EXECUTIVE SYSTEMS and FRONTOTEMPORAL DEMENTIA

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Kirk R. Daffner, MD, FAAN

J. David and Virginia Wimberly Professor of Neurology
Harvard Medical School

Director, Center for Brain/Mind Medicine
Brigham and Women’s Hospital

Disclosures: none

Case

39 year old right-handed woman, former childcare provider

- Presenting symptoms
  - Brought by best friend for evaluation of progressive changes in personality and behavior
  - Husband divorced her because of erratic behavior
  - Currently jobless; days spent on the street or at McDonalds; sleeping on the street or in her ex-husband’s van

- Family and Social History
  - Mother with progressive neuropsychiatric syndrome in early 40s
    - Died at 52 after 9 years in psychiatric wards and nursing homes
  - High school graduate
  - Worked as a childcare provider and foster care mother for > 10 years
- Past psychiatric history
  - No prior psychiatric or substance abuse history
  - No known encounters with the law

- Initial Clinical Examination
  - No impairments in memory, language, or composing a detailed narrative
  - 30/30 on MMSE
  - Behaviorally, very inappropriate, labile affect; quickly shifting from jocularity to tearfulness
  - No insight into her predicament

Course of the illness
- Guardianship was sought and finally obtained by her best friend
- In the nursing home, she was not closely supervised
- Got involved with a man in his 70s who she met at a bar while she was supposed to be attending church
- Taken to his secluded trailer in the woods for sexual favors
- Turned out that this man was a Level-2 sex offender
• PET Imaging
  – Marked hypometabolic activity within the orbitofrontal cortex, extending to the cingulate gyrus and caudate bilaterally

• Genetic Testing
  – Mutation of the MAPT gene on Chromosome 17

• Diagnosis: Behavioral Variant Frontotemporal Degeneration (bvFTD)

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Executive Systems and FTD

• Neuroanatomy, Cognitive Processing, Affect Regulation, Social Cognition
• Evaluation
• bvFTD Clinical Diagnosis and Epidemiology
• bvFTD Markers of the disease
  – bvFTD Neuropathology and Genetics
  – bvFTD Management

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Frontal Networks

• Are critical for countering the default mode of the brain, which is to be reactive to environmental and internal stimuli

• Allow us to be proactive, to anticipate potential outcomes, monitor consequences of decisions, and adjust actions accordingly

• Play a crucial role in negotiating the uncertainties of the social terrain, essential for successfully carrying many of our goals
Functions Attributed to the Frontal Lobes

- Judgment
- Foresight
- Insight
- Abstract Reasoning
- Self-Governance
- Perspective Taking
- Mental Flexibility
- Perseverance
- Curiosity
- Initiative and Drive
- Planning and Sequencing of Complex Behavior
- Delay of Gratification
- Inhibition of Inappropriate or Overlearned Behavior
- Context Appropriate Behavior

Divisions of the Frontal Lobe

- Frontal-Parietal Control Network

Frontal-Parietal Control Network

- Willment and Daffner, 2014
- Niendan et al., 2012
- Nivitch et al., 2013
**Frontal-subcortical Networks**

- Frontal Lobe
- Striatum (Caudate/Putamen)
- Globus Pallidus/Substantia Nigra
- Thalamus

**Executive Control Functions**

Complex set of cerebral processes that operate to exert top-down, volitional control over sensory input, cognition, emotion, motor output, allowing individuals to carry out goal-directed behaviors.
The Frontal Lobe Team

- Dorsolateral PFC
- Ventrolateral PFC
- Anterior Cingulate Cortex
- Orbitofrontal Cortex
- Rostromedial PFC
- Fronto-insular Cortex

The Executive Control Team

- Keeping Task-Relevant Goals On-Line (Task-setting)
- Initiating (Starting) and Sustaining Activity (Energization)
- Anticipating and Monitoring Outcomes/Rewards
- Inhibiting (Stopping) Activity
- Predicting the mental states/responses of others
- Evaluating and responding to changes in salience

Keeping Task-Relevant Goals On-Line (Task-setting/Processing Priorities)

- Critical function of Working Memory
  - Holding on-line and manipulating internalized representations to guide future behavior
- Executive Control Network
  - Dorsal (and Ventral) Lateral PFC
  - Posterior Parietal Cortex

