76.3 (7.7)	75.8 (8.0)	75.1 (8.0)	73.8 (7.1)
Sex (M:F)	15:5	65:80	33:25	110:93
Education	17.4 (2.4) ^d	16.1 (2.5)	15.3 (2.5)	16.3 (2.3)
MMSE	25.9 (2.7) ^d	26.9 (2.6) ^{b***}	23.3 (4.2)	29.0 (1.2)
CDR-SB	3.3 (2.2)	1.8 (1.7) ^{b***}	4.2 (3.1)	0.1 (0.3)
Hippocampal Volume	2075 (292) ^d	3194 (241) ^{b***}	2237 (229)	3282 (361)
Centiloids	-1.6 (11.9) ^{d***}	80.1 (37.1) ^{b*}	97.7 (38.7)	1.2 (9.2)
Global Tau-Max	5.5 (7.8) ^{d***}	21.4 (26.0) ^{b***}	44.2 (30.9)	0.5 (2.0)
MTL Tau-Max	2.5 (3.9) ^{d***}	12.7 (18.6) ^{b***}	30.4 (28.2)	0.4 (1.7)

Note: MMSE = Mini Mental State Examination, CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes, MTL = Medial temporal lobe, NPI = Neuropsychiatric Inventory

a = AD+sLATE+ vs. Aβ-CU, b = AD+sLATE+ vs. AD+sLATE-, c = AD+sLATE- vs. Aβ-CU, d = AD-sLATE+ vs. AD+sLATE+

*p < .05, **p < .01, ***p < .001

Results

Aim 1: Characterize NPI scores in suspected LATE, AD, and co-occurring AD+sLATE+

Table 2. NPI scores by group

	AD-sLATE+ (n = 20)	AD+sLATE- (n = 115)	AD+sLATE+ (n = 58)	Aβ-CU (n = 193)
	M (SD)	M (SD)	M (SD)	M (SD)
NPI Total Score	4.85 (6.94)	4.62 (6.11)	9.90 (12.19)	1.62 (4.75)
Delusions	0.00 (0.00)	0.13 (1.14)	0.34 (1.34)	0.01 (0.14)
Hallucinations	0.00 (0.00)	0.06 (0.42)	0.06 (0.39)	0.00 (0.00)
Agitation/Aggression	0.00 (0.00)	0.20 (0.75)	1.14 (1.94)	0.14 (0.86)
Depression/Dysphoria	0.45 (1.00)	0.36 (0.80)	1.10 (2.37)	0.26 (1.03)
Anxiety	0.40 (1.10)	0.40 (1.44)	1.00 (2.20)	0.12 (0.71)
Elation/Euphoria	0.20 (0.89)	0.04 (0.31)	0.14 (0.66)	0.01 (0.10)
Apathy	1.15 (2.23)	0.55 (1.52)	1.43 (2.59)	0.17 (0.97)
Disinhibition	0.85 (1.90)	0.19 (0.70)	0.41 (1.28)	0.07 (0.61)
Irritability/Lability	0.00 (0.00)	0.66 (1.64)	1.38 (2.25)	0.28 (1.07)
Aberrant Motor Behavior	0.35 (1.09)	0.16 (0.72)	0.84 (2.41)	0.01 (0.07)
Sleep	0.05 (0.22)	1.13 (2.36)	0.62 (1.42)	0.45 (1.45)
Appetite Change	1.40 (2.68)	0.66 (2.14)	1.43 (2.97)	0.10 (0.66)

