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Optimizing longitudinal β-amyloid PET measurement: The challenges of intensity normalization

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Accurate measurement of β-amyloid (Aβ) PET tracer retention has become an increasingly important feature of neuroimaging research in Alzheimer's disease (AD). While initial Aβ PET work mostly focused on abnormal/normal (+/-) categorization, the field has moved towards more precise measurement techniques in order to detect Aβ at and even below the positivity threshold in hopes of understanding the initial stages of pathological change as well as points of potential effective intervention. Clinical trials such as A4 using PET to screen for Aβ positivity rely on the definition of an SUVR threshold or threshold range that can identify those who are early enough in the course of disease to still benefit from an Aβ-targeting therapy[1]. In addition, recent research has emphasized the earliest detection of Aβ pathology, how it changes over time, and how it relates to neurodegenerative and cognitive changes[2-6], all of which depend on the accurate and precise measurement of Aβ on a continuous scale.

While the selection of a reference region may appear to be a technical detail in PET image analysis, it has a major influence on Aβ PET SUVRs. Cross-sectional Aβ PET analyses have frequently used cerebellar cortex or the whole cerebellum (white plus grey matter) since these regions are known to be relatively free of Aβ in AD. Few studies have compared PET SUVRs calculated using different regions to one another, but existing work suggests that different reference regions are far from interchangeable[7, 8]. For example, longitudinal florbetapir-PET cortical SUVRs calculated using a whole cerebellum reference region are only minimally predictive of the same cortical change calculated using a white matter (WM) reference region[9]. This reinforces the idea that reference region selection is a methodological decision worthy of careful consideration since it is likely to significantly influence study findings.

For longitudinal studies in particular, where accumulation may be less than 1% per year, the reference region that is selected may determine whether any change is detected at all. Several studies have reported that longitudinal florbetapir-PET[9-11] and PiB-PET[12] SUVRs are more stable and more plausible (e.g. roughly linear, non-decreasing) when the reference region contains WM than when it does not (e.g. whole cerebellum alone). WM may result in more stable signal because it is a larger, less influenced by registration problems or poor regional definition or

segmentation, and less vulnerable to problems with scatter correction due to being close to the edge of the field of view.

On the other hand, WM signal is poorly understood, complicating its utility as a reference region. The majority of Aβ pathology in AD is located in cortex, but Aβ pathology has also been observed in WM[13, 14]. In Aβ PET imaging, tracer retention in WM is frequently as high as in cortex and is considered nonspecific. This WM retention may be explained by slower tracer clearance compared with grey matter[15], tracer lipophilicity[16], and the β-pleated sheet structure of myelin binding protein[17]. However, PIB retention is also reduced in WM lesions[18, 19]. Importantly, these factors are ligand-specific, and could account for differing proportions of WM signal depending on which ligand is used. Furthermore, isolating WM from cortical signal is challenging because of their proximity to one another; elevated signal in cortex can influence WM signal and vice versa.

The lack of a gold standard for longitudinal measurement also makes evaluation of the "correct" reference region challenging. Nonetheless, stability of a reference region stability over time and over the course of disease is a critical feature. In this issue, Lowe and colleagues perform an unusually comprehensive set of PiB-PET analyses to determine whether WM is an acceptable reference region for measuring cortical PIB retention across the spectrum of disease and Aβ burden[20]. The authors use both cross-sectional and longitudinal analyses across the spectrum of disease to show that WM retention (but not cerebellar crus or whole cerebellum retention) increases with age and at moderate levels of cortical Aβ (SUVR of about 1.9-2.1).

The authors performed several critical analyses to examine cortical and WM regions separately and ensure that there was minimal contamination between signal these regions that would complicate interpretation of the behavior of WM tracer retention. First, they performed two-compartment partial volume correction, which adjusts for the influence of CSF on neighboring WM or grey matter, but not for the influence of WM on grey matter or vice versa. To address the latter issue, the authors examined periventricular WM separately from the rest of subcortical WM, since periventricular regions are far enough away from cortex to eliminate the influence of cortex on WM via partial volume effects. Compared with subcortical WM that neighbors cortex, periventricular WM regions were less elevated with older age and at moderate levels of cortical Aβ, supporting the assumption that rising cortical Aβ contributes to the observed WM signal elevations. However, importantly, elevations in periventricular WM were still significant, so these elevations seem to be independent of cortical signal. Finally, they examined WM SUVs (using participant weight and injected dose) in order to verify that the SUVR increases they observed in WM (in this case, as the SUVR numerator or target region) were not driven by reductions in cerebellar grey matter (the SUVR denominator).

There are a several important implications of these results. First, while the study cannot determine the neurochemical basis of WM binding, the pattern of findings is consistent with the possibility that slower clearance in WM accounts for increased WM signal, since this would be expected to worsen with age. On the other hand, the findings argue against the idea that

reduced signal associated with WM lesions (such as WM hyperintensities) have a major influence WM retention overall, since we would expect to see age-related reductions in WM retention accompanying age-related increases in WM hyperintensities, instead of the increasing, age-related WM retention that was observed. More importantly, the findings indicate that instability of WM over time could compromise longitudinal cortical PIB measurements when a WM reference region is used, perhaps underestimating cortical increases at older ages and for those with moderate Aβ burden. On the other hand, the authors acknowledge that problems in cortical longitudinal PIB SUVR measurement due to WM instability are likely to be minimal for studies lasting just a few years (which is the majority of Aβ PET studies). For these shorter studies, the reduction in variability resulting from using a larger WM reference region might exceed the drawback of the WM instability.

Examining the behavior of WM binding of other ligands and other samples will be critical for continuing to optimize longitudinal PET measurement in future AD research and clinical trials aimed at screening for the presence of Aβ and tau, and tracking longitudinal changes in this pathology over time. Aβ PET has had a head start in defining tools and strategies for accurate measurement that may also eventually benefit tau PET despite the initial challenges of greater regional specificity and complex patterns of off-target binding[21].

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