Baddeley, 1992; Goldman-Rakic, 1987; Miller et al., 1996; Miller et al., 2000; Owen et al., 2000; Smith et al., 1999; Courtney et al., 1999; Wilson et al., 1998; D'Esposito et al., 1998; Smith et al., 1996; Courtney et al., 1996; Miller & Cohen, 2001
Keeping Task-Relevant Goals On-Line
(Task-setting/Processing Priorities)

Task Setting – coordination of executive/WM processes to establish a goal-directed plan upon which motor or mental activity is enacted

Planning – mental representation of intermediate steps/tasks needed to accomplish a goal

Organization – ordering of tasks/responses into a scheme that directs the execution of subroutines to accomplish a goal

Posterior – Anterior gradient in the lateral PFC
  • Posterior (closer to motor cortex) – immediate/less abstract tasks or actions
  • Anterior (towards the frontal pole) – more abstract, less temporally immediate tasks or action rules

Initiating and Sustaining Activity
(Energization)

• Purposeful, self-generated commencement and maintenance of an overt act or mental activity
• Anticipating the potential reward value of actions serves as the basis of motivating/energizing behavior

• Medial Prefrontal Cortex

Seeley et al., J Neurosci., 2007

Passingham, 1985; Ritter et al., 2004; Fias, 2001; Cohen et al., 1996; Sasu, 1998; Ullsperger et al., 2014
Anticipating and Monitoring Outcomes/Rewards

• Decoding/anticipating the reward value of sensory signals, objects, and choices

• Orbital Frontal Cortex

Anticipating and Monitoring Outcomes/Rewards

• Keeping track of a designated set of external or internal stimuli. Discrepancies from expectation are registered and can trigger additional processing and response.

• Dorsal Anterior Cingulate

Stroop Effect: Color/Word Tests

Instructions: print on card stock and cut each page into horizontal strips. See the Science Buddies project What Conflicting Mental Tasks Reveal About Thinking: The Stroop Effect for complete information.
Inhibiting (Stopping) Activity

- Suppression of a specific behavioral output, mental activity, or emotional response (usually an automatic, prepotent, or overlearned)
- Lateral Prefrontal Cortex—cognitive
- Orbitofrontal Cortex—emotional

Liddle et al., 2001; Kanwisher et al., 1999; Brass et al., 2005; Andersen et al., 2004; Wagner et al., 2003; Knight et al., 1991; Davidson & Mounts, J. Neurophysiol., 2000; Ochsner, Bunge, Gross, & Gabrieli, J.Cogn Neurosci., 2002)

Understanding and predicting the mental states and responses of others

- Representations of the self
- Monitoring of one’s emotional states
- TOM (representations of the mental states and intentions of others)
  - TPJx, STS, TP, PCC
- Prosocial emotions (e.g., empathy, compassion, gratitude, reputation)
  - Reward system/ventral striatum, STS

Amodio, Frith 2006; Sanfey 2007; Rillings, Sanfey 2011; Moll et al. 2007

Regions commonly activated during social decision-making studies

Sanfey, 2007
A common neural currency underlying social and monetary rewards

Gateway to Social-Emotional Semantics
- Representations of social-emotional experience
- Stored knowledge underlying social rules and expectation
- R Temporal Lobe

Evaluating and responding to changes in salience
- Identifying the most homeostatically relevant stimuli through the rapid integration of sensory, visceral, autonomic, and hedonic signals
- Frontoinsular Cortex
<table>
<thead>
<tr>
<th>Executive Control Functions</th>
<th>Sensory Input</th>
<th>Thought/Cognition</th>
<th>Emotion</th>
<th>Motor Output</th>
<th>Social/Interpersonal</th>
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<tbody>
<tr>
<td>Sensory Deficits</td>
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<tr>
<td>Enhancement Deficits</td>
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<td>Inhibition Deficits</td>
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**Sensory Input**

**Selective attention**
- Facilitates processing of sensory input that is most relevant to task demands or behavioral goals
- Biases sensory processing by enhancement of neural activity in response to task relevant features and/or suppression of neural activity in response to task irrelevant ones

