



Neuroimaging and Neuropsychological Aspects of Frontotemporal Degeneration

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3 Distinct Syndromes

- 3 major subtypes of Frontotemporal Lobar Degeneration (FTLD):
 - Frontotemporal dementia (FTD; >50% of cases)
 - Decline social/interpersonal conduct, self-regulation of behavior, emotional blunting, loss of insight
 - Semantic dementia (SD)
 - Fluent but empty spontaneous speech, loss of word meaning, agnosia for faces/objects, preserved repetition
 - Primary progressive aphasia (PPA)
 - Non-fluent spontaneous speech with agrammatism, phonemic paraphasias or anomia
- Goal of neuropsychological assessment and neuroimaging:
 - To distinguish between these specific subtypes and to discriminate FTLD subtypes from other dementias such as Alzheimer's disease
 - Imperative for accurate treatment planning

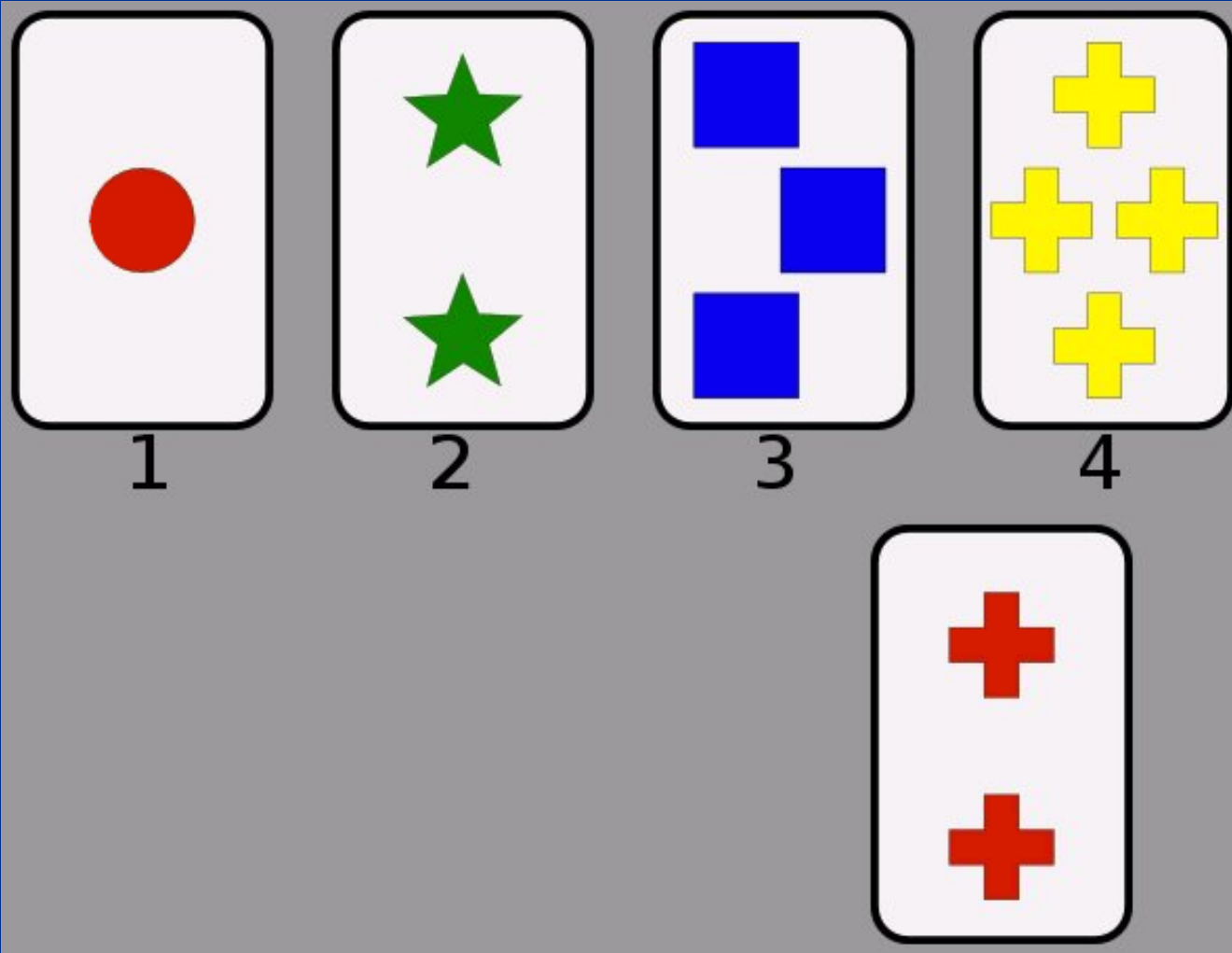
Features of FTD

- FTD is the most common subgroup of FTLD
 - Between 55 and 65 years of age
 - Personality and behavioral changes
 - Apathy and depression mistaken for clinical depression
 - Lack of insight, disinhibition, inappropriate behavior
 - Poor financial judgment
 - Inappropriate sexual behavior
- Frontal lobe functions impaired but memory less so
 - If memory problems, due to lack of attention/effort
 - Formal memory testing may be abnormal, but can track day-to-day events (not the typical amnesic syndrome as in AD)
 - Language not affected early in the disease → mutism

What is Neuropsychological Assessment?

- The use of objective measures (i.e., paper/pencil tests; computerized tests) to assess brain activity
- Distinct patterns of performance on these tests involving various cognitive domains (i.e., memory, attention, executive function), which are a reflection of the underlying brain regions
- Performance patterns on neuropsychological tests in the assessment of the various cognitive domains is helpful in differentiating among the various types of dementia in neurodegenerative disease and other neurological disorders

Wisconsin Card Sorting Test



- Cognitive flexibility
- Self-regulation of behavior
