Fronto-temporal dementias

OUTLINE

- Introduction
- History
- Epidemiology
- Etiology
- Clinical Features
- Pathology
- Differential Diagnosis
- Treatment

- Dementia associated with atrophy of the frontal and temporal lobes encompasses both sporadic and familial diseases.

- The hallmark of FTD is a progressive change in personality and behaviour

HISTORY

- Arnold Pick in 1892 provided initial descriptions of the clinical syndrome of a dementia with associated circumscribed atrophy of the frontal and temporal lobes
- Alzheimer subsequently described associated neuropathological abnormalities including the presence of intraneuronal inclusions and ballooned neurons
- The inclusions were later named Pick bodies, and syndrome of dementia with frontotemporal atrophy and Pick bodies was named Pick disease

- FTD includes two broadly accepted subgroups:

1. Behavioural-variant FTD (bv-FTD)

2. Language predominant FTD (including progressive nonfluent aphasia and semantic dementia).

- diagnostic criteria for the bv-FTD were updated most recently in 2011, by the International Behavioural Variant FTD Consortium
- For diagnosis of possible bv-FTD, 3 of 6 behavioural and cognitive symptoms must be demonstrated :
  1. behavioural disinhibition
  2. apathy or inertia
  3. loss of sympathy or empathy
  4. perseverative, stereotyped or compulsive/ritualistic behavior
  5. hyperorality or dietary changes
  6. executive or generation deficits with relative sparing of memory and visuospatial functions).
- A diagnosis of "probable" bv-FTD also requires significant functional decline, and imaging consistent with bv-FTD.

- “Definite” diagnosis of bvFTD needs either documentation of frontotemporal lobar degeneration by **histopathological confirmation or a pathogenic mutation**

- In 2011, an international work group published criteria for the language predominant forms of FTD

- The DSM-5 includes both a behavioural variant and a language variant in its description of Major Frontotemporal Neurocognitive Disorder

DSM-5 Diagnostic Criteria

- A. The criteria are met for major or mild neurocognitive disorder.
- B. The disturbance has insidious onset and gradual progression.
- C. Either (1) or (2);
- 1. Behavioral variant;
- a. Three or more of the following behavioral symptoms:
  - i. Behavioral disinhibition.
  - ii. Apathy or inertia.
  - iii. Loss of sympathy or empathy.
  - iv. Perseverative, stereotyped or compulsive/ritualistic behavior.
  - v. Hyperorality and dietary changes.
- b. Prominent decline in social cognition and/or executive abilities

- 2. Language variant:
  - a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension.

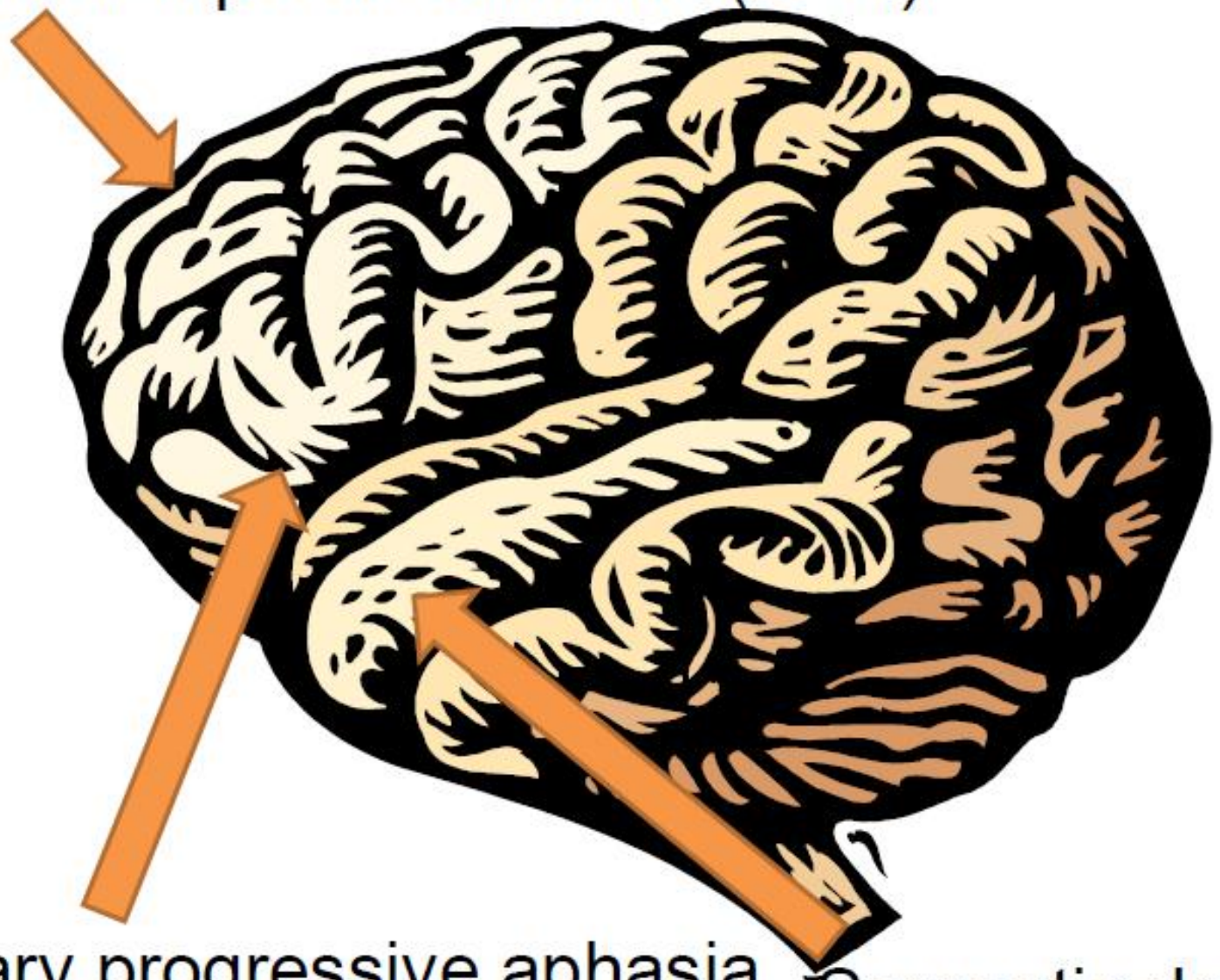
- D. Relative sparing of learning and memory and perceptual-motor function.