**Enhancement Deficits**
- Reduced Ability to focus attention

**Inhibition Deficits**
- Increased distractibility by task-irrelevant sensory input

**Executive Control Functions**

**Thought/Cognition**

**Working Memory**
- Control over the on-line content of internal thought
- Active maintenance of current processing priorities (task setting)
- Management of the execution of multiple cognitive operations and the shifting of mental sets

**Enhancement Deficits**
- Inability to hold information or task priorities on-line
- Loss of mental set
- Poor planning and organization

**Inhibition Deficits**
- Increased distractibility by task-irrelevant cognitive input
<table>
<thead>
<tr>
<th>Emotion/Motivation</th>
<th>Executive Control Functions</th>
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</thead>
<tbody>
<tr>
<td>Regulation of affective and motivational states</td>
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<tr>
<td>Initiation and sustaining of mental activity and engagement</td>
<td></td>
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<tr>
<td>Mapping and integration of visceral, autonomic, and hedonic markers of experience</td>
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<tr>
<td>Determination of affective weights/values of objects, actions, and potential outcomes</td>
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<table>
<thead>
<tr>
<th>Enhancement Deficits</th>
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<tbody>
<tr>
<td>Apathy – motivational inability to carry out goal-directed behavior</td>
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<td>Emotional blunting</td>
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<thead>
<tr>
<th>Inhibition Deficits</th>
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<tr>
<td>Disinhibited behavior</td>
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<tr>
<td>Emotional lability</td>
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<tr>
<th>Motor Output</th>
<th>Executive Control Functions</th>
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<tbody>
<tr>
<td>Eye movements</td>
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<td>Reaching behaviors</td>
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<table>
<thead>
<tr>
<th>Enhancement Deficits</th>
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<tr>
<td>Reduced ability to initiate movements</td>
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<tr>
<td>Impersistence</td>
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<tr>
<th>Inhibition Deficits</th>
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<tr>
<td>Impulsivity</td>
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<td>Perseveration</td>
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<td>Utilization Behavior</td>
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<td>Impairments in motor sequencing</td>
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<table>
<thead>
<tr>
<th>Social/Interpersonal</th>
<th>Executive Control Functions</th>
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<tbody>
<tr>
<td>Representations of the self</td>
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<tr>
<td>Representations of mental states/intentions of others</td>
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<tr>
<td>Monitoring of emotional states of oneself and others</td>
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<thead>
<tr>
<th>Deficits</th>
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<tbody>
<tr>
<td>Decreased self-monitoring/awareness of one’s internal states</td>
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<tr>
<td>Failures of empathy/compassion</td>
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<tr>
<td>Inability to distinguish one’s own mental states from those of others (TOM impairment)</td>
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<tr>
<td>Diminished capacity for “affect sharing”</td>
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</table>
Frontal Anatomy

<table>
<thead>
<tr>
<th>Dorsolateral PFC</th>
<th>Ventrolateral PFC</th>
<th>Anterior Cingulate Cortex</th>
<th>Orbitofrontal Cortex</th>
<th>Rostromedial PFC</th>
<th>Fronto-insular Cortex</th>
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<tbody>
<tr>
<td>WM/ Goals-on-Line</td>
<td>Initiating/ Sustaining</td>
<td>Anticipation/ Monitoring</td>
<td>Inhibition</td>
<td>Social/Interpersonal</td>
<td>Salience Integration</td>
</tr>
</tbody>
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Executive Systems, Aging, and Dementia

- Normal Age-related Cognitive Changes
- Alzheimer’s Disease
- Vascular Cognitive Impairment
- Dementia with Lewy bodies
- Parkinson’s Disease
- bvFTD
Evaluation

- History/History/History
- Neuromedical Assessment
- Toxic-metabolic screen
- Mental State Examination
  - Behavioral Observations
  - Focused, Divided, and Sustained Attention
  - Working Memory
  - Inhibition
- Inventories
  - Clinical Dementia Rating Scale
  - Neuropsychiatric Inventory

Frontal Assessment Battery

1. Similarities (Conceptualization) “Banana/orange, Table/Chair, Tulip/Rose/Daisy.”
2. Lexical Fluency (Mental Flexibility/Sustained Output) “S words”
4. Conflicting Instruction (Sensitivity to Interference) “Tap twice when I tap once; Tap once when I tap twice.”
5. Motor Go –No –Go (Inhibitory Control) “Tap once when I tap once. Do not tap when I tap twice.”
6. Prehension behavior (Environmental Autonomy) “Do not take my hands.”

