Rapporti tra disturbi di personalità, psicopatie e demenza frontotemporale

La degenerazione frontotemporale lobare e gli aspetti di confine

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As we enter the next millennium, neurology and psychiatry are trying to define their future roles.

We review the initially common, then divergent relationship between neurology and psychiatry.

We trace the emergence of neuroscience over the last two decades that has informed both disciplines. Recent advances have fundamentally changed brain science, requiring the abandonment of several central dogmas while compelling improvement in reciprocal relationships.
Neurology and psychiatry have, for much of the past century, been separated by an artificial wall created by the divergence of their philosophical approaches and research and treatment methods.

Scientific advances in recent decades have made it clear that this separation is arbitrary and counterproductive.

Further progress in understanding brain diseases and behavior demands fuller collaboration and integration of these fields.
Closing the great divide

- After World War II, a doctrinaire approach in psychiatry emerged during which almost exclusive psychoanalytically based, socially oriented investigations were favored.

- Psychiatry’s roots within biology and experimental medicine were abandoned.

- Knowledge about the brain as the organ of cognition and behavior was considered largely irrelevant.

- Nevertheless, this mind/brain dichotomy was resisted by a small group within psychiatry who contested the view that psychiatric diseases were without brain pathology.
The contemporary forces of change

• The emergence of revolutionary advances in neuroscience over the last two decades that have produced a common foundation and language for both disciplines.

• Certainly the single most important advance in psychiatry, neurology, and psychology has been the invention of modern imaging technology to study the living normal and diseased human brain.

• A secondary reason calling for further integration has been the increasing recognition that psychiatric symptoms are common and important contributions to morbidity in neurologic diseases and that many attributes of psychiatric diseases may in fact be neurologic in origin.
Inseparability of mind and brain

Other recent advances in neuroscience have compelled paradigmatic shifts within both disciplines:

- the brain’s demonstrable plasticity,
- the redefinition of major mental illnesses as biologically based diseases,
- and the era of molecular biology
FTLD: a bridge between neurology and psychiatry
Outline

• Psychiatric phenotypes as presenting symptoms of FTLD
• Sociopathy, criminal behavior and FTLD
• FTLD genes and psychiatric diseases
• Network dysfunction in FTLD: implications for personality disorders
• FTLD and psychiatric diseases: are there common mechanisms?
• Differential clinical diagnosis between FTLD and psychiatric diseases
Recent advances in FTLD
The problem of polysemy

- Pick’s disease
- Pick-complex disorder
- Progressive subcortical gliosis
- Dementia lacking specific pathology
- Frontal dementia of the non-Alzheimer type
- Frontotemporal dementia (FTD)
- Frontotemporal lobar degeneration (FTLD)
The term frontotemporal lobar degeneration (FTLD) was coined to describe a pathology associated with atrophy of the frontal and temporal lobes. FTLD describes a spectrum of clinically, pathologically and genetically heterogeneous neurodegenerative disorders. The diagnosis of FTLD often remain a diagnostic challenge.
While traditionally they were considered as two separate identities, it is now thought that FTLD and ALS form one clinical continuum, in which pure forms are linked by overlap syndromes.

Christine Van Broeckhoven, 2012
New diagnostic criteria for bvFTD

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms must be present to meet criteria

A. Early behavioural disinhibition
B. Early loss of sympathy or empathy
C. Early perseverative, stereotyped or compulsive/ritualistic behaviour
D. Hyperorality and dietary changes
E. Neuropsychological profile of executive deficits with relative sparing of memory and visuospatial functions
Heritability in FTLD

- Approximately 20-50% of individuals with frontotemporal lobar dementia have a first-degree-relative affected with a neurodegenerative disease.
- However, only 10%–30% of family pedigrees show an autosomal dominant inheritance pattern.
- In most of the cases FTLD is a genetic-based disease, even in the elderly. However, different inheritance modality might be considered in future work, beyond autosomal dominant disease (Borroni et al, 2014).
Molecular genetics of FTLD

More to come…

- MAPT gene
- PGRN gene
- VCP gene
- CHMP2B gene
- TARDBP gene
- FUS gene
- UBQLN2 gene
- SQSTM1/p62 gene
- PROFILIN gene
- C9orf72 gene
- OPTN gene

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VCP gene

CHMP2B gene

TARDBP gene

FUS gene

OPTN gene

C9orf72 gene
Neuroimaging in FTLD
Psychiatric phenotypes as presenting symptoms of FTLD
A. FTLD presenting with Heterosexual Pedophilia
A 49-year old man with a 12-month history of inappropriate sexual behavior with his 9-year old daughter was admitted in 2003 to the Memory Clinic of our Neurological Department.

