Brain Amyloid and the Transition to Dementia in Down Syndrome

David B. Keator[1], Eric Doran[2], Lisa Taylor[1], Michael J. Phelan[3], Christy Hom[1], Katherine Tseung[4], Theo G.M. van Erp[1,8], Steven G. Potkin[1], Adam M. Brickman[5], Diana H. Rosas[6], Michael A. Yassa[1,7,8], Wayne Silverman[2], Ira T. Lott[2].

[1] Department of Psychiatry and Human Behavior, University of California, Irvine, CA, 92697 USA.

[2] Department of Pediatrics, University of California, Irvine Medical Center, Orange, CA, 92868 USA.

[3] Department of Statistics, University of California, Irvine, CA, 92697 USA.

[4] Keck Science Department, Scripps College, Claremont, CA, 91711 USA.

[5] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University New York, NY., 10025 USA.

[6] Massachusetts General Hospital, Harvard University, Boston, MA., 02114 USA.

[7] Department of Neurobiology and Behavior, University of California, Irvine, CA, 92697 USA.

[8] Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA, 92697 USA.

Corresponding Author:

David B. Keator, M.S., Ph.D.

University of California, Irvine

Irvine Hall rm. 163, ZOT-3960

Irvine, CA. 92697

dbkeator@uci.edu

949-824-7870

Running Title: **Brain Amyloid and the Transition to Dementia in Down Syndrome**

Highlights

- Regional [18F]-Florbetapir PET predicts future transition to dementia in Downs Syndrome.

- Increased amyloid in prefrontal, inferior parietal, superior frontal, rostral middle frontal, and posterior cingulate cortices detect transitioiners, with prefrontal and superior frontal being best overall.

- Amyloid PET-based classification able to discriminate between transitioners and non-transitioners.

Keywords

- Down Syndrome, Amyloid, PET, SUVR, Dementia, Alzheimer's, Classification, Predict, Transition

Abstract

INTRODUCTION: Down syndrome (DS) is associated with elevated risk for Alzheimer's disease (AD) due to beta amyloid (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 PET scans from 19 nondemented individuals with DS at baseline and monitored them for four years, with five individuals transitioning to dementia. Machine learning classification determined features on ^{18}F-Florbetapir standardized uptake value ratio (SUVR) 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.

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 (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 since 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 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.

In this study, a small sample of cognitively stable (non-demented) participants with DS were followed clinically for four years after acquiring a baseline [^{18}F]-Florbetapir PET scan. During the four-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 the baseline PET scan. 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 and are consistent with late Braak and Braak stages [5]. We hypothesized these regions would show preferential uptake during dementia transition.

2. METHODS

2.1 Participant Characteristics

Nineteen cognitively stable adult participants with DS were evaluated at baseline and after nine, 18, 27, and 48 months. Informed consent was obtained according to IRB protocols for persons with intellectual disabilities. During the period of follow-up, five participants progressed (age=50.4+/-4.3yrs.; sex=2 Male, 3 Female; average transition time from PET scan=1.9±1.3yrs.) to dementia based on clinical evaluations; fourteen remained cognitively stable (age=52.1+/-5.7yrs.; sex=10 male, 4 female). The groups did not differ in mean age (t(17)=0.70;p<0.49 two-tailed) or sex (p<0.30 Fisher's). Baseline PET scans were acquired along with longitudinal neuropsychological assessments (supplement S3).

2.2   Diagnosis of the Transition to Dementia

Dementia was diagnosed in accordance with ICD-10 and DSM-IV-TR criteria as outlined by Sheehan et al. [6]. 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 (e.g. sensory deficit, untreated thyroid dysfunction, and major depression) were excluded. Details regarding transition symptoms of individual participants are given in the supplemental material (supplement S1).

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) [7]. Image acquisition followed the Alzheimer's Disease Neuroimaging Initiative (ADNI) [8] protocol. PET

reconstructions were performed using the 3D ordinary Poisson ordered subset expectation maximization (3D OP-OSEM) algorithm with scatter and attenuation corrections [9]. Structural T1-weighted MPRAGE scans were acquired on a 3-Tesla Philips Achieva scanner (sagittal orientation, TR/TE=6.8/3.2ms, flip angle=9°, NEX=1, field of view=27cm^2, voxel resolution=0.94x0.94x1.20mm, matrix size=288x288x170, SENSE acceleration factor=2).