0-3 points per item (Maximum score 18).
Score <17 raises the possibility of frontal dysfunction.

FTLD-modified Clinical Dementia Rating Scale (CDR)

<table>
<thead>
<tr>
<th>Category</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
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<tbody>
<tr>
<td>Memory</td>
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<tr>
<td>Orientation</td>
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<tr>
<td>Judgment + Problem Solving</td>
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<tr>
<td>Community Affairs</td>
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<tr>
<td>Home + Hobbies</td>
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<tr>
<td>Personal Care</td>
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<tr>
<td>Language Deficits</td>
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<tr>
<td>Behavioral Disturbance</td>
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Neuropsychiatric Inventory
Questionnaire

- Delusions
- Hallucinations
- Agitation or aggression
- Depression or dysphoria
- Anxiety
- Elation or euphoria
- Apathy or indifference
- Disinhibition
- Irritability or lability
- Motor disturbance
- Nighttime behaviors
- Appetite and eating

bvFTD: Brief Summary

- Salient changes in personality, behavior, and social interactions
- Poorly modulated behaviors (apathy / impulsivity)
- Impaired executive functions, insight, judgment
- C9ORF72 cases may include psychotic sx; delusions
- Relative sparing of memory (storage) and spatial orientation (early)
- MRI/CT: Disproportionate anterior atrophy (early)
- PET/SPECT: Hypometabolism/Hypoperfusion in anterior regions (early)
- Genetics: Chromosome 9—C9ORF72; Chromosome 17 – MAPT gene, PGRN gene
- Pathology: Neuronal loss and gliosis
  - Tau pathology (~40-50% of cases)
  - TDP-43 Protein Inclusions (~40-50% of cases)
  - AD (plaques & tangles) pathology – relatively rare
- Prominent Distribution of Pathology:
  - Frontal lobes and anterior temporal lobes

Behavioral Variant FTD
Diagnostic Criteria, International bvFTD Criteria Consortium

<table>
<thead>
<tr>
<th>Level</th>
<th>Criterion</th>
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<tbody>
<tr>
<td>Possible</td>
<td>3 of the following 6: 1) disinhibition; 2) apathy/inertia; 3) loss of sympathy/empathy; 4) perseverative, stereotyped, or compulsive/studialtic behavior; 5) hyporality and/or dietary changes; 6) neuropsychological evidence of executive deficits with relative sparing of episodic memory and visuospatial functions</td>
</tr>
<tr>
<td>Probable</td>
<td>Criteria for “possible” FTD</td>
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<td></td>
<td>Evidence of significant functional decline</td>
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<tr>
<td>Definite</td>
<td>Evidence of structural or functional imaging abnormalities c/w bvFTD</td>
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<tr>
<td>Exclusionary Criteria</td>
<td>Deficits due to other non-degenerative CNS or medical disorders, or to psychiatric disorders</td>
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<tr>
<td>Biomarkers strongly indicative of AD or other neurodegenerative processes</td>
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</table>
Clinical-Pathological Correlations

<table>
<thead>
<tr>
<th>Behavioral Dysfx</th>
<th>Critical Anatomical Nodes</th>
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</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>ACC, dlPFC, OFC</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>OFC, vlPFC</td>
</tr>
<tr>
<td>Perseverative behaviors</td>
<td>dlPFC, ACC</td>
</tr>
<tr>
<td>Loss of Empathy</td>
<td>mPFC, R ant temp</td>
</tr>
<tr>
<td>Hyperorality/Dietary change</td>
<td>FI cortex, OFC</td>
</tr>
<tr>
<td>Executive Deficits</td>
<td>dlPFC, vlPFC</td>
</tr>
</tbody>
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Massimo et al., 2009; Shallice et al., 2006; Joseph et al., 2007; Whitwell et al., 2007; Velayos 2007; Breeze et al., 2010

