

Differences in Cognitive Performance across Atrophy-Defined Alzheimer's Disease Subtypes



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Background: Heterogeneous atrophy-defined subtypes of have been linked to differences in cognitive decline, *APOE4* genotype, and other factors [1]. We sought to define differences in demographic and cross-sectional and longitudinal change in cognition by atrophy-defined subtype in patients diagnosed with dementia due to AD from three cohorts within the Alzheimer's Disease Sequencing Project – Phenotype Harmonization Consortium (ADSP-PHC).

Methods:

- 1978 stable AD participants were included from three ADSP-PHC cohorts, including ADNI, NACC/SCAN, and HABS-HD. 762 of these individuals were confirmed to be A β -positive by PET or CSF. AD patients were divided into four groups based on atrophy patterns following a method modified from [1]. Briefly, AD patients with hippocampal and cortical volume >-0.5 SD relative to CNs were assigned to a minimal atrophy (Min. Atr.) sub-group. Hippocampal to cortex volume ratio was calculated and divided into quartiles. Those in the lowest quartile were assigned considered to be Limbic Predominant (LP), the highest quartile were defined as hippocampal sparing (HpSp). The remaining two quartiles were defined as typical AD (tAD).
- Memory, executive function, language, and visuospatial function composite scores were generated as previously described [2]. Additional cognitive and clinical tests that were common across the cohorts were included (MoCA, Digit Span, Trail Making, CDR) .
- Demographics and clinical/cognitive performance at the first visit diagnosed with AD (baseline for prevalent, first visit with AD diagnosis for incident) were compared between groups using an ANCOVA or chi-square tests, covaried for age, sex, and education where appropriate. Changes in longitudinal cognitive performance (up to 7 years) were assessed using linear mixed effect models, adjusted for age, sex, and education. Analyses were performed in full sample (n=1978) and the A β -positive only subgroup (n=762).

