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SHORT REPORT

Brain amyloid and the transition to dementia in Down syndrome

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Alzheimer's Disease in Down Syndrome

Abstract

Introduction: Down syndrome (DS) is associated with elevated risk for Alzheimer's disease (AD) due to amyloid beta (Aβ) lifelong accumulation. We hypothesized that the spatial distribution of brain Aβ predicts future dementia conversion in individuals with DS.

Methods: We acquired ^{18}F-florbetapir positron emission tomography scans from 19 nondemented individuals with DS at baseline and monitored them for 4 years, with five individuals transitioning to dementia. Machine learning classification using an independent test set determined features on ^{18}F-florbetapir standardized uptake value ratio maps that predicted transition.

Results: In addition to "AD signature" regions including the inferior parietal cortex, temporal lobes, and the cingulum, we found that Aβ cortical binding in the prefrontal and superior frontal cortices distinguished subjects who transitioned to dementia. Classification did well in predicting transitioners.

Discussion: Our study suggests that specific regional profiles of brain amyloid in older adults with DS may predict cognitive decline and are informative in evaluating the risk for dementia.

KEYWORDS
Alzheimer's, amyloid, classification, dementia, Down syndrome, positron emission tomography, predict, standardized uptake value ratio, transition

1 | INTRODUCTION

Individuals with Down syndrome (DS) have a high age-related prevalence of Alzheimer's disease (AD) and life-long accumulation of brain amyloid beta (Aβ) in part due to the triplication of amyloid precursor protein (APP) on chromosome 21.[1] Early identification of those at highest risk for early onset dementia is paramount for intervention trials in DS because potential disease modification is less effective after symptoms of cognitive decline are observable.[2] Current approaches for detecting brain Aβ include positron emission tomography (PET).[3,4] One important issue is whether amyloid-PET alone could be predictive of dementia transition in DS as demonstrated in the growing literature in the neurotypical population.[5] Hartley et al. demonstrated a relationship with increased neocortical Aβ accumulation and a decline in certain cognitive capabilities in the transitional phase before a dementia diagnosis in patients with DS.[6] As Aβ accumulates in the brain across the lifespan in DS, it may be possible to identify regional Aβ distributions that predict future conversion to dementia using PET.

In this study, a small sample of cognitively stable (non-demented) participants with DS were followed clinically for 4 years after acquiring a single baseline [^{18}F]-florbetapir PET scan. During the 4-year follow up, a subset progressed to dementia. Here we report on differential amyloid accumulation as a function of transition time and classification results of predicting those who transitioned, using only the baseline PET scan data. Regions of particular interest of amyloid uptake were the frontal regions, middle and inferior temporal cortices, and the inferior parietal cortex, as these areas have been linked to executive functioning, visuospatial processing, and memory. We hypothesized these regions would show preferential uptake during dementia transition.

2 | METHODS

2.1 | Participant characteristics

Participants were male or female with DS who were at least 40 years old; other inclusion and exclusion criteria can be reviewed in the supporting information (supplement S1). Nineteen cognitively stable adult participants with DS were evaluated at baseline and after 9, 18, 27, and 48 months. Informed consent was obtained according to institutional review board protocols for persons with intellectual disabilities. During the period of follow-up, five participants progressed (age = 50.4+/−4.3 years; sex = two male, three female; average transition time from PET scan = 1.9 ± 1.3 years) to dementia based on clinical evaluations; 14 remained cognitively stable (age = 52.1+/−5.7 years; sex = ten male, four female). The groups did not differ in mean age (t[17] = 0.70; $P < 0.49$ two-tailed), sex (Fisher's exact: $P < 0.30$, two-tailed), or intellectual functioning (X^2[3, N = 19] = 1.69; $P = 0.64$). PET scans were only acquired at the baseline visit whereas clinical and neuropsychological visits continued for up to 48 months (supplement S3 in supporting information).

RESEARCH IN CONTEXT

1. **Systematic review**: Down syndrome (DS) is a condition marked by brain amyloid accumulation and elevated risk for Alzheimer's disease (AD). The authors reviewed the DS literature in PubMed, conference publications, abstracts, and posters along with current research from the Alzheimer's Biomarkers Consortium-Down Syndrome (ABC-DS). This article fills a gap in our understanding of how predictive regional brain amyloid is of future conversion to dementia in DS and its potential use in a composite risk profile.