Potential Misdiagnoses of bvFTD

- “Phenocopies”—unmasking developmental or psychiatric syndromes
  - Cluster C Personality Disorders
- Frontal variant of Alzheimer’s disease
- Sagging Brain Syndrome
- Manic-Depressive Illness
- Sociopathy
- OCD
- High functioning Autism Spectrum Disorders

Mychack et al., 2001; Gossink et al., 2015; Khan et al., 2012; Saeger et al., 2017

Epidemiology of FTLD

- Prevalence
  - Usual Age of Onset: 45-65 years old
  - 2nd most common cause of presenile dementia
  - Estimates vary from 1-35 per 100,000 in patients <65 y.o.
  - bvFTD much more common than agrammatic PPA and semantic PPA
- Sex Ratio: Male = Female (Pickering-Brown, 2007; McKann et al., 2001), although some have suggested Male > Female (Hodges, 2003; Velayos et al., 2007)
- Duration (onset of symptoms to death): 4-8 years (Rasovski et al., 2002; Pasquier et al., 2004; Snowden et al., 2007; Vernooij et al., 2010; Xie et al., 2008)
- Delay to Dx (onset of symptoms to diagnosis) tends to be longer for FTD than AD (Pasquier et al., 2004)
- Family History 30-40% of cases (Rasovski et al., 2002; Pasquier et al., 2004; Snowden et al., 2007)
- First degree family members of patients with FTD: 3.5-10 fold increased risk of developing FTD

Rasovski et al., 2002; Ghiasfar et al., 2003; Kavanagh et al., 2014; Velayos et al., 2007; http://www.dementia.ion.ucl.ac.uk
Epidemiology
Does FTD only afflict relatively young patients?

- Manchester Brain Bank (Baborie et al., 2010)
  - 25% of all FTLD autopsy cases over 25-year period had onset 65+ yo
  - Most cases bvFTD
  - Compared to young onset, smaller percentage with lobar atrophy and higher percentage with hippocampal sclerosis

- Newcastle Brain Bank (Baborie et al., 2012)
  - Behavioral symptoms more than language/semantic dysfunction
  - Frequent memory loss
  - Prominent hippocampal sclerosis; less prominent lobar atrophy

Neuropsychological Tests Discrimination between FTD and AD

- Meta-analysis suggesting that neuropsychological tests do not tend to discriminate FTD from AD patients. Large overlap in performance between the 2 groups (Hutchinson and Mathia 2007)

- FTD pts tend to do relatively better on episodic memory than executive fxs (Pachana et al., 1996)

- AD pts either do relatively poorly in both realms (Bennett et al. 2004) or are more impaired on tests of episodic memory than executive fxs (Pachana et al., 1996; Parnia et al., 2001)

- Perry & Hodges (2000)
  - fvFTD severe deficits in attention/executive fxs with preserved semantic memory
  - bvFTD severe deficits in semantic memory with preserved attention/executive fxs
  - Attention/executive fxs separated bvFTD pts from early AD pts, who were densely amnestic
  - Memory Tests: AD worse than all groups, bvFTD > NC

- Some bvFTD patients exhibit prominent memory impairment (Hornberger et al. 2011; Graham et al. 2005)

- ~50% evidence of memory storage lost = AD pts (Hornberger et al. 2011)

- Hippocampal volume similar for bvFTD and AD (de Souza et al. 2013)

Non-Traditional Tests

- “Ecologically-valid Neuropsychological Tests” (Knight et al. 2002; Sheehan et al. 2002)

- Theory of Mind (Gregory et al., 2002)
  - Faux Pas recognition test (Stone et al., 1998)
  - Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001)

- Social cognition and Emotion Assessment (SEA) (Farthing et al. 2012)

- Moral Judgments (Millar et al., 2002)

- Decision Making Paradigm (Rankin et al., 2006)

- Interpersonal Reactivity Index (Rankin et al., 2006)
Structural MRI

- The earliest tissue loss in bvFTD is observed in frontal paralimbic cortices (Seeley et al., 2008)
  - CDR 0.5: Paralimbic (ACC, frontoinsular, lateral OF); Frontal Neocortical (DLPFC, rostromedial, frontopolar); limbic (R hippocampus); subcortical (ventral striatum, MD thalamus). R>L hemisphere involvement
  - CDR 1.0: Regions similar to CDR 0.5 but more confluent and bilateral. Development of lateral frontal regions. White matter atrophy in subfrontal, parahippocampal, mid collosal regions
  - CDR 2-3: Additional posterior insula, hippocampus, and parietal involvement. More extensive white matter loss

