Neuroimaging and Dementia

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One of the remarkable milestones in human history is to explore the hidden organs of its own with the technology developed by itself. With the discovery of X-rays, in vivo brain imaging has become possible, and more comprehensive information about the brain has been acquired with the new technologies and large-scale imaging projects (Human brain project, Human connectome project, Chinese brain project). Using open code applications in the developing technologies and open access to the data in neuroimaging are indicators of solidarity of scientists, and symbolize the future of the world. The past two decades have shown that the free share of technology and data give rise to production of more knowledge.

Neuroimaging has made a significant contribution to the diagnosis of dementia, and understanding the dementia process. Neuroimaging is a valuable technique to understand the disease process of Alzheimer's Disease (AD), the most common type of dementia, as well as being an elaborate laboratory test for Alzheimer's disease (AD). Today, with multi-modal imaging studies, it is possible to see and track the changes in the structure, perfusion, and metabolism of the brain, and accumulation of amyloid and tangle from the presymptomatic period to the terminal period of the disease.

Magnetic resonance imaging (MRI) is the most common neuroimaging modality in the diagnosis of AD. Detection of selective atrophy in the course of the disease with structural MRI helps the clinician in the diagnosis of dementia, and studies using voxel-based volume analysis, cortical thickness measurements, and tractography analyzes have shown that structural changes in AD are detectable even in the presymptomatic period. The volume of healthy human brain tends to decrease towards the end of middle ages, but in AD, rate of volume reduction is 3 times more than normal brain volume reduction (1). MRI and voxel-based methods showed the rate of atrophy is not always stable, and the rate of temporal lobe atrophy differs as the disease progresses (non-linear atrophy) (2). Another contribution of structural MR studies in AD is to show the involvement of the white-matter. It has become clear that 70% of the AD patients have mild or severe white-matter lesions, and these are correlated with some clinical parameters (3, 4).

The MRI also has a capacity to show functional changes in AD. Even the task-based functional MRI (fMRI), especially with memory paradigms, was popular in AD; groundbreaking information have been gathered with another fMRI technique called "resting-state fMRI". This technique allows in vivo examination of large-scale brain networks, and has helped to show the alterations and pattern of alterations of these networks in AD. Default mode network located on anatomical regions including anterior and posterior midline structures, and parietal and medial temporal areas shows alterations in the presymptomatic period before the structural changes in AD (5). In normal people, default mode network is the most active network when the brain is in resting state, and the person is relatively closed to external stimuli. Alzheimer's disease seems to disrupt the basal working capacity of the brain in the very early phase of the disease. Why does AD selectively involve this network at the beginning of the disease? The answer to this question is the location of amyloid accumulation, one of the two major pathological protein accumulations of AD. Both positron emission tomography (PET) studies using specific radio ligands and postmortem pathologic studies showed that amyloid deposition, the earliest pathological accumulation in the course of the disease, starts from the brain areas which are part of default mode network. The question still remains, what is the relationship of default mode network alterations with structural changes and clinical symptoms? Recently, multi-modal imaging studies have started to provide data for the answer to this question.

One of the most popular topics in AD is molecular-based PET imaging targeting amyloid and tau depositions using specific radio ligands. The most important characteristic of this method is allowing the in vivo observation of pathologic changes in the brain as pathologists do in post-mortem brains. Amyloid imaging is a more established method than tau imaging and fourth generation ligands have been developed. Advantages and disadvantages of the method have also been learned. With amyloid imaging, over 90% of patients with

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mild cognitive impairment that will progress to AD can be identified (6). With this method, the question we expect to answer with longitudinal studies today is how much and how far amyloid accumulation is normal in normal people. Tau imaging is in principle similar to amyloid imaging, and it shows a correlation with disease course and clinical findings. Presence of tau accumulation in the brain means loss of neuron and atrophy of the tissue, and consequent impairment of functionality. This method has a potential to be used in the differential diagnosis, and detection of functionality in dementia patients. However, major limitations of the method are the high cost of the procedure, the difficulty of supplying ligands, and radiation issue. Tau imaging is also useful in other degenerative diseases with tau accumulation, and this promises more widespread use of this method.

PET imaging using fludeoxyglucose (FDG) shows brain metabolism and synaptic activity, and hypometabolism appears in the presymptomatic period of AD in patients. The signature of AD in FDG-PET imaging is the involvement of posterior midline structures including precuneus and posterior cingulate cortex and parietal cortex. This technique has a potential to predict conversion from mild cognitive impairment to AD with a sensitivity and specificity approaching to 80% (6). Interestingly, infants have also same pattern of brain metabolism observed in AD patients, and it seems that metabolism of the brains of the patients exhibiting childish behaviors become similar to the brains of the children.

In conclusion, neuroimaging is used as a powerful diagnostic tool in AD, but more importantly it gives valuable information about disease processes. Future neuroimaging is expected to be molecular-based and gene-mediated imaging at a more micro level.

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