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Short Communication

Reference Region Normalization in Amyloid and Tau Imaging with Positron Emission Tomography (PET)

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Abstract

Tau and amyloid imaging with positron emission tomography (PET) will play an increasingly important role in the design of Alzheimer's disease trials, both for the subject stratification and to evaluate the biological effects of drugs. Clinical PET acquisition protocols utilize short static scans with no arterial blood sampling. These images are normalized by a reference region's activity before semi-quantitative regional or voxel-based analyses. The selection of an appropriate reference region for PET normalization is a critical factor for data interpretation. This study provides an overview on some of the challenges associated with PET normalization process in Alzheimer's disease.

Short Communication

Pathological biomarkers of Alzheimer's disease (AD), such as amyloid beta plaques (Aβ) and neurofibrillary tau tangles, will play an increasingly important role in the design of AD trials to identify appropriate subjects and to track the effects of drugs. For instance, Aβ biomarkers have helped to identify Aβ+ individuals, thus presumably on the AD trajectory, and improved the ability of more recent trials to detect anti-Aβ treatment effects [1]. Abnormal levels of Aβ and tau can be detected with the analysis of the uptake of layer-specific PET tracers, such as [^{18}F] Florbetapir [2], [^{11}C]PIB [3], [^{18}F] Flutemetamol [4], [^{18}F] Florbetaben [5] for Aβ and [^{18}F] T807 (AV-1451) [6], [^{11}C] PBB3 [7], [^{18}F] THK5317 [8] for tau. Aβ/tau-PET images are normalized by a reference region's activity. The PET intensity normalization process is a simple way of determining activity in PET images and allows semi-quantitative comparisons between different scans and subjects. These normalized images serve as starting points for subsequent analyses. PET data analysis techniques can be as simple as the regional/global mean of standardized uptake value ratio (SUVR) [9] or sophisticated data-driven, voxel-based analyses [10-12] or machine learning diagnostic techniques [13], which have found wider applications in research settings than in routine clinical diagnosis. Most clinical Aβ-PET images are visually assessed by trained experts [14]. However, quantitative methods will continue to play an increasingly important role in AD trials.

In the past, Aβ-PET studies in AD used cerebellum as the reference region. Price and colleagues [15] showed that in amyloid-negative subjects, the pharmacokinetics of [^{11}C] PIB in the cerebellar gray matter are similar to the cerebral gray matter target regions. This pharmacokinetic similarity was one of the main factors for the selection of cerebellum as the reference region in previous Aβ-PET studies. However, recent research with Florbetapir [16-19] has found variabilities associated with the cerebellar normalization of PET images, presumably due to the location of the cerebellum, which falls on the edge of the scanner's axial field of view (FOV). Pathological effects could also contribute to the cerebellar amyloid uptake. Based on the Braak staging [20], the cerebellar amyloid deposit is present in stage three. Knight and colleagues [21] reported increased cerebellar retention of [^{11}C] PIB in presenilin-1 (PS1) mutation carriers. Catafau and colleagues [22] used post-mortem immunohistochemistry on 64 AD subjects and nine non-demented volunteers to demonstrate parenchymal and vascular Aβ deposits in cerebellum and determine their impact on [^{18}F] Florbetaben SUVR values. While they found diffuse plaques in 6% and vascular Aβ in 25.3% of their samples, the effect of cerebellar plaques on cortical SUVRs appeared to be negligible in this study. In comparison to cerebellar gray matter, the clearance of [^{11}C] PIB in the pons and subcortical white matter (WM) is different than in cerebral gray matter target regions. Nevertheless, The utilization of white matter (and pons) as an alternative reference region has reduced variabilities in the longitudinal progression of Aβ-PET retention [16-19], improved discrimination power between subject groups [16] as well as increased the association between Aβ-PET and clinical decline [17] and cerebrospinal Aβ1-42 [19].

Several cross-sectional tau-PET studies [6] have used cerebellar gray matter as the reference region. Given that longitudinal studies are of particular interest in tau imaging, the selection of cerebellum as the reference region for tau can obscure the subtle longitudinal changes in tracer uptake due to the additional noise created by its axial position in the scanner. While WM can be used as an alternative reference region in tau-PET to reduce the scan-to-scan variability, there are potentially other problems related to WM normalization. These include the presence of physiological and structural damages that can influence the non-specific uptake of amyloid [23,24] and possibly also tau radiotracers. For instance, Veronese and colleagues [24] showed that [^{11}C] PIB uptake is sensitive to myelin changes in both preclinical models and humans. WM damages are prevalent in the aging population and are related to vascular risk factors, cognitive impairment and dementia [25]. Therefore, the utility of WM as a PET reference region may depend on its structural and functional integrity, which can vary among individual subjects. WM damages appear as hyperintensities on T2-weighted, proton density and fluid-attenuated inversion recovery sequences (FLAIR) of magnetic resonance imaging (MRI). Other advanced MRI imaging techniques, such as Diffusion Tensor Imaging (DTI) [26,27] can provide additional information on the micro structural integrity of the white matter by measuring fractional anisotropy (FA), which reflects the diffusion directionality

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and mean diffusivity (MD), which shows the magnitude of water diffusion. DTI-MRI techniques can detect decreased structural integrity in normal-appearing white matter (NAWM) surrounding white matter hyperintensities [28]. Partial volume effects pose additional challenges to WM normalization, particularly in tau-PET imaging. Unlike amyloid tracers, tau retention in gray matter spreads into the nearby white matter, and the PET spatial resolution is too poor to separate the gray matter contribution from the white matter signal [29]. The presence of other pathophysiological conditions could also impact the non-specific radiotracer uptake in both cerebellum and WM. For instance, a history of traumatic brain injury (TBI) may pose an additional challenge to cerebellar normalization due to the increased likelihood of Aβ accumulation in the cerebellum of TBI subjects [30]. After age, family history, and APOE-ε4, TBI is the strongest risk factor for AD [31,32]. TBI affected subjects, such as Veterans and retired athletes will be increasingly recruited into AD drug trials. Therefore, cerebellum may not be a suitable reference region for this population. The binding characteristics of amyloid/tau radiotracers in the study of WM diseases are not entirely understood. There is a need for further studies related to this topic. Additional MRI scans to evaluate WM damages in individual subjects would be a good idea in clinical trials. Recent work by Fleischer and colleagues [33]. Found that the longitudinal percent change between placebo and solanezumab groups was not significant when cerebellum was used as reference region but became significant when the subcortical white matter was used as the reference region. This study is a good example of where the detection of damaged white matter regions (e.g. due to ARIA-E [34]) and their exclusion from the reference region ROI could further increase the effect size between treatment and placebo groups.

In summary, we have identified that the PET normalization process is a critical challenge for Aβ/tau-PET imaging in the aging population and Alzheimer's disease. One alternative solution would be to eliminate the reference region normalization from semi-quantitative PET studies. For amyloid imaging, this can be done by using topographic techniques, such as weighted two-point correlation functions [19], Haralick features [35], and peak cortical laminar deposition [36] that can be performed on non-normalized PET images. The idea behind these techniques is based on previous pathological observations on the spatiotemporal progression of amyloid in AD. For instance, from studies by Bruce and colleagues [37], we know that over the time the progressive amyloid deposition encompasses a greater extent of cerebral cortical laminae. The same pattern of progression is observed in PET radiotracer uptake, which starts from the interface between gray matter and white matter and gradually expands toward the brain surface.

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