2. **Interpretation**: Our findings suggest that the spatial distribution of amyloid in DS, measured by [^{18}F]-florbetapir positron emission tomography, is predictive of transition to dementia and identifies a binding pattern in addition to "AD signature regions" important for accurate prediction.

3. **Future directions**: Future studies with larger samples, longer follow-up, and comprehensive biomarker assessments will be needed to replicate these findings and understand their utility in a risk profile for dementia. A large-scale National Institutes of Health–supported cooperative study, ABC-DS, is currently underway.

2.2 | Diagnosis of the transition to dementia

Dementia was diagnosed in accordance with International Classification of Diseases 10th edition (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria as outlined by Sheehan et al.[7] Transition classification followed comprehensive baseline and longitudinal assessments including history, neurological examination, and consideration of previous studies in the medical record. Transition to dementia was decided at a consensus conference, blinded to the PET scan and neuropsychological results. Participants with confounding conditions (eg, sensory deficit, untreated thyroid dysfunction, and major depression) were excluded. Adults with DS experience health co-morbidities that can mimic AD dementia or impact an existing dementia. Relevant conditions include thyroid dysfunction, sensory impairment, depression and other neuropsychiatric conditions, seizures, medication side effects, and other systemic illnesses. To address these potential confounds, a thorough medical and behavioral health history, medical chart review, and neurological and physical examinations were performed at each visit and this information was used at the consensus diagnosis conference of dementia status and the process of differential diagnosis. Details regarding transition symptoms of individual participants are given in the supporting information (supplement S2). For transitioned participants, the

transition times corresponded to the clinical visit at which a new diagnosis was given.

2.3 | Image acquisition

[^{18}F]-Florbetapir PET scans were acquired at the University of California, Irvine Neuroscience Imaging Center using the high resolution research tomograph (HRRT).[8] Image acquisition followed the Alzheimer's Disease Neuroimaging Initiative (ADNI)[9] protocol. PET reconstructions were performed using the 3D ordinary Poisson ordered subset expectation maximization (3D OP-OSEM) algorithm with all standard corrections applied.[10] Structural T1-weighted magnetization prepared rapid gradient echo (MPRAGE) scans were acquired on a 3-Tesla Philips Achieva scanner (sagittal orientation, TR/TE = 6.8/3.2 ms, flip angle = 9°, NEX = 1, field of view = 27 cm^2, voxel resolution = 0.94 × 0.94 × 1.20 mm, matrix size = 288 × 288 × 170, SENSE acceleration factor = 2).

2.4 | Image processing

The PET frames were realigned, averaged, and co-registered with their respective magnetic resonance imaging (MRI) scans. MRI segmentations were computed with the FreeSurfer (FS6; RRID:SCR_001847). Regions of interest (ROI) were extracted in the native MRI space from the FS6 Desikan/Killiany atlas[11] segmentations. The PET counts were converted to standardized uptake value ratio (SUVR) units using the cerebellum cortex reference region. Correction for partial volume effects was performed using PETSurfer.[12] Voxel-weighted ROI averages for inferior parietal, entorhinal, lateral occipital, anterior/posterior cingulate, inferior/middle/superior temporal, prefrontal, superior frontal, rostral-middle frontal, medial/lateral orbito-frontal, precuneus, dorsal striatum, hippocampus, and whole-brain were computed for each subject.

2.5 | Statistical analysis and classification

To evaluate the risk of conversion to dementia given the variable transition times relative to the PET scan acquisitions, Cox regression models were built with the R survival package (RRID:SCR_001905). Separate regression models were evaluated for each ROI after removing the linear effects of region volume on ROI SUVR average and including age at the time of PET scan as a covariate.

To evaluate the predictive capacity of using only the baseline amyloid PET data to predict future transition to dementia, we trained logistic regression classifiers for each ROI independently after removing the linear effects of region volume and age. Because of the small sample size, we used an independent dataset of 11 participants with DS from the Alzheimer's Biomarkers Consortium-Down Syndrome (ABC-DS) with an initial consensus-based diagnosis of mild cognitive

impairment-Down syndrome (MCI-DS),[13] six of which transitioned (range: 1.0–1.4 years after PET scan) to a diagnosis of dementia (age = 54.1+/−4.6 years; three women, eight men)[LT1]. Participants with MCI-DS were selected from the ABC-DS project as being the closest in level of disease severity to the "cognitively stable" group in this study as the diagnosis procedures in ABC-DS were different (eg, consensus-based using clinical, neuropsychological assessments, and caregiver reports) from the clinically focused process used for the current study. This allowed us to test the logistic regression classifiers trained with the primary dataset in an independent sample.