CT scan showed mild frontal atrophy.
Over a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges or behaviors involving sexual activity with a pre-pubescent child or children (generally age 13 or younger).

The fantasies, sexual urges, or behaviors cause clinically significant distress or impairment in social, occupation, or other important areas of functioning.

The person is at least age 16 years and at least 5 years older than the child or children in Criterion A.
The neurobiological basis of the disorder is still unidentified. Several data suggests that pedophilia is linked to early neurodevelopment perturbations. A role for genetic factors in the development of the disease has been hypothesized but, at present, no genetic clue is available. Recent studies with fMRI demonstrated that heterosexual pedophiles showed an alteration of prefrontal networks associated with stimulus-controlled behaviors.
Additional Examinations

- PET-FDG showed significant frontal and temporal lobe hypometabolism.

- CSF concentration of phospho-Tau resulted slightly increased (37.7 pg/ml - n.v. < 35 pg/ml) while total Tau and beta-amyloid were normal.

- MAPT, PGRN and TARDBP genes were sequenced.
A point mutation (R177H) in the \textit{PGRN} gene was found.

In \textit{silico} analyses suggested a possible damaging role for this mutation.
Our case supports the results of studies in experimental animals suggesting a key role for progranulin in the male-specific phenotypic differentiation of the brain.

In addition, the present report suggests that patients with mutation in the PGRN gene may present abnormal sexual behavior and suggests to screen patient with late-onset abnormal sexual behavior for frontotemporal dementia.
B. FTLD presenting with Pathological Gambling
BACKGROUND: Pathological gambling (PG), which is characterized by consistent, repetitive gambling and unsuccessful quitting attempts, is classified as an impulse control disorder. PG has also been reported in patients with Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis.

CASE REPORT: A 53-year-old male visited the outpatient clinic due to excessive gambling and personality changes. Based on electrophysiological findings and neuropsychiatric assessment, he was diagnosed as frontotemporal dementia-amyotrophic lateral sclerosis.

CONCLUSIONS: This case report underlines that PG can also be seen in patients with neurological disorders involving the orbitofrontal cortex.
C. FTLD complicated by Comorbid Bordeline Personality Disorder
The patient was a 46-year-old woman who presented after a suicide attempt with a strawberry daquiri and diphenhydramine.

Her past psychiatric history was significant for three prior psychiatric admissions, each following a suicide attempt, as well as bulimia and a remote history of self-mutilation.

Borderline traits were also acknowledged in the patient, including binge drinking, self-mutilation, and emotional lability dating back to age 16.

In addition, she had an existing diagnosis of major depressive disorder (MDD) and had been treated with a selective serotonin reuptake inhibitor (SSRI) for 11 months.
FTLD and Personality Disorder
FTLD and Personality Disorder (Salzbrenner et al, 2009)

• This case emphasizes the importance of recognizing an atypical presentation of a well-documented clinical syndrome, frontotemporal dementia, specifically in a patient previously diagnosed with borderline personality.

• When the individual’s outpatient psychiatrist was contacted following admission, the patient’s major depressive disorder was considered largely refractory to treatment.

• This case illustrates the difficulty faced by the clinician in recognizing a relatively uncommon condition, frontotemporal dementia, when a patient presents with psychiatric symptoms.
D. FTLD and suicidal behaviour
• Suicide risk in frontotemporal lobe degeneration: to be considered, to be prevented (Padovani et al, 2012).

• Suicide attempt as the presenting symptom of C9orf72 dementia (Synofzik et al, 2012).

• Suicidal behaviour in frontotemporal dementia patients - a retrospective study (Fonseca et al, 2014).

Retrospective study of 86 FTLD patients. Suicidal behaviour was defined here as a deliberate act of self-harm with the clear purpose of a fatal outcome. The odds ratio between patients with FTLD and age-and gender-matched controls was 3.810 [p=0.040 (Pearson's chi-square test)]. All the patients with suicidal behaviours [17% (n = 10)] had the behavioural variant of FTD. These data suggest a relevant association between FTD and suicide that can be addressed later by a prospective study.
Sociopathy, criminal behavior and FTLD
Sociopathy in dementia

- There is a relationship between criminal behavior and brain disorders.
- Epidemiological information indicates that as many as 94% of homicide offenders, 61% of habitually aggressive people, and 78% of sex offenders may have brain dysfunction.
- Investigators have studied acquired sociopathy or antisocial acts from acute, focal lesions but have not clarified the nature of sociopathy from dementia.

