Recent Advancements & the Hope Ahead

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Frontotemporal Dementia (FTD)

- 1892, Arnold Pick describes a focal neurodegenerative condition
- Pick’s disease preferentially affects the frontal and temporal lobes
- Pick body (Alzheimer 1911)
Frontotemporal Dementia (FTD)

- **Common** cause pre-senile dementia
  - 1:1 with AD 45–64 years (Ratnavalli, Hodges 2002), most common dementia <60 (Knopman 2004)
  - More common if ALS, PSP & CBD, CTE considered

- Also occurs after 70
  - 25% FTD over 65, late onset tau more common (SW Seo 2018)
Psychiatric Misdiagnosis

Rates of Psychiatric Diagnosis within each Neurodegenerative Disease

Psychiatric Syndromes in FTD

- Bipolar
- Antisocial personality
- Schizophrenia
- Borderline personality
- Schizoaffective disorder
- Borderline
- Conversion

- Addiction
- Body dysmorphic disorder
- Schizotypal
- Schizoidal
- OCD
- Unipolar depression
International Research Criteria for bvFTD

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 & 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
# Crime with Dementia

<table>
<thead>
<tr>
<th>Dx</th>
<th>Number</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>AD</td>
<td>545</td>
<td>7.7%</td>
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<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>
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<tr>
<td>MCI</td>
<td>243</td>
<td>3.3%</td>
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Liljegren & Naasan, Englund et al JAMA Neurol 2015; Lillegren JAMA 2019
Loss of Empathy

- R temporal pole
- R medial OFC
- R caudate
- R medial frontal
- Only right hemisphere mediates these empathy changes
Frequency of Psychotic Symptoms
Across Neuropathological Cohorts

Naasan et al., Brain 2021
Brain Atrophy Caregiver Health

Caregiver Psychopathology

Patient Psychopathology

Brain Global Health

Covariates:
- caregiver age and sex
- patient diagnosis, disease severity, cognitive functioning, head size
- MRI scanner field strength

Hua. Dementia Geriatric Cognitive Disorder 2019
Consequences of Behavioral Symptoms in Dementia

- Significant caregiver stress (professional & non-professional)
- May endanger the individual/caregiver
- Reduced quality of care/life
- Accelerated functional decline and higher risk of placement in more restrictive setting
- High risk chemical restrain with concomitant side effects
Treatment of Behavior

- Identify problem
- Should it be treated?
- Consider protection of caregiver and family
- Try environmental intervention (Care Ecosystem)
- Is the deficit due to a serotonergic deficit?
- Antidepressants may be helpful
3 Types Frontotemporal Dementia

Behavioral Variant:
- Often genetic
- Tau, TDP, FUS
- 50% TDP

Language Variants:
- Semantic Variant:
  - Rarely genetic
  - 83% TDP-C

- Nonfluent Variant:
  - Some genetic
  - 85% Tau, TDP-A

Slide courtesy of Bill Seeley
Three Main Genetic Mutations

1. **MAPT**
   - 52 years, symmetrical MRI, bvFTD with parkinsonian syndromes, 1998 (tau aggregation)
   - **Therapy:** turn off or degrade tau

2. **GRN**
   - 62 years, asymmetric MRI, bvFTD, PPA, PD, AD, 2006 (TDP A), haploinsufficient
   - **Therapy:** replace PGRN

3. **C9orf72**
   - 56 years, symmetric MRI, cerebellar involvement (subtler frontal involvement), bvFTD and ALS, 2011 (TDP B, dipeptides) (hexanucleotide repeat)
   - **Therapy:** turn off gene

Rohrer 2015
Disease Progression in FTLD

- Clinical status
- Brain volume
- Neurofilament
- Molecular pathology
- Inflammation

FTLD-CDR:
- Asymptomatic (0)
- Questionable (0.5)
- Symptomatic (≥1.0)
Neurofilament Predicts State/Decline

