Navigating the Cognitive Internet
Part II

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Networks
Characteristics of Networks

• Fundamental neurobiological system with physiological and neurobiological properties that distinguish it from other systems

• Contains interacting brain areas that are connected and distinct from other systems within the brain
Schematic representation of the 36 canonical expanded seed regions used for evaluating composite scores for 5 brain resting state networks (RSNs).
DMN- Default Mode Network,
DAN- Dorsal Attention Network,
CON- Control Network,
SAL- Salience Network,
SMN- Sensory Motor Network.

Regions associated with the brain’s default network

Ventral medial prefrontal cortex
Posterior cingulate/retrosplenial cortex
Inferior parietal lobule
Lateral temporal cortex
Dorsal medial prefrontal cortex
Hippocampal formation

Default Network

• Internally directed cognition
  – Freely wandering past recollections
  – Future plans
  – Other personal thoughts and experiences
  – Generation and manipulation of mental images
  – Reminiscence of past experiences based on episodic memory
  – Making plans
DMN and AD

• AD pathology forms preferentially throughout the DMN, suggesting that activity within the network may facilitate disease process.

• Metabolism hypothesis
  – Synaptic activity increases extracellular α-beta
  – Map of rest state glycolosis correlates well with distribution of amyloid plaques
WHERE IT’S ALL HAPPENING

Slide courtesy of Dr. R Shatz
Global Network Dysfunction in AD

- All networks showed ↓ activity with higher CDR score, except salience network (slightly ↑ between CDR 0 and 0.5)
- Reduced anti-correlation among networks with ↑ CDR
- DMN is anatomical and functional connectivity hub
- Synaptic dysfunction spreads across all networks
DYSFUNCTION: THE LAST STRAW

- Network change before cognitive change
- Function preserved in damaged networks by compensatory changes
- Cognition insensitive to earliest pathologies
- Cognitive impairment represents failed compensation

**Network goal:** 
Preserve Function

Slide courtesy of Dr. R Shatz
Current treatment options

- Tacrine [Cognex (1993)]
- Donepezil [Aricept (1996)]
- Rivastigmine [Exelon (2000)]
- Galantamine [Razadyne (2001)]
- Memantine [Namenda (2003)]
Preclinical AD

• Stage I: Asymptomatic amyloidosis
  – Low CSF Aβ42 or elevated brain amyloid by PET imaging
  – Normal cognition for age and education.

• Stage II
  – Normal cognition with an AD-like pattern of abnormality on downstream markers. (synaptic dysfunction as per FDG hypometabolism, functional connectivity MRI, increased CSF tau/phospho-tau, or MRI findings of cortical thinning or atrophy in the hippocampus or entorhinal cortex.)
Biomarkers

• CSF Tau/A-beta
• Hippocampal Atrophy
• FDG PET
• Amyloid Imaging
**Indication**: PET imaging of brain in cognitively impaired adults undergoing evaluation for AD and other causes of cognitive decline

- As part of a comprehensive diagnostic evaluation, **negative** scan should prompt investigation for **non-AD**
- Error in categorization small but more **false negative**
- **Not been tested** for
  - **predictive value** MCI/at risk
  - **monitoring response to AD therapies**

Slide courtesy of Dr. R Shatz

**FLORBETAPIR: AN AD TEST?**

Clinical trials.gov number NCT01447719
Amyloid Imaging

Current data support amyloid imaging for:
- Pts with memory complaints and impairments on cognitive tests
- Pts diagnosed with AD with unusual presentation
- Pts with dementia <65 years of age

Committee recommends against scanning for:
- People who have normal cognitive exams
- Pts >65 years old with clear AD diagnosis
Brain amyloid is a risk for Alzheimer’s dementia
Pre-plaque amyloid reduces expansion and maintenance of default network
Initially the brain compensates for amyloid induced changes
fMRI reveals changes in nodes and connections
Cognitive change occurs late and represents failure of brain’s compensatory abilities

Networks are the basis of dementia

Alzheimer’s: a chronic disease
Preclinical MCI Dementia

Slide courtesy Dr. R Shatz
Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade

*The Lancet Neurology*, Volume 9, Issue 1, Pages 119-128

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Increases AD</th>
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<tbody>
<tr>
<td>Diabetes</td>
<td>40%</td>
</tr>
<tr>
<td>Mid-life HTN</td>
<td>60%</td>
</tr>
<tr>
<td>Mid-life obesity</td>
<td>60%</td>
</tr>
<tr>
<td>Inactivity</td>
<td>40-80%</td>
</tr>
<tr>
<td>Low education</td>
<td>40-80%</td>
</tr>
<tr>
<td>Smoking</td>
<td>60%</td>
</tr>
<tr>
<td>Depression</td>
<td>90%</td>
</tr>
<tr>
<td>Cognitive inactivity</td>
<td>(unknown)</td>
</tr>
</tbody>
</table>
Minimize network burden
- Diabetes HgbA1C <5.7
- Anticholinergics
- High body weight
- Depression
- Hypertension 120/80
- Hyperlipidemia LDL<70
- Cerebrovascular disease
- Head injury, contact sports
- Sleep apnea, RBD
- Inflammatory diseases

Maximize network maintenance
- Early learning and variety of activity
- Complexity
- Physical exercise 1 hour daily
- Acetylcholinesterase inhibitors

Slide courtesy of Dr. R Shatz
ANTICHOLINERGICS
RISK FOR DEMENTIA

Medical Research Council's Cognitive Function and Aging Studies (CFAS)

Mortality
ACB >4: 20%
Each point ACB >5, increased odds 26%

Cognitive impairment (ACB>5)
Score 4% lower on cognitive tests
Associated with a diagnosis of MCI.

Risk
Accumulates with chronic use
Varies with strength of ACD

Most anticholinergic drug use
Elderly
Greater number of health conditions

Cocktail of Popular Drugs May Cloud Brain
By RONI CARYN RABIN
February 27, 2012, 5:39 pm 81

Religious orders study
Prospective study
/>= 1 anticholinergic drug
>65y

3X risk of cognitive decline

Slide courtesy of Dr. R Shatz

Wilson et al 2009; Fox et al 2011
Muscle relaxers
Bentyl, Flexeril, Robaxin, Soma

Anti-anxiety
Ativan, Serax, Valium, Xanax

Bladder control
Detrol, Ditropan

Antidepressants
Elavil, Paxil, Tofranil, Desyrel

OTC
Cold & cough, Benadryl, Tylenol PM

Antacids
Tagamet, Zantac

Antipsychotics
Clozaril, Prolixin, Zyprexa, Seroquel
ACTIVITY PROMOTES NEUROGENESIS

Physical Activity

New Learning Novelty

Socialization

Slide courtesy of Dr. R Shatz
Types of PPA

- Fronto-Temporal Dementia
  - Non-fluent Primary Progressive Aphasia (PPA)
    - Non-fluent
    - Frontal
  - Semantic Dementia (SD)
    - Fluent
    - Temporal
- Alzheimer’s Disease
  - Logopenic Dementia (LD)
    - Non-fluent +/-
    - Temporal/Parietal
Basic PPA criteria

• **Inclusion criteria**
  – Language difficulty
    • the most prominent clinical feature
    • principal cause of impaired ADL
    • most prominent deficit at symptom onset and initial disease phases

• **Exclusion criteria**
  – Deficit pattern
    • better explained by nondegenerative CNS or medical disorder
    • better explained by psychiatric diagnosis
    • Parkinsonian syndrome
    • prominent initial
      – episodic memory
      – visual memory
      – visuospatial deficit

Progressive nonfluent agrammatic

Motor speech

• Clinical diagnosis
  (At least 1 core feature)
  – Agrammatism
  – Effortful halting speech with inconsistent speech sound errors and distortions (apraxia)
  (At least 2 of the following)
  • Impaired comprehension of syntactically complex sentences
  • Spared single word comprehension
  • Spared object knowledge

• Imaging supported
  – Clinical diagnosis established (At least 1)
    - Predominant left posterior fronto- insular atrophy on MRI
    - Predominant left posterior fronto- insular hypometabolism (PET) or hypoperfusion (SPECT)

• Definite pathology
  – Clinical diagnosis (At least 1)
    – Histopathologic evidence of specific neurodegenerative pathology (FTLD-tau, FTLD-TDP, AD, other)
    – Presence of a known pathogenic mutation
Logopenic

