MRI BIOMARKERS IN NEURODEGENERATIVE DISORDERS

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ABSTRACT

The neurodegenerative disorders all share a broad common mechanism: accumulation of abnormal protein within the nervous system leads to excess neuronal loss. Alzheimer's disease (AD), the prototypic neurodegenerative disease, is associated with accumulation of amyloid plaques and neurofibrillary tangles composed of phosphorylated tau which preceded excess neuronal loss within specific brain regions, notably the medial temporal lobes. Other neurodegenerative disorders (including frontotemporal dementia and dementia with Lewy bodies) are associated with deposition of different proteins, and different patterns of regional brain loss. Cross-sectional neuroimaging is widely used for diagnostic purposes and research, with MRI (and more recently PET) being used as inclusion/exclusion criteria and safety outcome measure for clinical trials. Serial MRI is widely used to assess the extent and pattern of progression in neurodegenerative diseases both for observational and therapeutic studies. In observational studies, longitudinal MRI-based measures of brain volume change (reflecting cerebral atrophy) are used to provide insights into the timing, extent and correlates of neurodegeneration. For clinical trials serial MRI based measures of atrophy are widely used as outcome measures, both to distinguish symptomatic from disease-modifying drug effects – under the premise that the latter but not the former will lead to attenuation of atrophy rate in the treated group compared to placebo – and to reduce sample size requirement. If atrophy based measures are to be used as outcome measures, it is essential that image acquisition is carefully planned and undertaken to provide appropriate tissue classification and stability over time. Thereafter, it is over to the image analyst. In this talk I will discuss the end-user requirements of an image-analysis tool, focusing on the need for clinicians and image analysts to work closely together to ensure that any such techniques produce not only robust but also clinically relevant results. In the absence of a gold standard means of assessing the validity of any methods of determining brain volume change over time, safeguards to help provide reassurance will be discussed, including the use of simulated atrophy; comparison with manual techniques; and ensuring techniques are commutative/symmetric and transitive, reproducible and biological plausible. The importance of striving to reduce variance – the key factor influencing sample size – will be emphasized, with the caveat that the most that can be asked of any image analytical tool is to reduce within subject variability. The advantages and pitfalls of using sample size reduction per se as a criterion for comparing techniques will also be covered, with particular regard to data produced from the Alzheimer's disease Neuroimaging Initiative.

Index Terms— magnetic resonance imaging (MRI), clinical trials, Alzheimer's Disease, biomarker validation, neurodegeneration