Gray Matter Loss

<table>
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<tr>
<th>CDR</th>
<th>Image</th>
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<tbody>
<tr>
<td>0.5</td>
<td>![Image](Seeley et al. 2008)</td>
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<tr>
<td>1.0</td>
<td>![Image](Seeley et al. 2008)</td>
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<tr>
<td>2+</td>
<td>![Image](Seeley et al. 2008)</td>
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PET/SPECT

Compared to structural MRI, functional imaging with FDG PET reveals more extensive areas of hypometabolic activity at the earliest stages of bvFTD and a progression over ~20 months to involve parietal and temporal regions (Diehl-Schmid et al. 2007)
Baseline FTG-PET
22 bvFTD pts:  
62.7 yo; MMSE 24.5; NPI 17.3  
6 pts CDR 0.5 16 pts CDR 1.0;  

Diehl-Schmid et al, 2007

Biomarkers

Structural Imaging
• Increased white matter disruption (DTI) in Tau than TDP-43 (McMillan et al., Hum. Brain Mapp., 2014)
• Data-driven volumes of interest (VOI) (combining GM MRI and DTI)  
  – Better classification accuracy (FTLD vs AD) than global measures (e.g., ventricular volume) or anatomic VOI

Functional Imaging
  – Overlap/Mixed
• Tau imaging (18F) (Chien et al., 2013; Dickerson et al, 2014)

Ghetti, Oblak, Boeve, Johnson, Dickerson, Goeder, Neuropathol Appl Neurobiol. 2015
**Biomarkers**

**CSF**

- **R/O AD Pattern (increase Tau/AB42 Ratio)** (Irwin et al., Front Aging Neurosci., 2013)
- **P-Tau/Tau ratio lower in FTLD-TDP43 vs Tau (Hu et al., Neurology, 2013)**
- **Increased neurofilament light chain (NFL)**
  - Higher in TDP-43 or FUS than Tau (Landqvist Waldo et al., BMC Neurol., 2013)
  - Higher in FTLD than AD or Normal Controls
  - Higher in bvFTD and SD than AD or a-PPA (Landqvist Waldo et al., BMC Neurol., 2013)
- **Increased Tau levels predict shorter survival time** (Padovani et al., J. Alzheimers Dis., 2013)
- **Increased TDP-43 in plasma or CSF in C9 or GRN mutations** (Suarez-Calvet et al., J. Neurol. Neurosurg. Psychiatry, 2014)

**FTD — Neurochemistry**

- **Serotonin Deficits**
  - 5-HT Projections from brainstem raphe nuclei to frontal cortex
  - Evidence via autopsy, imaging, and CSF studies
  - Postsynaptic > Presynaptic Deficits
  - Abnormal serotonergic activity has been associated with aggression, impulsivity, mood disturbance, OCD symptomatology, perseverative responses, increased appetite, and weight gain
- **Dopamine Deficits**
  - DA Projections from brainstem VTA and SN
  - Evidence via imaging and CSF studies
  - Decreased presynaptic DA transporter in caudate and putamen
  - Abnormal dopaminergic activity has been associated with frontoexecutive dysfunction and thought disorders)
- **Cholinergic and NE systems relatively intact**

(Huey et al., 2006)
## FTLD: 2 Major Types of Pathology

- Tau-positive inclusions (40 - 50% of cases)
- FTLD-U: Tau-negative, ubiquitin-positive (40 - 50% of cases)
  - TAR DNA-Binding Protein 43 (TDP-43 protein inclusions)
    - Proteins targeted for degradation are ‘ubiquitinated’
  - FUS (fused in sarcoma) inclusions (5-10% bvFTD)

### FTLD

<table>
<thead>
<tr>
<th>Major Molecular Class</th>
<th>Recognized Subtypes</th>
<th>Associated Genes</th>
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<tbody>
<tr>
<td>FTLD-Tau</td>
<td></td>
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<tr>
<td>Type A</td>
<td>Many NCI</td>
<td>MAPT</td>
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<td>GRN Mutations</td>
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<td></td>
<td>type B moderate NCI</td>
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<td>type C many long DN</td>
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<td>FTLD-UPS</td>
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<td></td>
<td>type C many long DN</td>
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</tbody>
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## Neuropathology—How often do clinically dx’d FTD pts have underlying AD pathology?

