Overview

- Introduction of FTD (it’s important)
- Brief neuropathology/genetics
- Clinical bvFTD
  - Crime
  - Emotion
- Tau imaging
- Progranulin therapeutics
- Tau therapeutics

Frontotemporal Dementia (FTD)

- 1892, Arnold Pick describes a focal neurodegenerative condition
- Pick’s disease preferentially affects the frontal and temporal lobes
- Pick body (Alzheimer 2011)

VBM of FTD & AD vs Controls

Concept from Delay, Brion et al., 1950s, Thibodeau MP, Miller BL. Neurocase, 2013
Frontotemporal Dementia (FTD)

- Common cause pre-senile dementia
  - 1:1 with AD 45–64 years (Hodges 2002), most common dementia <60
  - 40% familial, 10% dominant (Chow, 1999)
- Rare after 70?
  - Strong links with ALS, PSP, CBD

Chronic Traumatic Encephalopathy/Tau


3 Types Frontotemporal Dementia

- Behavioral Variant
- Language Variants
  - Semantic Variant
  - Nonfluent Variant

- Often genetic Tau, TDP, FUS
- Rarely genetic TDP-C
- Some genetic 83% TDP-C, 85% Tau, TDP-A
Network-based Neurodegeneration

Syndrome-specific regional atrophy patterns: patients vs. controls

Seeley et al. Neuron 2009

C9ORF72 Small Medial Pulvinar
Salience Network Disruption

Lee SC et al. Brain 2014

FTLD-tau

Pick 3R PSP 4R CBD 4R FTLD-FUS

TDP-A TDP-B TDP-C Dipeptides (C9ORF72)

FTLD-TDP
Three Main Genetic Mutations

- **MAPT**: 52 years, MRI symmetrical, bvFTD with parkinsonian syndromes, 1998
- **GRN**: 62 years, MRI asymmetric, bvFTD, progressive aphasia, PD, AD, 2006
- **C9ORF72**: 56 years, MRI symmetric, cerebellar involvement (subtler frontal involvement), bvFTD and ALS, 2011

*Adeline Ng Neurology 2015

How Many Familial FTLD Do You Follow?
Rare Variants with FTD-ALS Syndromes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Phenotype</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>TARDBP</td>
<td>P112H</td>
<td>FTD</td>
<td>Moreno et al 2015</td>
</tr>
<tr>
<td>FUS</td>
<td>Q140H</td>
<td>tauopathy</td>
<td>Ferrer et al 2015</td>
</tr>
<tr>
<td>LRRK2</td>
<td>C2154F</td>
<td>tauopathy</td>
<td>Chen-Plotkin et al 2008</td>
</tr>
<tr>
<td>TBK1</td>
<td>Nonsense variant</td>
<td>FTD-ALS</td>
<td>Le Ber et al 2015</td>
</tr>
<tr>
<td>PRNP</td>
<td>Q160X</td>
<td>dementia</td>
<td>Fong et al 2016</td>
</tr>
<tr>
<td>OPTN</td>
<td>deletion, nonsense &amp; missense mutation</td>
<td>ALS</td>
<td>Maruyama et al 2010</td>
</tr>
<tr>
<td>UBQLN2</td>
<td>PXX</td>
<td>ALS</td>
<td>Deng et al 2011</td>
</tr>
</tbody>
</table>

Giovanni Coppola personal communication

Behavioral Variant Frontotemporal Dementia (bvFTD): A Socioemotional Disease

- Behavioral disinhibition
- Apathy or inertia
- Loss of sympathy or empathy
- Perseverative, stereotyped, or compulsive behavior
- Hyperorality and dietary changes
- Executive dysfunction

International Consortium Brain 2011

Medial Versus Lateral Orbital Cortex

+ monitoring reward value
+ punishers leading to change in behavior

(Kringelbach & Rolls 2004 meta-analysis)
### Crime with Dementia

<table>
<thead>
<tr>
<th>Dx</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>545</td>
<td>7.7%</td>
</tr>
<tr>
<td>bvFTD</td>
<td>171</td>
<td>37.4%</td>
</tr>
<tr>
<td>svPPA</td>
<td>89</td>
<td>27%</td>
</tr>
<tr>
<td>HD</td>
<td>30</td>
<td>20%</td>
</tr>
<tr>
<td>MCI</td>
<td>243</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Liljegren & Naasan et al JAMA Neurol 2015