FTLD and criminal behavior


**OBJECTIVE:** Our aim was to compare the frequency of criminal conduct in patients with behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and Alzheimer disease.

**METHODS:** We used a standardized caregiver interview to assess criminal behavior in 83 outpatients: 32 with bvFTD, 18 with SD, and 33 with Alzheimer disease.
RESULTS: We found criminal behavior (theft, willful damage to property, housebreaking, assault, or indecent behavior) in 54% of the patients with bvFTD and 56% of those with SD, but only 12% of those with Alzheimer disease.

CONCLUSIONS: Just over half of our patients with bvFTD or SD had committed crimes. When middle-aged or older patients commit minor crimes, frontotemporal lobar degeneration should be considered as a possible cause. If an affected person faces criminal charges, the court might take incapability or diminished responsibility into account in reaching a verdict.
Neurodegeneration behind bars

• The prison population is aging and developing neurodegenerative disorders at a faster pace than general population.

• Hidden among this group of recidivist, career criminal, there is a group of first offenders with bvFTD.

• The criminal justice system and the correctional institutions were not designed for persons with dementia.

• Appropriate care of these patients require the development of preventative programs for screening and placement in palliative care facilities.

Closing the great divide

FTLD genes and psychiatric diseases
C9orf72 gene and FTLD
C9orf7: abnormal RNA expression is the key

(A) Haploinsufficiency of C9ORF72 gene
(B) Repeat RNA-mediated toxicity
(C) Dipeptide protein toxicity

- Reduction of C9orf72 mRNA levels
- Repeat RNA foci
- Repeat Associated non-AUG (RAN) translation
- Dipeptide protein aggregation
C9orf72 and bipolar disorder

- C9ORF72 expansion in a family with bipolar disorder (Meisler MH et al, 2013).
- C9ORF72 hexanucleotide repeat expansion as a rare cause of bipolar disorder (Galimberti D et al, 2014).
- C9ORF72 repeat expansion and bipolar disorder - is there a link? No mutation detected in a Sardinian cohort of patients with bipolar disorder (Cannasa A et al, 2014).
C9orf72 and schizophrenia

- The C9ORF72 hexanucleotide repeat expansion is a rare cause of schizophrenia (Galimberti D et al, 2014).

- No abnormal hexanucleotide repeat expansion of C9ORF72 in Japanese schizophrenia patients (Yoshino Y et al, 2014).
• Mutations in *VCP* account for a minority of familial FTLD cases.

• Mutations in VCP gene cause a range of neurological conditions including a form of dementia called Inclusion Body Myopathy, Paget’s Disease of the Bone and Frontotemporal Dementia (IBMPFD). More, recently mutations in VCP have been associated with ALS.

• VCP has an important role in the mechanisms of neuronal autophagy.
We report the case of a patient who developed progressive weakness of the limbs in his fifties, until he was confined to a wheelchair.

At that time, he developed acute behavioural changes including irritability, severe anxiety and major depression, which led to him being hospitalised in a psychiatric hospital.

He also suffered from aphasia and executive function impairment, which helped us to diagnose a behavioural form of frontotemporal dementia (FTD).
VCP and Psychiatry
Network dysfunction in FTLD: implications for psychiatry
Personality, defined broadly as a dynamic and organised set of characteristics that uniquely influences an individual’s cognition, motivation and behaviour, is a complex and challenging concept.

The ‘five factor’ model of personality has met with wide acceptance due to its robustness across ages, genders and cultures. According to this model, personality results from the stable balance of five key traits, extraversion, agreeableness, conscientiousness, neuroticism and openness to new experiences.

FTLD patients frequently present with complex behavioural changes, and therefore potentially provides a disease model in which to investigate brain substrates of personality.
The FTLD group showed a significant decline in extraversion, agreeableness, conscientiousness and openness and an increase in neuroticism.
Change in particular personality traits was associated with overlapping profiles of grey matter loss in more anterior cortical areas and relative preservation of grey matter in more posterior areas.

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Neurodegenerative Dementias: Connecting Psychiatry and Neurology Through a Shared Neurobiology
Neuronal autophagy and FTLD genes

SQSTM1

VCP

OPTN

CHMP2B
Schizophrenia and FTLD: shared causation?