- E. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

Epidemiology

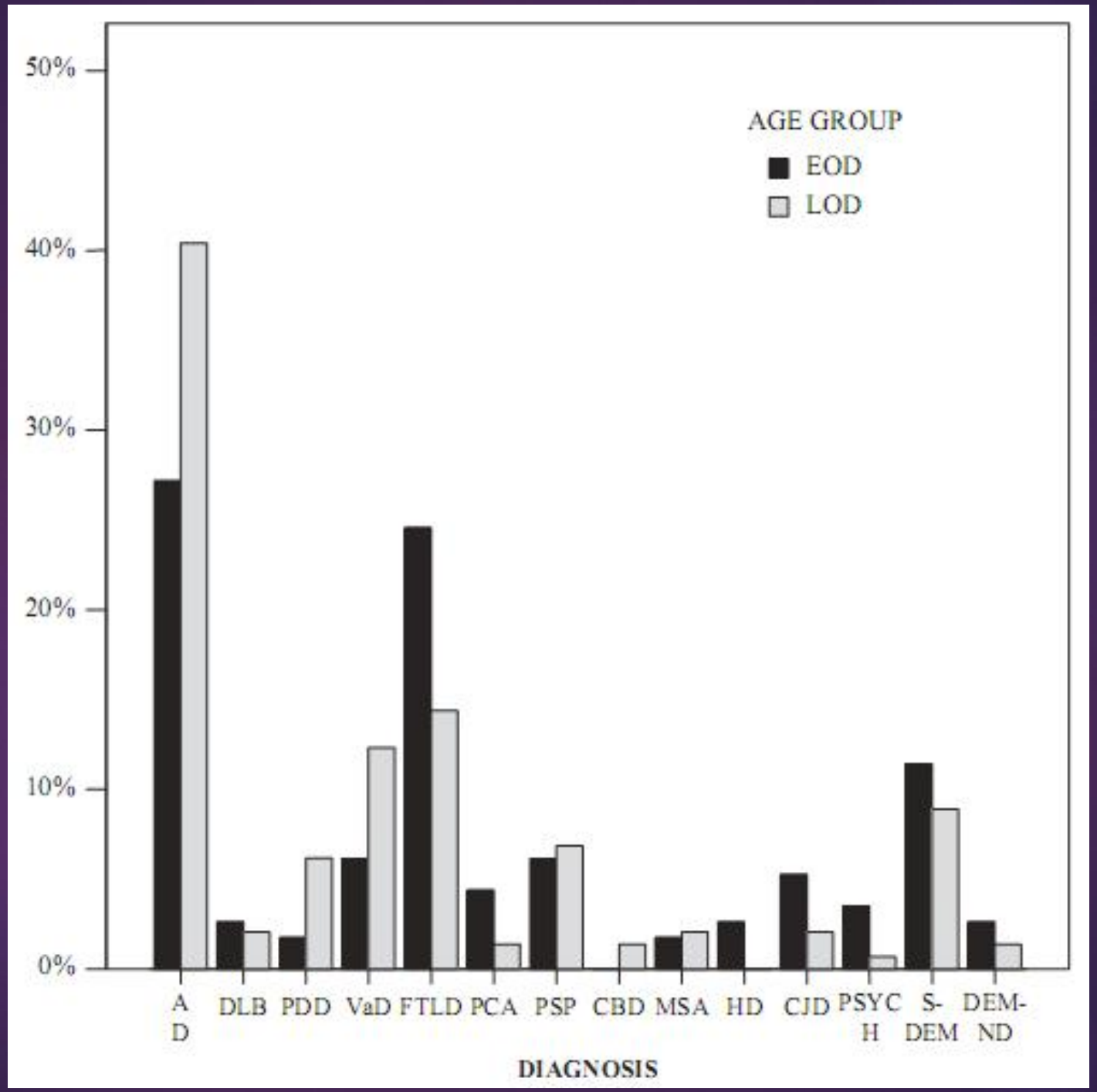
- The prevalence and incidence of FTD has been reported to be similar to that of early onset Alzheimer dementia
- Incidence rates 3.5 per 100,000 person years in a 45 to 64 years age group
- 3.3 per 100,000 person years in a 50 to 59 years old age group
- Age at presentation is most commonly in the sixth decade
- can range from the third to the ninth decade.
- male predominance in the behavioral variant and semantic dementia
- female predominance in progressive nonfluent aphasia.

