Frontotemporal Dementia

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Objectives

Review
- Clinical features of FTD, PA, and SD
- Treatment of FTD

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Terminology

Frontotemporal Lobar Degeneration (FTLD)

- Frontotemporal dementia (FTD)
- Progressive non-fluent aphasia (PA)
- Semantic dementia (SD)

FTD, PA, and SD have same spectrum of pathologies but different site of lesions

Neary et al. Neurology 51:1546-1554, 1998

Core Diagnostic Features (Need All)

- Early decline in social interpersonal conduct
- Early loss of insight
- Early emotional blunting
- Early impaired regulation of personal conduct
- Insidious onset and gradual progression

Neary et al. Neurology 51:1546-1554, 1998

Decline in Social Interpersonal Conduct

Breaches of etiquette, such as:

- Decline in manners and social graces
- Disinhibition (eg. speech, gestures, sexual behaviour, shoplifting)
- Violation of interpersonal space

Emotional blunting

- Emotional shallowness with unconcern
- Loss of emotional warmth
- Indifference to others
- Loss of empathy and sympathy

Neary et al. Neurology 51:1546-1554, 1998

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Impaired Regulation of Personal Conduct

Inactivity, passivity, inertia, pacing, wandering, increased talking laughing, sexuality, singing, and aggression

Neary et al. Neurology 51:1546-1554, 1998

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Early Behavioural Changes

- Decline in social interpersonal conduct
- Loss of insight
- Emotional blunting
- Impaired regulation of personal conduct
- Insidious onset and gradual progression

Neary et al. Neurology 51:1546-1554, 1998

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Hyperorality

- Overeating
- Food fads
- Oral exploration of objects

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Frontotemporal Dementia

Early anatomical lesions
Orbitofrontal, superior medial frontal (including anterior cingulate), hippocampus

(Stage 1, Broe et al. Neurology, 2003)

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Frontal Cognitive Tests

FTD

- Orbitofrontal and medial frontal dysfunction underlie social cognitive deficits

Majority of neuropsychological tests are

- Sensitive primarily to dorsolateral frontal lesions
- Relatively insensitive to early FTD

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Need

Neuropsychological and behavioural measures for early FTD that

1) Are sensitive to orbitofrontal and medial frontal lesions
2) Assess social cognition

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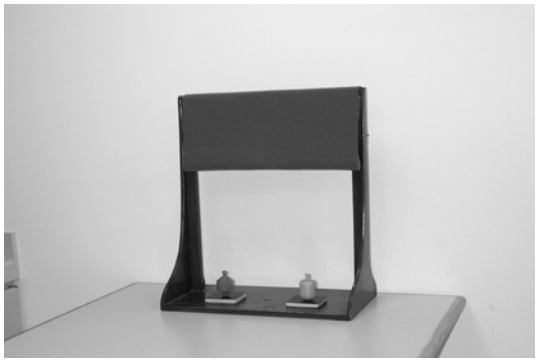
Object Alternation

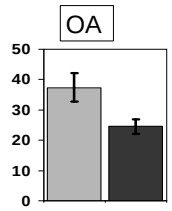
In humans:
Sensitive to ventrolateral – orbitofrontal and medial frontal lesions

Freedman et al. Cerebral Cortex, 1998



Freedman, Black, Ebert, Binns. Cerebral Cortex 8:18-27, 1998

Errors on Object Alternation

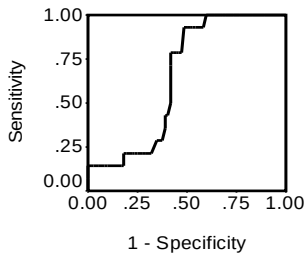


p=0.04

FTD ☐ Controls ☐

Freedman, Binns, Black, Levine, Miller, Stuss. Neurology. Suppl 1 A264, 2003.

