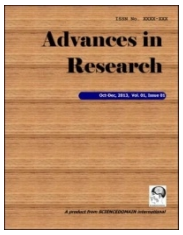

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En Attendant Centiloid

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Short Research Article

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ABSTRACT

Aims: Test the robustness of a linear regression transformation of semiquantitative values from different Aβ tracers into a single continuous scale.

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Study Design: Retrospective analysis.
Place and Duration of Study: PET imaging data acquired in Melbourne and Perth, Australia, between August 2006 and May 2014.
Methodology: Aβ imaging in 633 participants was performed with four different radiotracers: flutemetamol (n=267), florbetapir (n=195), florbetaben (n=126) and NAV4694 (n=45). SUVR were generated with the methods recommended for each tracer, and classified as high (Aβ+) or low (Aβ-) based on their respective thresholds. Linear regression transformation based on reported head-to-head comparisons of each tracer with PiB was applied to each tracer result. Each tracer native classification was compared with the classification derived from the transformed data into PiB-like SUVR units (or BeCKeT: Before the Centiloid Kernel Transformation) using 1.50 as a cut-off.
Results: Misclassification after transformation to PiB-like SUVR compared to native classification was extremely low with only 3/267 (1.1%) of flutemetamol, 1/195 (0.5%) of florbetapir, 1/45 (2.2%) of NAV4694, and 1/126 (0.8%) of florbetaben cases assigned into the wrong category. When misclassification occurred (<1% of all cases) it was restricted to an extremely narrow margin (±0.02 BeCKeT) around the 1.50 BeCKeT threshold.
Conclusion: While a definitive transformation into centesimal units is being established, application of linear regression transformations provide an interim, albeit robust, way of converting results from different Aβ imaging tracers into more familiar PiB-like SUVR units.

Keywords: Alzheimer's disease; the Australian imaging biomarkers and lifestyle study of ageing; Aβ imaging; dementia; centiloid.

ABBREVIATIONS

***AD**: Alzheimer's disease*
***Aβ**: β-amyloid*
***AIBL**: Australian Imaging, Biomarkers, and Lifestyle study of ageing*
***PET**: positron emission tomography*
***PiB**: Pittsburgh compound B*
***FLUTE**: flutemetamol*
***FBP**: florbetapir*
***FBB**: florbetaben*
***NAV**: NAV4694*
***SUV**: standardized uptake value*
***SUVR**: Standardized uptake value ratio*
***BeCKeT**: Before the Centiloid Kernel Transformation*
***Aβ+**: "high" Aβ burden*
***Aβ-**: "low" Aβ burden*

1. INTRODUCTION

Aβ imaging with PET allows accurate detection of Alzheimer's disease (AD) pathology in those neurodegenerative conditions where Aβ plays a role [1]. Aβ imaging also provides unique information on the relationship between brain Aβ and different cognitive parameters as well as genetic, central nervous system or peripheral markers [2]. Researchers often validate their assessments against the amount of Aβ in the brain. Most researchers are

familiar with the 11C-PiB spectrum of SUVR values, and what PiB SUVR constitutes a “high” or “low” Aβ burden.

The introduction of novel F-18 labeled Aβ imaging with their different kinetics and recommended quantification procedures as well as different autopsy-validated SUVR thresholds to determine “high” and “low” Aβ burden, [3-10] highlighted the need to standardize all these results and display them along a single universal scale. A recent publication reports on a three-tracer (PiB, florbetapir and flutemetamol) comparison where, despite having different pharmacodynamic behavior, different quantitative ranges and different degrees of white matter retention, yielded highly correlated and consistent results between them [11]. There is an international effort to establish this single scale under the name of Centiloid [12]. The Centiloid project proposes to perform head-to-head comparison between PiB and all the different Aβ tracers in both young and elderly as well as Alzheimer’s disease patients, aimed at covering the whole spectrum of Aβ deposition. While the Centiloid is established and implemented, large cohort studies like the Australian Imaging, Biomarkers, and Lifestyle (AIBL) study of ageing require both categorical and continuous variables of brain Aβ burden in order to validate biomarker results right now. This cross-validation is crucial for biomarker discovery and being able to display in the same continuous scale estimates of Aβ burden generated using different Aβ imaging radiotracers increases the sample size and the robustness of the findings. Therefore, a linear regression approach to transform the results of each Aβ tracer generated with their own validated quantification method into PiB-like units was adopted.

The purpose of this study was to test the robustness of such linear regression transformations.

2. MATERIALS AND METHODS

Aβ imaging in 633 participants was performed with four different radiotracers: ^{18}F-flutemetamol (FLUTE), ^{18}F-florbetapir (FBP), ^{18}F-florbetaben (FBB), and ^{18}F-NAV4694 (NAV). Written informed consent was obtained from all participants. Approval for the study was obtained from the Austin Health, St. Vincent’s Hospital, Edith Cowan University and Hollywood Private Hospital Human Research Ethics Committees. Participants included in the study underwent positron emission tomography (PET) examinations in either Melbourne or Perth between August 2006 and May 2014. While those participants that underwent FBB PET were enrolled in the Women Healthy Ageing Project (WHAP), the majority of participants were enrolled into the longitudinal AIBL study of ageing which has been described in detail elsewhere [13,14].