Frontotemporal dementia (55%)



Primary progressive aphasia (25%)

Semantic dementia (20%)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AGE GROUP
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LOD
AD
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VaD
FTLD
PCA
PSP
CBD
MSA
HD
CJD
PSYCH
S-DEM
DEM-ND
DIAGNOSIS

Etiology

- FTD occurs in both sporadic and familial forms
- Family history is present in up to approximately 50 percent of cases
- typically with an autosomal dominant pattern of transmission
- etiology of the sporadic forms is currently unknown
- most commonly affected gene is *C9ORF72*
- Approximately 26 percent of familial, and 5 percent of sporadic, FTD cases may carry *C9ORF72* expansions
- often present as the behavioral variant, and up to 30 percent of cases may include concomitant motor neuron disease

- **Mutations in *GRN*,** found on chromosome 17 that result in loss of function may account for up to 5 to 10 percent of FTD cases
- **Mutations in the gene for *MAPT*,** also located on chromosome 17, similarly result in FTD
- less common, FTD, has also been reported due to mutations in *CHMP2B, VCP, FUS, and TARDBP*.

Clinical Features

Behavioral-variant FTD

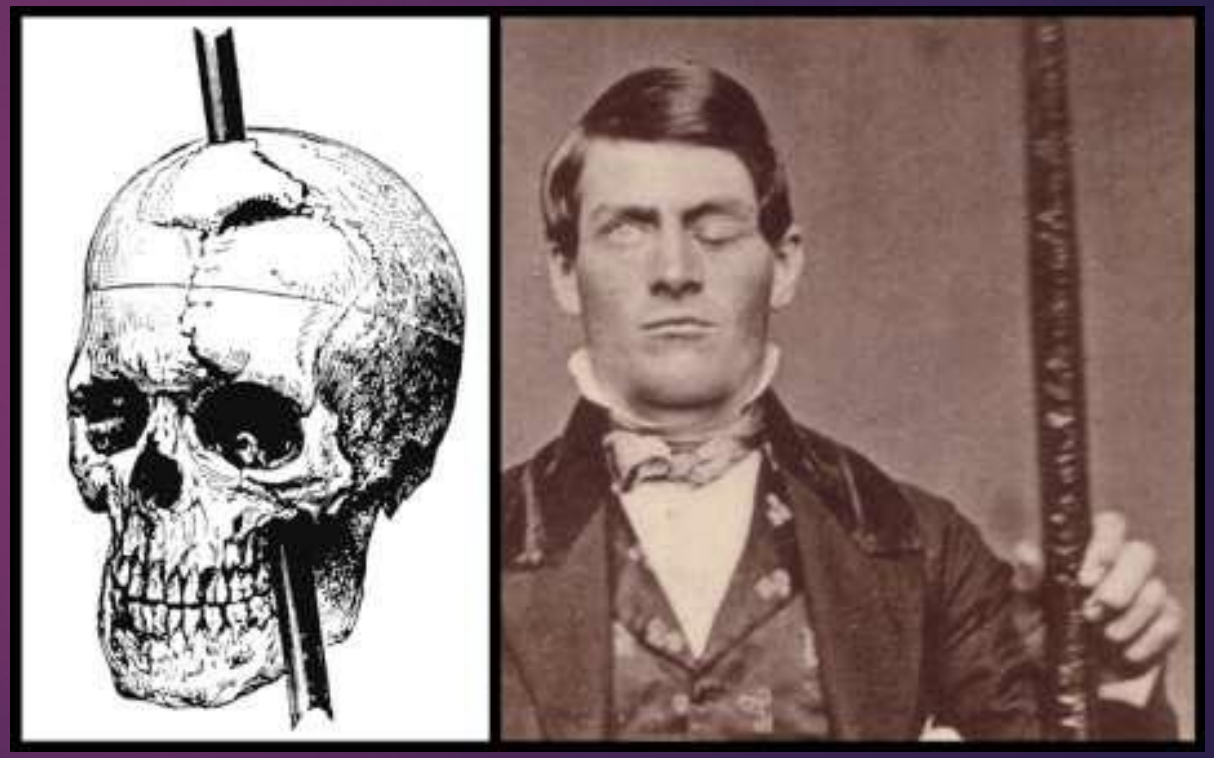
- In the bv-FTD, apathy, disinhibition, and loss of self and other awareness are early signs
- Behavioral disinhibition characterized as socially inappropriate behavior or a loss of manners or decorum. An individual may begin to make impulsive, rash or careless actions
- Apathy or inertia
- early loss of sympathy or empathy, with an individual displaying diminished reactivity to other's needs or feelings, or diminished social interest, interrelatedness, or personal warmth.

