Le spectre des DFT



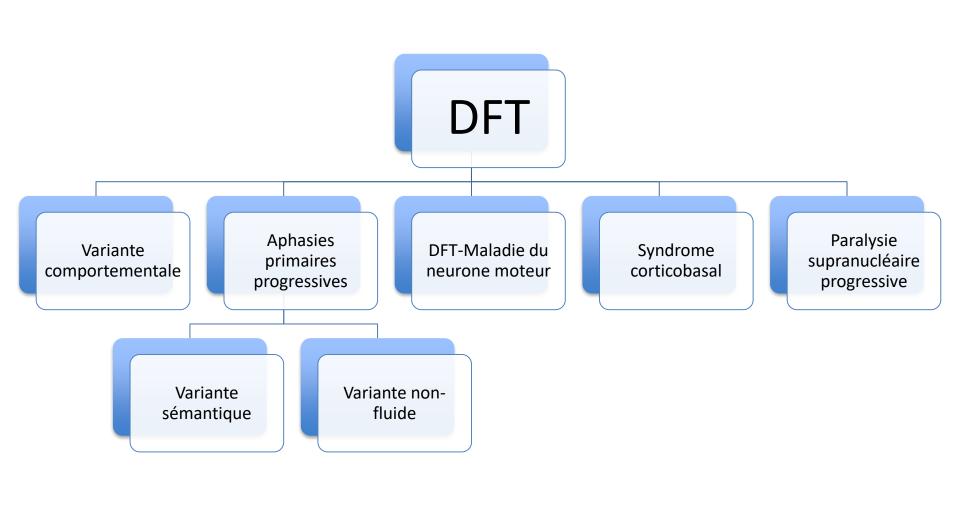
Robert Laforce Jr, MD PhD

Neurologue et Neuropsychologue Département des Sciences Neurologiques Professeur Agrégé de Clinique, Université Laval

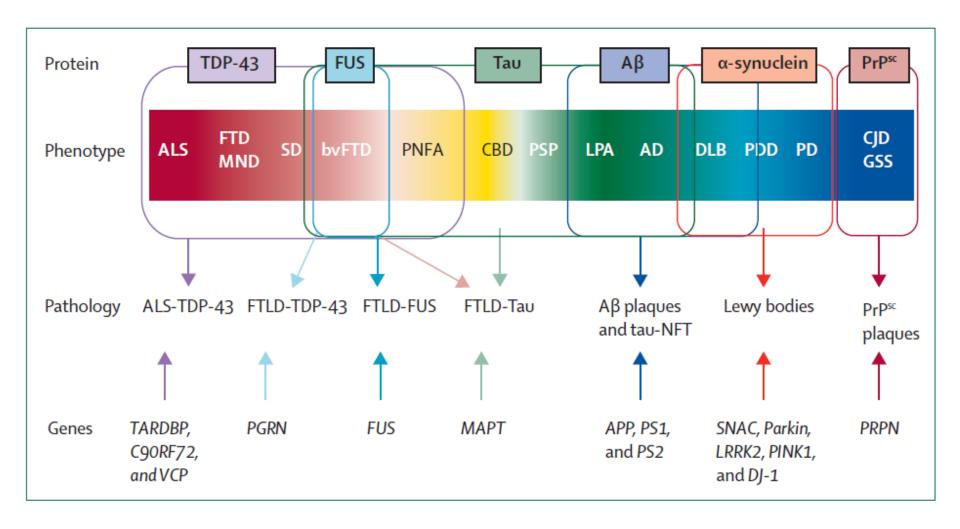
7 novembre 2018







Le spectre des DFT





The molecular basis of frontotemporal dementia

Manuela Neumann¹, Markus Tolnay² and Ian R.A. Mackenzie^{3,*}

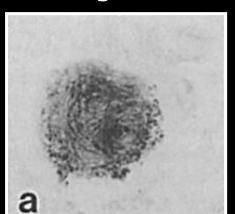
Tau (1986)

TDP-43 (2006)

Fused in sarcoma (FUS) (2009)