3 | RESULTS

In the following sections, we describe analyses designed to evaluate: (1) the relationship between transition time to clinical dementia and regional amyloid burden, (2) the effect size of differences between transitioned and non-transitioned participants, and (3) our ability to predict who would transition to frank dementia.

3.1 | Brain amyloid and risk of clinical conversion

The results of evaluating the relationship between transition time and regional amyloid burden using Cox regression models are shown in Table 1 where regions are ordered by the magnitude of the Cohen's D effect sizes of the group differences using the partial volume corrected data. The average whole-brain SUVR for transitioned participants was 1.46+/−0.17 while the non-transitioned participants were lower at 1.26+/−0.09. For whole-brain voxel-wise effect size estimates between transitioned and non-transitioned participants see the supplement S3.

3.2 | Amyloid classification of future clinical transition

Given the robust findings from the regression analyses, we were interested in evaluating the performance of a classification algorithm in detecting future dementia transitions using amyloid PET data prior to conversion. Using the PET scan data from the independent test set, prior to transition and after removing the linear effects of region volume and age, we evaluated whether the trained classifiers could discriminate between those who transitioned to dementia and those who did not (Table 2). We found, similar to the Cox regression analysis, that amyloid burden in prefrontal, inferior parietal, superior frontal, rostral middle frontal, and posterior cingulate were among the most sensitive regions for detecting who would eventually transition. Broadly looking across the metrics, we found prefrontal and superior frontal cortices to be the best overall regions, with high sensitivity, balanced accuracy, area under the receiver operating characteristic (AUC) curve, and reasonably good specificity (0.80).

TABLE 1 Cox regression analysis results with and without partial volume correction (PVC) by region of interest

	PVC				Without PVC			
Regions of interest	Z	P	P Adj	Cohen's D	Z	P	P Adj	Cohen's D
Brain Average	2.53	0.006	0.044	1.87	2.51	0.006	0.041	1.19
Superior Frontal	2.53	0.006	0.044	1.86	2.50	0.006	0.041	1.85
Prefrontal	2.24	0.012	0.056	1.81	2.39	0.009	0.047	1.80
Middle temporal	2.45	0.007	0.047	1.74	2.00	0.026	0.077	2.18
Posterior cingulate	2.25	0.012	0.056	1.67	2.44	0.007	0.045	2.18
Rostral middle frontal	2.20	0.014	0.056	1.66	2.37	0.009	0.047	1.65
Inferior parietal	2.64	0.004	0.037	1.60	2.71	0.003	0.030	1.77
Superior temporal	2.20	0.014	0.056	1.55	2.32	0.010	0.051	1.43
Precuneus	2.62	0.004	0.040	1.52	2.61	0.004	0.035	1.65
Lateral orbitofrontal	1.92	0.027	0.074	1.29	2.11	0.017	0.063	1.90
Medial orbitofrontal	1.98	0.024	0.072	1.18	2.26	0.012	0.052	1.24
Anterior cingulate	1.97	0.024	0.073	1.13	2.13	0.017	0.063	1.29
Dorsal striatum	1.83	0.033	0.074	1.10	1.86	0.031	0.094	0.95
Inferior temporal	1.65	0.049	0.098	0.89	2.65	0.004	0.032	1.62
Hippocampus	0.18	0.431	0.431	0.13	0.66	0.254	0.259	0.35
Entorhinal cortex	−1.39	0.083	0.083	−0.73	−0.46	0.323	0.323	−0.23
Lateral occipital	−1.93	0.027	0.054	−1.32	0.65	0.259	0.259	0.09

Notes: Table shows the z-score from Cox regression, uncorrected P-values (P), adjusted (Hommel method) P-values (P Adj), and Cohen's D effect size of transitioned versus non-transitioned participants.