Receiver Operating Characteristic (ROC) Function for OA



Cutoff = 23 errors
Sensitivity = 93%
Specificity = 51%

Tests of Social Cognition

- Theory of mind (ability to infer other people's mental states)
- Emotional processing (eg recognition of facial emotion)
- Empathy

NB There are deficits in the above in FTD

Lough et al. Neuropsychologia 2006

Theory of Mind (ToM)

Awareness of content of other people's minds

Tests of ToM

- Measure social cognition
- Sensitive to orbitofrontal lesions

Stone et al. J. of Cognitive Neuroscience 10:640-56, 1998
Stuss et al. Brain 124:279-86, 2001

Ist Order False Belief Tasks

- Person A and B are in room
- Person A puts object somewhere
- Person A leaves room
- Person B moves object
- Person A returns

Belief Question

Where does A think that object is?

Progressive Non-Fluent Aphasia

Lesion: Left perisylvian

- Nonfluent agrammatic speech
- Stuttering quality to speech
- Phonemic paraphasias
- Anomia
- Comprehension initially relatively preserved
- Poor repetition

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Semantic Dementia

Language
- Fluent grammatical speech
- Semantic paraphasias
- Lose meaning of words and objects
- Repetition relatively good

Visual recognition deficits
- May be very mild and hard to detect

Lesion

Bilateral temporal pole and inferolateral cortex

Drugs Tested in FTD

- Trazodone *
- Idazoxan *
- Paroxetine *
- Galantamine*
- Methylphenidate*
- Lithium + Fluoxetine
- Lithium + Paroxetine
- Fluoxetine
- Sertraline
- Fluvoxamine
- l-deprenyl
- Moclobemide
- Piracetam
- Donepezil
- Rivastigmine
- Paroxetine

* DBPC

Benefit in all cases except piracetam.
Mixed results with idazoxan and paroxetine

DBPC Trials in FTD

- Trazodone
- Idazoxan
- Paroxetine
- Galantamine
- Methylphenidate

1) Benefit in FTD with all drugs except paroxetine and galantamine
2) Galantamine benefited only in PPA
3) Mixed results with idazoxan

Trazodone (Serotonergic Drug)

- DBPC cross-over design/150-300 mg daily
- 6 wk trial / n=31 (26 completed study)
- Benefit on NPI total score (p=0.028) with improvement on Eating Disorders, Agitation, Irritability, Depression/Dyshporia
- No benefit on CGI-I (global measure) or MMSE

Lebert et al. Dement Geriatr Cogn Disord, 2004

Galantamine

- 4 wk DBPC withdrawal study after 18 weeks open label on 16 or 24 mg galantamine
- n=18 FTD and 18 PPA (34 completed trial)
- No benefit in FTD (FBI, WAB, CGI, NPI, DRS-2, ADCS-ADL-Inventory, MMSE)
- CGI in PPA (p=0.009)

Kertesz et al. Presented at ANA 2005

Genetics of FTLD

- 40% have a positive family history
- 2 autosomal dominant genes on chromosome 17
  tau gene (tau +ve)
  progranulin gene (tau –ve)
- Both genes together represent 10% of total cases and 23% of familial
- Mutations in both genes are equally frequent

Gass et al. Hum Mol Genet Advance Access 2006

Neuropathologies in FTLD

With Tau Inclusions	Without Tau Inclusions
• Pick's disease • CBD • PSP • Neurofibrillary tangle dementia • Argyrophilic grain disease • FTDP 17	• FTLD-U and FTD-MND • Neuronal intermediate filament inclusion disease • Basophilic inclusion body disease • FTD with inclusion body myopathy and Paget's dis. • Dementia lacking distinctive histology (DLDH)

Strong M (In Press). See chapters by Cairns NJ and by Bigio EH

Classification Issues

Behavioural	FTD, fvFTD
Language (nonfluent)	PA, PPA
Language (fluent) plus semantic knowledge	SD, tvFTD, PPA
All of above plus CBD, PSP, FTD-MND	Pick Complex

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Frontotemporal Dementia

Onset usually under age 70 years

Clinical studies

- 12% of dementia cases under age 65 years

Neuropathological studies

- 8 - 17% of dementia cases under age 70
- 5 -13% of all dementia cases

Conclusions

- FTD is a disorder of personality and social conduct
- FTD, PA, and SD share same spectrum of pathologies but differ clinically due to lesion site
- Multiple pathologies produce FTLD
- More clinical neuropsychological measures of orbitofrontal function are needed
- Motor neuron disease pathology common in FTLD
- Treatment studies in FTD are now emerging