Brain Circuits: Breakdown in Dementia and Hopes for Repair
11/8/12

Gil D. Rabinovici, MD
William Seeley, MD
Adam Boxer, MD, PhD

BIOGRAPHY:
Born and raised in Jerusalem, Dr. Rabinovici received his BS degree from Stanford University and MD from Northwestern University Medical School. He completed an internship in internal medicine at Stanford University, neurology residency at UCSF and a behavioral neurology fellowship at the Memory and Aging Center, where he has remained on faculty as an attending neurologist. His research focuses on how structural, functional and molecular brain imaging techniques can be used to improve diagnostic accuracy in dementia and to study the biology of neurodegenerative diseases. Dr. Rabinovici’s work is supported by the National Institute on Aging, the Alzheimer’s Association, the John Douglas French Alzheimer's Foundation and the Hellman Family Foundation. He is the recipient of the 2012 American Academy of Neurology Research Award in Geriatric Neurology, and the 2010 Best Paper in Alzheimer’s Disease Neuroimaging: New Investigator Award from the Alzheimer’s Association.

BIBLIOGRAPHY:


Sgt. M: The Forgetful Veteran

- 70 year-old right-handed veteran with diabetes, high cholesterol
  - “My memory is terrible”
- Wife notes that in last 3-4 years
  - Forgets conversations, TV programs
  - Repeats questions, stories
  - Memory for remote events spared
  - More quiet in social settings
  - Last month lost on the way home from medical appointment in SF

Sgt. M: Memory Testing

After fourth recitation of the list

- "hat"
- "cherries"
- "wrench"
- "sweater"
- "lemon"
- "pliers"
- "belt"
- "peaches"
- "drill"

10 minutes later…

- "hat"
- "cherries"
- "wrench"
- "sweater"
- "lemon"
- "pliers"
- "belt"
- "peaches"
- "drill"

Sgt. M: Diagnostic Evaluation

Cognitive testing
- Moderate-severe memory impairment
- Mild impairment in language, visuospatial, executive domains

Laboratory testing
- Normal electrolytes, liver and kidney function, cell counts, vitamin B12, thyroid function

Brain Atrophy in Alzheimer’s Disease

- Temporoparietal cortex
  - Memory
  - Language (left)
  - Math, tool manipulation (left)
  - Navigation, spatial reasoning (right)
- Lateral frontal cortex
  - Executive function
  - Medial frontal cortex spared
  - Behavior, social function

Rabinovici et al., AJADOD 2008
AD Pathology: Plaques & Tangles

Amyloid plaques
- Extra-cellular
- Amyloid-β (Aβ)

Neurofibrillary tangles
- Intra-cellular
- Tau

The Amyloid Cascade

Neurofibrillary Tangles

Microtubule

Tau protein

AD Pathophysiology is Complex

Detecting AD Pathology in Cerebrospinal Fluid

- CSF changes in AD
  - Decrease in Aβ1-42
  - Increase in total and phosphorylated tau

- CSF Tau/Aβ1-42 ratio
  - 85% accurate in discriminating autopsy-confirmed AD from controls

Imaging Amyloid Plaques (PIB-PET)

Klunk et al. Ann Neurol 2004
### AD Risk Factors

**Increase risk**
- Genes
  - 1% have disease-causing gene (APP, PS1, PS2)
  - Apolipoprotein E4 is major risk modifying gene
- Age
  - Prevalence 1% age 60-64, 35-40% over age 85
- Female sex
- Head trauma
- Vascular risk factors
- Reduced mental and physical activity

**Decrease risk**
- Education
- A little alcohol
- Increased mental and physical activity
- Heart-healthy diet
  - Mediterranean

### Clinical Evolution of AD

- **Normal Aging**
  - Decline in memory or other cognitive functions
  - Beyond expected for age
  - Does not interfere with day to day function
  - Multiple causes; may or may not progress to AD

- **Mild Cognitive Impairment**
  - Decline in memory
  - or other cognitive functions
  - Beyond expected for age
  - Interferes with day to day function