2.4   Image Processing

The PET frames were realigned, averaged, and co-registered with their respective 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 [10] 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 [11]. 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. To understand whether regional amyloid burden was predictive of transition, we modeled the logit of the probability of transition as a linear function of average amyloid burden for each ROI after removing the linear effects of region volume and age.

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; (3) our ability to predict who would transition to frank dementia.

3.1 Brain Amyloid and Risk of Clinical Conversion

Cox regression models were built with the R survival package to evaluate the risk of conversion given the variable transition times relative to the PET scan acquisitions (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. The results are shown in Table 1 where regions are ordered by magnitude of risk. The Cohen's D effect sizes of the group differences for each ROI is included.

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. Because of the small sample size, we used an independent dataset of eleven 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) [12], six of which transitioned (range: 1.0-1.6 yrs. after PET scan) to a diagnosis of dementia (age=53.1+/-4.3yrs.;1 woman, 10 men). This allowed us to test the logistic regression classifiers trained with the primary dataset. 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).

4.   DISCUSSION

This retrospective case-control study evaluated a cohort of nineteen participants with DS, five 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 [13], 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 [14] and neurotypical populations [15].

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 [16].   Other groups have found the rate of β-amyloid accumulation in the brains of individuals with DS differ according to the pre-existing amyloid burden [17,18] 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 [19]. 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. 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 [12]. 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, regional amyloid is likely a useful quantitative measure to include in a composite risk score for dementia transition in DS.

References

[1] Mann DMA, Esiri MM. The pattern of acquisition of plaques and tangles in the brains of patients under 50 years of age with Down's syndrome. J Neurol Sci 1989;89:169–79.

[2] Lott IT, Doran E, Nguyen VQ, Tournay A, Head E, Gillen DL. Down syndrome and dementia: a randomized, controlled trial of antioxidant supplementation. Am J Med Genet A 2011;155A:1939–48.

[3] Chiotis K, Saint-Aubert L, Leuzy A, Rodriguez-Vieitez E, Nordberg A. Tau pet imaging in neurodegenerative tauopathies – a multimodal paradigm. Neurobiol Aging 2016;39:S29.

[4] Grimmer T, Wutz C, Drzezga A, Förster S, Förstl H, Ortner M, et al. The usefulness of amyloid imaging in predicting the clinical outcome after two years in subjects with mild cognitive impairment. Curr Alzheimer Res 2013;10:82–5.

[5] Braak H, Braak E. Morphological criteria for the recognition of Alzheimer's disease and the distribution pattern of cortical changes related to this disorder. Neurobiol Aging 1994;15:355–6; discussion 379–80.

[6] Sheehan R, Sinai A, Bass N, Blatchford P, Bohnen I, Bonell S, et al. Dementia diagnostic criteria in Down syndrome. Int J Geriatr Psychiatry 2015;30:857–63.

[7] Eriksson L, Wienhard K, Eriksson M, Casey ME, Knoess C, Bruckbauer T, et al. The ECAT HRRT: NEMA NEC evaluation of the HRRT system, the new high-resolution research tomograph. IEEE Trans Nucl Sci 2002;49:2085–8.

[8] ADNI Home n.d. http://www.adni-info.org/ (accessed December 8, 2016).

[9] Keller SH, Svarer C, Sibomana M. Attenuation correction for the HRRT PET-scanner using transmission scatter correction and total variation regularization. IEEE Trans Med Imaging 2013;32:1611–21.

[10] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968–80.

[11] Greve DN, Svarer C, Fisher PM, Feng L, Hansen AE, Baare W, et al. Cortical surface-based analysis reduces bias and variance in kinetic modeling of brain PET data. Neuroimage 2014;92:225–36.

[12] Keator DB, Phelan MJ, Taylor L, Doran E, Krinsky-McHale S, Price J, et al. Down syndrome: Distribution of brain amyloid in mild cognitive impairment. Alzheimers Dement 2020;12:e12013.

[13] Pepe MS. The Statistical Evaluation of Medical Tests for Classification and Prediction. Oxford University Press on Demand; 2004.