Rojas et al, for the LEFFTDS & ARTFL Research Consortium. 2018
Baseline Activity Levels and Rate of Plasma NfL Progression in FTLD Variant Carriers

- Higher physical activity is associated with slowed cognitive and functional declines over time
- Even in autosomal dominant variants of frontotemporal lobar degeneration (FTLD)

Casaletto et al. JAMA Neurology 2023;80:82–90.
Treatment of FTD

- **MAPT**
  - Antibody delivery
  - CRISPR

- **C90rf72**
  - Antisense oligonucleotides
  - CRISPR
  - Small molecules

- **GRN**
  - Antibody delivery via transferrin receptor
  - AAV delivery
  - Anti-sortilin antibody
Creativity
Cave Painting Lascaux 15,000 BCE
Creativity Networks in the Brain

The whole is more than the sum of its parts.

LEFT

Lorem ipsum dolor sit amet

RIGHT

\( ax^2 + bx + c = 0 \)
Clinical Diagnosis of svPPA

- **Both** core features must be present:
  - Impaired **confrontation naming**
  - Impaired **single-word comprehension**

- ≥3 of the following must be present:
  - Impaired **object knowledge**, particularly for low-frequency or low-familiarity items
  - **Surface dyslexia** or **dysgraphia**
  - **Spared repetition**
  - **Spared speech production** (grammar and motor speech)

Gorno-Tempini et al. *Neurology*. 2011
Creativity in FTD Not Rare

Anatomy is Evident

Patients with FTD can develop new artistic skills after disease onset.

Visual creativity more common when anterior temporal lobes or left frontal lobe show focal degeneration.

12 patients showing emergence of musical or visual ability, all with FTD.

Art in FTD is not a coincidence!

Associated with language variants.

*Miller BL et al. Neurology. 1998
Each Bar Favorite Note Has a Color
Meter 321 Change of Key

"The colored, treble parts are embellished with geometric shapes in black and also engraved into the paper to represent the quality of tone of each note. When the modulation finally does occur I use gaudy fluorescent colors to make the few #’s in the piece. The music soon collapses and dies in the final two bars. I find Bolero an exciting experiment in sound, one which Ravel didn’t really consider true ‘music’.”
Right Posterior Cortex is Hypermetabolic and Thicker than Matched Controls
Complementary Network Strengths

Focal left frontal injury accompanied by right posterior enhancements

Gray matter increases
Gray matter decreases
Review of 17 Artists with Dementia

- Of 689 FTD-spectrum patients, 17 artists (2.5%)
  - 8 of 17 artists had temporal variant of FTD (6.7%)
  - 8 de novo, 7 some interest, 2 artists who changed
  - Most severe atrophy anterior temp, amygdala striatum insula (left > right), amygdalae, striatum, and left insula

- Same region correlated with left motor strip (hand), no correlation in FTD or healthy controls
- Visual artistic creativity occurred early in FTD
- Disproportionately temporal lobe degeneration
- Damaged brain regions normally suppress dorsomedial greater occipital cortex function
Prevalence, Timing, and Network Localization of Emergent Visual Creativity in FTD

- Bright colors common, art rarely focused on human faces
- 2 svPPA patients generated animal sculptures lacking features of species
- When present, facial expressions bizarre and did not convey natural emotions

Conclusions

- Art uses both hemispheres
  - Double consciousness?
- Artistic creativity may emerge in association with left hemisphere dysfunction
  - Rewiring of posterior brain?
- Insights into the degenerative process: strengths important in diagnosis & care
- Insights into our humanity: brain asymmetry is at core of our strengths and weaknesses
Join Us for UnRavelled
a play by Jake Broder

Award-winning cast, with projection, sound design and a finale of Ravel's Bolero performed by musicians from the San Francisco Conservatory of Music.

July 21, 2023, at the San Francisco Conservatory of Music

In association with the Global Brain Health Institute, The Association for Frontotemporal Degeneration and San Francisco Conservatory of Music, Jake Broder, James Bonas and Cath Brittan