- **Alzheimer’s Dementia**

### Amyloid Deposition in Genetic AD

- Pre-symptomatic carriers
- MCI (median age 44)
- Dementia (median age 49)

### PIB in Normal Elderly Correlates with Hippocampal and Cortical Atrophy

- Mormino et al., Brain 2009
- Oh et al., NeuroImage 2010

### Model for AD Cascade

- Jack et al., Lancet Neurol 2010
Take Home Messages

- AD attacks brain networks involved in memory, language, visuospatial and executive function
- Misfolded proteins form toxic plaques and tangles 10-15 years before symptoms
- Increasing focus on disease prevention: 
  - Mens sana in corpore sano
- Future of therapy will include early detection and intervention with biologically specific agents

Acknowledgments

Bruce Miller
Bill Jagust
Adi Alkalay
Nick Block
Adam Boxer
Brendan Cohn-Sheehy
Mary DeMay
Michael Geschwind
Pia Ghosh
Marilu Gorno-Tempini
Lea Grinberg
Robin Katzell
Joel Kramer
Baber Khan
Suzee Lee
Manja Lehmann
Cindee Madison
Katya Rascovsky
Kate Rankin
Howie Rosen
Bill Seeley
Trishna Subas
Marissa Urbano
Mike Weiner
Teresa Wu

Funding sources:
NIA K23-AG031861
NIA P01-AG1972403
NIA R01 AG027859
ADRC P50 AG223501
CA DHS 04-33516
Alz Association
French Foundation
Hellman Foundation
Predicting regional neurodegeneration from the healthy brain functional connectome

William W. Seeley, MD
Associate Professor of Neurology
UCSF
Alzforum Webinar
April 10, 2012

**Take home messages**

- The human brain is composed not of isolated and specialized brain regions but of large-scale distributed networks
- Network science and brain imaging has provided new tools to examine neural networks in humans
- Neurodegenerative diseases represent organized, network-based degenerations
- A network-based approach may allow us to predict and follow a patient’s trajectory

**Network hypothesis of Alzheimer’s disease**


**Patient F.T.**

58 y.o. business executive with 2 high school children

Brought in by wife for increasingly uncharacteristic behaviors:

- Disinterest in kids’ school and sports activities
- Speaking out of turn, commenting on strangers’ weight or hairstyle
- Circles the kitchen island 3 times (counterclockwise) upon entering room
- New penchant for sweets, overeating in general

Language, memory, navigation, skilled movements all normal. Denies low mood, sleep disturbance, life stressors.

FTD Prevalence

Common cause early age-of-onset dementia
- Prevalence ~1/5000 in persons 45-64 years old, 1:1 with AD (Ratnavalli et al., Neurology 2002)
- Higher incidence than AD when symptoms begin before age 60 years (Knopman et al., Neurology 2004)
- Broader FTD spectrum even more common

Less common after 70?

Intrinsic connectivity measured with fcMRI

“Salience Network” (Intrinsic connectivity network)

bvFTD

bvFTD atrophy pattern
VBM, patients vs. controls N = 24
Functional connectivity Right FI seed
dMRI, healthy controls N = 19
Network-based neurodegeneration

Lingering questions

- Does each disease involve a focal “epicenter” from which disease spreads?
- What are the mechanisms of network-based vulnerability?
- Can we use network-based imaging in the clinic?
bvFTD atrophy pattern
VBM, patients vs. controls
N = 24

Does each disease involve a focal "epicenter" from which disease spreads?

Correlation between functional connectivity in health and disease vulnerability

AD pattern  bvFTD pattern  SD pattern  PNFA pattern  CBS pattern
Graph metrics in health predict atrophy severity across target and off-target networks

Healthy connectivity graph

Atrophy severity in disease

Graph metrics in health predict atrophy severity across target and off-target networks

Healthy connectivity graph

Atrophy severity in disease

Graph metrics in health predict atrophy severity across target and off-target networks

Healthy connectivity graph

Atrophy severity in disease

Graph metrics in health predict atrophy severity across target and off-target networks

Healthy connectivity graph

Atrophy severity in disease

Graph metrics in health predict atrophy severity across target and off-target networks