- Perseverative behavior

FTD versus AD

- Early behavioral symptoms
- Apathy is pervasive; indifference to others
- Memory loss less prominent; lack of effort/concern
- Little effort to perform simple tasks
- Spatial difficulties are rare
- Motor difficulties
- Socially appropriate behavior
- Apathy in confusing situations
- Profound difficulty in learning and retention of info
- Complain little of cognitive loss; fake it
- Spatial difficulties are prominent
- No motor problems

Neuropsychological Differences

FTD versus AD

- Controversy - Applied neuropsychological findings of cognitive deficits found in AD to FTD patients
- Resulted in many studies with different findings
- Methodological problems in these studies
- Problem with diagnosis based upon cognitive data - both can include executive dysfunction and language impairment; both can include alterations in behavior
- Trends observed – better recall/recognition memory in FTD vs. AD; executive function (memory organization, perseverations, verbal fluency) more impaired in FTD vs. AD

Distinctive Neuropsychological Patterns in FTD, SD, and PPA

- FTD vs. PPA - patients with PPA have normal executive functioning and more intact episodic memory function than FTD
- SD patients are worse than FTD patients on naming and other language-based tasks and have severe deficits in semantic memory (attention and executive function ok). *FTD patients show the reverse pattern*
- PPA and SD differences are between a pure speech/language impairment (PPA) vs. a relatively pan-modal agnosia (SD) which includes (but is not limited to) language-based expression
 - Repetition is perfect in SD, but the definitions are generalized or lacking in detail (e.g., “Can you say hippopotamus?,” “Hippopotamus,” “What is a hippopotamus?,” “A big animal”) or simply absent (“I think I've heard of a hippopotamus but I can't say what it is”). Patients with PPA show the opposite pattern (can define but not repeat)
- In general, neuropsychological findings along with neuropsychiatric and neurobehavioral information increases the probability of an accurate diagnosis that will be confirmed post-mortem

