

Brain imaging in early diagnosis and monitoring treatment effect in dementia disorders*

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There has recently been a surge of investigations assessing the use of brain imaging in diagnosis and monitoring treatment effect in dementia disorders. In addition, major new methods to image brain pathology in vivo such as amyloid markers have been developed, and although their clinical utility has not yet been subjected to extensive investigation, they hold considerable promise. In what follows the main findings but also the main issues related to applications of structural MR, PET and SPECT will be summarized.

Applications of brain imaging to dementia diagnosis raise some general issues, mainly the existence of significant overlap among the main types of dementias (e.g. Alzheimer's disease (AD) and vascular dementia (VD), AD and Lewy body dementia (LBD)), and the fact that the vast majority of the dementias represent simple acceleration of "normal" age-related processes. It also raises issues more specifically related to imaging, mainly :

- 1) the lack of specificity of imaging markers - be it hippocampal atrophy, perfusion, glucose metabolism, alterations in neurotransmitters or even amyloid - to dementia subtypes and aging
- 2) the pathology long predates the clinical manifestations, probably because of compensatory processes, involving the risk of "incipient pathology" in "normal" aged people;
- 3) disease definition is in principle pathological, but pathological confirmation is rarely possible because of the long wait, especially in studies of early diagnosis, exposing to the risk of large drop-out and co-morbidities as time elapses.

Finally, the diagnostic value of a given imaging modality should in principle be tested against clinical, neuropsychological and other more routine imaging data, in other words the question should be what is the 'added value' of the particular imaging modality, rather than its value separately from other more simple and readily available information. This however involves rather difficult studies to complete.

Studies of early diagnosis in mild cognitive impairment (MCI) aim to predict conversion to clinically-probable AD (cpAD). The valid target here is by comparing converters to non-converters since otherwise differences with normal subjects may be present in both groups. Specific issues involve:

- 1) which MCI subtype to study, i.e., 'amnesic' (aMCI) or 'multiple-domain', knowing that they represent distinct topography of pathology so although merging them may represent the 'real-world', it entails a loss of accuracy
- 2) what length of follow-up (F/U)? Since more MCI will convert with longer F/U, the F/U should depend on the scientific aim, and F/U for studies intended for drug trials should be realistic (e.g. 18 months), while studies aiming to detect incipient AD should be longer (e.g. 5 years).

These caveats in mind, volumetric studies published [1] so far have shown that hippocampal atrophy has a significant but small added predictive value over and above neuropsychological data and age, due to the overlap with normal aging. However, adding entorhinal cortex and considering other neocortical particularly temporal and fusiform regions markedly improves specificity, with reported accuracies up to 96%. This specificity of neocortical, particularly temporal, regions in predicting conversion has been confirmed in mapping studies such as Voxel-based morphometry (VBM), which serve as hypothesis-generating for future volumetric studies [2,3]. A different approach uses annual rates of atrophy, which appear to have good predictive value. Although the latter requires serial MRI with sophisticated co-registration and image analysis, it could be useful in drug studies when a long wash-in period is feasible.

Hypometabolism (FDG PET) and hypoperfusion (SPECT) in the left or right temporo-parietal association cortex and/or posterior cingulate region have been consistently shown to have significant added predictive value for aMCI conversion over and above cognitive tests, APO-E genotype and hippocampal volume, using either ROIs or voxel-based methods [4]. Recent reports using the PET amyloid ligand PIB indicate a robust difference in tracer retention in neocortical areas in AD brain compared to healthy controls [5]. MCI shows an intermediate PIB retention between AD and healthy controls [6,7]. The PIB retention in MCI converters was as high as AD while the non-converters showed low PIB retention comparable to healthy controls [6]. The mixed amyloid-tau ligand FDDNP has also shown an intermediate uptake in MCI brains compared to healthy controls [8]. Further studies with different amyloid ligands in AD and MCI patients are expected.

Studies assessing the value of imaging in improving the diagnosis of mild cpAD or possible AD as compared to other dementias have almost exclusively focused on volumetric measures of hippocampus of medial temporal lobe (MTL), showing overall the expected poor specificity and sensitivity of this variable, since hippocampal atrophy is also present in other dementias in part because currently memory impairment is required in the criteria for dementia [2]. However, lack of MTL atrophy has a high negative predictive value for AD, which is clinically useful as well as for drug trials. The pattern of neocortical hypometabolism in FDG PET and to a lesser extent perfusion SPECT have been shown to have significant added value in differentiating AD against any type of dementia as well as specifically against LBD and frontotemporal dementia (FTD) in several studies with autopsy confirmation. Studies also suggest FDG PET may help differentiating AD from VaD. FDG PET also significantly helps predicting progression of dementia when assessed at the mild stage. A high neocortical PIB retention has not only been found in cpAD as compared to controls, but also in LBD [9] and probably multi-tracer imaging are needed to discriminate between AD and LBD. However, early reports indicate almost constantly normal PIB uptake in FTD [10,11,12] and PD [13,14].

Overall, volumetric MR, FDG PET and amyloid PET appear to have significant predictive value for the early diagnosis of AD, and the recently proposed new diagnostic criteria for cpAD (15). However, their relative added value and cost-effectiveness remain to be determined with precision before such a radical change is implemented.

There is as yet limited experience in the use of mapping neurotransmission and inflammation in the early diagnosis of dementia, due to the complexity and cost of the techniques. However, marked reductions in cortical presynaptic acetylcholine esterase (AChE) activity [16] as well as in post-synaptic receptors such as nicotinic [17, 18] and 5HT_{2a} [19], have been reported in converter aMCI and cpAD, together with marked elevations in microglial activation [20]. Likewise, reductions in presynaptic nigro-striatal dopamine markers appear to afford a good separation between AD and LBD [21]. However, the role of these markers in early diagnosis remains to be formally assessed.

Apart from its use in diagnosis, imaging can also be used in monitoring treatment effect, as 1) marker of disease burden (e.g., amyloid); 2) surrogate marker of disease progression (e.g., annual rate of hippocampal atrophy, FDG uptake deterioration); and 3) marker of pharmacodynamic efficacy (e.g., receptor/enzyme occupancy). Substantial results concern only the latter, where it has been shown that treatment with AChE inhibitors in patients with cpAD can improve or stabilize cerebral blood flow /glucose metabolism [22] and induces a reduction in cortical AChE activity the magnitude of which negatively correlates with the improvement in tests of general attention [23]. It is assumed that both structural as well as functional imaging will be used more extensively in the future for evaluation of new treatment strategies [24].

** This session is held at the occasion of the ECNP Targeted Expert Meeting 2007 Dementia, 12-13 October 2007, Vienna, Austria. For further details see the ECNP website www.ecnp.eu*

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