Healthy connectivity graph

Atrophy severity in disease

Graph metrics in health predict atrophy severity across target and off-target networks

Healthy connectivity graph

Atrophy severity in disease
Salience Network breakdown and DMN enhancement track bvFTD severity

Acknowledgments
Seeley Lab  Stephanie Gaus  Christine Guo  Alex Larkin  Norbert Lee  Alissa Nana Li  Manu Sidhu  Andrew Trujillo
Cal Tech  John Allman  MSSM  Patrick Hof
UCSF ADRC  Pathology Core  Ben Andrews  Kelly Craigton  Steve Dammond  Clair Waites
UCSF Memory & Aging Center  Adam Boxer  Marilu Gorno-Tempini  Suzee Lee  Bruce Miller  Howard Rosen  Virginia Sturm  Michael Weiner
Funding Sources:
Frontotemporal degeneration (FTD) Treatment Advantages

Adam L. Boxer, MD, PhD
Director, Neuroscience Clinical Research Unit
Director, AD and FTD Clinical Trials Program
Associate Professor of Neurology
University of California, San Francisco

UCSF Mini Med School; November 8, 2012

Current Management of AD

Cognitive complaint (patient or family)
Investigations (cog. testing, brain image, labs [vitamin B12, thyroid function])
Diagnosis (exclusion of other causes):
Mild Cognitive Impairment (no functional decline)
Alzheimer’s Disease (functional decline)

Interventions (manage symptoms):
Acetylcholinesterase inhibitor (Aricept® or Razadyne®)
Memantine (Namenda®)
Exercise (physical/mental)
Minimize CV risk factors
Minimize other CNS drugs
Treat behavioral/psychiatric symptoms
Caregiver support

End of Life Care

Current AD Therapies

• Donepezil (Aricept)
• Rivastigmine (Exelon)
• Galantamine (Razadyne)
• Memantine (Namenda)

Impact of Alzheimer’s Treatment

Delay onset by 2 years
Delay onset by 5 years

Millions of people with AD in the U.S.

Cost to society: $ billions

Year

2003 2010 2020 2030 2040 2050
Alzheimer’s disease under the microscope: plaques and tangles

Amyloid plaques
Neurofibrillary tangles

Alzheimer’s vs. Mouseheimer’s

- Introduce human dementia causing genes (tau, APP, PS1)
- Memory deficits, amyloid plaques but no neurofibrillary tangles

Targets for disease modifying agents

- Anti-amyloid vaccines
- Antibodies
- Aggregation inhibitors
- R-flurbiprofen
- Gamma secretase inhibitors
- Beta secretase inhibitors
- Bapineuzumab removes amyloid

Bapineuzumab removes amyloid

Bap
Pbo
Frontotemporal dementia

- Common early onset (<65 yrs)
- Behavior, social function, language (primary progressive aphasias)
- Molecular pathology: Tau or TDP-43
- Low hanging fruit for drug development:
  - TDP-43: progranulin-related FTD (GRN)
  - Tau: Progressive supranuclear palsy (PSP) or MAPT mutation carriers (FTDP-17)
- Overlap with ALS, tauopathies including chronic traumatic encephalopathy (CTE)
- No approved medical therapies
Neuropathology of bvFTD

- Tau
- TDP-43
- FUS
- ALS
- PSP
- CBD
- C9ORF72
- GRN
- MAPT
- Tau + Aβ
- Alzheimer's

Amyloid imaging in FTD diagnosis

No FDA approved therapies

- **AD medications**
  - Acetylcholinesterase inhibitors
    - No RCT bvFTD; worse behavior (Mendez)
    - PPA: benefit in logopenic variant (AD pathology)?
  - Memantine
    - 52 wk RCT in bvFTD: no benefit (Vercelleto, 2011)
    - 26 wk RCT in bvFTD & svPPA
  - Trazodone: improved behavior (NPI) 6 wks RCT (Lebert, 2004)
  - SSRIs: commonly used; behavior, diet
  - Atypical antipsychotics: suppress all behavior; efficacy; worse Parkinsonism (Pijnenburg, 2003)

Medication use (NACC)