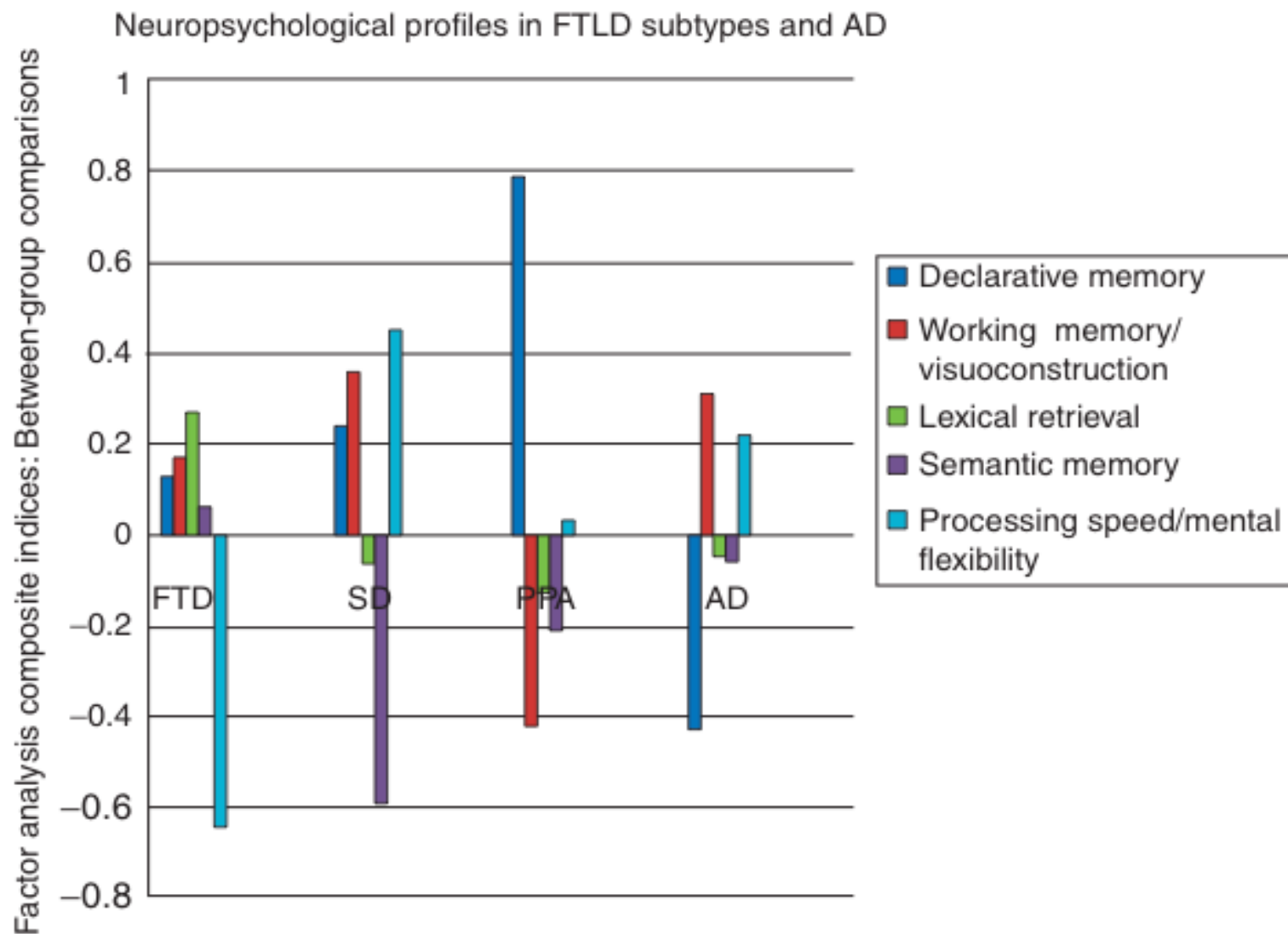


FIG. 2. Factor analysis of a multitest neuropsychological battery demonstrated five major cognitive factors. Between- and within-group analyses of the factors demonstrate that each patient group is associated with a specific profile of neuropsychological impairment, in which each group is significantly worse than the others on at least one factor (data from Libon *et al.*, 2007).

Detection of FTL D Syndromes

- Some problems – extensive neuropsychological batteries used in research studies are not available in clinical settings
- Not established whether neuropsychological differences can reliably discriminate between diagnostic groups
- Need for consensus on types of tests to use, across many sites, and guidelines to be established to differentiate FTL D from AD, and to differentiate among the FTL D syndromes

