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Featured Article

Dissociation of Down syndrome and Alzheimer's disease effects with imaging

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Abstract

Introduction: Down Syndrome (DS) adults experience accumulation of Alzheimer's disease (AD)–like amyloid plaques and tangles and a high incidence of dementia and could provide an enriched population to study AD-targeted treatments. However, to evaluate effects of therapeutic intervention, it is necessary to dissociate the contributions of DS and AD from overall phenotype. Imaging biomarkers offer the potential to characterize and stratify patients who will worsen clinically but have yielded mixed findings in DS subjects.

Methods: We evaluated 18F fluorodeoxyglucose positron emission tomography (PET), florbetapir PET, and structural magnetic resonance (sMR) image data from 12 nondemented DS adults using advanced multivariate machine learning methods.

Results: Our results showed distinctive patterns of glucose metabolism and brain volume enabling dissociation of DS and AD effects. AD-like pattern expression corresponded to amyloid burden and clinical measures.

Discussion: These findings lay groundwork to enable AD clinical trials with characterization and disease-specific tracking of DS adults.

Keywords: Down syndrome; Alzheimer's; Imaging; Amyloid; AV-45; Glucose metabolism; FDG; PET; MRI; Clinical trials; Prodromal; Biomarker initiative; DSBI; Classifier; NPAIRS

1. Introduction

Down syndrome (DS) is associated with an increased rate of Alzheimer's-like dementia, prevalent in up to 55% of individuals in their forties and 77% of age >60 years [1]. Neuritic plaques and neurofibrillary tangles consistent with Alzheimer's disease (AD) have been identified in nearly all DS adults examined of age >40 years [1,2]. Because of this, DS adults may provide a naturally enriched population

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in which to evaluate the potential of pharmacological candidates to prevent AD progression. Ideally, trials would initiate treatment at a common, well-defined point before AD dementia [2]. This would require individual characterization of the degree of AD-related pathology and neurodegeneration distinct from DS effects. Detection of disease-modifying treatment effects would require distinguishing impact on AD-related pathology from that on underlying DS.

The primary objectives of our work were to: (a) dissociate within DS subjects the effects attributable to DS versus those associated with AD, and (b) to quantify the degree of AD progression. To pursue this, we applied multivariate analysis advances to baseline 18F fluorodeoxyglucose (FDG) PET structural magnetic resonance imaging (MRI) images and examined relationships with amyloid and clinical endpoints. We hypothesized that nondemented DS subjects with emerging AD would exhibit a pattern of neurodegeneration characteristic of prodromal AD. We postulated that standard image analysis methods might not be able to fully dissociate effects attributable to DS vs AD within subjects, and that multivariate analysis software capable of identifying different contributing networks or patterns to overall effect could isolate DS and AD components.

The source of DS data for our work was a 3-year DS Biomarker Initiative (DSBI) study was initiated by Janssen Research and Development in collaboration with the University of California San Diego (UCSD) and the Alzheimer's Disease Cooperative Study (ADCS). This study was designed to demonstrate methodology feasibility for a larger natural history trial. Endpoints include neuropsychological testing, positron emission tomography (PET) imaging of cerebral amyloid and glucose metabolism, MRI, and blood biomarkers [2,3].

In AD, a characteristic pattern of glucose hypometabolism emerges in hippocampus and posterior cingulate, expands to temporo-parietal regions, and gradually affects most cortical tissue, whereas pons, cerebellum, and motor and visual cortices are relatively preserved [4–6]. Changes are found in genetically at-risk individuals [7,8], begin years before symptom onset [9], and correlate with clinical decline [4,10]. In DS, results of FDG PET studies have been mixed [11]. Some studies in young adults (<25 years) have found no differences or only hypermetabolism compared to normals [12–14]. Other studies in DS adults have found hypometabolism in AD-relevant regions, more pronounced in demented than nondemented subjects [15–17]. Findings have not dissociated DS from AD effects within-subject nor quantified degree of AD progression.

AD also causes structural atrophy that initiates in entorhinal cortex, spreads to hippocampus, and expands to parietal and most cortical and subcortical structures [18–20], correlating with clinical progression [21,22]. In young DS persons (ages 5 to 23 years), MRI studies have shown reduced brain volume, shortened frontal lobes, reductions in cerebellum and brainstem, hippocampus, amygdala, and white matter but preservation of parietal and subcortical regions [23–25]. Studies in DS adults have found lower volumes overall and in cerebellum, cingulate gyrus, frontal lobe, superior temporal lobes, and hippocampi and associations between dementia, regional atrophy typical of AD, and ventricular enlargement [17,26–30]. However, structural effects of DS have not been dissociated within subject from those attributable to AD.

Consistent with postmortem findings, amyloid imaging studies in DS adults have found a high prevalence of AD-like amyloid associated with age and dementia [17,31–34].

Our work builds on these findings by differentiating, at the subject level, the effects attributable to DS independent of amyloid burden from those associated with emerging AD, and furthermore, provides a quantitative measure of the degree of AD progression. We demonstrate that these measures correlate with amyloid and clinical endpoints at baseline.

2. Methods

2.1. Subject selection

Twelve nondemented adult individuals diagnosed with DS, age 32–61 years, were enrolled. Exclusion of a diagnosis of dementia was based on absence of evidence of recent deterioration in cognitive function not secondary to medical illness (e.g., hypothyroidism, sleep apnea) or mental illness (e.g., depression), with absence of a significant decline in function over a period of 6 months or more. The diagnosing neurologist was experienced with premorbid deficits in DS and incorporated dementia diagnosis recommendations from the National Task Group on Intellectual Disabilities and Dementia Practices [35]. Ten subjects were female; six were *APOE* ε4 carriers. Assessments were conducted by UCSD in collaboration with the ADCS under IRB-approved protocols with patient informed consent [3].

2.2. Image data acquisition, processing, and analysis

All subjects received FDG PET, florbetapir (amyloid) PET, and structural MRI (sMRI) scans, acquired and processed as described in the Supplementary Material and [3]. FDG PET and MRI analyses were performed while blinded to amyloid, *APOE* ε4, and clinical status. Image analysis consisted of three parallel, complementary approaches.

2.2.1. Analyses with NPAIRS

The NPAIRS [36,37] multivariate analysis software framework was applied to detect patterns in FDG PET and T1-weighted sMRI characterizing similarities and differences between the DS group and pre-defined comparator groups. In brief, NPAIRS uses canonical variates analysis (a form of linear discriminant analysis) to identify uncorrelated spatial patterns that when mathematically combined account for overall variance across groups of image data. Importantly, NPAIRS uses an iterative resampling process