- Perseverative, stereotyped, compulsive or ritualistic behaviors can also be seen (collecting specific objects, or hoarding)
- hyperorality or dietary changes, including altered food preference, such as eating foods that are just one color, or binge eating
- behavioral variant often have very limited insight into their alterations of behavior
- executive function deficits, with relative sparing of memory and visuospatial functioning

- 20 percent of individuals with the behavioral variant also show signs of parkinsonism
- akinetic rigid form present in about 60 percent of these individuals
- tremor predominant present in 40 percent
- Five to ten percent of individuals with FTD have co-occurring motor neuron disease as well, with symptoms including muscle wasting, weakness, and fasciculations

Frontotemporal lesions and antisocial acts

- It has been known for almost a century that frontotemporal lesions lead to antisocial acts



- Three different language variants have been described:

Semantic dementia

- impaired confrontation naming and impaired single word comprehension
- impaired object knowledge and surface dyslexia (difficulty with recognition of irregular sounding words, like yacht)
- Dysgraphia
- may substitute categories for words (“food” for “apple”)
- As the disease progresses speech becomes empty of content
- right sided predominant atrophy show behavioral features, including emotional detachment or lack of empathy, or impairments in facial recognition

Semantic Dementia

Animal

Bird

Progressive nonfluent aphasia

- requires one of the two core features for a diagnosis

1. agrammatism in language production
2. apraxia of speech

- Speech is often described as slow, labored, effortful or halting.
- Speech sound errors are made and there is abnormal prosody.
- **Impaired comprehension of syntactically complex sentences.**
- **Single-word comprehension and object knowledge are spared.**
- Individuals with progressive nonfluent aphasia tend to have more insight into their deficits maintain social norms