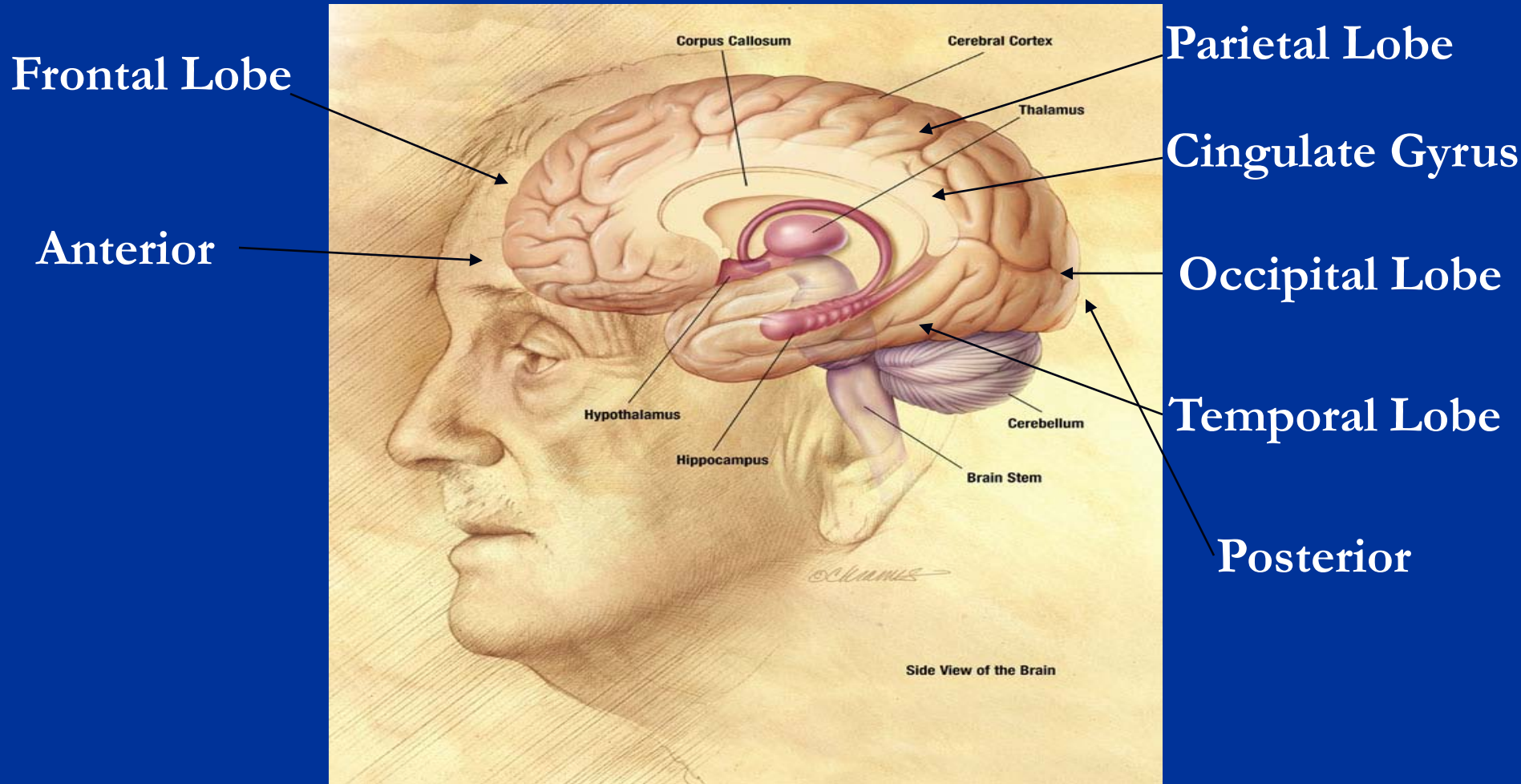
Neuroimaging

- The advent of brain imaging techniques (various types) has opened up a window into the living human brain allowing us for the first time to identify, and track, disease process and its progression
- Advances in brain imaging will undoubtedly add important information for the prevention and treatment of degenerative disorders, and in identification at early stages

Why imaging?

