FOUR-YEAR COGNITIVE DECLINE IN MILD COGNITIVE IMPAIRMENT PATIENTS WITH VARYING BASELINE NEUROANATOMICAL ATROPHY PROFILES: A MEMENTO AND QYSCORE® STUDY.

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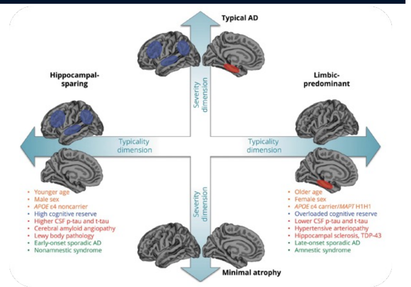
QYNAPSE

BACKGROUND

Three patterns of brain atrophy have been consistently identified in cases of Alzheimer's dementia[1] and may provide important prognostic information about future cognitive decline in mild cognitive impairment (MCI) [2,3]

- limbic-predominant (LP): atrophy of the hippocampus but relatively spared neocortex
- hippocampal sparing (HS): atrophy in the cortex (especially lateral temporal and parietal lobes) but sparing of the hippocampus
- typical/diffuse (TD): atrophy in both hippocampus and cortex



Schematic illustration of brain atrophy subtypes (from ref. [1])

OBJECTIVES

To assess differential patterns of cognitive decline over 48 months in the MEMENTO population using a volumetric quantitative approach to define atrophy subtypes using the automated output of QyScore® an FDA-approved and CE-marked image analysis software[4].

METHODS

IMAGING DATA

- **N=1153 3DT1 images** from mild cognitive impairment (MCI) participants from the MEMENTO cohort were included (Age=71±8, 688 (59%) female; baseline MMSE = 27.8±2.0, CDR-SB = 0.6±0.7)
- **N=461 (40%)** had amyloid status from CSF or PET, with **145 amyloid-positive (A+).**
- Neurodegeneration-positive **(N+) atrophy subtypes (LP, HS or TD**) were defined on individual scans using z-scores from parietal cortex and hippocampus volumes referenced to 1290 cognitively normal individuals using **QyScore® v1.10**
- Volumes were corrected by **intracranial volume** (ICV).

Atrophy subtype	N- (no or minimal atrophy)	LP	HS	TD	TOTAL
Total Cohort	1012	37	84	20	1153
Amyloid positive	114	8	21	2	145

NEUROPSYCHOLOGY DATA AND ANALYSIS

- All **1153** participants underwent cognitive and functional assessments **at baseline** and **48 months**, including mini-mental state examination (**MMSE**), clinical dementia rating scale (**CDR**), Free and Cued Selective Reminding Test (**FCRST**) and Instrumental Activities of Daily Living (**IADL**) scale.
- Linear regression analysis (correcting for age, sex and baseline performance) investigated the relationship between the baseline neuroanatomical subtype and subsequent 4-year cognitive decline. Bonferroni correction was applied.

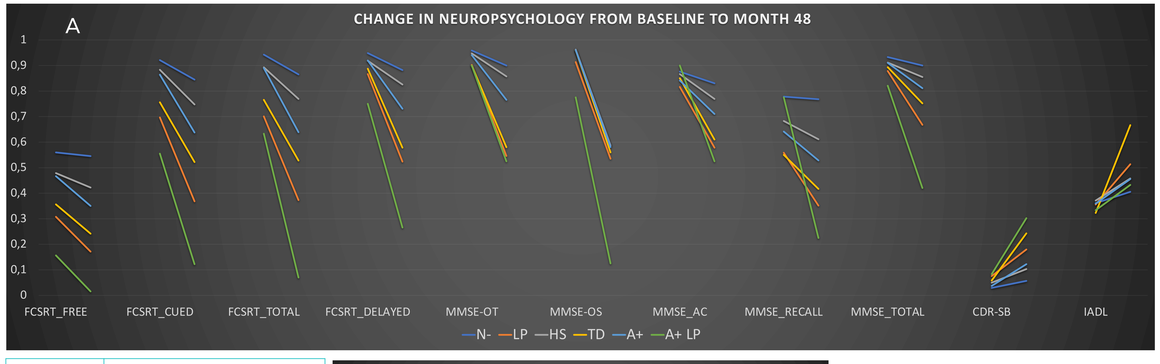
CONCLUSIONS

- This work highlights the utility of quantifying early atrophy profiles in MCI to provide insights into the domains and severity of patient progression over 4 years.

