Selective Vulnerability of von Economo Neurons in Frontotemporal Dementia

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Why study selective vulnerability?

Dementia diagnosis and treatment

- **Dx:** Selective vulnerability dictates early, disease-specific symptoms & signs

- **Rx:** Global targeting of aberrant proteins may not be enough
  - Need to stop disease early, while confined to most vulnerable cells and circuits…may prevent downstream degeneration
  - Vulnerable neurons may express susceptibility or response genes that relate to pathogenesis and impact treatment
  - Invulnerable neurons may employ cell-protective mechanisms that could be used to rescue vulnerable cells
  - Disease-related proteins have normal functions. Systemic treatments may confer toxicity.
Why study selective vulnerability?

Neuroscience

- Selective vulnerability provides an opportunity to study the function of specific cells and circuits targeted by disease

- Selective vulnerability provides a window into human brain systems that cannot be modeled in laboratory animals
Frontotemporal dementia

Behavioral variant

Language variants

Semantic Dementia

Progressive Nonfluent Aphasia

Also:
“Frontal variant” FTD
“FTD”
Frontotemporal lobar degeneration (FTLD)

- Behavioral variant
- Semantic Dementia
- Progressive Nonfluent Aphasia

- Tau-positive
  - Pick’s
  - CBD
  - PSP

- Tau-negative
  - FTLD-U TDP-43
  - FTLD-MND TDP-43
BvFTD social cognitive deficits: Representations of self and others

- Self-concept
  Miller 2001

- Self-conscious emotion
  Sturm 2006

- Empathy
  **Rankin 2005, 2006

- Social self-monitoring
  **Rankin unpublished

- Theory of Mind
  **Gregory 2002
  Snowden 2003
  Lough 2006

- Metacognitive judgment
  **Eslinger 2005

- Moral reasoning
  **Mendez 2005
  Lough 2006
Early bvFTD network: Very mild dementia (CDR 0.5)

9 bvFTD imaging studies (PET/SPECT/MRI)

132 bvFTD patients
166 controls

Pregenual ACC/rmPFC
Frontal insula
Frontal pole

Activation likelihood estimate
Early bvFTD network: very mild dementia (CDR 0.5)

Voxel-based morphometry
P < 0.05, corrected

N = 15

Seeley, Crawford et al, *Arch Neurol*, in press
Very mild bvFTD:

CDR = 0.5

P<0.05 FWE corrected

N = 15
Mild bvFTD:

CDR = 1

P<0.05
FWE corrected

N = 15
Moderate-to-severe bvFTD:

CDR = 2-3

P<0.05 FWE corrected

N = 15
In healthy subjects, baseline low frequency fMRI BOLD signal fluctuations in R FI are correlated with...

An ACC-FI network in healthy humans?

Seeley, Menon et al, J Neurosci 2007
Early bvFTD targets an ACC-FI paralimbic network

R FI intrinsic connectivity

bvFTD CDR 0.5 atrophy
Very mild FTD
CDR 0.5

Cytoarchitecture

von Economo and Koskinas, 1925
von Economo Neurons

- 1881 Betz
- 1899 Cajal
- 1925 von Economo
- 1927 Rose
- 1979 H. Braak
- 1995 Nimchinsky & Hof
Von Economo neurons: Phylogeny

von Economo 1925  Nimchinsky *PNAS* 1999
**Structure**
- Simplified architecture
- Layer Vb, Fl>>ACC
- Columnar clusters parallel to small arterioles
- Project axons into WM, targets unknown
- R/L hemisphere = 1.3

**Neurochemistry**
- Somata & prox dendrites express receptors:
  - D3
  - 5HT1b/2b
  - Vasopressin 1a

**Ontogeny**
- Emerge late in gestation (34-38 wks)
- Peak total # = 8 mo-4 yrs
- Pruned to adult prevalence by 8-10 yrs

**Phylogeny**
- Absent in monkeys and lesser apes
- Orangutan<Gorilla<Chimps
- Great apes<<<Human
- Whales
What drove VEN specialization in primates?

Hof & Van Der Gucht, Anat Rec A Discov Mol Cell Evol Biol, 2006
VENs: The key vulnerable neuron in bvFTD?

**bvFTD**
- Self-awareness
- Social cognition
- Early ACC-FI injury
- Asymmetric right-sided degeneration

**VENs**
- Late-evolving
- Late-developing
- Restricted to ACC and FI
- 30% more abundant on right
VENs: The key vulnerable neuron in bvFTD?

Seeley, Carlin et al, Ann Neurol, 2006
FTLD

Pick’s

FTLD-U

0.4% (0.1-0.7%)

N = 7

AD

1.5% (0.7-2.2%)

N = 5

CBD

1.4%

N = 1

Tau immunohistochemistry
VEN tauopathy: Pick’s disease

Tau immunohistochemistry (CP-13 antibody)
Healthy human VENs in FI

Ongur & Price, JCN 2003
VEN Hypothesis: Summary

1. In bvFTD, VENs show early selective vulnerability, akin to the early loss of ERC Layer 2 projection neurons in AD

2. Early VEN injury incites a degenerative cascade throughout an anterior paralimbic network rooted in the ACC and FI

3. VENs may provide the ACC-FI network with new information processing capacities in humans that are lost in early FTD
Next steps

- VEN neurochemistry
- VEN connectivity
- Early VEN pathogenesis in FTD
- VEN physiology
- VEN gene and protein expression profiles
Next steps

- VEN neurochemistry
- VEN connectivity
- Early VEN pathogenesis in bvFTD
- VEN physiology
- VEN gene and protein expression profiles
48 y.o. man w/ familial FTD-MND

CDR = 0

GFAP
Normal ACC/FI neuronal morphology

Pyramidal

VEN

Watson et al 2006
Early VEN pathogenesis?
Early VEN pathogenesis?
Alzheimer’s disease

Episodic Memory

ERC-DG-CA3-CA1-subic-FF-PCC

ERC Layer II pyramidal

Aβ42, tau

Presenilins ApoE, APP

Known
Hypothesized

RX
FTD

Social cognition
Self-representation
Response inhibition

ACC-FI network

Tau, TDP43

1999 → 2002 → 2006

Known
Hypothesized

MAPT
PGRN

1999
2002
2006

RX
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