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.9±8.8</td>
<td>64.8±9.8</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>56%</td>
<td>34%</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>11±2 (34%)</td>
<td>10±2 (34%)</td>
</tr>
<tr>
<td>RACE (% caucasian)</td>
<td>83%</td>
<td>95%</td>
</tr>
<tr>
<td>CDR Sum of Boxes</td>
<td>6.88±4.4</td>
<td>7.89±4.9</td>
</tr>
</tbody>
</table>

- Donepezil 26%
- Memantine 33%
- Antidepressant 37%
- Antipsychotic 10%
- Anxiolytic 18%
- Mood stabilizer 3.8%
- Dementia medication 25%
- Psychiatric medication 68%

Tartaglia et al., submitted
Memantine and dementia

- FDA/EMA approved for mod-severe Alzheimer’s
  - Not efficacious mild AD (Schneider, 2011)
  - Better agitation/aggression, eating/appetite, irritability/lability (+donep; Cummings, 2006)
- Global, behavioral benefits in PDD/DLB
  - Aarsland, 2009; Emre, 2010
- Small cog benefit VaD?
  - Kavirajan, 2007

- Case reports in FTD (+/-)
- Open label study

Multicenter, 26 week, randomized, double blind, placebo controlled trial memantine 20 mg daily in bvFTD and svPPA

- Nine academic centers
- Primary outcomes: NPI, CGIC
- Secondary: CDR-sb, FAQ, FTD neuropsych battery (Knopman, 2008), TEFA, ZBI, EXIT25
- Included bvFTD and svPPA with characteristic neuroimaging; MMSE > 15
- AChI, memantine, antipsychotics within 1 month excluded

Memantine in bvFTD, svPPA

- Case reports in FTD (+/-)
- Open label study

Multicenter, 26 week, randomized, double blind, placebo controlled trial memantine 20 mg daily in bvFTD and svPPA

- Nine academic centers
- Primary outcomes: NPI, CGIC
- Secondary: CDR-sb, FAQ, FTD neuropsych battery (Knopman, 2008), TEFA, ZBI, EXIT25
- Included bvFTD and svPPA with characteristic neuroimaging; MMSE > 15
- AChI, memantine, antipsychotics within 1 month excluded
Trend towards worse ADLs (FAQ)

Worse digit symbol substitution (no learning effect?)

Worse Boston Naming

Memantine bvFTD svPPA summary

- Small improvement behavior 6 weeks. Underpowered to detect NPI effects?
- No difference in CGIC
- Trend towards worse ADLs (FAQ)
- Worse processing speed (DSST), naming (BNT)
- No effect on CDR-SB decline (twice AD rate)
- Memantine not useful in FTD
  - Adverse cognition, ADLs outweigh small, transient behavioral benefit
Drug development: FTD advantages

- Unmet need (no effective treatments)
- Help other indications due to overlapping pathology, genetics
  - C9ORF72 links to ALS
  - GRN links to inflammation, AD
  - MAPT links to AD, tauopathies, CTE
- Defined populations (neuropathology)
  - Younger, fewer co-pathologies
  - Genetics, biomarkers (progranulin)
- Rapid disease progression allows more efficient clinical trials
- Orphan drug incentives FDA
  - Accelerated approval possible
- Low hanging fruit (correct progranulin deficiency)
  - First win in neurodegeneration

Boxer, Alzheimer’s and Dementia, 2012

Tau is an ideal target

- Alzheimer Mice
- Neurotoxin seizures

Roberson et al. Science 2007;316:750-754

Trans-synaptic (prion-like) spread
1. Fross and Diamond Nature Rev Neuroscience 2010;316:750-754
3. de Calignon, Neuron 2012; 73, 685–697

Why develop tau drugs for tauopathies (CBD, PSP, FTDP-17)?

- Response to tau therapy could predict AD
- Pure tau; little co-pathology (Aβ, TDP, LB, vasc)
- Clinical PSP strongly predicts 4R tau (closer to mice!)
  - Many tau “AD” mouse models are FTD/PSP tau with AD anatomy
- Strong tau genetic links (PSP, FTDP-17)
- AD treatment will change if successful therapy
  - Increased recognition of non-AD dementia (Aβ PET)
  - How to test tau therapies in setting of successful Aβ therapy?

