Supratentorial white matter appears to be a better reference region than standard infratentorial regions for longitudinal quantification of [^{18}F]flutemetamol scans

Salvadó G[1], Foley C[2], Grecchi E[2,3], Cardoso MJ[4,5], Lopes Alves I[6], Markiewicz P[5], Falcon C[1], Battle M[2], Lammertsma AA[6], Schmidt M[7], Molinuevo JL[1], Barkhof F[5,6], Gispert JD[1], *on behalf of the AMYPAD Consortium*

1)BarcelonaBeta Brain Research Center (Spain), 2) GE Healthcare (United Kingdom), 3) IXICO (United Kingdom), 4) King´s College London (United Kingdom),
5) University College London (United Kingdom), 6) VU University Medical Center (The Netherlands), 7) Janssen Pharmaceutica (Belgium)

Introduction

Change in amyloid load as measured by PET is a common outcome measure in clinical trials, but they are typically small.

The Centiloid (CL) scale [1] aims to standardize amyloid PET quantification across different tracers and includes four reference regions (RR). Supratentorial white matter (sWM) is not included, but has been proposed as an alternative RR for longitudinal analysis [2,3].

Objective

To compare the performance of different sWM RRs with those of the standard Centiloid method for longitudinal [^{18}F]flutemetamol PET scans.

Methods

Participants: 125 participants from AIBL (Australian Imaging Biomarkers and Lifestyle Study of Ageing) [4] who had MRI and longitudinal PET scans (577±22 days)

Diagnostic groups: Subjects were classified both by:

- Diagnostic group: Cognitively healthy, subjective cognitive decline (SCD), mild cognitive impairement (MCI) or Alzheimer's Dementia (AD)
- Amyloid status: positive if baseline PET CL > 25 [5]

Preprocessing: Cortical SUVr values were calculated from each PET scan using the standard Centiloid pipeline with different RRs.

Reference regions: Three types of RRs were used:

- Atlas-based sWM using different atlases and erosion levels (8)
- Standard infratentorial Centiloid RRs (4)
- Subject-specific sWM based on SPM WM segmentation with successive erosions (5)

Performance:

- Effect size: Cohen's d of SUVr changes (only SCD and MCI participants included)
- Test-retest stability: assessed only in non-accumulators (ΔSUVr < 0.004)[6] and stratified by amyloid status
- Plausibility: the percentage of subjects with a non-negative amyloid change (all subjects included)

Results

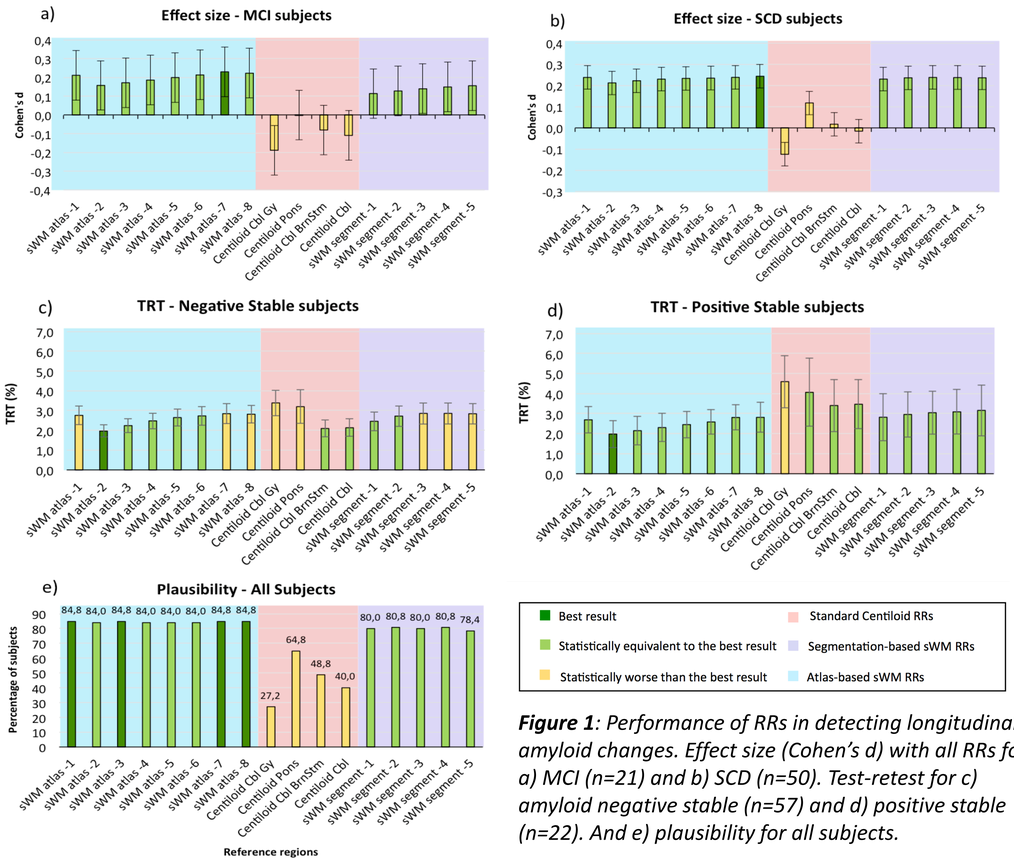

***Figure 1**: Performance of RRs in detecting longitudinal amyloid changes. Effect size (Cohen's d) with all RRs for a) MCI (n=21) and b) SCD (n=50). Test-retest for c) amyloid negative stable (n=57) and d) positive stable (n=22). And e) plausibility for all subjects.*

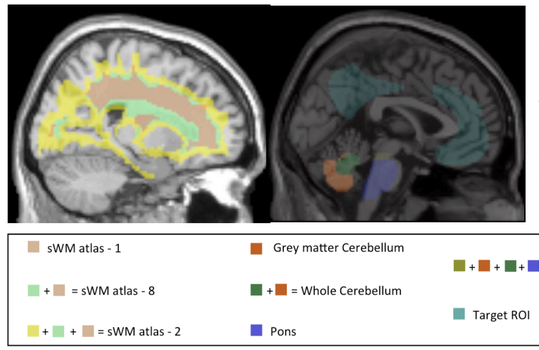

***Figure 2**: Illustration of some of the RRs used. On the left some of the atlas-based sWM and, on the right standard Centiloid RRs and target ROI.*

- Effect size: All sWM RRs showed significantly (p<0.05) larger effect sizes than standard Centiloid RRs in both MCI and SCD (Figure 1a and 1b)
- Test-retest stability: Most sWM RRs showed better reproducibility, but differences did not reach statistical significance against some Centiloid RRs (Figures 1c and 1d)
- Plausibility: All sWM RRs rendered higher % of plausible changes compared to all standard Centiloid RRs (Figure 1e)

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References; [1] Klunk et al., Alzheimer's. [2] Landau et al., J. Nucl. Med., 56(4), 2015. [3] Chen et al., J. Nucl. Med., 56(4), 2015. Dement., 11(1), 2015. [4] Ellis et al., Int. Psychogeriatrics, 22(4), 2009. [5] Villemagne et al., J. Nucl Med. 58(S1), 2017. [6] Jack et al., Neurology, 80(10), 2013.

Discussion

- ✓ sWM RR yields superior statistical performance for detecting **longitudinal change**s in amyloid load as effect size in MCI and SCD participants
- ✓ Further studies should assess the potential influence of **white matter alterations** in amyloid uptake

Contact:
gsalvado@barcelonabeta.org
info@amypad.org
www.amypad.eu

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