### Crime: bvFTD, svPPA & AD

<table>
<thead>
<tr>
<th></th>
<th>bvFTD</th>
<th>svPPA</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>37.40%</td>
<td>27%</td>
<td>7.70%</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Early</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td><strong>Types</strong></td>
<td>Sexual advance, theft, public urination, violence</td>
<td>Theft, traffic violation</td>
<td>Traffic violation, trespass/wander</td>
</tr>
<tr>
<td><strong>Cause</strong></td>
<td>Disinhibition, impulsivity, reward/punish</td>
<td>Compulsive attracted to visual stimuli</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td><strong>Anatomy</strong></td>
<td>Anterior insular, orbitofrontal, ventral striatum</td>
<td>Ant. temporal orbitofrontal, ventral striatum</td>
<td>Hippocampus, parietal lobe</td>
</tr>
</tbody>
</table>

Liljegren & Naasan et al JAMA Neurol 2015

### International Research Criteria for Behavioral Variant FTD

1. Early (2–3 yrs) behavioral disinhibition
2. Early (2–3 yrs) apathy or inertia
3. Early (2–3 yrs) loss of emotional reactivity, sympathy and empathy
4. Perseverative, stereotyped or compulsive/ritualistic behavior
5. Hyperorality and dietary changes
6. FTD neuropsychological profile
7. Frontal or anterior temporal atrophy on MRI
8. Presence of known mutation

International Consortium, Brain, 2011
Abnormal Behavior Driven by Right Hemisphere Dysfunction

- Aberrant Motor Behavior
- Apathy
- Disinhibition

Rosen et al. Brain, 2005

Loss of Empathy

- R temporal pole
- R medial OFC
- R caudate
- R medial frontal

Only right hemisphere mediates these empathy changes

Rankin et al. Brain 2006

Leaders of the Neuroscience of Emotion

Guillaume-Benjamin-Amand Duchenne de Boulogne
Paul Ekman
Robert Levenson
**Disgust: Levenson Lab Methods**

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Physiological reactivity</th>
<th>Self-report</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>film (~1 min.)</td>
<td></td>
</tr>
</tbody>
</table>

Eckart et al., 2012

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**Eliciting Disgust in the Laboratory**

- Autonomic Reactivity: change from baseline
- Facial Expression: disgust behavior
- Subjective Experience: self-report

Eckart, Sturm, Miller & Levenson, 2012

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**Impaired Disgust Reactivity in bvFTD**

![Graph showing impaired disgust reactivity in bvFTD](chart.png)

Self-Reported Experience: bvFTD< controls when controlling for total emotion

Eckart, Sturm, Miller & Levenson, 2012
**Loss of Disgust in FTD**

Self-Reported Experience: FTD < controls

- Disgust Behavior
- ANS Reactivity

Eckart et al., 2012

* p < .05

**Disgust Behaviors**

**Disgust Recognition**

**Overlap**

Woolley et al., Biol Psych 2015

**Frontoinsula Atrophy Relates to Diminished Disgust**

- Lower disgust reactivity (ANS and self-reported experience) related to smaller bilateral insula volume
- Frontoinsula atrophy related to real-world disgust behavior and disgust recognition deficits

Kurth et al., 2010; Verstaen et al., 2015; Woolley et al., 2015
Overlapping Anatomy of Reward Processing and bvFTD

Haber and Knutson, Neuropsychopharmacology, 2010

Seeley et al, Archives of Neurology, 2008

Reward Seeking in bvFTD

Perry, Brain, 2014

Olfactory Reward Tasks
Less aversion to unpleasant smells in bvFTD

Perry et al, unpublished
Reward Changes in FTD Relate to Atrophy in Reward Processing Structures

- Greater atrophy with smaller gaps between ratings of pleasant and unpleasant
- Greater atrophy with more positive rating of unpleasant smells

Displayed at p<.001 within regions known to be involved in reward.

Psychiatric Misdiagnosis

Rates of Psychiatric Diagnosis within each Neurodegenerative Disease

- bvFTD (n=89)
- AD (n=65)
- svPPA (n=41)
- nfvPPA (n=17)
- CBD (n=25)
- PSP (n=15)
- ALS (n=20)

Men
Women
Total


Treatable Disorders Missed

- NPH
- Sagging Brain
- K channel ab

Klassen & Ahlskog 2011
M Hong et al. 2002
M Geschwind et al. 2008
Therapies

- bvFTD
  - Environment, social, legal
  - Consider antidepressant
  - Avoid other meds
  - Clinical trials beginning

AD vs FTD Amyloid PET > FDG-PET

47 autopsy-proven cases
Amyloid (PIB) PET visual reads
  - 100% sensitivity
  - 90% specificity

FDG-PET visual reads
  - 87% sensitivity
  - 79% specificity

Rabinovici et al. Neurology 2011

Tau PET: The New Frontier

Amyloid, tau & brain metabolism
57 year-old AD
Brain dysfunction correlates with tau but not amyloid