Fig. 1. AD Atrophy Subtypes

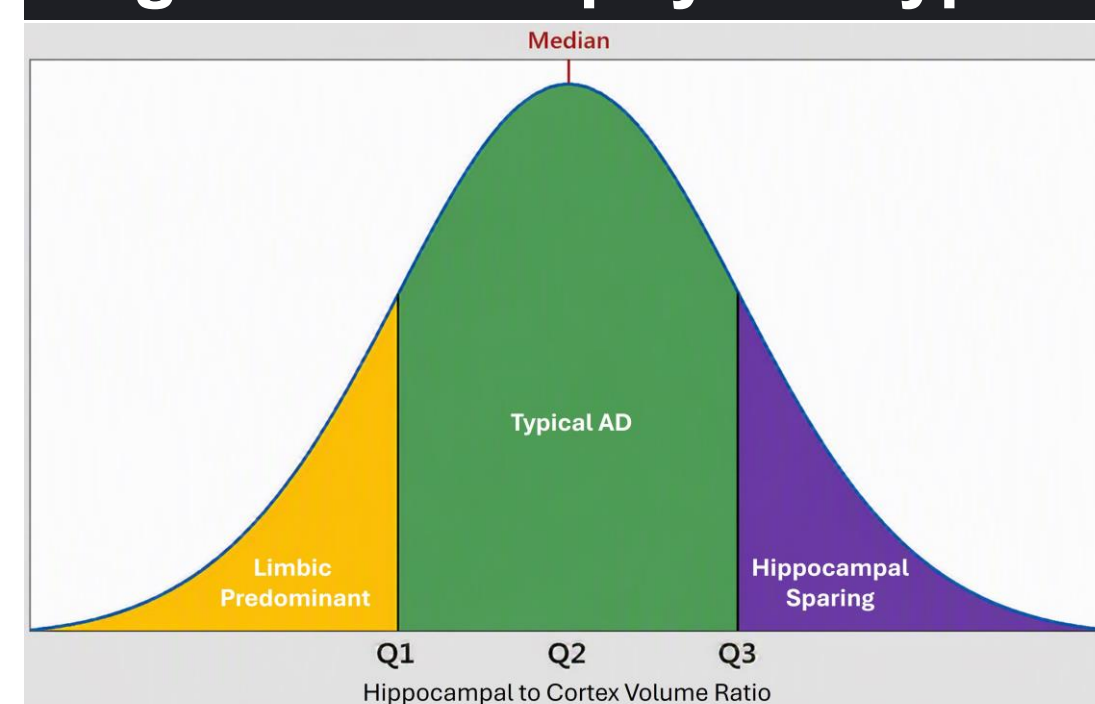


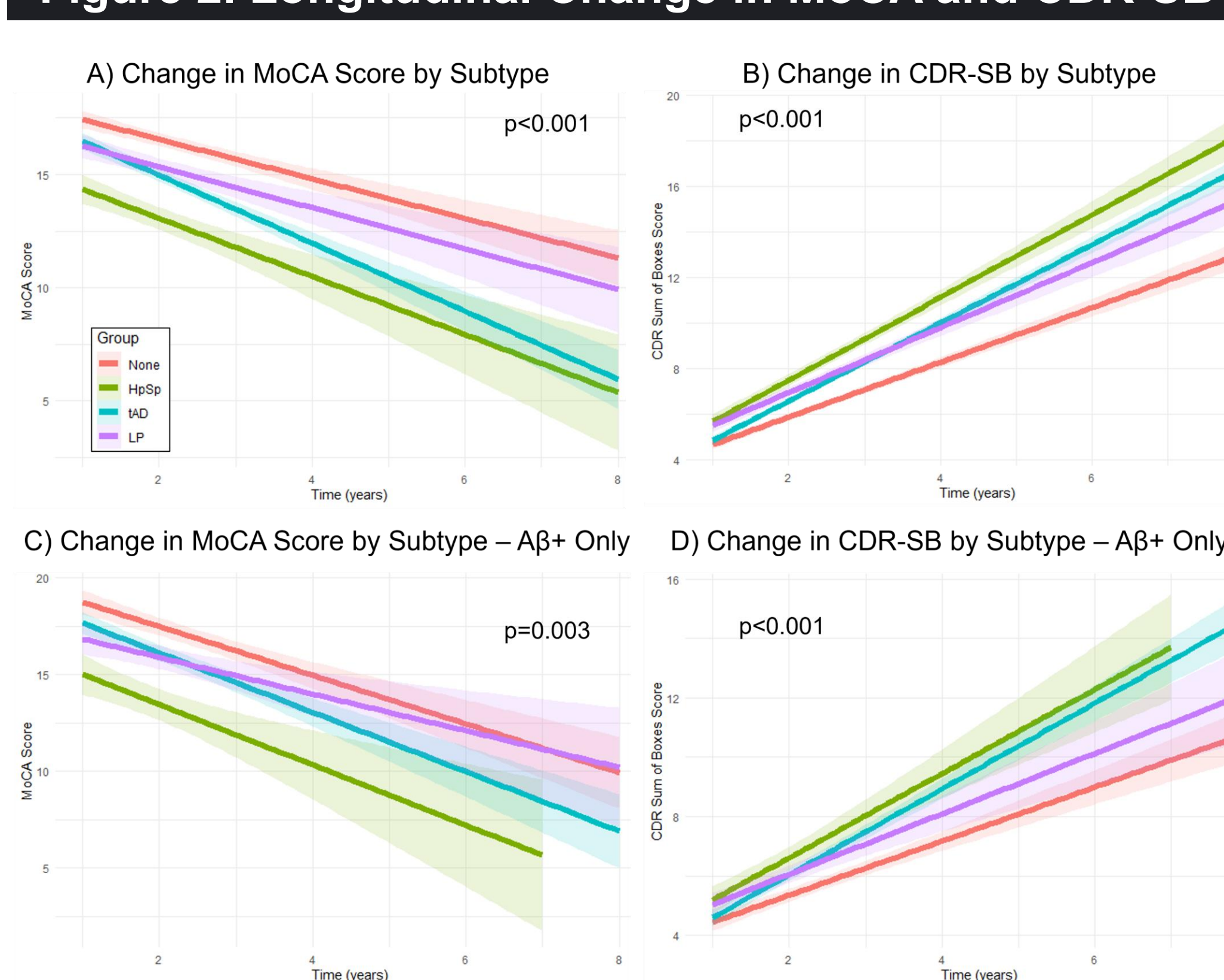
Table 1. Sample Characteristics and Cognitive Performance – Full Sample

