Differentiating the Effects of Down Syndrome and Alzheimer's Disease upon Neuronal Function and Brain Volume

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BACKGROUND

Down Syndrome (DS) is associated with a high incidence of dementia concomitant with the presence of the amyloid plaques and tangles found in AD. Adults with DS may provide an enriched population for the study of AD-targeted treatments in preventative trials. However, to initiate therapy at a well-defined point in disease development, and to longitudinally monitor clinical effects arising from AD progression, it is necessary to dissociate the contributions of DS and AD to the overall, complex phenotype.

OBJECTIVES

The objective of our work was to discriminate between effects attributable to DS vs. AD pathology, and to quantify the degree of predementia AD progression within-subject. We evaluated 18-F fluorodeoxyglucose (FDG) PET, structural MRI, and florbetapir PET imaging biomarkers, and relationships among imaging markers and between imaging and clinical endpoints. We hypothesized that although standard methods of image analysis would not be able to dissociate effects attributable to DS vs. AD, application of advanced multivariate methods could identify the relative contributions of these syndromes to overall effect.

METHODS

We evaluated the baseline FDG PET and structural MRI data of 12 nondemented adults with DS (age 32 to 61 yrs, 83% F, 50% ApoE e4 carriers) while blinded to amyloid burden and cognitive status. FDG scans were scored using a previously developed AD Progression Classifier that quantifies the degree to which an individual subject expresses a pattern of relative hypometabolism reflecting progression from Normal (NL) amyloid negative (Am-) status to amyloid positive (Am+) AD. Separately, we applied NPAIRS multivariate analysis software (Strother 2002, 2010) to identify uncorrelated patterns (Canonical Variates, CVs) characterizing similarities and differences between the DS group and four pre-defined, previously processed groups of ADNI subjects characterized by clinical diagnosis, amyloid status, and age: (1) Am- NL, (2) Am+ AD, (3) Am+ early MCI (EMCI), and (4) Am+ late MCI. NPAIRS was used to compare groups. Apriori regions of interest were also measured on the FDG scans and compared across groups. After unblinding to amyloid, cortical cerebellar SUVRs were calculated for the DS florbetapir scans (Am+ threshold of 1.11). Relationships were evaluated between FDG and MRI CV scores and age, amyloid burden, and clinical endpoints.

RESULTS

In each of FDG PET and MRI, two distinct patterns were identified. The first differentiated DS from either NL or AD, while the second differentiated AD from NL. The DS-related pattern did not correlate with age or amyloid status, but the AD pattern in each case correlated with these and with clinical endpoints.

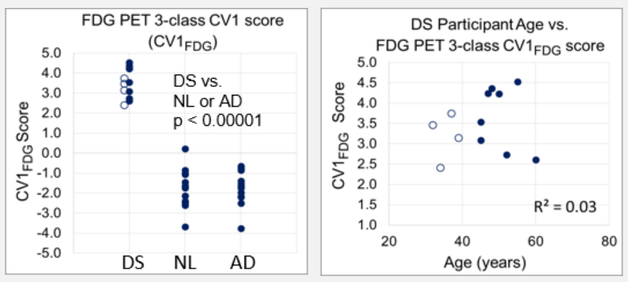

Figure 1. FDG PET $CV1_{FDG}$. The first pattern differentiated DS from NL Am- (p<0.00001, effect size (ES) 5.93) and AD (p<0.00001, ES 6.58), and did not correlate with age or amyloid status. Blue= relative decreases, red= relative increases. Unfilled DS circles = Am- or threshold; filled DS circles = Am+.