Inclusions Tau

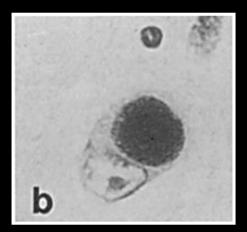
PSP NFT globose



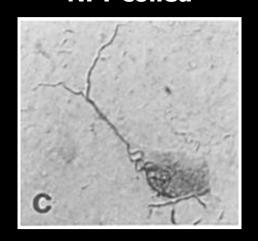
Neurones

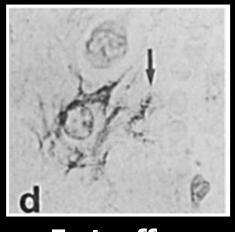
Astrocytes

Maladie de Pick Corps de Pick



SCB NFT coiled

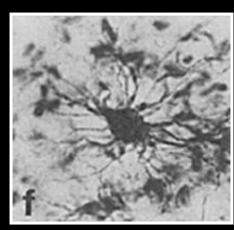




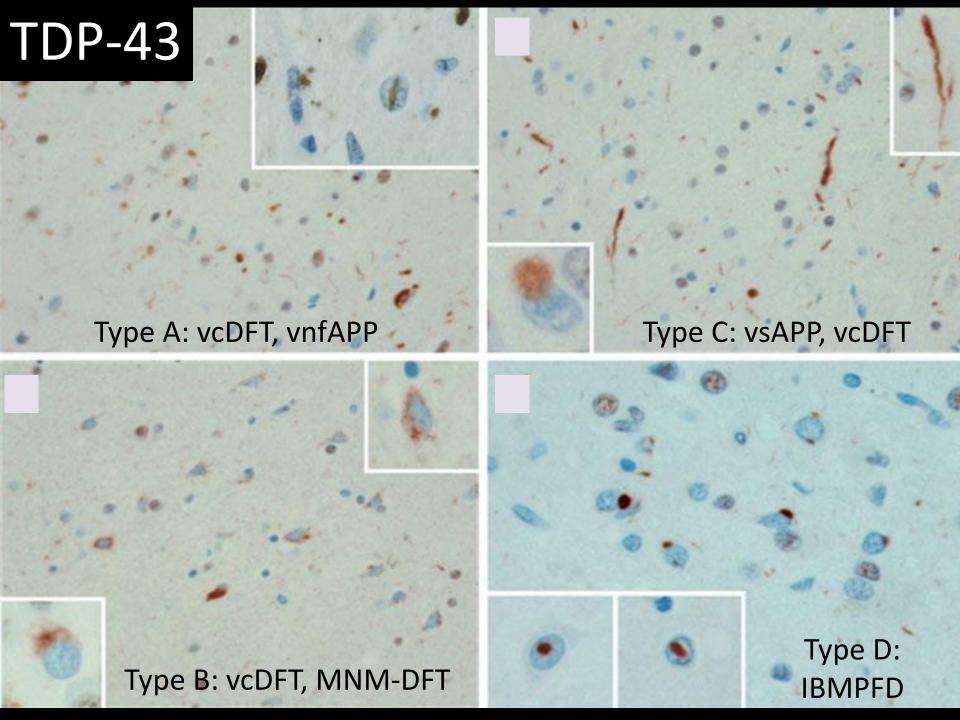
En touffes



Dystrophiques



Plaques

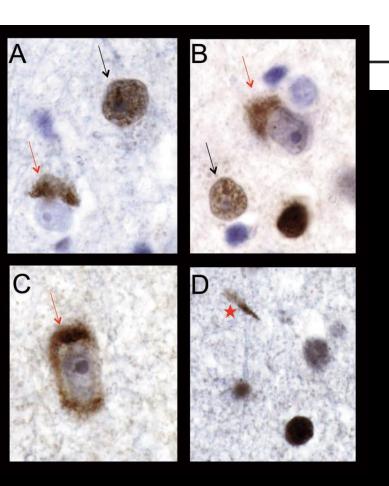


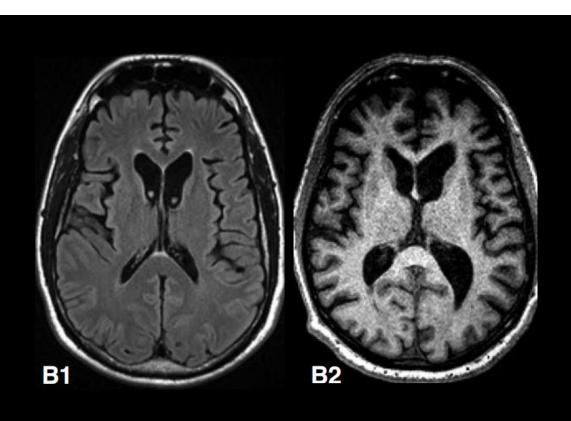
BRIEF COMMUNICATIONS

A 44 Year-Old Man with Profound Behavioural Changes

R. Laforce Jr, G.A. Kerchner, G.D. Rabinovici, J.C. Fong, B.L. Miller, W.W. Seeley, L.T. Grinberg

Can J Neurol Sci. 2012; 39: 527-530





FUS

- Début tôt dans la vie (âge moyen de 41 ans)
- Pas d'histoire familiale
- Comportements obsessionels, ritualisés, et stéréotypés avec 1/3 montrant des hallucinations et/ou délires
- Peu ou pas de symptômes moteurs (3%)
