BrainWire LLC

Predicting the future progression of dementia

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National Institutes of Health

Research highlighted in:
Problem

- Alzheimer’s disease and other dementias are debilitating, incurable diseases
- Affects 1 in 5 elderly, **10 million** in US
- Current diagnosis, prognosis highly subjective, cannot predict future course
- Based on cognitive test, visual assessment of MRI

- **When/whether will I get Alzheimer’s?**
- **Which brain regions will I lose?**
- **Will I lose memory, attention, behavior or executive?**

- **Life/financial planning**
- **Targeted brain stimulation**
- **Therapeutic options (aggressive or not?)**
- **Cognitive reserve, memory exercises**
Enter BrainWire Technology

- A diagnostic and predictive software tool
- Based on cutting edge graph theoretic models
- Barrier to entry: new, emerging technology, IP
- Not possible 2 years ago

Baseline MRI

Computer algorithms, machine learning

The Brainwire product:
- Prognostics on likely future disease patterns
- Risk of conversion assessment
- Best anatomic targets for therapy
- Full neuroradiologist report
How does it work

- BrainWire captures the latest basic science of trans-neuronal transmission of misfolded proteins

Stereotyped atrophy patterns, not random

(but considerable variations amongst patients)

Caused by stereotyped spread of misfolded proteins (A-beta, tau)

Apostolova, Arch Neurol 2007

Alzheimer Association
The Science
Diffusion on Graphs and Relationship to Dementias

- “Signal” $x(t)$: amount of disease agent (Ab, tau) in brain regions
- We mathematically model neurodegeneration as a diffusive process

\[ \frac{dx_1}{dt} = \beta c_{1,2}(x_2 - x_1) \]

Spread of tau pathology from entorhinal cortex traces classic Braak stages (left).
We model the trans-neuronal spread from region 2 to 1 as a diffusion process whose rate is regulated by network connectivity (right).

Closed form solution gives $x(0) \rightarrow x(t)$, for any future time $t$, starting at baseline pathology/atrophy pattern $x(0)$.
How to get the “connectome”?
High Angular Resolution Diffusion Imaging (dMRI)

credit: P Mukherjee
Whole brain tractogram from dMRI

“Connect the dots” to draw tracts between dMRI voxels

Graphic designed by Eve LoCastro
Neuroimaging pipeline to obtain atrophy patterns and connectome from human brains

MRI scans are atlased, parcellated and volumed → diffusion MRI scans are reconstructed, tractograms drawn → Datasets are combined to achieve atrophy and connectivity defined on the same set of nodes.
From DTI to tractography to network or “graph”
Results:

Correlation between atrophy pattern and diffusion model: The seed regions providing the best match with the observed atrophy pattern were the hippocampus ($R_{left}=0.48$, $R_{right}=0.45$), caudate ($R_{left}=0.49$, $R_{right}=0.47$), putamen ($R_{left}=0.44$, $R_{right}=0.42$) as well as left amygdala ($R=0.43$) – all at around the same time $t_{max}$ (Figure 4). The ones with worse correlation were superior and middle frontal gyri.

Evolution of AD according to the diffusion model: When seeding from the hippocampus (Fig 3 – left), the modeled disease spread to mesial temporal lobe (Fig 3 – middle) before continuing to the frontal-temporal-parietal association areas (Fig 3 – right).

ND Model seeded at Hippocampus recapitulates classic AD progression:

ND Model “eigen-modes” match AD atrophy topography:

The eigen-mode of ND model


Measured atrophy pattern from Alzheimer’s subjects
Statistical correlation results on 18 AD, 18 HC, 19 FTD patients


Diagonal plots show strong correlations, off diagonals show weak correlations

This supports the conclusion that there is a one-to-one relationship between the Brainwire model and various dementias
Parkinson’s disease is initiated at a brainstem region called substantia nigra, then spreads outwards.

Network diffusion was seeded at SNpc ➔ predicted future PD pathology

Spread of Parkinson’s pathology traces 6 Braak stages (left). This spread is modeled as a network diffusion process whose rate is regulated by network connectivity.
Predicted spatial pattern from the Network Diffusion Model applied to (directional) mouse brain network accurately predicts the regional distribution of tau deposition, early stage APP concentration and tau-induced atrophy

1st network eigenvector versus regional increase in tau burden (Clavaguera, 2009)  
$r^2 = 0.56, p < 0.01$

1st network eigenvector versus relative regional APP level (Harris, 2010)  
$r^2 = 0.86, p < 0.01$

1st network eigenvector versus future regional atrophy (de Calignon, 2012)  
$r^2 = 0.88, p < 0.01$
Clinical Implications

- One of the first predictive, testable, mathematical models of spread of neurodegeneration
- Model is fully predictive
  - Can use baseline MRI to predict future atrophy
  - Just “play out” the diffusion equation
- Utility in monitoring of clinical trials
- Preliminary results promising:
  - Alzheimer
  - Parkinson
  - Frontotemporal dementia
Predicting future atrophy patterns

- Alzheimer’s Disease Patient

Predicted atrophy of AD, subject #5, t = 0, 5, 10, years

- Baseline
  - Projected: 5 years
  - 10 years

Predicting future atrophy patterns

MCI subject who converted to AD

Predicted atrophy of MCI-C, subject #104, t = 0, 5, 10, years

MCI subject who did not convert to AD

Predicted atrophy of MCI-N, subject #100, t = 0, 5, 10, years

Baseline

Projected: 5 years

10 years

Temporal lobe

Predicting future atrophy patterns

- 687-subject ADNI T1 volumetrics using Freesurfer, 2-4 year longitudinal follow up
- Baseline was applied to ND model, “future” prediction tested against follow up scans

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Stats (measured)</th>
<th>Stats (model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI-N atrophy</td>
<td>0.85</td>
<td>0.97</td>
</tr>
<tr>
<td>MCI-C atrophy</td>
<td>0.87</td>
<td>0.96</td>
</tr>
<tr>
<td>AD atrophy</td>
<td>0.89</td>
<td>0.96</td>
</tr>
<tr>
<td>MCI-N FDG</td>
<td>0.92</td>
<td>0.96</td>
</tr>
<tr>
<td>MCI-C FDG</td>
<td>0.89</td>
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Significant improvement in correlation between measured and predicted out-year atrophy

Back to the Business...
The Clinical Market Opportunity, Based on Dementia Research Roadmap

- Key focus areas in AD research includes biologic / imaging biomarker.