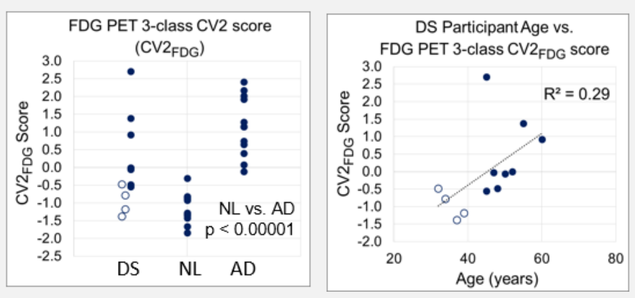

Figure 2. FDG PET $CV2_{FDG}$. The second pattern separated NL Am- from AD (p<0.00001, ES 3.48), while DS scores were distributed across the range from NL to AD. All Am- or threshold subjects had $CV2_{FDG}$ scores in the range of NL.

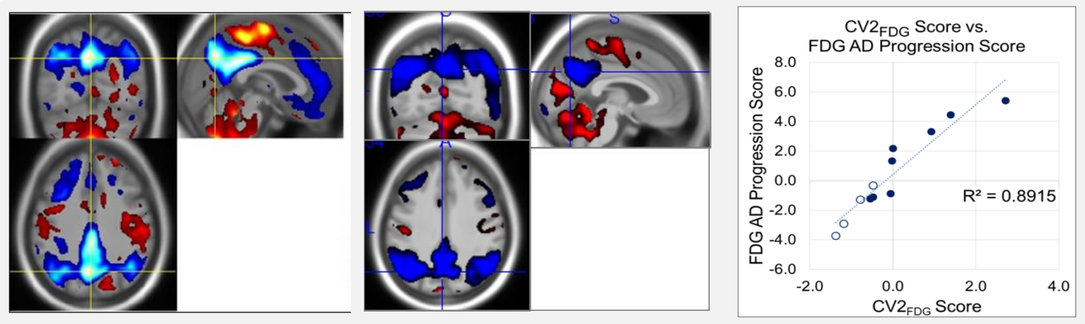

Figure 3. Comparison to AD Progression Pattern. The $CV2_{FDG}$ pattern is very similar to that of an FDG AD Progression classifier developed independently using 166 ADNI subjects, DS $CV2_{FDG}$ scores correlate with FDG AD Progression scores (R^2=0.89, p<0.00001)

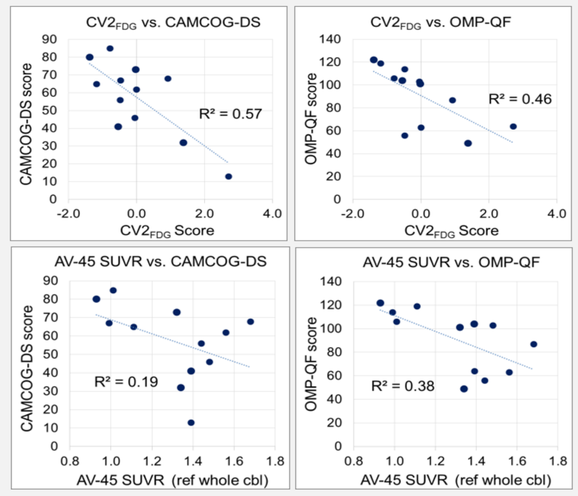

Figure 4. FDG and Amyloid correlations with clinical endpoints. $CV2_{FDG}$ score in DS subjects vs. clinical endpoints at baseline (top row), and Amyloid SUVR in DS subjects vs. the same measures at baseline (bottom row). The FDG values correlate with clinical endpoints throughout the spectrum of scores. In contrast, although there is a general correlation between Am- vs. Am+ status and clinical endpoints, the correlation no longer holds within the Am+ subgroup.