- Atrophie modérée sévère des noyaux caudés
- Durée courte (en moyenne 8 ans)

Historique

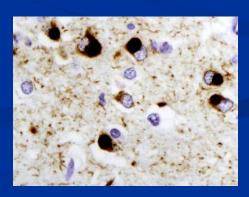
 En 1892, Arnold Pick décrit une entité neurodégénérative focale



La maladie affecte
 préférentiellement les lobes
 frontaux et temporaux



La présence d'inclusions cellulaires (corps de Pick) était nécessaire au Dx



Historique

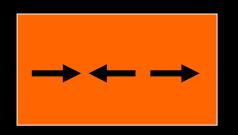
- Pick (1892)
- Alzheimer (1911)
- Delay, Brion & Escourolle (1957)
- Neary (1986)
- Critères de Neary (1998)
 - Catégorisation en différents sous-types

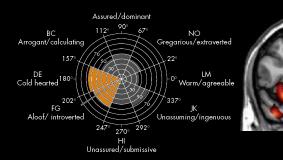
UCSF Memory and Aging Center 2010



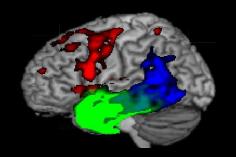
Personality, Social cognition Kate Rankin

FTD Neuropsychology Joel Kramer

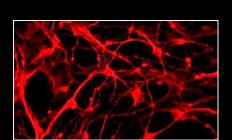




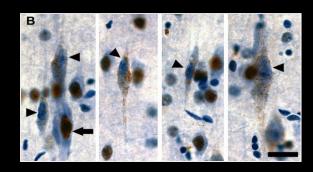
Primary Progressive Aphasia M. L. Gorno-Tempini