Ossenkoppele R et al. Brain 2016
Tau PET Patterns Correlate with AD Phenotype

byFTD V337M MAPT Mutation

Consortium for Frontotemporal Dementia Research (progranulin)

- Progranulin knockout mouse
  (B Farese, Harvard)
- Behavior
  (E Roberson, UAB; L Gan, UCSF)
- Progranulin & granulin pathways
  (L Gan, UCSF)
- High throughput screen
  (J Herz, Y Gang, UT)
- Consortium pathology/gene carrier
  (B Seeley, S Lee, B Miller, UCSF)
  - Early detection: clinical, fMRI
- Skin/iPS/neuron (B Farese, M Ward, NIH)
- PGRN genetics (R Rademakers, Mayo)
- Lysosome (S Ferguson, Yale; B Farese)
- Treatments (Adam Boxer, UCSF)
Restoring Progranulin Levels

THERAPEUTIC GOAL: Increase GRN transcription from the remaining WT allele
SCREEN: FDA-approved compound library using luciferase-tagged PGRN reporter
SAHA greatly altered progranulin levels

Joachim Herz & Gang Yu labs, UTSW

Lysosomal Storage Features

- Homozygote GRN lysosomal storage disease neuronal ceroid lipofuscinosis (NCL) (Smith K 2012, Almeida M 2016)
- Heterozygous GRN mutation show autofluorescent NCL-like storage material in the CNS

Michael E. Ward et al., Sci Transl Med 2017

Chronic Neuroinflammation Contributes to Neurodegeneration

Loss PGRN activates innate immune cells

Kao et al., Nat Rev Neurosci 2017
Ahmed et al., Am J Pathol 2013
Critical Role of Microglia and TNFα Signaling in Progranulin Deficient FTD

Minami et al., Nat. Med., 2014
Krabbe et al., PNAS, 2017

PGRN Deficient FTD Patients Exhibit OCD-like Behavior

David Perry, Bruce Miller, UCSF
Krabbe et al., PNAS, 2017

Reducing TNFα Restored the Firing Frequency in PGRN Deficient Striatal Neurons to WT Levels

Krabbe et al., PNAS, 2017
In Vivo Imaging of Microglial Motility

Yang et al., Nature Protocols, 2010

Progranulin Deficiency Impairs Microglial Baseline Motility in Vivo

Krabbe et al., PNAS, 2017

n=6, 4-5 mice, Student’s t-test, p=0.04

Microglia’s Response to Injury is Attenuated PGRN Deficient Mice

Krabbe et al., PNAS, 2017

n=4 independent experiments, Student’s t-test, p<0.05

n=7, 4-5 mice
PGRN Loss Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation

Removing C1qa in Grn−/−;C1qa−/− Mice Protects Synaptic Pruning, Restores Thalamic Microcircuit Function, Mitigates OCD-like Behaviors, and Improves Survival

Tau Consortium

Stem cells
David Cook, Haggerty, Ichida, Karp, Karp, Temple

Genomics
Gampa, Gershbein, Goate, Lee, Nakayama

Biomarkers
Kozlov, Gradwohl, Ginberg, Jagust, Komar, Mathis, B. Miller, Neylan, Rebischuk, Rainov, Surai, Stein, Wald, Walsh

Treatments
Miller, Sudlow, Diamond, Stryer, Gen, Gestwicki, Hageman, Kosik, Knuckey, L. Miller, Prusiner, Rebischuk

Synthesis
Bateman, Disney, Gan, Kao, T. Miller

Propagation
Haggarty, Goate, Haggarty, Ichida, Kampmann, Karp, Karp, Temple

Clearance
Cuervo, Gestwicki, Haggarty, Rubinsztein

Models
(Models, Rubinsztein)
Pure Tauopathies vs. Mixed Tauopathy

- Mutations – bvFTD, nfvPPA, PSP, CBD
- Pick – bvFTD, nfvPPA
- CBD – bvFTD, nfvPPA, executive/motor
- PSP – falls, gaze, axial PD, dementia
- AD*
- CTE*
- Guam-PD-Dementia
- Postencephalitic Parkinson’s
- Niemann-Pick disease

 Tau Spreads Like a Prion

Functional Connectivity Dorsal Midbrain Tegmental Network & Tau PET in PSP

2017

- Better diagnosis of tau-related FTD
- New causal and risk genes
- U grants (Boxer Orphan Disease, Boeve, Rosen FTD Genetics, GENFI (Jonathan Rohrer))
- Tau-lowering trials with antibodies
- For TDP-43 subtypes
  - Anti-inflammatory compounds for svPPA
  - Progranulin-elevating therapies
  - Genetic therapies silence gene in C9orf72 forms of FTD-ALS