- Provides a unique way to detect age- and disease-related changes in the human brain
- Monitors structural and functional changes *in vivo*
- To improve our understanding of the physiology of aging
 - Previously only in post-mortem brain
- To improve our understanding of the pathogenesis of neurodegenerative disease
- May facilitate early diagnosis for intervention before onset of behavioral problems and dementia syndrome

Schematic of the Brain



Types of Neuroimaging Techniques

Structural Imaging

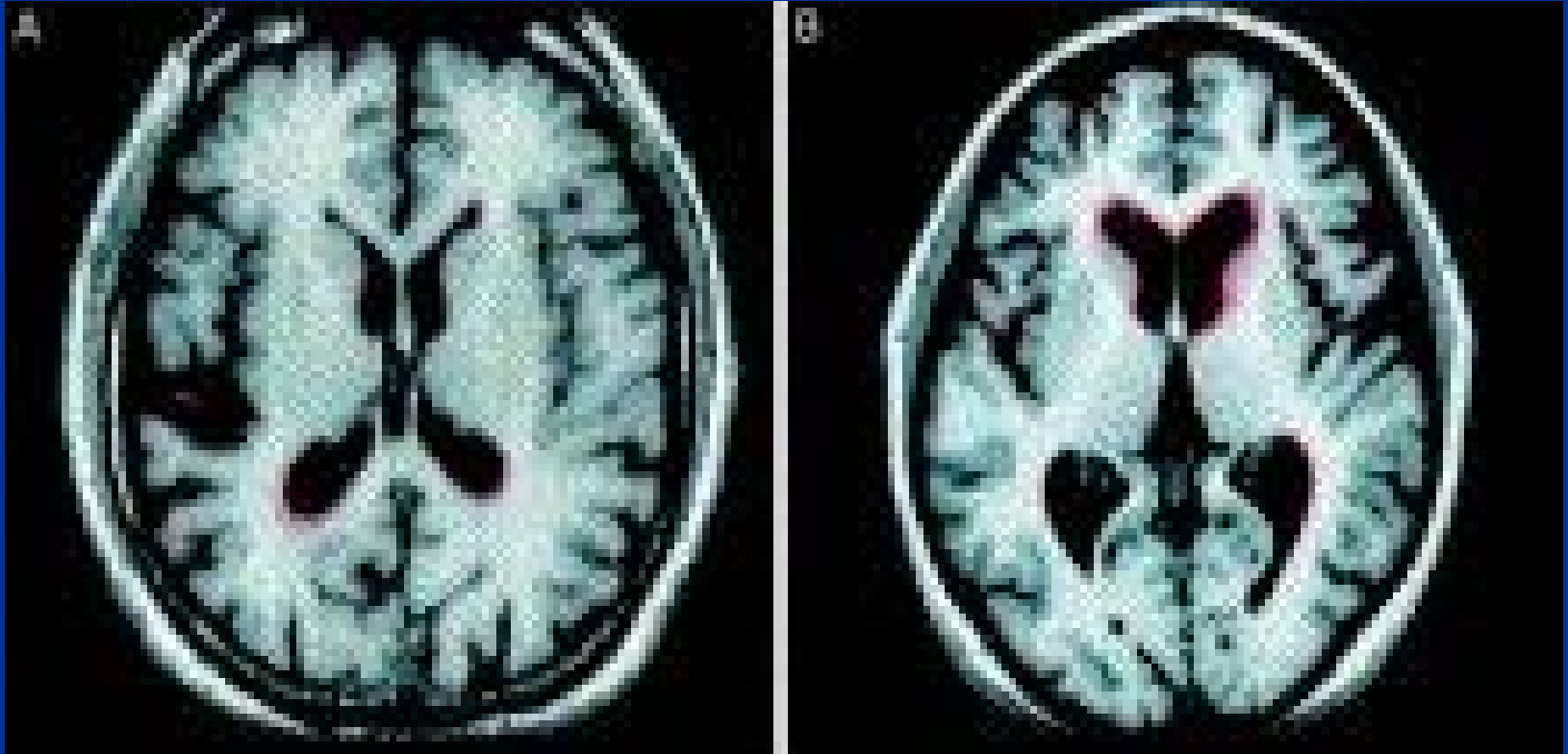
- Used for years in the evaluation of medical disorders
 - brain tumor, hydrocephalus, vascular disease
- Computed Tomography (CT)
 - Emerged in the 1970s
 - Hope was to use as confirming diagnosis
 - Became possible to document focal anterior brain atrophy *in vivo*