“The use of biomarkers in both Alzheimer’s dementia and MCI due to Alzheimer’s disease is intended only for research at this time. However, some biomarkers, especially those using advanced imaging techniques, could enter clinical practice in the near future, though much remains to be learned about their utility in this setting.”*

*a hypothetical intervention that delayed the onset of Alzheimer’s dementia by five years would result in a nearly 45 percent reduction in the number of people with Alzheimer’s by 2050, and reduce the projected Medicare costs of Alzheimer’s from $627 billion to $344 billion dollars.”*

*Source: Alzheimer Association publication, NEW CRITERIA AND GUIDELINES FOR THE DIAGNOSIS OF ALZHEIMER’S DISEASE PUBLISHED FOR FIRST TIME IN 27 YEARS, April 2011*
Market

- Very large market, rapidly growing
- 10m+ dementia patients in US
- Growth drivers:
  - aging, baby boomers
  - better diagnostic technology
- 16740 neurologists in the US, 3628 neuroradiologists
- 3000 primary care in dementia
- 330 memory clinics

2500 clinics to reach
Plan: reach 10% each year post-launch
Requires sales force ramp up, 7-10 sales professionals required

US spending on AD (billion $)*

* Total disease-related expenses
Source: AHRQ report, NEJM 2013
## Products and Markets

<table>
<thead>
<tr>
<th>Product</th>
<th>Market</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PACS-integrated neuro reporting tool</strong></td>
<td><strong>patient</strong></td>
</tr>
<tr>
<td>Full integration into EHR/PACS</td>
<td>Academic center, large hospital</td>
</tr>
<tr>
<td>Workstation model</td>
<td>Radiology PACS</td>
</tr>
<tr>
<td>Customized reports based on requirements</td>
<td>Brainwire</td>
</tr>
<tr>
<td><strong>Neuro report tool for clinicians</strong></td>
<td><strong>Neurology clinic</strong></td>
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<tr>
<td>Cloud-served, SaaS</td>
<td>Cognitive testing</td>
</tr>
<tr>
<td>Neuro report sent automatically, Push to clinic EHR</td>
<td>Upload</td>
</tr>
<tr>
<td><strong>Trial cohort selection, stratification tool</strong></td>
<td>If cog is diagnostic</td>
</tr>
<tr>
<td>Cloud-served SaaS or custom install</td>
<td><strong>MRI</strong></td>
</tr>
<tr>
<td>No report, but quantitative tables and decision points</td>
<td>Brainwire</td>
</tr>
<tr>
<td></td>
<td><strong>Clinical trials organization, big pharma</strong></td>
</tr>
</tbody>
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Clinical Trials Market

- Earliest commercial opportunity
- Does not require FDA clearance
- Clinical trials applications:
  a) screening: cohort stratification
  b) monitoring: improve ability to detect small changes from untreated disease trajectory, reduce sample size, hence reduce $$

“at any given point of time there are 150 clinical studies on AD/dementia underway in the US, need at least 50,000 participants. To reach that goal, researchers will need to screen at least half a million potential participants”**

Competition
Players in dementia diagnostics

* Venture backed  ** post-IPO!

Cognitive

- GPCOG, MoCA, ADAS-cog
  - free, screen
- Cognistat, Screen*, Cantab**
  - $300-$500, screen
- Cognoptix *
  - >$400

Imaging

- Only available prognostic tool
- BrainWire
  - $200
- Genomics+imaging
- i2Dx *
  - $??
- NeuroQuant *
  - ~$1000
- Glucose PET
  - $2000
- Amyvid *
  - PET
  - $5000
- Closest comparable MRI-based atrophy measurement
  - Only meant for Dx

- Spinal tap (CSF amyloid)
  - $3000

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Financial Projections

- Seed investment was obtained from ADDF
- Plan NIH SBIR funding (Phase I, II)
- Break even in year 5
- Require VC investment of $3m in 2018
Management Team

Ashish Raj, PhD (Founder, CEO)
- Faculty at Weill Cornell
- 3 NIH grants
- Director of Advanced imaging Lab

Development team

Michael Dayan, PhD (chief s/w architect)
- 5 years experience designing image processing s/w for brain scans

Eve LoCastro (engineer)
- 4 years experience designing in image processing
- Systems administrator

Clinical / business advisors

Manish Raj, MBA (Business Dev)
- 15 years experience in IT consulting, finance, I-banking
- MBA from Wharton B-school

Gloria Chiang, MD
- Faculty in neuroradiology at Weill Cornell
- Expert in reading MRI exams in dementia

John Tsiouris, MD
- Faculty in neuroradiology at Weill Cornell
- Expert in reading MRI/PET exams in dementia
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- Brain imaging-based prognostic software technology
- Technology, validation data and team in place
- Seeking:
  - Seed and venture capital
  - Developers, marketing/business advisors
  - FDA regulatory, s/w guidelines experts
  - Clinical advisors

Contact: Ashish Raj (ashish.raj@gmail.com)

THANK YOU !!