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Hot topic: Exploiting the Full Potential of Beta-Amyloid and Tau PET Imaging for Drug Efficacy Testing

Short running foot line: Amyloid and Tau PET for Drug Testing

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The feasibility of acquiring clinically relevant histopathological information on critical underlying amyloid and tau pathology in Alzheimer's (AD) and related diseases is the reason why therapeutic trials now incorporate PET imaging biomarkers in the vast majority of studies. Specifically, PET is used to assess eligibility for inclusion in trials, as 15-30% of clinically diagnosed AD participants may have no demonstrable brain amyloid or tau deposition, the very targets of treatment. Furthermore, PET imaging is used to longitudinally monitor both disease-related changes in AD brains and effects of a drug on the biological target of interest [1].

Although longitudinal studies require both high precision and quantitative accuracy of the PET signal, there is a vigorous ongoing debate on how these PET studies should be carried out and what kind of PET measures should be generated. This debate is based on the fact that PET is capable of deriving - depending on the data acquisition and analysis protocols used - a wide spectrum of quantitative measures of different quality. This ranges from semiquantitative tissue ratios (a static measure at a certain time-point after tracer administration relative to a reference region) such as standardized uptake value ratios (SUVR), to fully quantitative data on the regional concentration of amyloid or tau aggregates that can be expressed as binding potentials, distribution volumes/distribution volume ratios (DVRs) or rate constants. The latter are derived from dynamic brain scans, using either non-invasive (reference region) or invasive (arterial blood sampling) tracer input information, and by applying pharmacokinetic compartmental models.

To decide on what kind of quantitative amyloid/tau PET parameters are used for drug efficacy testing, different aspects need to be considered. On the one hand one may advocate fully validated quantification (using a dynamic scan protocol together with tracer kinetic modelling) as the optimal measure of amyloid/tau for assessing drug effects. On the other hand, based on both patient comfort and scanning costs, a short static scan protocol may be attractive. Finally, there is the desire of pharmaceutical companies to optimize the cost/benefit ratio of trials and to acquire scientifically strong and regulatory robust data that can support a potential filing for approval. These different perspectives require a compromise in order to maximize robustness

and reliability of the outcome data, whilst minimizing discomfort to the patient/costs. So far, in most studies, longitudinal SUVRs have been employed to determine pathological burden at baseline and after treatment. Here, we (an international group of amyloid and tau PET imaging and PET quantification experts) would like to provide a critical appraisal of this approach, and present some arguments on how to achieve a compromise that ensures robust, reliable and reproducible measures of pathological burden in the brain.

The SUVR has the seductive advantage of being simple to determine from a static short (15-20 min) scan. Consequently, it is less sensitive to head movements and indeed allows for higher patient throughput, i.e. reduced scanning costs. Nevertheless, important drawbacks are (i) the lack of an appropriate input function (i.e. delivery to tissues), (ii) its sensitivity regarding the scanning time-window used due to the fact that the tracer might not reach apparent steady-state as it happens with some amyloid and most tau PET tracers, and (iii) the inability to correct for confounding effects (e.g. it is not possible to distinguish between specific and non-specific uptake). As a result, SUVRs are vulnerable to changes in blood flow affecting tracer delivery and clearance, changes that can be induced directly by the treatment drug itself, as a consequence of the response to treatment, or as a result of the progression of disease. Furthermore, the lack of an input function precludes accounting for the likely drug-induced changes that might affect tracer delivery to the brain, such as changes in tracer metabolism, blood brain barrier permeability, or peripheral binding. Investigating this issue, van Berckel et al. (2013) found that changes in [^{11}C]PiB SUVR over time differed from those parameters derived from the gold standard kinetic modeling. This discrepancy was attributed to longitudinal changes in blood flow [2]. Although this may not have a strong effect in normal elderly controls, brain perfusion progressively becomes impaired in dementia patients, adding to the concern related to the use of SUVRs in longitudinal amyloid and especially tau PET imaging, where reductions in SUVR may be due to changes in these confounding effects rather than real changes in brain target density.