Types of Neuroimaging Techniques

Structural Imaging..continued

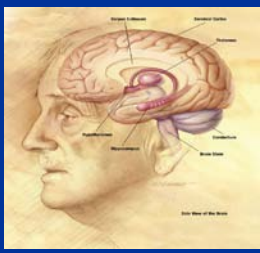
- **Magnetic Resonance Imaging (MRI)**
 - **Better spatial resolution**
 - **Better able to define anatomically distinct clinical subtypes of FTD**
 - **MRI showed that the presence of anterior frontal and temporal atrophy separated patients with FTD from AD**
 - **Medial temporal atrophy is present in both FTD and AD; so very distinct**
 - **FTD patients showed more asymmetry of hemispheric volume than AD or HC**

MRI of AD and FTD



Distribution of cerebral atrophy in a patient with AD (A) and frontotemporal dementia (FTD) (B). Both patients had similar inter-scan intervals (11 months) and annualized rates of global cerebral atrophy ($\sim 4\%$). Areas of volume loss are highlighted in red. Note the generalized distribution of atrophy in AD and the preferential anterior volume loss in FTD.

From Bozoki and Farooq, Intern. Rev. Neurobiol, 2004



Brain Regions affected in FTD and subtypes

- MRI differentiates subtypes through patterns of regional atrophy on volumetric analysis
 - FTD has bilateral frontal atrophy, SD predominantly left anterior TL atrophy, and PPA is associated with left perisylvanian atrophy
 - More frontal gray matter atrophy in FTD vs. SD
 - SD shows bilateral, asymmetrical atrophy of anterior TL (degree of semantic deterioration correlated with extent of left anterior TL damage)
 - Schroeter et al 2007 – very large study showing a triple dissociation between the 3 subtypes

