"Down Syndrome and Alzheimer’s Disease: Defining a Pathway Toward Prevention"

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Outline

- Rationale for Studying AD in Down Syndrome
- Background of Alzheimer’s Disease
- Imaging the Brain with PET and MRI
- Findings of the Role of Amyloid and Tau in Alzheimer’s Disease
- Neurodegeneration in Aging Down Syndrome
- Defining a Pathway for the Prevention of Alzheimer’s Disease
Alzheimer’s Disease and Down Syndrome

• General population:
  • Rare before age 50
  • 3% between 65-74yrs
  • 17% between 75-84yrs
  • 32% over 85yrs

• Down syndrome:
  • 9% of adults in 40
  • 33% of adults in 50s
  • 50% of adults in 60s+ yrs
Characteristics of Alzheimer’s Disease

- **Dementia** – progressive deterioration of cognitive function that ultimately prevents a person from independently performing their daily activities

- **Alzheimer’s Disease** – accounts for 70% of cases of dementia
  - Symptoms include difficulty in:
    - Language, memory, perception, emotional behavior, cognitive skills
    - (e.g. judgment)
Why is AD a public policy issue?

• AD is the most common form of dementia (60-80%)
  • 5.5M people in the US, estimated to double every 20yrs (16M by 2050)
  • Age is the largest risk factor
    • 3% between 65-74yrs
    • 17% between 75-84yrs
    • 32% over 85yrs

• Increasing elderly population
  • Medical advances and improved social and environmental conditions
  • In 2017 alone, there were
    • Estimated 64,000 new AD cases between 65-74yrs
    • Estimated 173,000 new AD cases between 75-84yrs
    • Estimated 243,000 new AD cases above age 85yrs

• Large socioeconomic burden on healthcare systems and families exacerbated by the decades long disease
  • National Alzheimer’s Project Act (NAPA; 2011): discover an effective treatment by 2025
  • 2019: $2.3B

Alzheimer’s Association, 2017; National Center for Health Statistics, 2017

Slide provided by Dr. Patrick Lao
Pathology of Alzheimer’s Disease
AD Pathology
- tangles and plaques

www.nia.nih.gov

Tangles and plaques are hallmarks of AD. Tangles are abnormal tangles of microtubules, which help transport materials and signals within nerve cells. Plaques are deposits of proteins outside the nerve cells, which can interfere with communication between cells.
β – Amyloid Plaques

Non-amyloidogenic

Amyloidogenic

www.nia.nih.gov
Tau Tangles in Alzheimer’s Disease
Why the Increased Risk for AD in Down Syndrome?

**Trisomy of chromosome 21**

- 234 protein encoding genes
- Overproduction (1.5x) of gene products, like amyloid precursor protein (APP)
- Amyloid deposition begins as early as 10-20yrs with DS
- Nearly ubiquitous in adults with DS by 40yrs at autopsy
- Same core protein as plaques in AD

Reprinted from Shaw, 2013
Down Syndrome – Trisomy 21

Life Expectancy

• Average life expectancy:
  9-12 yrs in 1929-1949
  55-60 yrs in 1991-2002

• Improved healthcare, lower infant mortality rate, shift away from institutional care

• Growing elderly DS population is resulting in a higher prevalence of adults with DS having Alzheimer’s Disease
Association of Dementia With Mortality in Down Syndrome

Cross-sectional data showing the distribution of age at dementia diagnosis in people with DS.

Alzheimers Dement. 2018; 4:703-713
Tracking Biomarkers for Alzheimer’s Disease

• Biomarker – ”Biological Markers” are medical signs which define a medical state from outside the patient and can be reproduced and measured accurately, unlike the medical symptoms which are mere indications of a patient’s condition described and perceived by the patients themselves.
Theoretical relation between dementia status and “IQ”

Figure Provided by Dr. Sharon Krinsky-McHale, Columbia University
Biomarkers for Alzheimer’s Disease

- amyloid
- tau
- neurodegeneration
Magnetic Resonance Imaging (MRI)  Positron Emission Tomography (PET)
Motivation: Why Study AD Biomarkers in Down Syndrome?