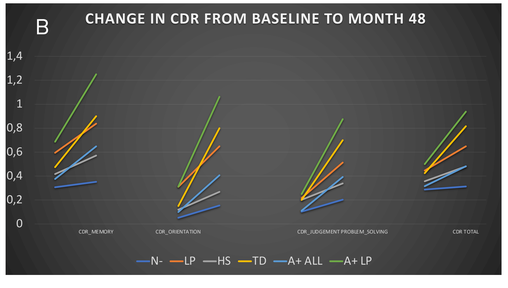
RESULTS

NEUROANATOMICAL PROFILE RESULTS

- At **Month 48**, all subtypes demonstrated significant (***p*<0.001**) decline across **memory, orientation**, and **executive function**.
- Severity of decline varied across subscales and subtype and was particularly **marked in A+ LP individuals** for **memory** and **orientation**.
- IADL remained stable for the N- and TD subgroups.
- 143 participants converted to **AD [N- = 102 (10%), LP = 18 (49%), HS = 15 (18%), and TD = 8 (40%)** subtypes
- Reflecting these fewer relative conversions, **HS** and N- individuals demonstrated the **least decline across all domains** and did not significantly differ on any tests (*p*>0.003 Bonferroni-corrected).
- **LP atrophy subtype** demonstrated the **greatest decline** across all **individual** cognitive domains as well as global CDR and **IADL** (*p*<0.001 compared with N- and HS subtypes).
- Similarly, **TD phenotypes** showed significantly decline across multiple cognitive subscales compared with N- and HS subtypes (*p*<0.001) particularly for orientation and global CDR rating.



FCSRT_FREE	Free recall trial of the FCSRT (Memory)
FCSRT_CUED	Cued recall trial of the FCSRT (Memory)
FCSRT_TOTAL	Total recall trial of the FCSRT (Memory)
FCSRT_DELAYED	Delayed recall trial of the FCSRT (Memory)
MMSE_RECALL	MMSE recall section (Memory)
MMSE-OT	MMSE Orientation in time (Orientation)
MMSE-OS	MMSE Orientation in space (Orientation)
MMSE_AC	MMSE Attention and Calculation (Executive function)
MMSE_TOTAL	TOTAL MMSE score (/30) (Global cognition)
CDR-SB	TOTAL CDR-sum of boxes (Global cognition) *
IADL	TOTAL IADL (functional measure of daily living) *



CDR 0 = no dementia,
CDR 0.5 = questionable dementia,
CDR 1 = MCI,
CDR 2 = moderate cognitive impairment and
CDR 3 = severe cognitive impairment

* Increasing values for all CDR scores and the IADL indicate greater deficit over time in contrast to declining score on the other neuropsychological assessments

References:
[1] Ferriera et al. (2020) Neurology 94:436;
[2] Dufouil et al. (2017). Alz Res Ther 9:67;
[3] Planche et al. (2021) Alz & Dem 17(4):651; [4] Cavedo et al. (2022) Eur Radiol 32(5):2949

Figure 1. A) Mean baseline and Month 48 scores on the cognitive and functional assessments, expressed as % of total possible score for each subscale. B) Absolute mean CDR rating score at baseline and Month 48, all presented by baseline atrophy subtype: N- (no/minimal atrophy), LP (limbic predominant), HS (hippocampal sparing), TD (typical/diffuse) A+ (amyloid positive).