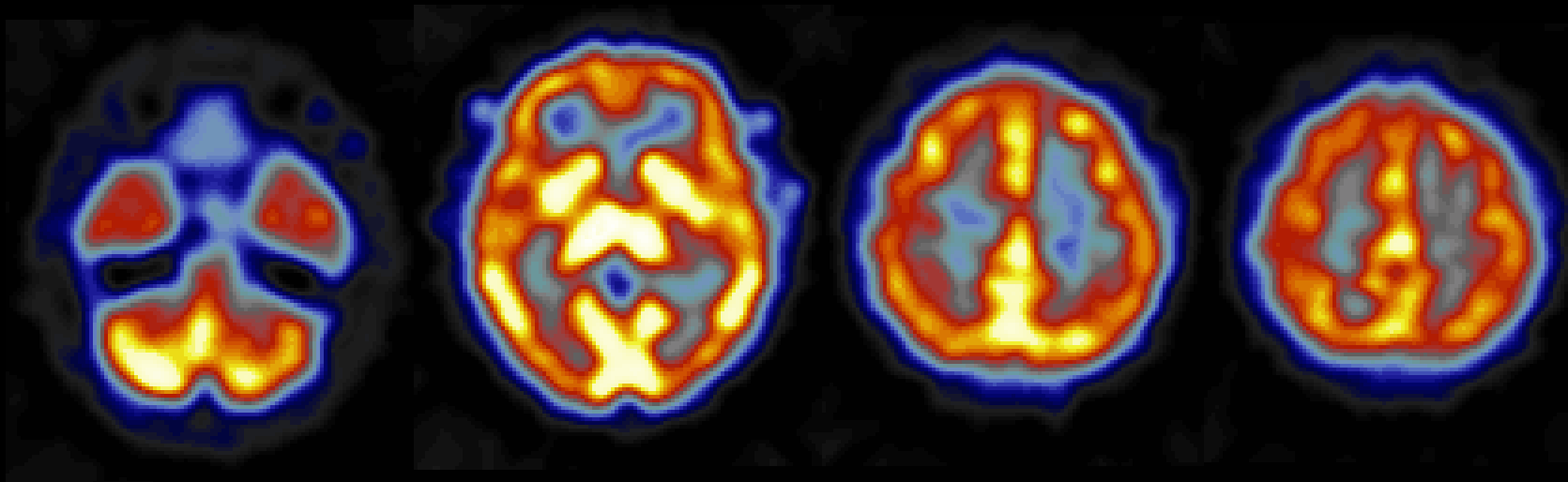
Types of Neuroimaging Techniques

Functional Imaging

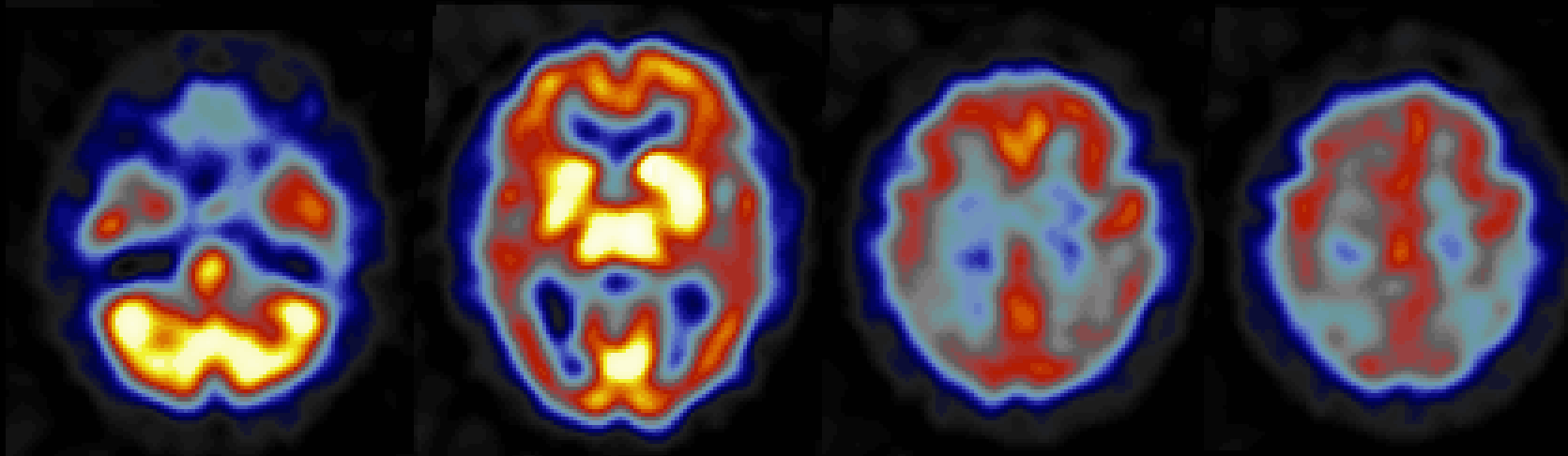
- **Single Photon Emission Computed Tomography (SPECT)**
 - Subtle asymmetries in frontotemporal regions in FTD
 - Consistent with asymmetric MRI-detected atrophy
 - Both SPECT and MRI asymmetry is the rule and not the exception