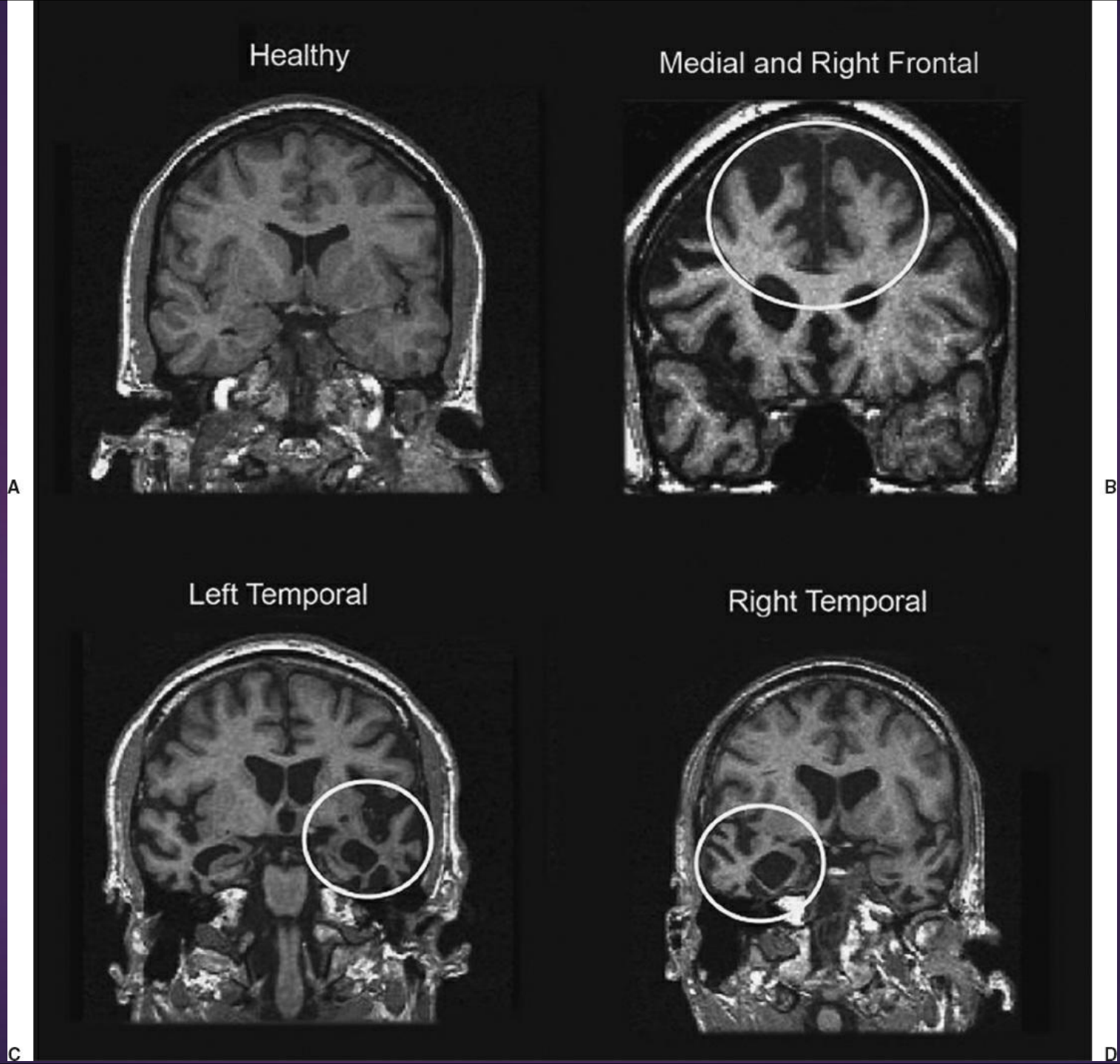
Logopenic variant

- impaired single-word retrieval in spontaneous speech and naming and impaired repetition of sentences and phrases
- Speech is slow due to word finding problems
- phonological errors in speech and naming
- Single-word comprehension, object knowledge, and motor speech are spared

Pathology

- behavioural variant, there is early degeneration of the paralimbic structures of the ventromedial prefrontal cortex, anterior cingulate cortex and anterior insula
- progressive nonfluent aphasia, there is degeneration of the dominant frontal operculum through the premotor area, and the insular cortex
- semantic variant, there is atrophy of the anterior temporal pole, which eventually spreads to the frontal areas, insula and anterior hippocampus