Phonologic processing deficits

• **Clinical diagnosis**

• **Core features** (need both)
  - Impaired single word retrieval in spontaneous speech and naming
  - Impaired repetition of phrases and sentences

• **At least 3**
  - Phonologic errors
  - Spared single word comprehension and object knowledge
  - Spared motor speech
  - Absence of frank agrammatism

• **Imaging supported**
  - Predominant left posterior perisylvian or parietal atrophy on MRI
  OR
  - Predominant left posterior perisylvian or parietal hypometabolism on PET or hypoperfusion on SPECT

• **Definite pathology**
  - Histopathologic evidence of a specific neurodegenerative pathology (AD, FTLD-tau, FTLD-ubiquitin, other)
  OR
  - Presence of a known pathologic mutation
Semantic dementia

**Conceptual and factual knowledge**

**Clinical diagnosis** (need both)
- Impaired confrontation naming
- Impaired single word comprehension
  (At least 1)
- Impaired object knowledge
- Surface dyslexia or dysgraphia
- Spared repetition
- Spared speech production
  (grammar and motor speech)

**Imaging**
- Predominant anterior temporal lobe atrophy
  OR
- Predominant anterior temporal lobe hypometabolism
  (PET) or hypoperfusion (SPECT)

**Definite pathology**
- Histopathologic evidence of a specific neurodegenerative pathology (FTLD-tau, FTLD-TDP, other)
  OR
- Presence of a known pathogenic mutation
PPA: correlates with regional atrophy

Agrammatic

Semantic

Logopenic

Epidemiology

Age of onset

20  45  65  90  years

FTD>AD  FTD=AD  AD>FTD

Duration

FTD-ALS  bvFTD  PNFA  SD

Gender

bvFTD  SD

PNFA
Inheritance

60% FTD accounted for by known genetic mutations
Nonfluency

- **Heterogeneous**
  - Agrammatism
  - Motor-speech (apraxia)
  - Hesitancy/effortfulness of articulatory planning
  - Slow rate of speech
  - Decreased phrase length
  - Executive dysfunction causing word finding difficulty

<table>
<thead>
<tr>
<th></th>
<th>+ Apraxia of speech</th>
<th>- Apraxia of speech</th>
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</thead>
<tbody>
<tr>
<td><strong>Agrammatism</strong></td>
<td>PNFA</td>
<td>GRN mutations</td>
</tr>
<tr>
<td><strong>No agrammatism</strong></td>
<td>PNFA?</td>
<td>Logopenic AD</td>
</tr>
</tbody>
</table>

Rohrer et al. Neurology 2010;75:603-610
Late Stage Mutism

- **SD**
  - Degradation of language content
  - Increasingly empty
  - Few stock phrases/words

- **LPA**
  - Increasing anomia
  - Decreased speech rate

- **NFPA**
  - Impaired generation of verbal thought
  - Dynamic aphasia

Semantic trees
Grammatical chains

Default network
Alzheimer’s
Meaning
Senses and making sense

Salience/Executive network
Frontal-temporal dementia
Grammar
Procedures
Movement
Timing
Left Parietal