Figure 2. NPI Total scores by group

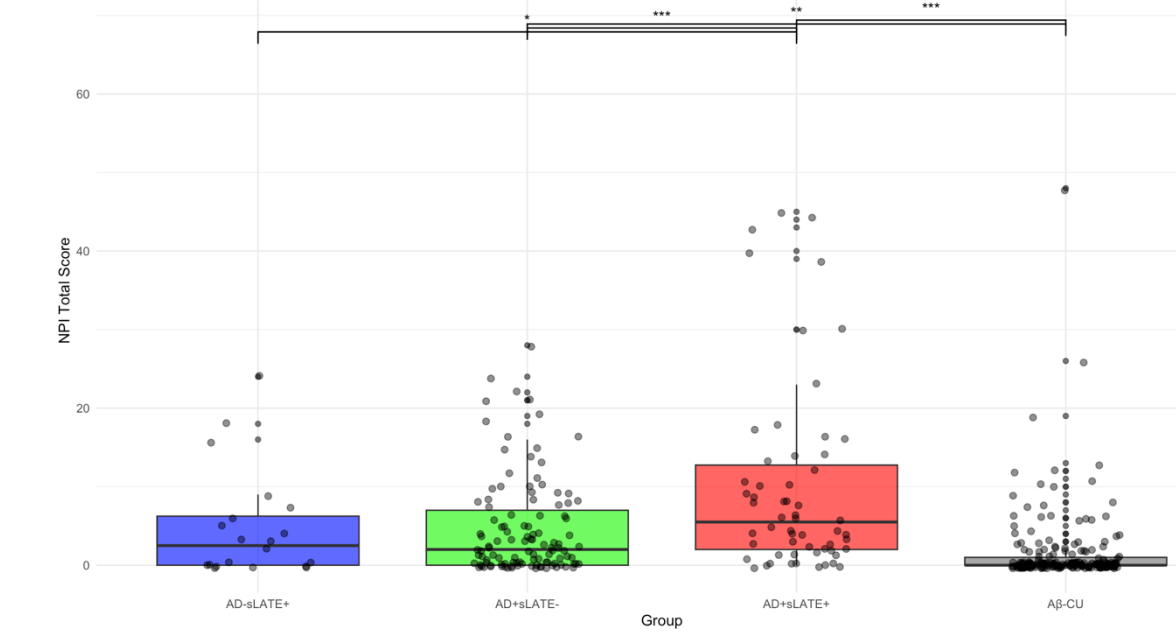
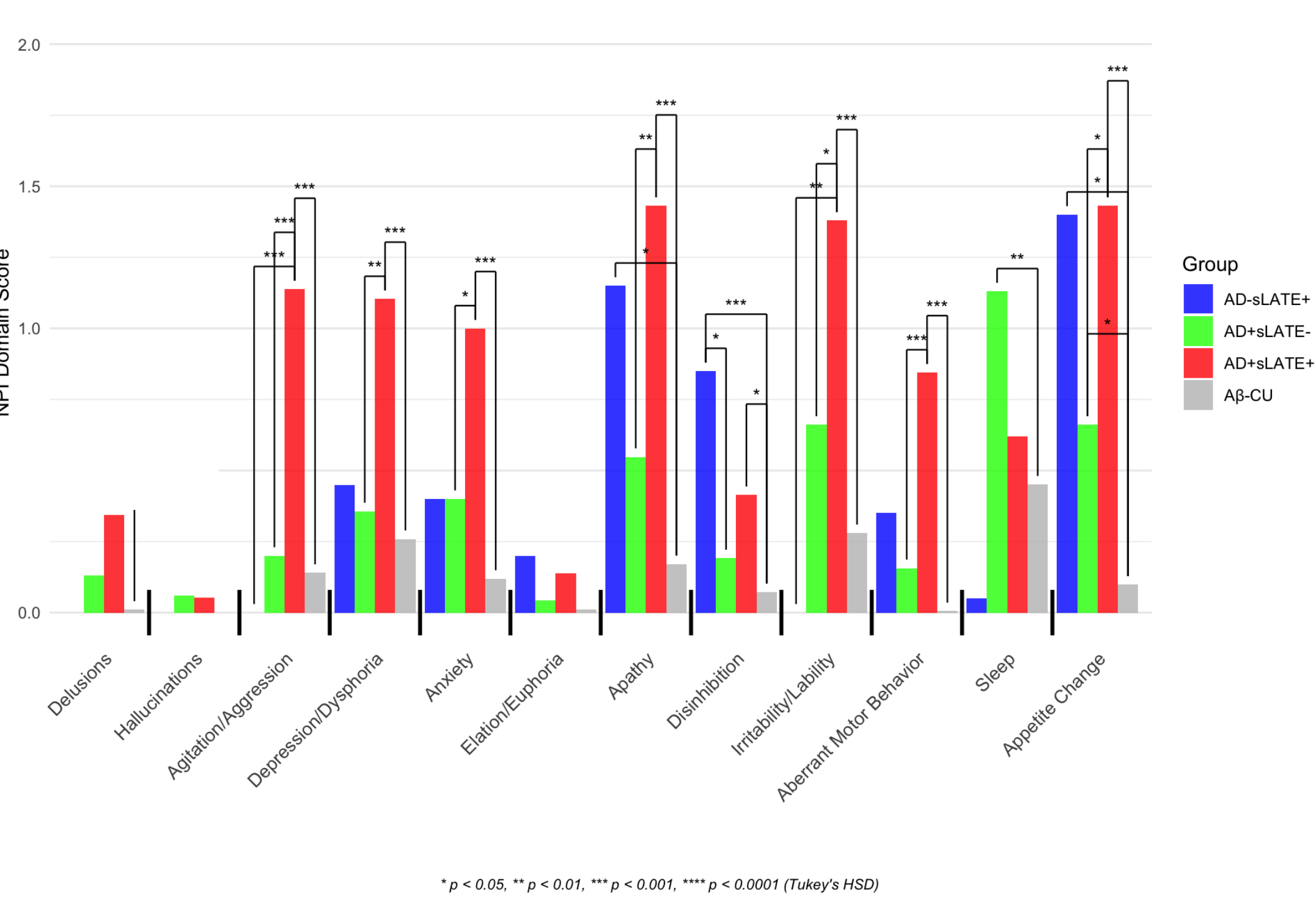