• Provide molecular information during the pre-dementia stage of amyloid-β accumulation

• Inform the timing of future studies (assuming generalizability to other populations)

• Motivate intervention trials, for which the DS population is particularly suited
• The goal of this project is to track amyloid deposition in adults with DS and to follow these individuals to understand the course of amyloid deposition and its effect on functioning over time.
Objectives

- Identify the patterns of amyloid burden in non-demented individuals with DS
- Examine the relation between amyloid burden and cognitive function
  - Identify the longitudinal changes in magnitude and regional distribution of changes in amyloid burden and gray matter volumes
  - Examine the relation of changes in neuropsychological measures with the presence of β-amyloid.
Methods: Participants

- Enrolled 79 non-demented participants with confirmed trisomy 21
  - Adults with DS ≥ 30 years of age
  - Excluded for any medical or psychiatric condition that would impair cognitive function or contraindicate a PET or MRI scan
  - Screened, but not excluded for any AD or memory enhancing medication

- Dependent Measures
  - Adaptive/Behavioral/AD measures
  - Neuropsychological measures
  - MRI (T1, T2, T2*)
  - PET (PiB, FDG)
  - Genetics (ApoE)
# Experimental Details

## Current Study Procedures and Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Informant/Participant</th>
<th>Time (minutes)</th>
<th>Screen/Baseline</th>
<th>Follow-Up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1 (Informant and Neuropsychological Measures)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>Caretaker &amp; Subject</td>
<td>45-60</td>
<td>X</td>
<td></td>
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<tr>
<td>DSDS Interview</td>
<td>Caretaker</td>
<td>30</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SIB/IQ/Neuropsych</td>
<td>Subject</td>
<td>120-150</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychiatric Assessment</td>
<td>Subject</td>
<td>15</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vineland/Reiss Screen</td>
<td>Caretaker</td>
<td>60</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical/Psychiatric Hx</td>
<td>Caretaker</td>
<td>15</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Day 2 (Neuroimaging Measures)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Subject</td>
<td>30</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PiB PET Scan</td>
<td>Subject</td>
<td>90</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Slide Provided by Dr. Sigan Hartley
PiB Status

- Tissue ratios calculated for cortical regions-of-interest (ROI) and normalized to cerebellum (SUVR) using 50-70 min PiB uptake.

- PiB(+) = above the cutoff in cortical areas defined using sparse k-means clustering
RESULTS: AMYLOID BURDEN BY PIB POSITIVITY

Cross-sectional patterns of amyloid burden

- PiB(-), n=59: predominantly white matter uptake

Slide provided by Dr. Patrick Lao
Cross-sectional patterns of amyloid burden

- **PiB(-), n=59**: predominantly white matter uptake
- **PiB(+), n=4**: elevated striatum uptake without elevated neocortical uptake
- **PiB(+), n=2**: elevated neocortical uptake without elevated striatum uptake
- **PiB(+), n=14**: elevated neocortical and elevated striatum uptake

*Lao et al., Alz & Dementia 2016.*
## Significant Neuropsychological Measures (Cycle 1)

<table>
<thead>
<tr>
<th></th>
<th>PiB+ (N=17)</th>
<th>PiB- (N=35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free Recall</td>
<td>14.2 (5.5)</td>
<td>16.9 (6.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cued Recall Intrusion</td>
<td>4.1 (5.3)</td>
<td>1.9 (2.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Visual Attention Time</td>
<td>94.2 (47.5)</td>
<td>77.0 (35.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Peg Board (both)</td>
<td>4.7 (1.9)</td>
<td>5.7 (1.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Expressive One-Word</td>
<td>66.1 (22.5)</td>
<td>77.4 (25.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Picture Recognition</td>
<td>4.4 (3.5)</td>
<td>6.5 (3.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table provided by Ben Handen, Ph.D.

Objectives

• Identify the regional distribution of amyloid burden in non-demented individuals with DS
• Examine the relation between amyloid burden and cognitive function
• Identify the longitudinal changes in magnitude and regional distribution of changes in amyloid burden and gray matter volumes
• Examine the relation of changes in neuropsychological measures with the presence of β-amyloid.
Longitudinal : Experimental Details

• Enrolled 79 non-demented participants with confirmed trisomy 21
• 52 participants with 2 cycles of data (3.0 ± 0.6 yrs after cycle 1)
  • Age at cycle 1
    • Range: 30-50 yrs
    • Mean ± SD: 37.5 ± 6.7 yrs
  • 46.2% Male / 53.8% Female
• N=5 APOE4 carriers