Aβ imaging with positron emission tomography (PET) was conducted using either FBP, FLUTE, FBB or NAV. Two hundred and sixty-seven participants underwent FLUTE imaging, 195 participants underwent FBP, 126 participants were scanned with FBB, and 45 with NAV. PET methodology for each tracer has previously been described in detail [3,5,6,10]. A 20-minute acquisition was performed 40 minutes post-injection of NAV, 50 minutes post-injection of FBP and 90 minutes post-injection of FLUTE and FBB. For semiquantitiative analysis, a volume of interest template was applied to the summed and spatially normalized PET images in order to obtain standardized uptake value (SUV). The images were then scaled to the SUV of each tracer recommended reference region to generate a tissue ratio termed SUV ratio (SUVR). A Global measure of Aβ burden was computed using the mean SUVR in the frontal, superior parietal, lateral temporal, occipital and anterior and posterior cingulate regions of the brain. For this analysis, NAV and FBB SUV images data were

normalized to the cerebellar cortex [3,10]. As advocated by the respective pharmaceutical company, the whole cerebellum was the reference region for FBP [4] while for FLUTE the reference region was the pons [8]. In the current study, the SUVR index was also considered as a dichotomous variable. The results generated with the tracer-specific methods were classified as "high" (Aβ+) or "low" (Aβ-) based on each radiotracer neuropathologically validated threshold [7,8,10]. Participants who underwent FBP were considered Aβ+ when SUVR ≥1.11 [7], for FLUTE when SUVR ≥0.62 [8], for FBB when SUVR ≥1.45, [15] for NAV when SUVR ≥1.50 [10] (Table 1).

A linear regression transformation, adapted from reported head-to-head comparisons of each of the tracers with PiB [6,9,10,16] was applied to the respective Aβ tracer SUVR to transform it into a "PiB-like" SUVR unit. Acknowledging the ongoing work aimed at establishing a single universal centesimal scale for all Aβ tracers (Centiloid) [12], these "PiB-like" SUVR were termed BeCKeT (Before the Centiloid Kernel Transformation). As with PiB, a BeCKeT ≥1.50 was classified as Aβ+ [14]. To assess the goodness of the transformation, discordant classification ratios were generated from the comparison between each tracer native categorical classification and the classification derived from the respective transformed data into BeCKeT. Statistical evaluations were performed using a Tukey-Kramer HSD test to establish differences between cohorts. Categorical differences were evaluated using Fisher's exact test.

3. RESULTS AND DISCUSSION

The demographic characteristics of the participants studied with each radiotracer are detailed in Table 1. A total of 568 of 633 (90%) participants underwent PET imaging in Melbourne while 65 participants (10%) were scanned in Perth.

Participants enrolled in WHAP, studied with FBB, were significantly younger and the prevalence of Aβ+ was lower than in those subjects who underwent FLUTE, FBP and NAV (Table 1). The intercept, slope and correlation coefficient for each Aβ tracer is also detailed in Table 1.

Misclassification after transformation to PiB-like SUVR compared to native classification was extremely low, with only 6/633 (0.9%) of all cases -3/267 (1.1%) of FLUTE, 1/195 (0.5%) of FBP, 1/126 (0.8%) of FBB and 1/45 (2.2%) of NAV cases- assigned into the wrong category (Table 1). Moreover, all six Aβ- cases were misclassified as Aβ+, and not the other way around. When this misclassification occurred it was restricted to an extremely narrow margin around the 1.50 BeCKeT threshold. In other words, if values falling above or below 0.02 BeCKeT around the 1.50 threshold (1.48-1.52) were discarded, the agreement between native SUVR and BeCKeT would be 100% for all tracers.

Despite using different reference regions and presenting with different pharmacokinetics and different dynamic SUVR ranges, (Fig. 1) all F-18 Aβ imaging radiotracers are highly correlated with PiB [6, 9-11, 16]. Given the disparity in analytical methods and resulting SUVR for the different F-18 labelled Aβ tracers, we aimed at transforming the respective native SUVR into a PiB-like spectrum of continuous values applying a linear regression analysis to the results of more than 600 Aβ PET studies with four different Aβ tracers: FBP, FLUTE, FBB and NAV (Fig. 1). The dichotomous classification into Aβ+ and Aβ- was essentially the same, with less than 1% discrepancy when using native SUVR or BeCKeT, suggesting that BeCKeT can be used in biomarker discovery and validation until the Centiloid scale can be implemented. Another relevant aspect of this approach is that after

the transformation there is a common threshold to distinguish high or low Aβ burden across tracers, (Fig. 1) where the combination of results from independent samples allows validation or discovery of genetic, cognitive or fluid markers or parameters in a large number of individuals in order to see if the findings are robust to be translated into clinical practice. Furthermore, as accurately pointed out recently [11], the selection of the cut-off value will depend on the needs of the study, either using a lower cut-off to increase sensitivity or a higher one to increase specificity.

