TUESDAY, JULY 17, 2012
SYMPOSIA: S3-01
IMAGING THE ONSET AND PROGRESSION OF NEURODEGENERATION

S3-01-01 ALZHEIMER'S DISEASE: WHERE DOES ATROPHY REALLY BEGIN?

Jennifer Whitwell, *Mayo Clinic, Rochester, Minnesota, United States.*

Background: Early imaging studies revealed characteristic patterns of atrophy involving the medial temporal lobes and temporoparietal neocortex in Alzheimer's disease (AD). Patterns of neuroanatomical progression matched the topographic progression of tau-positive neurofibrillary tangles through the brain, with earliest changes identified in the medial temporal lobe before subsequently spreading to association cortices. This traditional view of progression in AD has however been recently challenged. The advent of β-amyloid binding ligands that can be detected using PET has allowed investigators to assess even earlier stages of the disease, with studies assessing neuroanatomical signatures of AD in cognitively normal subjects that show β-amyloid deposition on PET, and hence presumed preclinical AD. Some of these studies have suggested that β-amyloid related neocortical neurodegenerative changes may in fact precede neurodegeneration in the medial temporal lobe. This suggests firstly that the presence of β-amyloid may be associated with neurodegeneration, and secondly that the earliest neuroanatomical changes in AD do not occur in the medial temporal lobe. This talk will discuss these issues and provide new data that suggests that the neuroanatomical signature of AD in cognitively normal subjects is weak at best and may not be reproducible across different image analysis techniques.

S3-01-02 IMAGING IN LEWY BODY DEMENTIA

John O'Brien, *Newcastle University, Newcastle upon Tyne, United Kingdom.*

Background: Dementia with Lewy bodies (DLB) has a distinct clinical and pathological profile when compared to Alzheimer's disease (AD). However, distinction between DLB and AD during life is often difficult, due to low sensitivity of current clinical diagnostic criteria. Both structural and functional neuroimaging have great potential to assist with better discriminating DLB from AD, but also to provide insights into similarities and differences in underlying neurobiology and disease progression. **Methods:** We have undertaken structural MR, diffusion imaging, arterial spin labeling and resting and activation BOLB studies in cohorts of subjects with DLB, AD and in normal controls. **Results:** Medial temporal lobe atrophy is robustly associated with AD but variably present in DLB. Resting BOLD studies demonstrate altered functional connectivity in subcortical areas in DLB, distinct from altered hippocampal connectivity seen in AD. Both resting and activation fMRI studies demonstrate normal functional of primary visual areas in DLB, while higher visual areas (motion detection) showed marked abnormalities. Diffusion imaging demonstrates global white matter abnormalities in both diffusivity and fractional anisotropy in AD, but much more localised posterior impairments in DLB. Longitudinal studies of these parameters are in progress to determine whether they are potential markers of disease progression. **Conclusions:** Multi-modal MR approaches have revealed a number of key differences between AD and DLB, with the latter associated with subcortical changes, abnormalities in higher visual processing areas and posterior white matter change. These imaging changes help explain the distinct symptom profile of DLB, provide further validation of DLB as a distinct clinical syndrome and provide new potential targets for both early recognition and diagnosis and the targeting of treatments.

S3-01-03 HUNTINGTON'S DISEASE

Elizabeth Aylward, *Seattle Children's Research Institute, Seattle, Washington, United States.*

Background: This presentation will cover structural neuroimaging results from studies of Huntington's disease (HD), with particular focus on PREDICT-HD, a longitudinal multi-site study of individuals who carry the gene mutation for HD but were not yet showing diagnosable symptoms of the disorder at the time of enrollment (PRE-HD). **Methods:** Participants include $>$ 800 PRE-HD individuals who have been followed every year for a decade with extensive neuropsychological and clinical testing, as well as structural MRI scanning every two years. MRI measures include volume of striatum, hippocampus, thalamus, cortex, and white matter. **Results:** Discussion will include cross-sectional and longitudinal findings of specific brain regions that change as individuals move from presymptomatic status through diagnosis and into the early stages of HD. Changes in striatal volume have been observed decades prior to diagnosis of HD symptoms, and atrophy progresses relatively quickly (3-5% per year) once it begins. Significant atrophy of white matter, particularly in the frontal lobe, is also observed early in the course of the disease. MRI variables will be related to genetic, cognitive, behavioral, psychiatric, and functional variables. **Conclusions:** The presentation will include discussion of the use of neuroimaging variables as potential biomarkers for assessing treatment effectiveness in future clinical trials in both presymptomatic and symptomatic HD.

S3-01-04 IMAGING THE ONSET AND PROGRESSION OF FRONTOTEMPORAL DEMENTIA

Jonathan Rohrer, *UCL Institute of Neurology, London, United Kingdom.*

Background: Frontotemporal dementia (FTD) is the second most common young onset degenerative dementia. Clinically it usually presents with either behavioural symptoms (behavioural variant FTD) or language symptoms (semantic dementia or progressive nonfluent aphasia). However there is overlap with both the atypical parkinsonian disorders (corticobasal syndrome and progressive supranuclear palsy) and motor neurone disease/ amyotrophic lateral sclerosis. Over a third of patients with FTD have an autosomal dominant family history with the genes most commonly involved being progranulin, tau and C9ORF72. Multiple studies have investigated the imaging features of FTD and its clinical, genetic and pathological subtypes. **Methods:** A number of key questions in the neuroimaging of FTD will be addressed: 1) What are the earliest detectable imaging features? 2) How can we use imaging in the diagnosis of FTD and in differentiating it from other neurodegenerative disorders? 3) How do imaging features change over time and how can we use imaging to track disease progression? **Results:** Studies of presymptomatic genetic cases that aim to identify the very earliest imaging changes in FTD will be highlighted. More commonly however, cross-sectional imaging studies have investigated affected subjects. Such studies have described characteristic patterns of atrophy and hypometabolism in the different clinical FTD subtypes, allowing these disorders to be differentiated from other neurodegenerative diseases. Specific imaging features of certain genetic and pathological subtypes have also been described. Changing patterns of atrophy over time are seen when patients are studied longitudinally. Such studies also allow the measurement of rates of global and focal brain atrophy which may be used as outcome measures in future trials. **Conclusions:** Studies of imaging in FTD have highlighted a variety of techniques which may be used as biomarkers for diagnosis and for tracking disease progression.

SYMPOSIA: S3-02
RNA-BASED THERAPEUTICS FOR NEURODEGENERATIVE DISEASE

S3-02-01 SHRNA TARGETING USING AAV FOR ALZHEIMER'S DISEASE

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Abstract not available.

S3-02-02 THE MIR-15/107 GENE GROUP IN NEURODEGENERATIVE DISEASES

Peter Nelson, Wang-Xia Wang, *University of Kentucky, Lexington, Kentucky, United States.*