TABLE 2 Logistic regression classifier results tested on an independent sample of participants with mild cognitive impairment (N = 11) prior to conversion to dementia (N = 6)

Region	Sensitivity	Specificity	Balanced accuracy	AUC
Prefrontal	1.00	0.80	0.90	0.93
Posterior cingulate	1.00	0.60	0.80	0.83
Inferior parietal	1.00	0.20	0.60	0.80
Superior frontal	1.00	0.80	0.90	0.97
Rostral middle frontal	1.00	0.60	0.80	0.90
Anterior cingulate	0.83	0.80	0.82	0.90
Superior temporal	0.83	0.40	0.62	0.67
Middle temporal	0.83	0.40	0.62	0.80
Brain average	0.67	0.80	0.73	0.80
Precuneus	0.67	0.40	0.53	0.73
Lateral Orbitofrontal	0.67	0.80	0.73	0.77
Medial Orbitofrontal	0.67	0.60	0.63	0.80
Dorsal striatum	0.50	0.80	0.65	0.77
Inferior temporal	0.50	0.80	0.65	0.70
Hippocampus	0.33	1.00	0.67	0.47
Entorhinal cortex	0.00	1.00	0.50	0.30
Lateral occipital	0.00	1.00	0.50	0.67

Note: Metrics shown include specificity, sensitivity, accuracy balanced for number of participants in each test group, and area under the receiver operating characteristic curve (AUC).

4 | DISCUSSION

This retrospective case-control study evaluated a cohort of 19 participants with DS, 5 of whom transitioned to dementia during the course of follow-up. The primary goal was to evaluate the regional distribution of amyloid prior to clinical transition and understand whether amyloid alone predicts future transition. Exploiting an advantage of logistic regression with retrospective study designs,[14] these analyses described the predictive potential for classifying cases based on regional amyloid distribution in scans prior to transition. We found that high amyloid burden in several regions, namely the prefrontal, superior and rostral middle frontal, and posterior cingulate provided excellent prediction of dementia transition. These regions are broadly associated with executive function, working memory, and attentional focus, which have been implicated in dementia progression in both DS[15] and neurotypical populations.[16] Interestingly, the hippocampus, a region implicated in the progression of AD,[17] was not related to transition in our sample. We speculate this region may have reached a plateau in its capacity to accumulate amyloid as there is virtually no difference in hippocampal amyloid between our two groups.

Comparing our classifier results with a study from Matthews et al. which evaluated [18F]-fluorodeoxyglucose (FDG) PET binding in DS, they found patterns of increased FDG metabolism in frontal regions and decreases in cingulate cortices compared to normal neurotypical participants[18] whereas we found amyloid binding in posterior cingulate to be as accurate as frontal regions in detecting future transition.

These data suggest that regional FDG metabolism may not track monotonically with amyloid load.

In the neurotypical population, the biomarker utility of increased cortical uptake as a result of amyloid binding on PET scans has been of interest in preclinical AD. However, it is not clear that the uptake data reliably predicts those who will subsequently transition to dementia.[3] Various working groups in nuclear medicine and AD have developed criteria for using amyloid PET in the diagnosis of patients with persistent or unexplained mild cognitive impairment in the neurotypical population but the diagnostic and predictive status of these measures remains uncertain.[19] Other groups have found the rate of amyloid beta accumulation in the brains of individuals with DS differ according to the pre-existing amyloid burden[20,21] and the presence of cortical Pittsburgh compound B (PiB)-binding, another PET amyloid ligand, as a function of age, which has been confirmed in *post mortem* studies.[22] It should also be noted that amyloid burden in *post mortem* studies has differed compared to PET imaging studies in DS. PET imaging in DS has shown amyloid accumulation in the subcortical regions appearing first before the areas in the neocortex such as the temporal lobes, while *post mortem* studies have found that accumulation likely begins in the neocortex before, if not simultaneously in, the subcortical regions including the striatum.[23] Given that our sample consists of older adults just prior to dementia conversion, we cannot speculate on where amyloid accumulates first. Our results suggest amyloid burden in the frontal, temporal, parietal, and cingulate cortices are the best correct classification of future dementia transition.

Our study suggests regional profiles of brain amyloid in older adults with DS may predict cognitive decline and are informative in evaluating the risk for dementia. Limitations of our study include the small sample size and imbalance in sex across the classifier training/testing groups, which may impact the generalizability of our findings. In a related study, we found increased amyloid in specific regions to be associated with MCI-DS, supporting the use of regional amyloid in tracking dementia progression in DS.[13] Our current study reinforces these observations, suggesting a role for regional amyloid measurements in a composite risk score for predicting dementia progression in individuals with DS. Pending replication in a larger sample, our small study suggests that regional amyloid may be a useful quantitative measure to include in a composite risk score for dementia transition in DS.

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CONFLICTS OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or nonfinancial interest in the subject matter or materials discussed in this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.