Semi-quantitative and even visual (qualitative) methods are valid techniques to demonstrate brain amyloid or tau deposition, which can serve as an inclusion criterion for clinical trials. Nevertheless, given the confounding effects mentioned above, it is strange that subsequently the same methods have also been used in longitudinal studies without critical assessment of their validity. We strongly believe that these simplified methods can only be used in longitudinal studies after proper validation against corresponding gold standard kinetic modeling measures. In principle, this validation needs to be repeated for each new drug, as confounding effects may be drug-dependent. This validation should also include determination of test-retest variability for the various PET parameters. Only then is it possible to determine if a simplified approach can be used. In addition, it allows for an appropriate power calculation concerning the study cohort size required to answer the trial question, and consequently to come to a scientifically reasonable and ethically justifiable study design [3]. Of note in this regard, the AMYPAD disease modelling group recently discovered that the use of DVRs can, as compared to SUVRs, reduce the sample size needed to detect longitudinal amyloid changes by around 40% in amyloid-negative populations [4], suggesting DVRs are much more sensitive to detect small amyloid changes over time than SUVRs. These results validate the approach and make it even more economically attractive to pharmaceutical industries, which are sometimes risking significant financial resources on unreliable outcome measures. Proper amyloid or tau PET drug efficacy testing protocols would at least shield against valid criticism of some trial reports, as were occasionally published in the past [5].

In therapeutic trials, as a viable alternative to static SUVRs to report on amyloid or tau PET or in those cases where it is not possible to perform fully dynamic imaging for kinetic modeling, dual time-window protocols should be employed (Figure) [6,7]. Here, it is - depending on the tracer used - only necessary to acquire PET data early after tracer administration and again at a later time-point, after a “coffee break”. The missing data on the in-between tracer dynamics is then interpolated from the information measured at the above two time-windows. This approach

allows for full quantification, including determination of a non-invasive reference tissue input function. At the same time, the overall length of the scan can be reduced significantly, thus minimizing patient discomfort. This approach is logistically feasible for most dementia patients while still providing robust high-quality quantitative drug efficacy outcome measures, and with the potential of higher patient throughput on the PET scanner compared to full dynamic scans.

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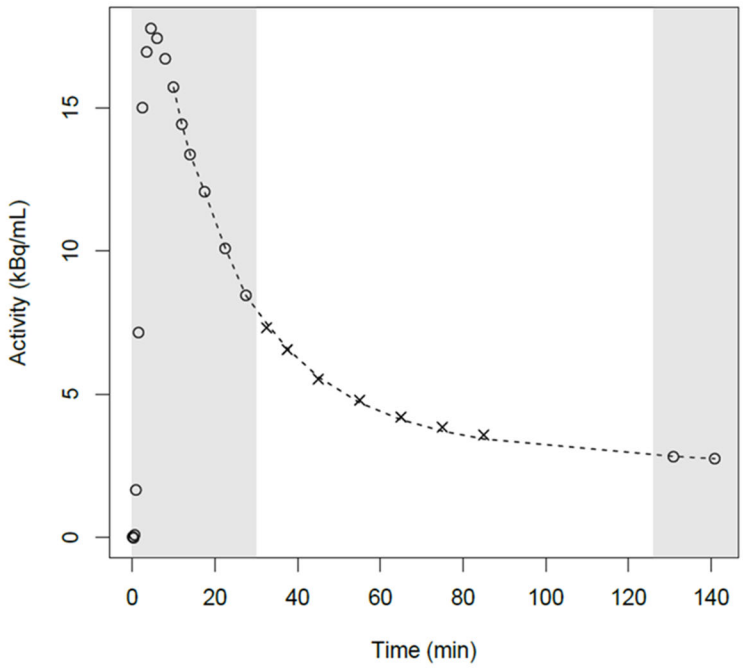
Figure



Example of a so-called "coffee break" or dual time-window imaging protocol, in this case for an [^{18}F]florbetaben amyloid PET scan. The grey-shadowed time windows represent the significantly shortened (as compared to full dynamic imaging) scan times for the patients, while the data in the in-between interval are interpolated. This protocol increases patient compliance, whilst still providing full-quality quantitative data. It even allows for high patient throughput via interleaved patient scheduling on the PET scanner. Figure taken from [6].