Figure 3. NPI domain scores by group



Aim 2: Characterize GDS scores in suspected LATE, AD, and co-occurring AD+sLATE+

Table 3. GDS scores by group

	AD-sLATE+ (n = 20)	AD+sLATE- (n = 115)	AD+sLATE+ (n = 58)	Aβ-CU (n = 193)
	M (SD)	M (SD)	M (SD)	M (SD)
GDS Total Score	2.20 (2.12)	1.81 (1.73)	1.92 (1.70)	1.11 (1.41)
Are you basically satisfied with your life?	0.00 (0.00)	0.09 (0.28)	0.07 (0.26)	0.05 (0.22)
Have you dropped many of your activities and interests?	0.10 (0.31)	0.25 (0.43)	0.15 (0.36)	0.09 (0.29)
Do you feel that your life is empty?	0.00 (0.00)	0.02 (0.13)	0.04 (0.19)	0.02 (0.14)
Do you often get bored?	0.15 (0.37)	0.13 (0.34)	0.15 (0.36)	0.08 (0.27)
Are you in good spirits most of the time?	0.00 (0.00)	0.03 (0.16)	0.05 (0.23)	0.03 (0.17)
Are you afraid that something bad is going to happen to you?	0.20 (0.41)	0.06 (0.24)	0.15 (0.36)	0.05 (0.22)
Do you feel happy most of the time?	0.00 (0.00)	0.04 (0.18)	0.07 (0.26)	0.07 (0.25)
Do you often feel helpless?	0.05 (0.22)	0.05 (0.22)	0.09 (0.29)	0.01 (0.10)
Do you prefer to stay at home, rather than going out?	0.40 (0.50)	0.23 (0.42)	0.16 (0.37)	0.24 (0.43)
Do you feel you have more problems with memory than most?	0.70 (0.47)	0.54 (0.50)	0.67 (0.47)	0.12 (0.33)
Do you think it is wonderful to be alive now?	0.00 (0.00)	0.04 (0.18)	0.05 (0.23)	0.04 (0.20)
Do you feel worthless the way you are now?	0.10 (0.31)	0.04 (0.21)	0.02 (0.13)	0.02 (0.12)
Do you feel full of energy?	0.30 (0.47)	0.28 (0.45)	0.22 (0.42)	0.28 (0.45)
Do you feel that your situation is hopeless?	0.10 (0.31)	0.05 (0.22)	0.02 (0.13)	0.01 (0.10)
Do you think that most people are better off than you are?	0.15 (0.37)	0.03 (0.16)	0.00 (0.00)	0.02 (0.12)