Lao et al. NRM 2016
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

Amyloid Accumulation in the PiB(-) subgroup
• PiB(-) at cycle 1
• PiB(-) at cycle 2
• Annual percent change = \[
\frac{[(\text{Cycle 2} - \text{Cycle 1})/\text{Cycle 1}] \times 100}{\text{(time between cycles)}}
\]
• Most areas have no change
• Slight positive change in:
  • Frontal cortex
  • Parietal cortex
  • Striatum
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

Longitudinal $[^{11}C]$PiB Age Associations

- Anterior Cingulate
- Frontal Cortex
- Parietal Cortex
- Precuneus
- Sulcus
- Temporal Cortex

PiB(-) subgroup

Slide provided by Dr. Patrick Lao
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

Amyloid Accumulation in the PiB converter subgroup
- PiB(-) at cycle 1
- PiB(+) at cycle 2
- Most areas have a positive change, namely:
  - Anterior cingulate
  - Frontal cortex
  - Parietal cortex
  - Precuneus
  - Striatum
  - Temporal cortex

Slide provided by Dr. Patrick Lao
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

Longitudinal $[^{11}C]PiB$ Age Associations

PiB converter subgroup
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

Amyloid Accumulation in the PiB(+) subgroup
- PiB(+) at cycle 1
- PiB(+) at cycle 2
- Most areas have a positive change, namely:
  - Anterior cingulate
  - Frontal cortex
  - Parietal cortex
  - Precuneus
  - Striatum
  - Temporal cortex
- Can see enlarged ventricle spaces in PiB(+) subgroup
RESULTS: LONGITUDINAL AMYLOID ACCUMULATION

Longitudinal $[^{11}C]PiB$ Age Associations

PiB(+) subgroup
Striatal First Patterns of Amyloid

Handen et al., Alzheimers Dement. 2012

Presenilin (PS1) Mutation Carriers

Klunk et al., J Neurosci. 2007
Results: Significant Correlations between change in Neuropsych & PiB retention

Longitudinal Group Comparisons (one-way ANOVA)

<table>
<thead>
<tr>
<th></th>
<th>PiB- to PiB-</th>
<th>PiB- to PiB+</th>
<th>PiB+ to PiB+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free Recall Total</td>
<td>Improved</td>
<td>Improved</td>
<td>Worse*</td>
</tr>
<tr>
<td>Free &amp; Cued Total</td>
<td>No change</td>
<td>Worse</td>
<td>Worse*</td>
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<tr>
<td>Cued Recall Intrusions</td>
<td>Improved</td>
<td>Worse</td>
<td>Worse*</td>
</tr>
<tr>
<td>Block Design</td>
<td>Improved</td>
<td>Improved</td>
<td>Worse*</td>
</tr>
<tr>
<td>Purdue (single)</td>
<td>No change</td>
<td>Worse</td>
<td>Worse*</td>
</tr>
<tr>
<td>Corsi forward</td>
<td>Improved</td>
<td>Improved</td>
<td>Worse*</td>
</tr>
</tbody>
</table>

Table provided by Ben Handen, Ph.D.

**Natural History of Amyloid Deposition of Amyloid in Aging Down Syndrome**

- Initiated in 2009: University of Pittsburgh, Waisman Center / UWADRC
- Goal: Recruit non-demented adults (n=84, age ≥ 30 yrs) to observe the change in amyloid deposition and its effect on functioning over time

**NIAD**

*Neurodegeneration in Aging Down Syndrome (NIAD) (U01)*

- Initiated in 2015: UPMC, UW, Cambridge U., Barrow/Banner, Washington U., LONI, Mayo, ATRI, NCRAD, NIA / NICHD
- Goal: This longitudinal study will examine progression of AD related neuroimaging, biofluid, genetic and cognitive/functional biomarkers in 180 adults with DS (>25 yrs of age) and 40 “biomarker-controls”
Alzheimer's Biomarkers Consortium — Down Syndrome (ABC-DS)

For Participants and Families
What is ABC-DS?
The Alzheimer's Biomarkers Consortium of Down Syndrome (ABC-DS) is a new initiative that aims to identify biomarkers that indicate Alzheimer’s disease in people with Down syndrome. It is a joint study conducted by two groups of research collaborators—Neurodegeneration in Aging Down Syndrome (NIAD) and Alzheimer’s Disease In Down Syndrome (ADDSD)—and is funded by the National Institute on Aging (NIA) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), both part of NIH.