- Currently there are no established biomarkers for the diagnosis of FTD
- In practice, use of MRI to establish the presence of circumscribed frontal and/or temporal atrophy
- Support for a diagnosis of FTD may similarly be obtained from functional imaging using PET or SPECT to demonstrate selective frontal and/or anterior temporal reduction in blood flow or metabolism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Right Temporal
C
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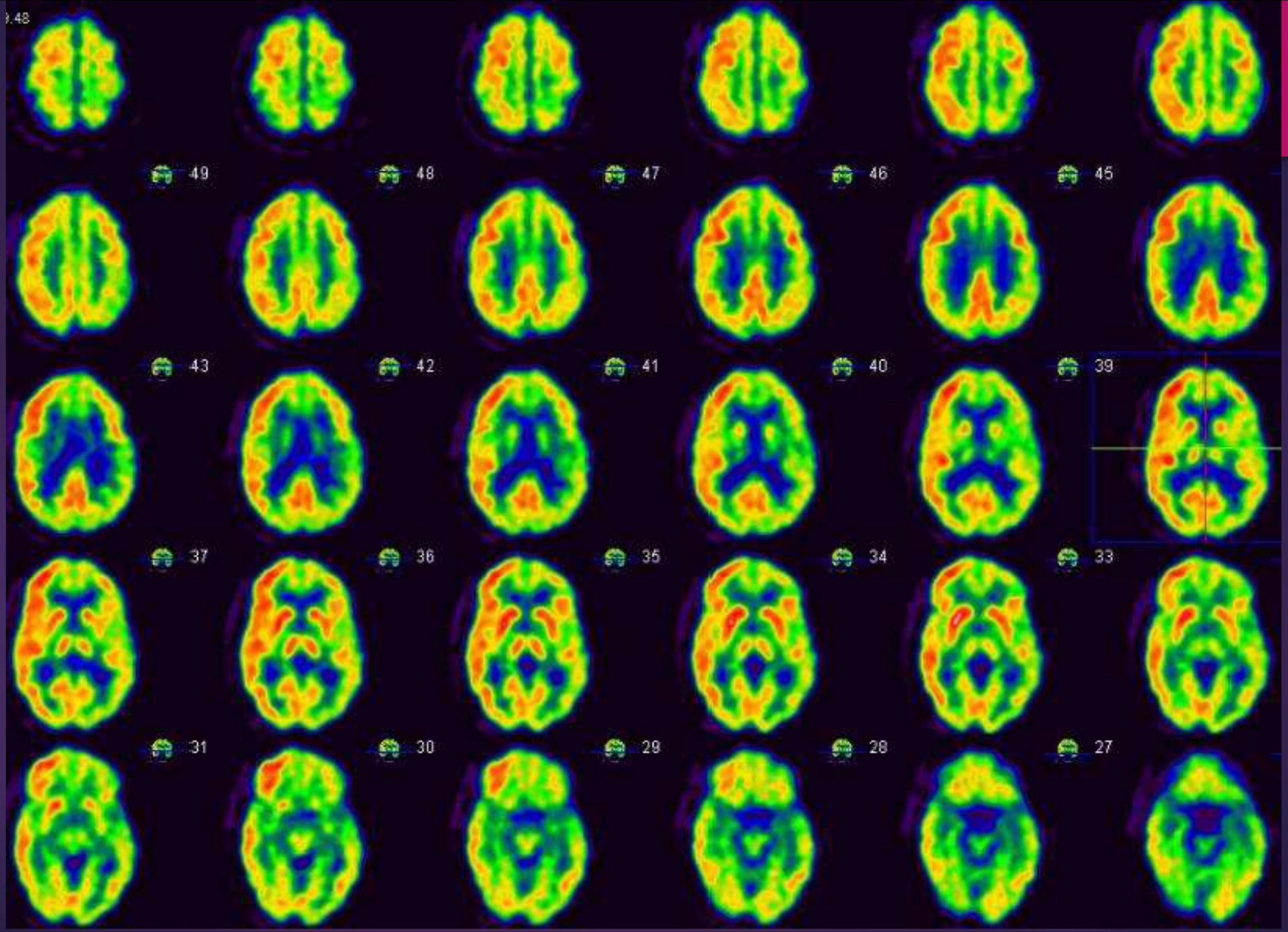
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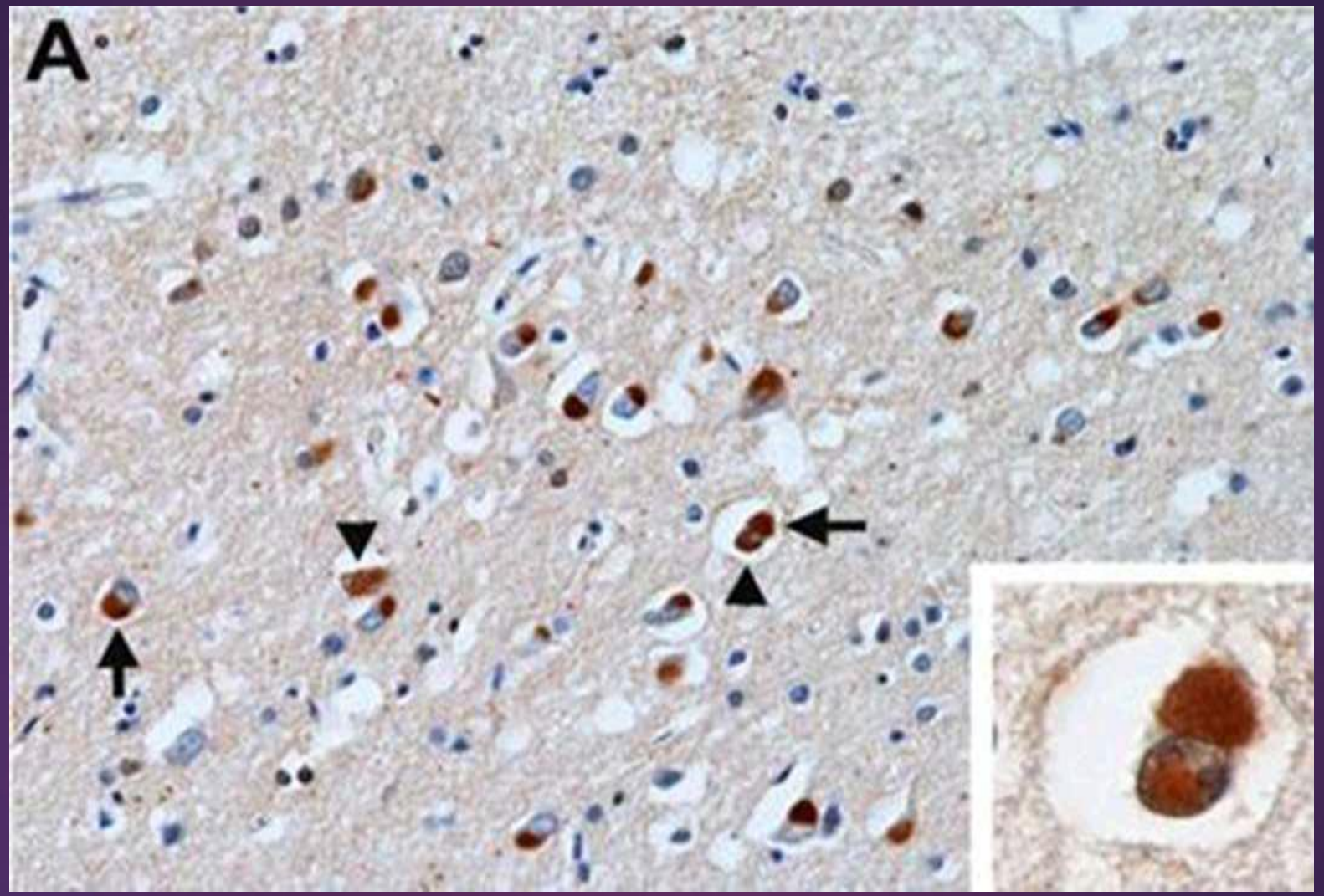
- Macroscopically, FTD is characterized by focal atrophy of the frontal cortex, the temporal cortex, or both
- Atrophy is usually symmetric, though asymmetry is sometimes present
- frontotemporal lobar degenerations can be divided into two major groups:

1. τ-positive inclusions
2. τ-negative and ubiquitin/P62-positive inclusions

- The frontotemporal lobar degenerations with τ-positive inclusions include classically described Pick disease, CBD, PSP, and dementia due to MAPT mutations

- distinguishing among subtypes may be more reliably achieved through the use of antibodies selective for τ isoforms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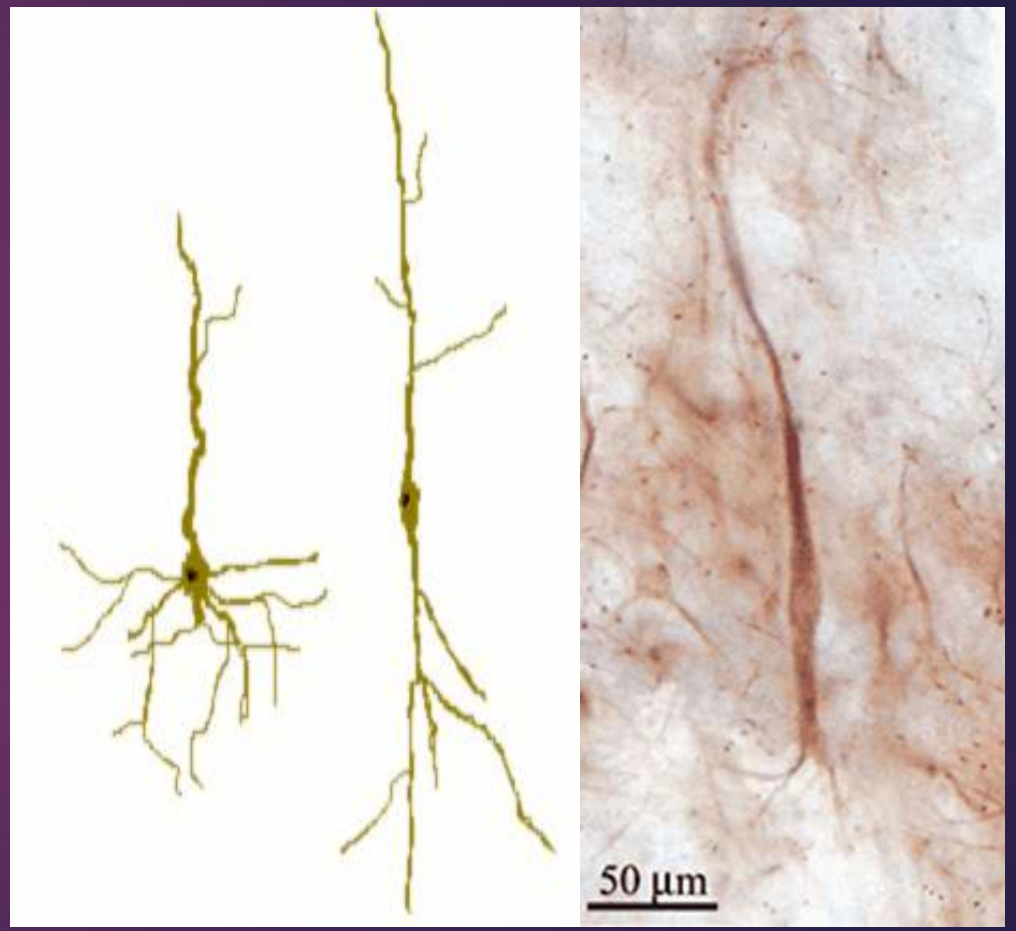
- most frequent pathological presentation in frontotemporal lobar degenerations **with τ-negative ubiquitin**/P62-positive inclusions is the presence of intracellular inclusions positive for TDP-43.

- Also most frequent pathological presentation among all cases of frontotemporal lobar degenerations

von Economo neurons (VENs)

- specific class of neurons that are characterized by a large spindle-shaped body
- reduced by an average of 74% in FTD



Differential Diagnosis

- given the frequent initial presentation of progressive alterations in behavior, **psychiatric syndromes are often initially suspected in individuals with FTDs**
- Depending on whether the initial behavioral symptoms are disinhibited, withdrawn and apathetic, or inattentive and disorganized : bipolar illness, major depression, and/or late-onset schizophrenia may be suspected
- Distinguishing FTD from these possibilities may be aided by structural and functional brain imaging
- Ultimately, **differentiation from these psychiatric disorders may rely on longitudinal observation of progressive cognitive decline or the identification of associated motor or extrapyramidal symptoms**