Figure 4. GDS Total scores by group

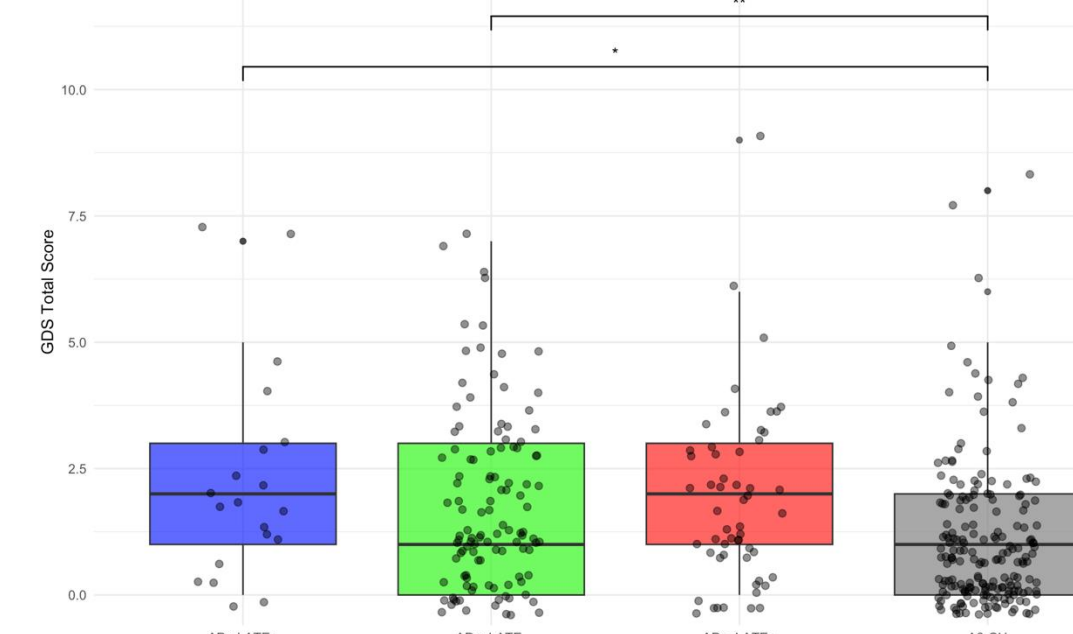
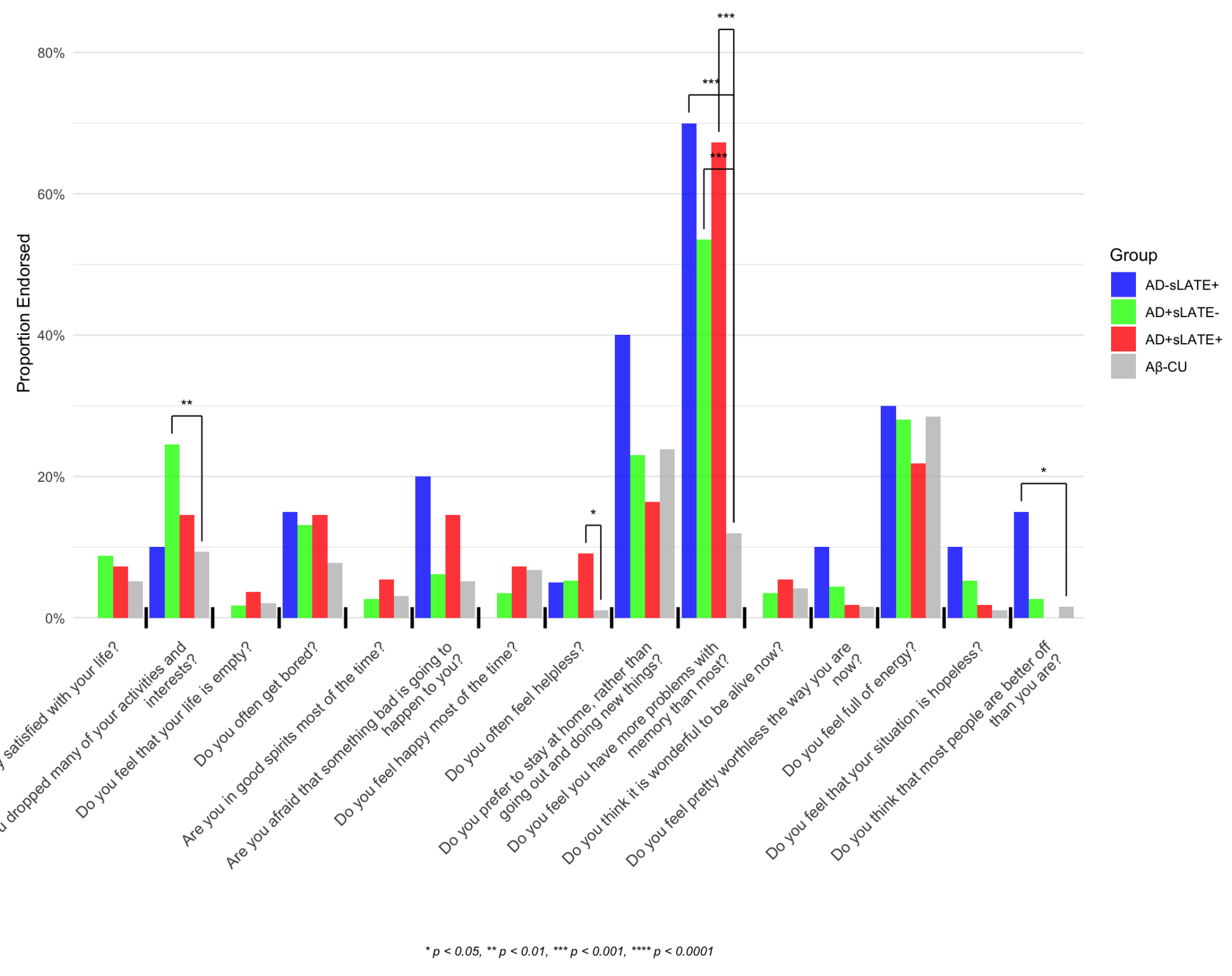


Figure 5. GDS item scores by group



Conclusions

- Co-occurring AD+sLATE+ showed a greater burden of BNPS relative to either pathology alone
 - More frequent and severe symptoms of agitation, depression, anxiety, apathy, irritability, and motor disturbance in AD+sLATE+ illustrate a profile characterized by mood dysregulation (apathy, depression, irritability/lability) and anxious distress with restlessness or compulsive behavior (anxiety, aberrant motor behavior)
- In contrast, AD-sLATE+ showed a lower overall BNPS burden relative to AD+sLATE+
 - Most frequent and severe disinhibition relative to other groups
 - More severe apathy and appetite change relative to controls
 - No reported instances of psychosis, agitation or irritability
- AD+sLATE- had an overall BNPS burden comparable to AD-sLATE+ but showed a distinct underlying profile
 - Less frequent and severe agitation, apathy,
 - More severe sleep disturbance relative to controls
- AD+sLATE+ may explain some previously reported cases of presumed AD+sLATE- with prominent BNPS
- Future studies should assess BNPS in large, autopsy confirmed samples of AD-LATE+ or prospective cohorts of AD-sLATE+ defined using clinical criteria to validate these findings

References

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