Mapping Of Pathological Inclusions in Human Brain Tissue with Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disorder which exhibits characteristic proliferation of pathological inclusions - β-amyloid plaques and neurofibrillary tangles (NFT) inside human brain. These plaques and tangles follow predefined trajectories to progressively involve different parts of the brain. Cryo-EM and ssNMR have derived many of the structures of pathological inclusions at high resolution, but are unable to provide detailed information about the way they interact with tissue in situ. X-ray microdiffraction in the small (SAXS) and wide (WAXS) angle regime can be carried out on histological thin sections of AD human brain tissue, making it possible to visualize their fibrillar and non- fibrillar structures in situ. In this work, we examined thin sections of tissue from AD subjects at different stages of disease by scanning with a 5μm diameter X-ray beam to generate diffraction patterns arrayed across a region of interest. This mapping of diffraction attributes across tissue sections elucidates the spatial distribution of amyloid plaques and NFTs.

Plaques and tangles have cross-beta structures and may be present as fibrillar or non- fibrillar structures, complicating the extraction of structural attributes from the X-ray data. The presence of mica substrate, subtle variation in sample preparation, the variability and heterogeneity of human brain tissue at every relevant length scale, all pose challenges to structural characterization. To analyze this data, we are harnessing state-of-art artificial intelligence techniques that can categorize tissue variations on the basis of X-ray microdiffraction with confidence. We have demonstrated that use of a Gaussian mixture model and neural networks can produce consistent mapping of β-amyloid plaques and NFTs. This in situ mapping of structural details of fibrils is producing new information on the way fibrils interact with brain tissue with the potential of improving our understanding of molecular basis of disease progression in AD.

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References

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