Tau drug targets and leads

- Methylene blue
- Tidegusib (GSK 3β inhibitor)
- Thiamet-G
- Coenzyme Q-10
- Rasagiline
- Mitochondrial cocktail
- Anti-tau mAb vaccine
- Devunetide
- Epothilone D
- anti-inflammatory
- Anti-oxidants
- Anti-microglial agents

Brunden, Nat Rev Drug Discov, 2009
Proteins and neurodegeneration

- Beta Amyloid
- Tau
- Synucleins
- TDP-43

AD DLB PD FTD PSP CBD

Beta Amyloid + + + +
Tau + + + +
Synucleins + + + +
TDP-43 + + + +

Tauopathies

PSP = Tau
Steele JC, Richardson JC, Olszewski J. 1964

Mitochondrial therapies

Stamelou, Brain 2010: 133; 1578–1590

Stamelou, Movement Disorders, 2008; 27: 942–949
Glycogen Synthetase Kinase (GSK3β) inhibitors

Tideglusib (NP-12) human clinical trial
- Not efficacious (-)
- 52 weeks, n=146 subjects
- PSP Rating Scale (PSPRS; primary endpoint)
- SEADL, cognitive battery, volumetric MRI results pending
- NCT01049399


Microtubule Stabilizers (Epothilone D)

- Aged 4RT P301S tau mice with pre-existing tau pathology
- Improves maze learning
- Zhang, J. Neurosci. 32: 3601–3611
- Human clinical trial Alzheimer’s disease underway

Tau immunotherapy

- Weight
- P301S mouse
- Rotarod (motor function)

Davunetide derived from ADNP

- Activity-Dependent Neuroprotective Protein
- 124 kDa growth factor released from glia in response to VIP
- (-/-) mice: embryonic lethal
- (-/+ ) mice: neurodegenerative phenotype
- Smallest active peptide (8 a.a.) NAPVSIPQ = NAP = Davunetide
- Exerts effects at 10^{-15} molar similar to growth factors
- Receptor unknown

Vulik-Shultzman, J Pharm Expert Therap (2007)
Summary (future treatment)

- Many failures with amyloid-directed therapies in Alzheimer’s
  - Prevention trials are next step
- No approved drugs to treat FTD
- Memantine and AChI commonly used
  - Worse cognition with memantine
- Tau and progranulin leading drug targets for FTD
- Many advantages to FTD drug development
  - May lead to new Alzheimer’s therapies
- New biomarkers under development will facilitate clinical trials
  - First international FTD clinical trial to begin this fall
  - First pivotal PSP tau drug trial completed this fall

Acknowledgments

- Memantine Clinical Trial: David Knopman, Dan Kaufer, Murray Grossman, Chiadi Onyike, Neill Graf-Radford, Mario Mendez, Jill Shapira, Diana Kerwin, Alan Lerner, Chuang-Kuo Wu, Mary Koestler, Kathryn Sullivan, Robert Nicholson, Jenn Ullah, Scott Fields, John Neuhaus, M. Marsel Mesulam and Bruce Miller
- FTD Treatment Study Group
  - Adam Boxer, M.D. Chair, UCSF
  - Jeff Cummings, M.D., Cleveland Clinic
  - Dave Knopman, M.D., Mayo Clinic, Rochester
  - Howard Fillit, M.D., ADDF
  - Howard Feldman, M.D., University of British Columbia
  - Mike Gold, M.D. Allon Therapeutics
  - Susan Dickson, M.S. AFTD
  - Maysy Grether, Ph.D., BrainWeb Project -> Rodney Pearlman, Ph.D.
- 4RTN: Howie Rosen, Carmela Tartaglia, Brad Dickerson, Norbert Schuff, Mike Weiner, Les Shaw, John Trojanowski, Anna Karydas, Art Toga, Paul Aisen, Jere Meredith
- Support: NIA, Tau Consortium, Association for FTD, Alzheimer’s Drug Discovery Foundation, BMS, Enviro, Beitman Foundation