[14] Lautarescu BA, Holland AJ, Zaman SH. The Early Presentation of Dementia in People with Down Syndrome: a Systematic Review of Longitudinal Studies. Neuropsychol Rev 2017;27:31–45.

[15] Kirova A-M, Bays RB, Lagalwar S. Working Memory and Executive Function Decline across Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. BioMed Research International 2015;2015:1–9. https://doi.org/10.1155/2015/748212.

[16] Mallik A, Drzezga A, Minoshima S. Clinical Amyloid Imaging. Semin Nucl Med 2017;47:31–43.

[17] Lao PJ, Handen BL, Betthauser TJ, Mihaila I, Hartley SL, Cohen AD, et al. Longitudinal changes in amyloid positron emission tomography and volumetric magnetic resonance

imaging in the nondemented Down syndrome population. Alzheimers Dement 2017;9:1–9.

[18] Jennings D, Seibyl J, Sabbagh M, Lai F, Hopkins W, Bullich S, et al. Age dependence of brain β-amyloid deposition in Down syndrome: An [18F]florbetaben PET study. Neurology 2015;84:500–7.

[19] LeVine H 3rd, Spielmann HP, Matveev S, Cauvi FM, Murphy MP, Beckett TL, et al. Down syndrome: age-dependence of PiB binding in postmortem frontal cortex across the lifespan. Neurobiol Aging 2017;54:163–9.

Regions of Interest	PVC				Without PVC			
	Z	P	P Adj	Cohen's D	Z	P	P Adj	Cohen's D
BrainAverage	2.53	0.006	0.044	1.87	2.51	0.006	0.041	1.19
SuperiorFrontal	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
MiddleTemporal	2.45	0.007	0.047	1.74	2.00	0.026	0.077	2.18
PosteriorCingulate	2.25	0.012	0.056	1.67	2.44	0.007	0.045	2.18
RostralMiddleFrontal	2.20	0.014	0.056	1.66	2.37	0.009	0.047	1.65
InferiorParietal	2.64	0.004	0.037	1.60	2.71	0.003	0.030	1.77
SuperiorTemporal	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
LateralOrbitoFrontal	1.92	0.027	0.074	1.29	2.11	0.017	0.063	1.90
MedialOrbitoFrontal	1.98	0.024	0.072	1.18	2.26	0.012	0.052	1.24
AnteriorCingulate	1.97	0.024	0.073	1.13	2.13	0.017	0.063	1.29
DorsalStriatum	1.83	0.033	0.074	1.10	1.86	0.031	0.094	0.95

InferiorTemporal	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
EntorhinalCortex	-1.39	0.083	0.083	-0.73	-0.46	0.323	0.323	-0.23
LateralOccipital	-1.93	0.027	0.054	-1.32	0.65	0.259	0.259	0.09

Table 1. Cox regression analysis results with and without partial volume correction (PVC) by region of interest. 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 vs. non-transitioned participants.

Region	Sensitivity	Specificity	Balanced Accuracy	AUC
Prefrontal	1.00	0.80	0.90	0.93
PosteriorCingulate	1.00	0.60	0.80	0.83
InferiorParietal	1.00	0.20	0.60	0.80
SuperiorFrontal	1.00	0.80	0.90	0.97
RostralMiddleFrontal	1.00	0.60	0.80	0.90
AnteriorCingulate	0.83	0.80	0.82	0.90
SuperiorTemporal	0.83	0.40	0.62	0.67
MiddleTemporal	0.83	0.40	0.62	0.80
BrainAverage	0.67	0.80	0.73	0.80
Precuneus	0.67	0.40	0.53	0.73
LateralOrbitoFrontal	0.67	0.80	0.73	0.77
MedialOrbitoFrontal	0.67	0.60	0.63	0.80
DorsalStriatum	0.50	0.80	0.65	0.77
InferiorTemporal	0.50	0.80	0.65	0.70
Hippocampus	0.33	1.00	0.67	0.47

EntorhinalCortex	0.00	1.00	0.50	0.30
LateralOccipital	0.00	1.00	0.50	0.67

Table 2: Logistic regression classifier results tested on an independent sample of participants with MCI (N=11) prior to conversion to dementia (N=6). Metrics shown include specificity, sensitivity, accuracy balanced for number of participants in each test group, and area under the ROC curve (auc).