The connection between these two conditions is not fully understood, but researchers believe that the presence of beta-amyloid plaques is one of the main contributors to the development of Alzheimer’s disease in people with Down syndrome.

ABC-DS researchers are building on what we know about Alzheimer’s disease in people with Down syndrome, as well as risk and protective factors, imaging scans and blood and tissue samples from adult volunteers with Down syndrome, along with other sources of data. These samples will be used to investigate biomarkers that may help predict the development of Alzheimer’s disease in people with Down syndrome.
## NiAD: Schedule of Biomarker Measures

<table>
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<tr>
<th>Measure</th>
<th>Month -&gt;</th>
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<th>16</th>
<th>32</th>
<th>48</th>
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<tr>
<td><strong>Day 1 (Informant Interview, Neuropsych., MRI)</strong></td>
<td></td>
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<tr>
<td><strong>Informed Consent</strong></td>
<td>B*</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>DSDS Interview &amp; DLD</td>
<td>C*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SIB/IQ/Neuropsych Tests</td>
<td>S*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Psychiatric Assessment</td>
<td>S</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vineland/Reiss Screen</td>
<td>C</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical/Psychiatric Hx</td>
<td>C</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>MRI</strong></td>
<td>S</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Day 2 (Fluid Biomarkers, Genetics and PET Scan)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Trisomy 21-blood</td>
<td>S</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td><strong>CSF</strong></td>
<td>S</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td><strong>PiB PET</strong></td>
<td>S</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td><strong>FDG PET</strong></td>
<td>S</td>
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<td></td>
<td>X</td>
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<tr>
<td>**ApoE, <strong>Genetics-blood</strong></td>
<td>S</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td><strong>Blood (Aβ, proteomics)</strong></td>
<td>S</td>
<td>X</td>
<td></td>
<td></td>
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<td><strong>Day 3 (PET Scan)</strong></td>
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<td></td>
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<td></td>
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<tr>
<td><strong>[F-18]AV-1451 PET</strong></td>
<td>S</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*C=Caregiver; S=DS Subject; B=Both  
**Biomarker Controls will have these measures
Longitudinal Amyloid Studies

N = 166 enrollment to date
Tau Imaging in Down Syndrome

- Acquired at baseline visit, and repeated at 32 months
- Scanned with [F-18]AV-1451
  - SUVR measured from 80 – 100 min
  - N = 166 Down syndrome subjects to date
Tau Imaging in Down Syndrome

26 yr, female

49 yr, female

48 yr, male

45 yr, male

Braak 0

Braak 1-2

Braak 3-4

Braak 5-6
Tau Imaging in Down Syndrome

Adapted from Braak, et al. J Neuropathol Exp Neurol. 2011

Zammit et al, Human Amyloid Imaging 2019
Amyloid cascade hypothesis

Note: sigmoid curves (slopes, spacing) are **arbitrary** in this illustrative figure

- Rates change over time

Selkoe et al, 1991; Jack et al, 2010; 2013
Amyloid cascade hypothesis

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- Rates change over time
- Proposed temporal order

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*Slide provided by Dr. Patrick Lao*
Amyloid cascade hypothesis

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- Rates change over time
- Proposed temporal order, but biomarkers become abnormal simultaneously

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Note: sigmoid curves (slopes, spacing) are **arbitrary** in this illustrative figure

- **Rates change over time**
- **Proposed temporal order**, but biomarkers become abnormal **simultaneously**
- Profile of biomarker abnormality can lead to **range of cognitive function** (cognitive reserve; neuroprotective effect)

Selkoe et al, 1991; Jack et al, 2010; 2013
**Amyloid cascade hypothesis**

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Selkoe et al, 1991; Jack et al, 2010; 2013

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*Slide provided by Dr. Patrick Lao*
Future Directions

• Alzheimer’s Clinical Trial Consortium (ACTC) launched in 2017
  • Initiating ACTC – Down Syndrome (DS)

• INCLUDE – INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome

• Project modeled after Dominantly Inherited Alzheimer Network (DIAN)
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