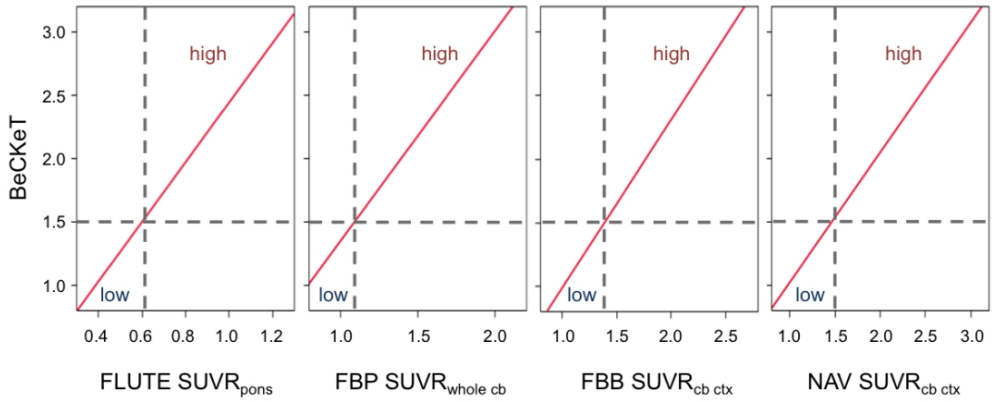

Fig. 1. A common scale and threshold for all Aβ tracers

All available Aβ radiotracers, due to their intrinsic pharmacological and pharmacokinetic characteristics, as well as their recommended analytical methods yield semiquantitative statements of Aβ burden in their own range of values and their particular thresholds. In order to render all this diverse spectra of native SUVR into a single continuous scale (BeCKeT), a linear regression transformation was applied to each radiotracer: FLUTE ($BeCKeT_{FLUTE}$=2.3529x FLUTE $SUVR_{pons}$+0.0802), FBP ($BeCKeT_{FBP}$=1.6667x FBP $SUVR_{wcb}$ -0.33), FBB ($BeCKeT_{FBB}$=1.32x FBB $SUVR_{cbctx}$ -0.3418), and NAV ($BeCKeT_{NAV}$=1.02656x NAV $SUVR_{cbctx}$ -0.0128). When the native categorical classification into Aβ- or Aβ+ for each radiotracer was compared with the classification resulting from the BeCKeT transformation, there were no significant differences (P=1.00) between them, with discrepancy being less than 1%

Table 1. Demographics, transformation parameters and results for four different F-18 Aβ tracers

	FLUTE	FBP	FBB	NAV
n	267	195	126	45
Age	74.4 ± 5.9	74.0 ± 6.2	69.3 ± 2.6*	73.6 ± 8.4
Gender (m/f)	122/145	84/111	0/126*	22/23
Aβ status (%Aβ+) (*based on native SUVR*)	32%	21%	10%*	36%
Reference region	pons	whole cb	cb cortex	cb cortex
Cut-off	0.62 [8]	1.11 [7]	1.42 [16]	1.50 [10]
Reported correlation with PiB	R^2=0.85 [6]	R^2=0.94 [9]	R^2=0.94 [16]	R^2=0.98 [10]
Native SUVR range	0.35 - 1.05	0.70 - 1.70	0.95 – 2.10	1.04 - 3.16
Intercept	0.08	-0.33	-0.342	-0.013
Slope	0.43	0.6	0.76	0.97
Discordant classification (*after BeCKeT transformation*)	3/267 (1.1%)	1/195(0.5%)	1/126 (0.8%)	1/45 (2.2%)

**Significantly different from FLUTE, FBP and NAV cohorts (P = 0.05)*

Abbreviations: FLUTE: flutemetamol; FBP: florbetapir; FBB: florbetaben; NAV: NAV4694; SUVR: Standardized uptake value ratio; cb: cerebellum; PiB: Pittsburgh compound B; Aβ-: low Aβ burden; Aβ+: high Aβ burden

There are limitations in this approach. For example, the linear transformation is based on comparison of elderly individuals that might already have some degree of Aβ deposition, therefore a true “0” for the scale cannot reliably be established. As proposed by the Centiloid project, lack of Aβ deposition is almost certain in young individuals, and their Aβ imaging results will provide a robust “0” for the scale. Another limitation is that a couple of linear regression transformations were derived from limited datasets. It might be possible that those parameters cannot be generalized to other, much larger groups.

4. CONCLUSION

Despite the aforementioned limitations, BeCKeT provide an interim and robust way of transforming SUVR results from different Aβ imaging tracers into more familiar PiB-like SUVR units, but most importantly, allowing integration into a single scale semiquantitative data obtained from different Aβ tracers.

CONSENT

All authors declare that written informed consent was obtained from all participants in the study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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