^{99m}Tc -HMPAO

HC



AD



10 mm

45 mm

70 mm

80 mm



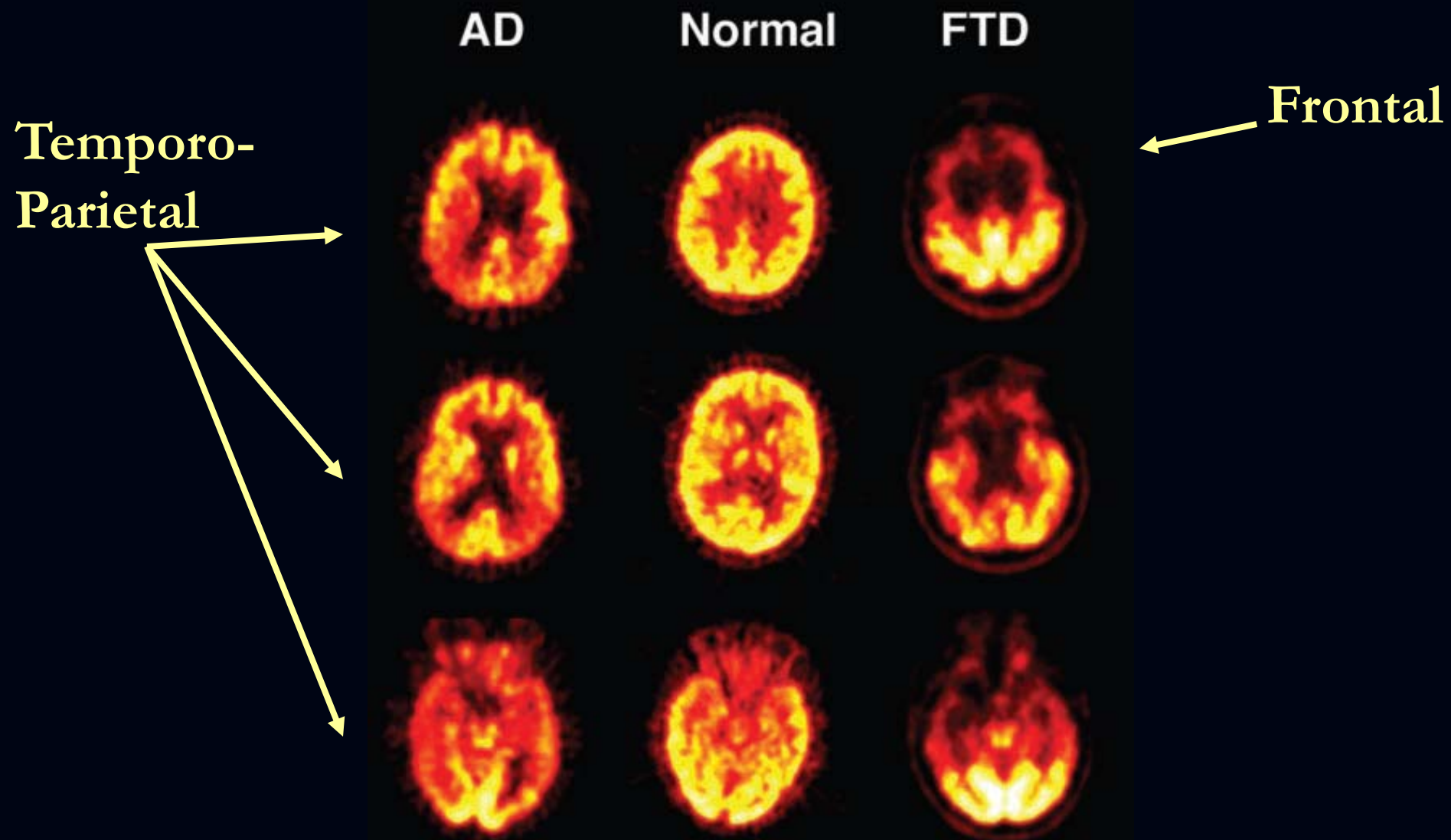
Types of Neuroimaging Techniques

Functional Imaging

- Positron Emission Tomography (PET)
 - Considered the ‘gold standard’ for many types of disorders
 - Diminished glucose uptake in FL
- Reduced glucose metabolic activity at the early stages of degenerative diseases, before atrophic brain changes are apparent on structural imaging (e.g., CT or MRI)
- One prospective study found patients with FTD have 5 points reduction in MMSE and decline of glucose metabolism exclusively in the *orbitofrontal* cortex from baseline to 17 mo f/u

Utility of Imaging for Diagnosis

- [¹⁸F]FDG PET – pattern of hypometabolic glucose activity used to differentiate type of dementia
- Similar sensitivity (identifies individuals who do have the disorder) and specificity (identifies individuals who do not have the disorder) with clinical assessment
- SPECT – difficult to separate out *type* of dementia but increases the accuracy of clinical assessment
- According to CMS guidelines
 - [¹⁸F]FDG PET useful in differential diagnosis of AD versus Fronto-temporal dementia



Glucose metabolism presented on a heat scale; brighter colors reflect greater glucose utilization

From Jagust, W. NeuroRx. 2004:206-212

Conclusion

- Prospective imaging studies, in combination with neuropsychological and neuropsychiatric data/studies has increased the accuracy of diagnosis between AD and FTD, as well as between the various subtypes of FTLD
- Consortium of NY sites will use a standard battery across sites, geared toward capturing the neuropsychological profile of FTD and will obtain genetics and imaging data to better characterize and understand FTD
- Goal is to increase diagnostic accuracy to enhance and inform treatment strategies