• Motivation to speak
  - Retained

• Structure to speak intact
  - Praxis, grammar
  - Order and sequence

• Discourse
  - Intact

• Motor production
  - Intact

• Semantics impaired
  - Loss of nouns, verbs
  - Phonological paraphasias

Left Frontal

• Motivation to speak
  - Laconic
  - Terse

• Structure to speak impaired
  - Praxis, grammar
  - Order and sequence

• Discourse
  - Impaired turn taking
  - Impaired topic maintenance

• Motor production
  - Dysarthria
  - Apraxia
<table>
<thead>
<tr>
<th>PASS</th>
<th>Normal</th>
<th>Possible/very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fluency</td>
<td>Normal flow of speech</td>
<td>Occasional blank pauses, fillers Reduced WPM Reduced phrase length</td>
<td>Short phrases Pauses or groping Occasional fluent speech</td>
<td>Mostly dysfluent Phrase&lt;/=3 Rare &gt;1 No speech</td>
<td></td>
</tr>
<tr>
<td>Syntax Grammar</td>
<td>No difficulty</td>
<td>Occasional odd sentence structure Effortful phrase or sentence construction</td>
<td>Simple sentence structure Frequent misuse or nonuse of grammatical words</td>
<td>Content words dominant Rare syntactic word group Rare functor words or morphologic markers</td>
<td>Single word utterances No speech No writing</td>
</tr>
<tr>
<td>Single word</td>
<td>No difficulty understanding in conversation or testing</td>
<td>Low frequency comprehension occasionally impaired Ask “what is a”</td>
<td>Lack of word in brief conversation Still converses meaningfully</td>
<td>Understands high frequency or familiar words Questions word meanings frequently</td>
<td>Minimal single word understanding</td>
</tr>
</tbody>
</table>

Behavioral symptoms in PPAs

- **SD**
  - Depression, irritability/lability, disinhibition, abnormal appetite/eating disorders, anxiety

- **PNFA**
  - Apathy, depression, agitation/aggression

- **LPA**
  - Irritability/lability, anxiety, apathy, agitation/aggression

- **GRN-PPA**
  - Apathy, irritability/lability

Motus

- Motivation
- Emotion
- Motor programs
- Executive function
- Sensory feedback
  - Proprioception
  - Vision
Frontal affect

- Apathy
- Restricted affect, hypomimia
- Lack of engagement
Disinhibition

- Hypomania
- Euphoria, moria, witzelsucht
- Disinhibition
Apathy and Depression
Socialization impaired

Behavioral concerns March 15, 2011

- I continue to find him at match.com and other sites
  - He told me that no one looks at women over 50
- Afraid that I will leave him and not take care of him
- He wants to be intimate frequently
  - There is no emotional contact between us when we are intimate
  - He masturbates very frequently, even nightly
Impulse

• “I lost my job because I was cursing too much”
• “Whenever he has money, he spends it or gives it away”
• “Greg will give you anything even if it isn’t his”.
• Three marriages back to back
• Two marriages to drug addicts
  – Stole computers, VCRs
  – Ransacked accounts
• Never bothered by wife’s behavior
How do you do again?

Frontal
- Lack of activity
- Simple repetitive acts
  - clap
  - sway
  - rock back and forth
  - sniff
  - grimace
  - lip pursing
  - words/phrases

Temporal
- Restlessness
- Complex compulsions
  - repetitive checking
  - cleaning
  - stereotyped phrases
  - collecting and hoarding
  - prolonged and bizarre toileting rituals
  - counting money
Fruits and vegetables

- Pepper
  - Red pepper
  - Green pepper
  - Yellow pepper
  - Spicy pepper
  - Mexican pepper
  - German pepper
  - Fried pepper
  - Pink pepper
  - Small peppers
  - Large peppers
House Perseveration
Perseveration
Pattern impaired
Behavioral concerns March 15, 2011

• Difficulty following conversations or answering questions.
  – Responds with random unrelated answers or lengthy stories
  – If cued, automatically agrees

• Difficulty making decisions
  – Order whatever I order in restaurant even if he doesn’t like what I’ve chosen
  – Doesn’t make any appointments, decisions on own
  – If given two items, says yes to both without realizing he hasn’t made a choice

• Believes the claims of every infomercial and thinks we should buy every item.

• Requires rigid schedule
  - If told why he can’t do or buy something, he’ll say okay
  - Then he does the thing we just discussed not doing

• Obsessed with military items, movies, and TV
  - If an actor plays a Navy SEAL, he doesn’t understand that it is not who the actor truly is
  - Tells complete strangers long fictional stories about his heroism, service to the country, awards, work record

• Buys one item at a time and returns to the store repeatedly
Not finger food

- Eating with fingers
- Wrong eating utensils
- Food fads
  - Maraschino cherries
  - In and Out burgers
  - Bananas
  - Coke
- Eating off of other’s plates
## Choices

- Answered automatically “yes” to questions
- Continuous nonverbal vocalizations
- Continued movements or tasks until physically stopped

<table>
<thead>
<tr>
<th>Latex Allergy:</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Directives:</td>
<td>Yes</td>
<td>Don't know</td>
</tr>
<tr>
<td>Prescription refills needed?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do you need test results?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reason for being seen today?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you smoke?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>