Alzheimer's disease dementia

The temporal relationship between sleep, Alzheimer's disease (AD), and cognitive impairment remain to be further elucidated.

The hippocampus and entorhinal cortex (EC), the earliest affected areas, are considered relative to early memory loss in Alzheimer's disease (AD). The hippocampus is composed of heterogeneous subfields that are affected in a different order and varying degrees during Alzheimer's disease pathogenesis.

Neuropsychiatric Inventory-Questionnaire (NPI-Q) assessed nighttime behaviors, a surrogate for sleep disorders, are associated with more rapidly deteriorating cognition in patients with AD neuropathology who are also carriers of APOEε4 or show cerebral amyloid angiopathy (CAA) [1].

In this study, we conducted a comprehensive proteomic analysis of the hippocampal subfields and EC region in human postmortem specimens obtained from the Chinese human brain bank. Bioinformatics analysis identified region-consistent differentially expressed proteins (DEPs) which associated with astrocytes, and region-specific DEPs which associated with oligodendrocytes and the myelin sheath. Further analysis illuminated that the region-consistent DEPs functioned as connection of region-specific DEPs. Moreover, in region-consistent DEPs, the expression level of S100A10, a marker of protective astrocytes, was increased in both aging and AD patients. Immunohistochemical analysis confirmed an increase in the number of S100A10-positive astrocytes in all hippocampal subfields and the EC region of AD patients. Dual immunofluorescence results further showed that S100A10-positive astrocytes contained apoptotic neuron debris in AD patients, suggesting that S100A10-positive astrocytes may protect brain through phagocytosis of apoptotic neurons. In region-specific DEPs, the proteome showed a specific reduction of oligodendrocytes and myelin markers in CA1, CA3, and EC regions of AD patients. Immunohistochemical analysis confirmed the loss of myelin in EC region. Above all, these results highlight the role of the glial cells in AD and provide new insights into the pathogenesis of AD and potential therapeutic strategies.

Frank et al. examined the ability of plasma hyperphosphorylated tau (p-tau)181 to detect cognitive impairment due to Alzheimer's disease (AD) independently and in combination with plasma total tau (t-tau) and neurofilament light (NfL).

Plasma samples were analyzed using the Simoa platform for 235 participants with normal cognition (NC), 181 with mild cognitive impairment due to AD (MCI), and 153 with AD dementia. Statistical approaches included multinomial regression and Gaussian graphical models (GGMs) to assess a network of plasma biomarkers, neuropsychological tests, and demographic variables.

Plasma p-tau181 discriminated AD dementia from NC, but not MCI, and correlated with dementia severity and worse neuropsychological test performance. Plasma NfL similarly discriminated diagnostic groups. Unlike plasma NfL or t-tau, p-tau181 had a direct association with cognitive diagnosis in a bootstrapped GGM.

These results support plasma p-tau181 for the detection of Alzheimer's disease dementia and the use of blood-based biomarkers for optimal disease detection [2].

Groot et al. compared regional gray matter (GM) volumes and associated gene expression profiles between cognitively-defined subgroups of amyloid-β positive individuals clinically diagnosed with AD dementia (age: 66 ± 7, 47% male, MMSE: 21 ± 5). All participants underwent neuropsychological assessment with tests covering memory, executive-functioning, language and visuospatial-functioning domains. Subgroup classification was achieved using a psychometric framework that assesses which cognitive domain shows substantial relative impairment compared to the intra-individual average across domains, which yielded the following subgroups in our sample; AD-Memory (n = 41), AD-Executive (n = 117), AD-Language (n = 33), AD-Visuospatial (n = 171). We performed voxel-wise contrasts of GM volumes derived from 3Tesla structural MRI between subgroups and controls (n = 127, age 58 ± 9, 42% male, MMSE 29 ± 1), and observed that differences in regional GM volumes compared to controls closely matched the respective cognitive profiles. Specifically, we detected lower medial temporal lobe GM volumes in AD-Memory, lower fronto-parietal GM volumes in AD-Executive, asymmetric GM volumes in the temporal lobe (left < right) in AD-Language, and lower GM volumes in posterior areas in AD-Visuospatial. In order to examine possible biological drivers of these differences in regional GM volumes, we correlated subgroup-specific regional GM volumes to brain-wide gene expression profiles based on a stereotactic characterization of the transcriptional architecture of the human brain as provided by the Allen human brain atlas. Gene-set enrichment analyses revealed that variations in regional expression of genes involved in processes like mitochondrial respiration and metabolism of proteins were associated with patterns of regional GM volume across multiple subgroups. Other gene expression vs GM volume-associations were only detected in particular subgroups, e.g., genes involved in the cell cycle for AD-Memory, specific sets of genes related to protein metabolism in AD-Language, and genes associated with modification of gene expression in AD-Visuospatial. We conclude that cognitively-defined AD subgroups show neurobiological differences, and distinct biological pathways may be involved in the emergence of these differences [3].

1)
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