Differences between FTD and Alzheimer's:
Opportunity for a New Approach to the Science?

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Toronto Dementia Research Alliance
Rolling back time may not be desirable
Clinical characterization

THE U of T FTD WORKGROUP
• Theory of Mind (OMHF)
• Primitive Reflexes?
• Emotional Valence and Non-verbal Memory
• Alexithymia
• Citalopram Challenge
• SLP interventions for semantic dementia and other PPAs
What’s happening?

- Neurons failing related to proteinopathy
  - Neuroreceptor # drops
  - GLU toxicity
    - Neuronal dysfunction, Apoptosis
    - Symptoms
Neurons failing related to proteinopathy

Additional proteinopathy? 
*PIB PET in early- vs late-onset FTD*

Neuroreceptor # drops

GLU toxicity

Neuronal dysfunction, Apoptosis

Symptoms

Could use a radioligand for TDP-43…
If reuptake inhibitors are helpful, does that indicate overcompensation by survivor-neurons or that neuroreceptor changes predate neuronal death?

Radioligands, such as 5HT2R tracer [18F]-setoperone, [11C]-WAY or [18F]-FP-TZTP.
Gender & Aging Effects on 5HT2aR binding

Uchida, *Int J Geri Psych* under review
Neurons failing related to proteinopathy

- Neuroreceptor # drops
- GLU toxicity

- Neuronal dysfunction, Apoptosis
- Symptoms

Memantine trial, FDG-PET

Subject referrals:
Memantine in Frontotemporal Dementia

- 24-week open-label trial: \( N = 43 \), transient NPI improvement, mixed signals on other measures
  - Boxer Alz Dis & Assoc Dis 2009
- Pre- and Post-Memantine FDG-PET Imaging in Frontotemporal Dementia
  - Co-Auths Ariel Graff-Guerrero, Morris Freedman, David Tang-Wai, Sandra Black, Bruce Pollock
SPM2: Single Condition and Covariates
Results at $p < .05$ (N=11)

- Colour = increased FDG signal after memantine
  $t = 2.25$

Right anterior cingulate gyrus

<table>
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<th>Pre</th>
<th>8 wks</th>
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<tbody>
<tr>
<td>AG011</td>
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<tr>
<td>HS015</td>
<td>-4</td>
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<tr>
<td>ST002</td>
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How might resting state functional connectivity relate to that peak?

Critical meltdown = ↓ salient network + ↓ default network?
Resting State Functional Connectivity Considerations over the Lifespan

- Individual variability on cogn testing increases with age
  - right on up to time of death!
  - C Grady tracking the changes in variability with aging.
Correlations between connected brain regions change with age, too

So watch where you’re putting those seeds!

Demonstrated here in resting state, but applies to Task Processing Network as well

Grady et al., Cerebral Cortex, in press
Functional Brain Networks and Aging

- Older adults:
  - “shrinking” of activity in the Default Network
  - reduced connectivity in the DN
  - “expanding” activity in the Task Network
  - maintained connectivity in the TN

- Default Network may be especially vulnerable to the effects of aging and Alzheimer disease
How might resting state functional connectivity relate to that peak?

Critical meltdown of salient network vs. additional ↓ default network?

When does window of opp’y for neuroprotection shut?

*longitudinal study & fMRI as outcome measure in clin drug trials*
Also at Baycrest, Quality of Life

**for Patient:**
- Pain-free
- Safe
- Meaningful activities
  - +/- meaningful social interactions
- Maximal autonomy

**For Cgr:** Meaningful interaction with patient
- Emotional connection
- “Doing for” ~ feeding
- Good downtime together (rest, or even- fun!?!)
- Everything that can be done IS being done
NO, IT’S NOT TOO COLD HERE, BUT YES, I DO MISS THE OCEAN!