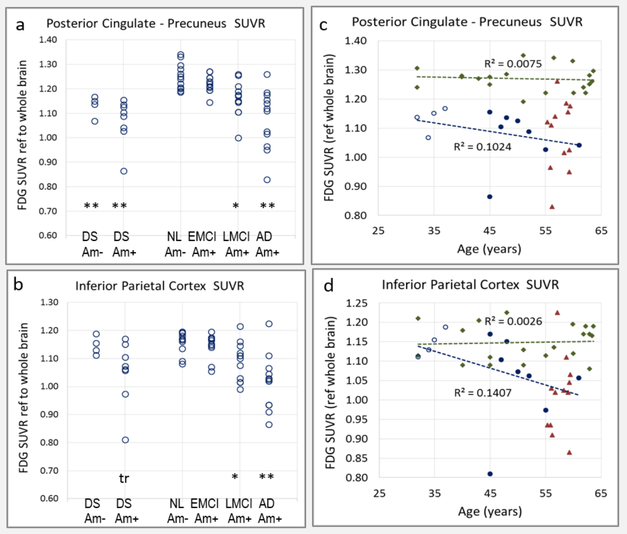

Figure 5. Region of Interest Analysis. The posterior cingulate-precuneus and inferior parietal cortex region of interest SUVR values are shown, normalized to whole brain, for DS Am-, DS Am+, NL Am-, EMCI Am+, LMCI Am+, and AD Am+ subjects. Asterisks indicate unpaired t-test significance (*p<0.05, **p<0.005, tr = trend). In c and d, relationships between SUVR values and age are shown for DS, NL (green diamonds), and AD subjects (red triangles). Unfilled DS circles = Am- or threshold; filled DS circles are Am+. PCC hypometabolism is noted all DS including Am- and ApoE e4 non-carriers.

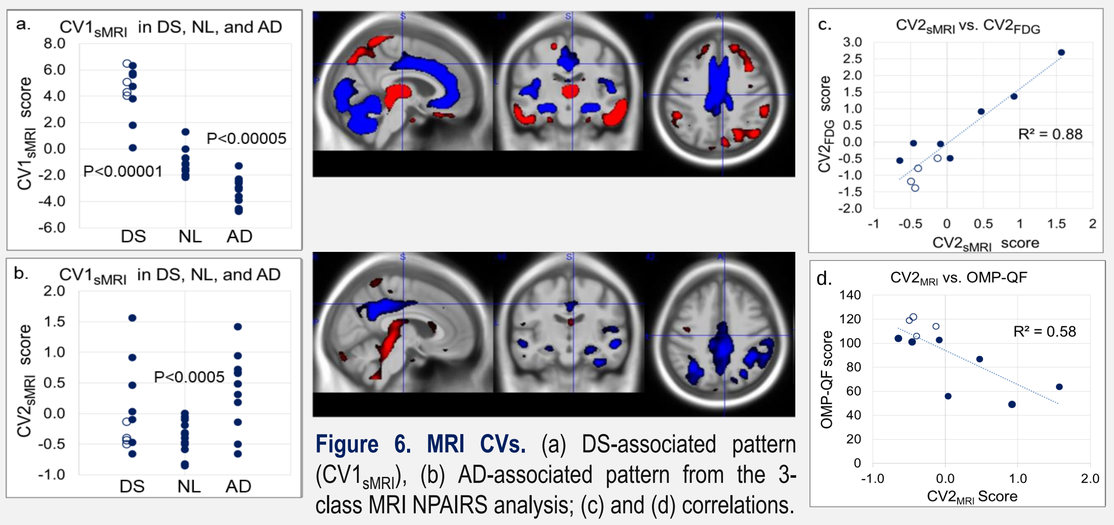

Figure 6. MRI CVs. (a) DS-associated pattern ($CV1_{sMRI}$), (b) AD-associated pattern from the 3-class MRI NPAIRS analysis; (c) and (d) correlations.

DISCUSSION AND CONCLUSIONS

Application of multivariate machine learning to FDG PET and MRI in DS adults enables dissociation of neuronal effects related to DS distinct from progressive AD. FDG and MRI AD-pattern expression correlate with clinical endpoints whereas amyloid burden does not once positivity is reached. By quantifying AD pattern expression using imaging biomarkers, it becomes possible to characterize degree of AD-related neurodegeneration for identification of suitable patients and detection of disease-specific treatment response.

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