

## Imaging Solutions I: Structural and Functional Imaging

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In this session, I will take a clinical approach towards structural and functional imaging in Alzheimer's disease (AD). Taking clinical practice as a starting point, I will focus on three topics: (1) early diagnosis, (2) monitoring disease progression, (3) endophenotypes; understanding heterogeneity of AD.

(1) Diagnosis: According to current guidelines, neuroimaging should be performed at least once during the diagnostic work-up of dementia. In the new research criteria coined by Dubois et al.,<sup>1</sup> atrophy of the medial temporal lobe is mentioned as one of the criteria for AD. Although this is a major step forwards in the nosological diagnostic paradigm, there are still a number of issues to solve. To date, there are no validated norm values for degree of atrophy of the medial temporal lobe. Visual rating scales can be easily applied, but are not highly sensitive and to some degree subjective in nature. Hippocampal volumes are more precise, but difficult to apply in clinical practice as these methods are still very time-intensive. Moreover, due to wide variability in MRI acquisition and post-processing techniques there are no norms available. Another issue is, that hippocampal atrophy is by no means present in all AD patients. Especially AD patients with early onset often display a typical atrophy pattern with relative sparing of the medial temporal lobe but prominent involvement of the precuneus.<sup>2</sup> Finally, the role of cerebrovascular damage, and how this should be taken into account in the diagnostic work-up of dementia is far from crystallized. We know that there is often a mix of neurodegenerative and cerebrovascular changes. But how these findings should be weighed and combined in the diagnosis of dementia is at present unclear. Microbleeds are a very interesting MRI finding in this respect. They seem to be related to cerebral amyloid angiopathy and potentially form the "missing link" between neurodegenerative disease and cerebrovascular disease. MBs have been shown to be related to both markers of small vessel disease (e.g. white matter hyperintensities, lacunes) and to increased levels of the protein amyloid-beta in the CSF.<sup>3</sup>

(2) Monitoring disease progression: The diagnosis of AD is not the end, but rather a starting point of ongoing deterioration. At present, a doctor has only very little to offer in terms of prognosis, while this kind of information would clearly benefit both patient and relatives. MRI seems to have value in this respect. First, we showed that a number of simple baseline MRI measures predict mortality.<sup>4</sup> Remarkably, while markers of atrophy are related to cognitive decline, cerebrovascular markers (especially microbleeds) more strongly predicted mortality. We then used serial MRI to track disease progression.<sup>5,6</sup> In a memory clinic sample of 147 patients (controls, mild cognitive impairment, AD), we were able to visualize how atrophy spreads through the cortex in a predictable way, with atrophy rates varying across regions according to the disease stage a patient is in. Most importantly, the rate of atrophy seems to be related to the rate of cognitive decline, which suggests that these measures can be used as surrogate outcome measures. Studies of natural disease progression are of the utmost importance, to effectively design trials in which MRI measures are used as an outcome. The USA Alzheimer's disease Neuroimaging Initiative (ADNI) was initiated as an attempt to measure disease progression in a large set of patients in a multi-center setting closely resembling that of clinical trials (www.ADNI-info.org). The ADNI study has now demonstrated that hippocampal volume loss over time, measured with MRI, has potential as a marker for progression in AD.<sup>7</sup> They were able to demonstrate hippocampal volume loss over a period as short as 6 months, and that the volume loss is related to cognitive decline and to other indicators of Alzheimer neuropathology. Experience with MRI markers as outcome measures in clinical trials is inconclusive, as positive trials are still awaited.

(3) Endophenotypes: understanding the heterogeneity of AD: Increasingly, AD is comprehended to be a heterogeneous disorder. Patients differ widely in terms of genetic make-up, age-at-onset, and the involvement of vascular factors, and these factors may be related to their response to future therapies. MRI may prove to be highly valuable to describe endophenotypes of AD. The pattern of atrophy differs according to age-at-onset,<sup>2</sup> and the same has been shown for APOE genotype.<sup>8</sup> Potentially, depending on genetic make-up and/or environmental factors, the AD pathology is "directed" towards specific regions in the brain, at the same time affecting specific networks. These involved regional networks in turn predispose for a specific clinical profile with prominent involvement of memory, or other –non-memory– functions. I would like to end with a few words on functional MRI in AD. Task-related fMRI does not seem to have future for AD for two reasons: (i) severe cognitive impairment is the hallmark of AD, so differential task performance will outweigh any difference in brain activity, and (ii) profound structural brain changes are present at an early stage ("dead neurons tell no tales"). Resting state fMRI is a promising alternative, as there is no cognitive performance involved. Using resting state fMRI, a number of brain networks have been shown, and these networks were shown to be compromised in AD.<sup>9,10</sup> Potentially, future studies will reveal differential networks to be involved in specific patient categories, and this may greatly help our understanding of the disease.

References 1. Dubois, B. et al. *Lancet Neurol* 6, 734-746 (2007); 2. Karas, G. et al. *Neuroradiology* 49, 967-976 (2007); 3. Goos, J.D. et al. *Stroke* 40, 3455-3460 (2009); 4. Henneman, W.J. et al. *Stroke* 40, 492-498 (2009); 5. Sluimer, J.D. et al. *Radiology* 248, 590-598 (2008); 6. Henneman, W.J. et al. *Neurology* 72, 999