¹ Mean (SD); ² Count (%)	Min. Atr.	HpSp	tAD	LP	p	Pairs (p<0.05*)
N	655	329	662	332		*Bonferroni corrected
Age (yrs) ¹	71.4 (9.85)	69.7 (10.4)	74.9 (8.45)	76.4 (7.39)	<0.001	tAD, LP>Min>HpSp
Education (yrs) ¹	14.6 (3.86)	15.3 (3.36)	15 (3.39)	15.2 (3.21)	0.009	HpSp>Min
Sex (Female) ²	321 (49.0%)	165 (50.2%)	321 (48.5%)	146 (44.0%)	0.381	n/a
Race (White, AA, Other) ²	554 (84.6%) 67 (10.2%) 34 (5.2%)	302 (91.8%) 19 (5.8%) 7 (2.4%)	591 (89.3%) 48 (7.3%) 23 (3.5%)	305 (91.9%) 22 (6.6%) 5 (1.5%)	0.003	Min. vs. HpSp, LP
Ethnicity (Non-Hisp.) ²	565 (86.7%)	301 (91.5%)	603 (91.4%)	309 (93.4%)	0.002	tAD, LP, HpSp > Min.
APOE4 Genotype ²	326 (55.5%)	159 (53.0%)	410 (67.2%)	201(65.7%)	<0.001	tAD, LP>Min., HpSp
Memory ¹	-0.60 (0.57)	-0.86 (0.66)	-0.82 (0.51)	-0.99 (0.50)	<0.001	Min.>HpSp, tAD>LP
Executive ¹	-0.44 (0.82)	-0.98 (0.80)	-0.57 (0.72)	-0.37 (0.77)	<0.001	Min., LP>tAD>HpSp
Language ¹	-0.30 (0.67)	-0.6 (0.68)	-0.43 (0.64)	-0.39 (0.63)	<0.001	Min.>tAD, LP>HpSp
Visuospatial ¹	0.13 (0.65)	-0.33 (0.83)	-0.05 (0.68)	-0.02 (0.67)	<0.001	Min.>tAD>HpSp; LP>HpSp
MoCA Score ¹	17.7 (5.25)	14.6 (6.25)	16.6 (5.07)	16.4 (4.78)	<0.001	Min.>tAD, LP>HpSp
Digit Span Forward ¹	6.96 (2.20)	6.28 (2.42)	6.94 (2.09)	7.21 (2.09)	<0.001	Min., tAD, LP>HpSp
Digit Span Backward ¹	4.51 (2.37)	3.54 (2.03)	4.49 (2.08)	4.87 (2.15)	<0.001	Min., tAD, LP>HpSp
Trail Making A ¹	64.10 (38.5)	81.9 (39.9)	67.2 (37.7)	56.7 (34.0)	<0.001	HpSp>LP>tAD; HpSp>Min
Trail Making B ¹	180 (89.2)	240 (78.1)	213 (94.1)	181 (87.4)	<0.001	HpSp>tAD>LP, Min.
CDR-global ¹	0.82 (0.45)	0.97 (0.54)	0.88 (0.46)	0.96 (0.52)	<0.001	LP>tAD>Min.; HpSp>Min.
CDR-sum of boxes ¹	4.42 (2.45)	5.43 (3.09)	4.86 (2.46)	5.39 (2.68)	<0.001	tAD>HpSp, LP>Min.