- FTLD and schizophrenia, defined on a syndromal basis by the DSM, are two neurobehavioral syndromes characterised by a profound alteration in personal and social conduct reflecting marked frontal dysfunction.

- Shared symptoms of both syndromes include emotional blunting, disorganised behaviours and language disturbances.

- However, specific features distinguish these two syndromes: age at onset, frequency of delusions and hallucinations, structural and functional imaging.

- The course of both conditions also differs: FTLD progresses in a constant way towards a decline, whereas the course is variable in schizophrenia.
FTLD and Schizophrenia

Schoder D, Hannequin D, Martinaud O, et al. Morbid risk for schizophrenia in first-degree relatives of people with frontotemporal dementia


• **BACKGROUND.** Familial co-occurrence of frontotemporal dementia and schizophrenia has never been investigated.

• **AIM.** To test the hypothesis that frontotemporal dementia and schizophrenia might have a common aetiology in some families in which both syndromes coexist (mixed families).

• **METHOD.** The morbid risk for schizophrenia, calculated in first-degree relatives of 100 FTLD probands, was compared with that calculated in first-degree relatives of 100 AD probands. In mixed families, sequencing analysis of known FTLD genes and detailed phenotype characterisation of individuals with FTLD and schizophrenia were performed.
FTLD and Schizophrenia

• RESULTS:

• The morbid risk for schizophrenia was significantly higher in relatives of frontotemporal dementia probands (1.35, s.e. = 0.45) than in relatives of Alzheimer’s disease probands (0.32, s.e. = 0.22).

• Ten mixed families were characterised. In three of them a frontotemporal dementia causal mutation was identified that was present in individuals with schizophrenia.

• Several specific clinical features were noted in people with schizophrenia and frontotemporal dementia in mixed families.

• CONCLUSIONS

• Co-occurrence of schizophrenia and frontotemporal dementia could indicate, in some families, a common aetiology for both conditions.
Schizophrenia and FTLD: shared causation?
Future perspectives

- Familial co-occurrence of frontotemporal dementia and schizophrenia: more than a coincidence?
- Possible diagnosis change from schizophrenia to frontotemporal dementia during the course of schizophrenia
- Implication of genetic findings
- Frontotemporal dementia and schizophrenia: single age-dependant continuum or phenotypic variable expression?
Multisystem Proteinopathy: a new conceptual framework
Recently, the new descriptor “multisystem proteinopathy (MSP)” has been suggested (Benatar M et al, Neurology 2013).

MSP nomenclature emphasizes the multisystem nature of the degenerative process (most prominently nerve, muscle, bone, and brain).

At present, four genes have been involved in MSPs: $VCP$, $hnRNPA2B1$, $hnRNPA1$ and $SQSTM1$).

Genetic defects in MSP implicate a range of biological mechanisms including RNA processing and protein homeostasis, providing links between FTLD, ALS, IBM and PBD.
Closing the great divide

Differential clinical diagnosis between FTLD and psychiatric diseases
Frontal and/or temporal lobar atrophy is sometimes detected on neuroimaging in patients with psychiatric disease. This observation leads to difficulty in distinguishing whether patients have FTLD or psychiatric illness. At first presentation, clinical profiles might be useful to distinguish these two population. Suggested criteria are:

A. Family history
B. Presenting complaints
C. Referral source
D. History of neurologic/psychiatric symptoms
E. Forensic compensation issues
F. Results of neurologic examination
G. Neuropsychometry
Atrophy and neurodegeneration


• RESULTS. In an experimental group of patients who had frontotemporal atrophy on neuroimaging and a psychiatric diagnosis, the developed criteria resulted in 25% of patients having FTLD and 75% of patients having a psychiatric diagnosis. At follow-up, all the psychiatric patients remained functionally stable while the FTLD patients had deteriorated.

• CONCLUSIONS. At first presentation frontotemporal atrophy has been found in some patients with psychiatric disease who do not develop evidence of neurodegeneration. This suggests that frontotemporal atrophy on neuroimaging might be a feature of a subgroup of patients with psychiatric diseases.
The revolutionary advances in neuroscience over the last two decades have produced a common foundation and language for both neurology and psychiatry.

A significant overlap between neurodegenerative dementias and psychiatric diseases has been shown.

FTLD as a unique profile in this context.

Knowledge of the different forms of FTLD and their associated phenotypes become essential in clinical practice in order to set up an adequate diagnostic and therapeutic strategy.

A new conceptual framework for neurodegenerative diseases is necessary.
Thank you for your attention