- FTLD overall: 17-20% [Karlawish et al., 2005; Forman et al., 2006]
- bvFTD: Studies vary
  - Some studies suggest bvFTD rarely due to AD pathology [Alladi et al., 2007; Karlawish et al., 2005]
  - Recent study suggests 22% of cases [Mendez, Joshi, Tassniyom, Teng, & Shapira, Neurology, 2013]
Pharmacologic Treatment Summary

• SSRIs—currently the first line drugs for behavioral symptoms, although evidence is very limited

• Trazodone – improved NPI (irritability, agitation, depression, eating disorder) (Sibert et al, 2004)

• Memantine—RCT: no evidence of benefit (Rosen et al, 2015)

• Oxytocin – 1 dose intranasal, improved NPI, change in emotional recognition tools (Jessel et al, 2011)
  – Recent safety/tolerability study. Twice/day x 1 week (Finger et al, 2015)

• Much more research is necessary

• Disease modifying agents (e.g., inhibition of tau aggregation)
Find and Treat Concurrent Medical Problems

- Concurrent Problems include
  - Cerebrovascular disease (strokes)
  - Sleep disorders
  - Endocrine abnormalities
  - Pain
  - Cardiac, pulmonary, renal abnormalities
  - Infection (e.g., UTI, bronchitis)
- Side-effects from Rx’d and OCT medications
- Need to advocate for appropriate medical care

Behavioral Issues and Their Management

- Driving Evaluation
- Determine Access to Weapons
- Safe Environment
  - OT / PT Consultation—home assessment
- Planning for the future
  - Power of Attorney
  - Guardianship


Behavioral Issues and Their Management

- Caregiver Education
  - Enhances empathy for patients
  - Increases tolerance for maladaptive behaviors
  - Establishes more realistic expectations
  - Promotes preparation for the future
- Caregiver Support
  - High incidence of depression among caregivers
  - Social Work Consultation
  - www.theafld.org
  - www.ftd-picks.org
  - www.ninds.nih.gov/disorders/picks/picks.htm
  - Alzheimer’s Association

Mittelman et al JAMA 1996
Multidisciplinary Team Approach

- Neurology
- Psychiatry
- Internal Medicine
- Neuropsychology
- Social Work
- Rehabilitation Services
  - Speech/Language
  - OT
  - PT
- Community Groups
  - www.fld-picks.org
  - www.theaftd.org
- Communication among team members is key
- Fewer behavioral and psychological symptoms
- Lower caregiver stress and depression

Update on patient presented earlier

- Further deterioration of her behavior over the next few years
- Section 12 for wandering from her unlocked facility and stealing from local stores
- Transferred to a locked dementia unit, where she is closely monitored
- Her very poor hygiene has improved substantially

Update on patient presented earlier

- Often walks around during meal times; eats off of others’ plates
- Currently puts anything she sees into her mouth
- Progressive reduction in verbal output – near mute
  - Had been singing songs learned 1960s-1980s
  - Most recent visit—unable to recall the words to songs
- The patient’s daughter sought genetic counseling and testing and was found to have the same mutation
bvFTD: Summary

- Salient changes in personality, behavior, and social interactions
- Poorly modulated behaviors (apathy / impulsivity)
- Impaired executive functions, insight, judgment
- Relative sparing of memory (storage) and spatial orientation (early)
- MRI/CT: Disproportionate anterior atrophy (early)
- PET/SPECT: Hypometabolism/Hypoperfusion in anterior regions (early)
- Genetics: Chromosome 9 – C9ORF72; Chromosome 17 – MAPT gene, PGRN gene
- Pathology: Neuronal loss and gliosis
  - Tau pathology (~40-50% of cases)
  - TDP-43 Protein Inclusions (~60% of cases)
  - AD (plaques & tangles) pathology -- rare
- Prominent Distribution of Pathology: Frontal lobes and anterior temporal lobes