Table 2. Sample Characteristics and Cognitive Performance – A β + Sample

¹ Mean (SD); ² Count (%)	Min. Atr.	HpSp	tAD	LP	p	Pairs (p<0.05*)
N	239	123	261	139		*Bonferroni corrected
Age (yrs) ¹	73.6 (8.44)	69.3 (9.67)	74.7 (7.94)	76.3 (7.21)	<0.001	LP>Min>HpSp; tAD>HpSp
Education (yrs) ¹	15.7 (3.01)	15.8 (3.45)	15.4 (3.00)	15.4 (2.93)	0.467	n/a
Sex (Female) ²	116 (48.5%)	65 (52.8%)	126 (48.3%)	53 (38.1%)	0.092	n/a
Race (White, AA, Other) ²	226 (94.6%) 12 (5.0%) 1 (0.4%)	115 (93.5%) 8 (6.5%) 0 (0.0%)	247 (94.6%) 12 (5.0%) 1 (0.4%)	133 (95.7%) 6 (4.3%) 0 (0.0%)	0.697	n/a
Ethnicity (Non-Hisp.) ²	226 (95.0%)	115 (93.5%)	247 (95.0%)	133 (95.7%)	0.942	n/a
APOE4 Genotype ²	149 (67.7%)	63 (56.8%)	183 (76.3%)	90 (69.2%)	0.003	tAD>HpSp
Memory ¹	-0.61 (0.50)	-0.92 (0.55)	-0.81 (0.47)	-0.99 (0.48)	<0.001	Min.>tAD>LP; Min.>HpSp
Executive ¹	-0.30 (0.76)	-1.01 (0.83)	-0.52 (0.68)	-0.39 (0.71)	<0.001	Min.>tAD>HpSp; LP>HpSp
Language ¹	-0.11 (0.65)	-0.51 (0.65)	-0.33 (0.62)	-0.32 (0.60)	<0.001	Min.>tAD>HpSp, Min.>LP
Visuospatial ¹	0.12 (0.67)	-0.43 (0.84)	-0.06 (0.69)	-0.10 (0.69)	<0.001	Min., tAD, LP>HpSp
MoCA Score ¹	18.9 (4.72)	15.2 (6.01)	17.8 (4.52)	16.9 (4.73)	<0.001	Min., tAD>HpSp; Min.>LP
Digit Span Forward ¹	7.13 (2.07)	6.58 (2.77)	7.30 (2.06)	7.39 (2.03)	0.427	n/a
Digit Span Backward ¹	4.77 (2.34)	3.25 (2.01)	4.79 (1.87)	4.74 (2.07)	<0.001	Min., tAD, LP>HpSp
Trail Making A ¹	56.4 (32.5)	81 (42.2)	63.4 (35.1)	56.1 (31.5)	<0.001	HpSp>Min., tAD, LP
Trail Making B ¹	167 (84.5)	242 (76.2)	205 (88.8)	180 (83.8)	<0.001	HpSp>tAD>LP, Min.
CDR-global ¹	0.76 (0.39)	0.92 (0.47)	0.84 (0.42)	0.91 (0.51)	0.002	HpSp, LP>Min.
CDR-sum of boxes ¹	4.27 (2.03)	5.11 (2.59)	4.64 (2.01)	4.82 (2.08)	0.003	HpSp>Min.

Figure 2. Longitudinal Change in MoCA and CDR-SB



Results/Discussion:

- AD patients with the hippocampal-sparing atrophy subtype showed poorer baseline cognition and faster longitudinal decline in general cognition (MoCA) and clinical dementia severity (CDR-SB), despite similar levels of dementia severity (CDR-global).
- Cognitive domain performance mapped onto atrophy subtypes, with the hippocampal-sparing atrophy subtype had the poorest performance at baseline in non-amnesic cognitive domains, while the limbic predominant had the poorest memory performance.
- APOE4* carrier status was less frequent in the hippocampal-sparing and minimal atrophy subtypes.
- AD patients with minimal hippocampal or cortical atrophy showed less clinical and cognitive impairment at baseline and slower clinical decline over time.
- Findings were similar in the full sample and in A β + subset.
- These findings support our previous work, suggesting that cortical predominant (hippocampal-sparing) atrophy patterns are associated with faster clinical decline in AD patients AD. Future studies should explore differences in these subtypes on tau PET, as well as neuropathological changes at autopsy to understand the role of other potential pathologies beyond A β and tau pathology.

References:

- [1] Risacher et al. (2017), *Neurology*. PMID: 29070667
[2] Mukherjee et al. (2023), *Neuropsychology*, PMID: 3592573