- also include the other causes of dementia

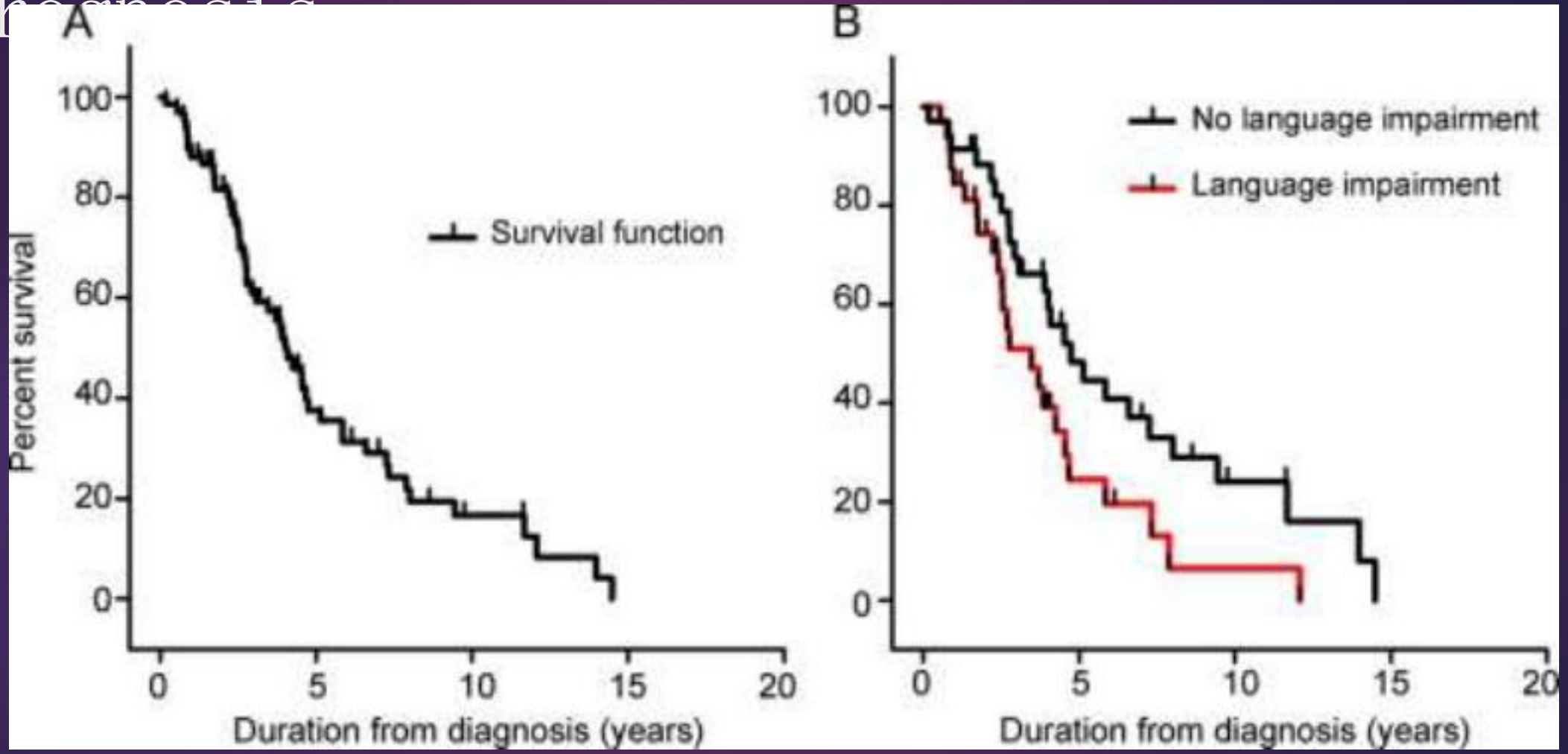
- commonly frontal predominant presentations of Alzheimer disease, particularly if the logopenic variant of primary progressive aphasia is diagnosed

- the combination of cognitive impairment and parkinsonism found in DLB

Course and Prognosis

- The course of FTD is one of **progressive deterioration**
- With progression, the differing initial presentations described above frequently merge
- ultimately loss of other cognitive functions may occur
- On average, **survival is 8 years from symptom onset, and 4 to 5 years from diagnosis**
- individuals with FTD and motor neuron disease have a significantly shorter survival time compared to those without motor neuron disease
- more rapid cognitive and functional decline than those individuals with Alzheimer disease

Survival and prognosis



Treatment

- no treatments for the cognitive deficits associated with FTD, and no treatments to prevent progression of the underlying pathologies
- Insufficient data exists to recommend cholinesterase inhibitors,
- recent randomized double-blind placebo controlled study showed no benefit of memantine in the treatment of frontotemporal lobar degeneration
- Symptomatic use of trazodone, second generation antipsychotics, SSRIs, and anticonvulsants may help agitation, disinhibited, and aggressive behaviour
- Second-generation antipsychotic medications should be used with caution and close observation, as individuals with FTD may be more sensitive to extrapyramidal side effects
- People experiencing language difficulties may benefit from speech therapy to learn alternate strategies for communication

refrences

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- Google Images

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Geezer Planet
I was unfaithful to you once. With some redhead. In the men's room of a pool hall in 1971. I was drunk.
That was me.
shoeboxblog.com