Development of a Multimodal Approach to the Neuroimaging of Alzheimer's Disease

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The focus of Alzheimer's disease (AD) research has shifted towards an investigation of the entire disease course, with a particular emphasis on early changes when intervention strategies would be most effective. The earliest stages of the amyloid cascade hypothesis of AD pathogenesis can be investigated in every young adult with Down syndrome (DS; trisomy 21) due to a deterministic genetic predisposition to APP overproduction, using PET and MRI imaging. The overall goal of this thesis project was to characterize the early spatial patterns of amyloid burden, glucose metabolism, and gray matter (GM) volume, as well as the early temporal changes in amyloid accumulation and GM atrophy, in the young, non-demented DS population and to extend these results to the more common sporadic AD, informing future AD therapeutic strategies. Additionally, the large heterogeneity in response to current AD therapeutics may be explained by PET imaging of concurrent brain changes, such as neuroinflammation or decreased cholinergic neurotransmission.

Quantitative *in vivo* interrogation of amyloid burden ([^{11}C]PiB), glucose metabolism ([^{18}F]FDG), and GM volume (volumetric MRI) was performed in a longitudinal PET and MRI imaging study (3-5yrs) in young DS adults. For atypical populations, special consideration must be placed on methods that rely on templates built from healthy controls, such as spatial normalization or tissue type segmentation templates. Radiochemical synthesis methods were amended for PET imaging studies of neuroinflammation ([^{11}C]PBR28) and receptors designed to

modulate neuron activity ([^{11}C]clozapine). A first-in-humans PET study of nicotinic acetylcholine receptors ([^{18}F]nifene) in healthy controls were evaluated for safety, distribution throughout the brain, and test-retest variability.

DS specific templates reflected the unique DS brain morphology and substantially improved spatial normalization and tissue type segmentation. DS specific PiB positivity thresholds identified elevated amyloid (36yrs) two decades prior to the median age of onset, a striatum-dominant pattern of amyloid accumulation, and decreased GM volume and glucose metabolism in AD-associated regions (parietal and temporal cortices). Longitudinally, the annual percent change in PiB depended on the existing amyloid burden (PiB(-): 0.5%/yr, PiB converter: 4.9%/yr, PiB(+): 3.7%/yr). The rate was slow initially and then faster with elevated amyloid, consistent with the sigmoid curve proposed in the amyloid cascade hypothesis. There was greater GM atrophy with elevated amyloid in regions involved in the default network (precuenus), but no change in overall cognitive function in young, non-demented DS adults.

The prevalence of elevated amyloid, the timing of elevated amyloid prior to dementia, and the subsequent patterns of neurodegeneration of the AD pathophysiological process in DS was similar to that in sporadic AD, despite the atypical striatum-dominant pattern of amyloid accumulation. Moreover, the longitudinal rates of amyloid accumulation and GM atrophy by existing amyloid burden are consistent with those in sporadic AD, suggesting an overall generalizability of findings in this DS work to the more common sporadic AD. Therefore, this thesis work provides a framework for evaluating anti-amyloid AD therapies in DS that could be effective two decades prior to dementia, or earlier, and assessed by reduced rates of AD biomarker change or the absence of subsequent AD-associated patterns of neurodegeneration. Novel, multi-factorial approaches can be adopted for non-responders to traditional AD

therapeutics by evaluating concurrent changes in the brain (e.g. neuroinflammation, cholinergic losses).