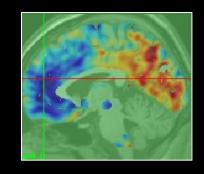




Robert Farese iPS with FTD mutations

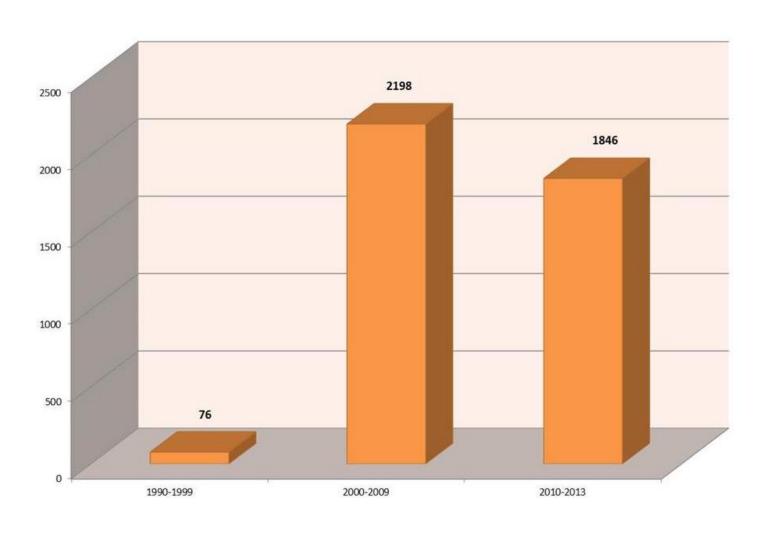


William Seeley
Von Economo neurons in FTD

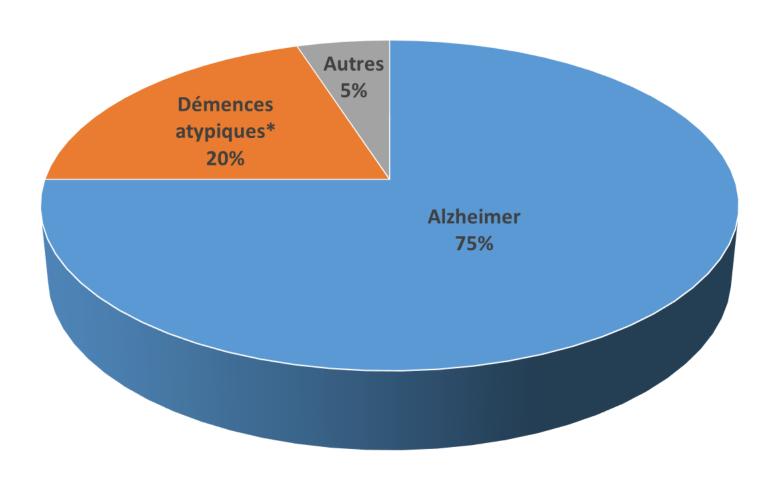


Howard Rosen FTD Longitudinal imaging

Citations DFT sur Medline

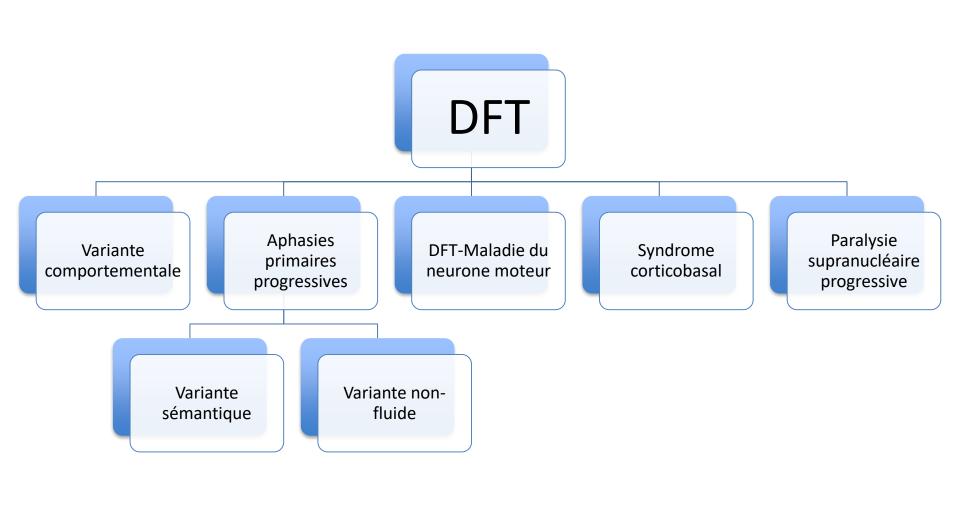


Épidémiologie



Épidémiologie

- 3ième cause de démence après MA et DCL
 - Sous-Dx (Mendez 1993)
- Cause fréquente de démence présénile
 - 1:1 avec MA 45-64 years (*Ratnavalli 2002*)
 - Plus fréquente que MA sous les 60 ans (*Knopman 2004*)
- Rare après 70 ans?
 - Prévalence de 3% chez 80-90 ans (*Skoog 2003*)
 - Encore plus fréquente si on inclue PSP, SCB, SLA
- Phénotypes et génétiques hétérogènes
 - Génétique (40%), sporadique (60%)
 - Frontale, temporale, prédominance gauche ou droite
 - Overlap moteur avec PSP, SCB, SLA





Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

Katya Rascovsky, ¹ John R. Hodges, ² David Knopman, ³ Mario F. Mendez, ^{4,5} Joel H. Kramer, ⁶ John Neuhaus, ⁷ John C. van Swieten, ⁸ Harro Seelaar, ⁸ Elise G. P. Dopper, ⁸ Chiadi U. Onyike, ⁹ Argye E. Hillis, ¹⁰ Keith A. Josephs, ³ Bradley F. Boeve, ³ Andrew Kertesz, ¹¹ William W. Seeley, ⁶ Katherine P. Rankin, ⁶ Julene K. Johnson, ¹² Maria-Luisa Gorno-Tempini, ⁶ Howard Rosen, ⁶ Caroline E. Prioleau-Latham, ⁶ Albert Lee, ⁶ Christopher M. Kipps, ^{13,14} Patricia Lillo, ² Olivier Piguet, ² Jonathan D. Rohrer, ¹⁵ Martin N. Rossor, ¹⁵ Jason D. Warren, ¹⁵ Nick C. Fox, ¹⁵ Douglas Galasko, ^{16,17} David P. Salmon, ¹⁶ Sandra E. Black, ¹⁸ Marsel Mesulam, ¹⁹ Sandra Weintraub, ¹⁹ Brad C. Dickerson, ²⁰ Janine Diehl-Schmid, ²¹ Florence Pasquier, ²² Vincent Deramecourt, ²² Florence Lebert, ²² Yolande Pijnenburg, ²³ Tiffany W. Chow, ^{24,25} Facundo Manes, ²⁶ Jordan Grafman, ²⁷ Stefano F. Cappa, ^{28,29} Morris Freedman, ^{24,30} Murray Grossman^{1,*} and Bruce L. Miller, ^{6,*}

vcDFT – Possible (3/6)

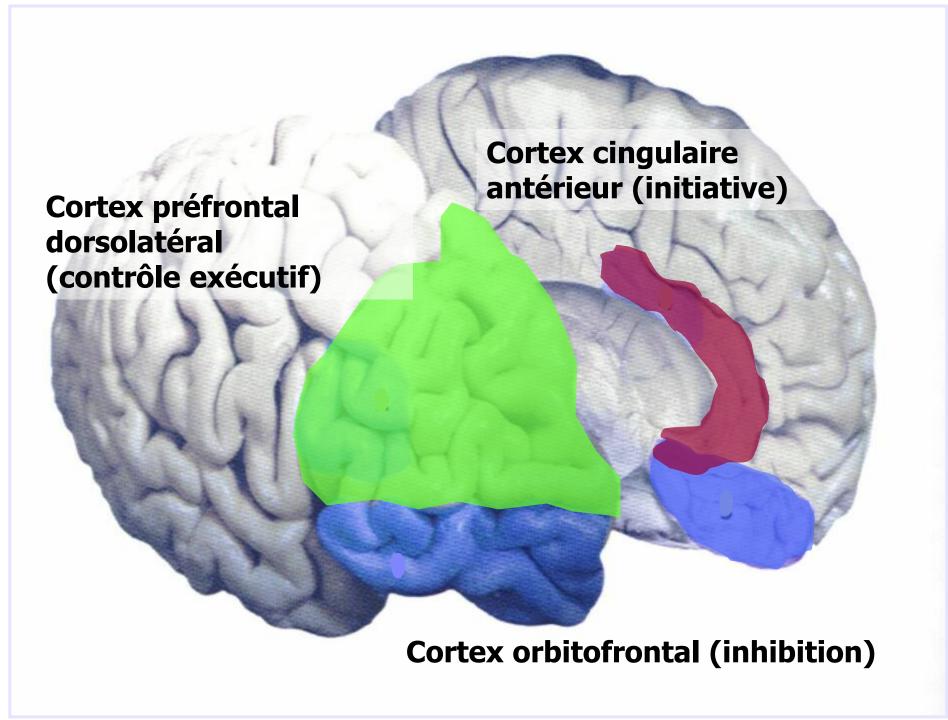
- 1. Désinhibition comportementale (précoce)
- 2. Apathie ou inertie précoce (le plus fréquent)
- 3. Perte d'empathie ou de sympathie (précoce)
- 4. Comportements persévératifs, stéréotypés ou compulsifs/ritualisés (précoce)
- 5. Hyperoralité et changements alimentaires
- 6. Profil neuropsychologique de troubles exécutifs avec préservation relative de la mémoire et des fonctions visuospatiales

vcDFT – Probable (3/3)

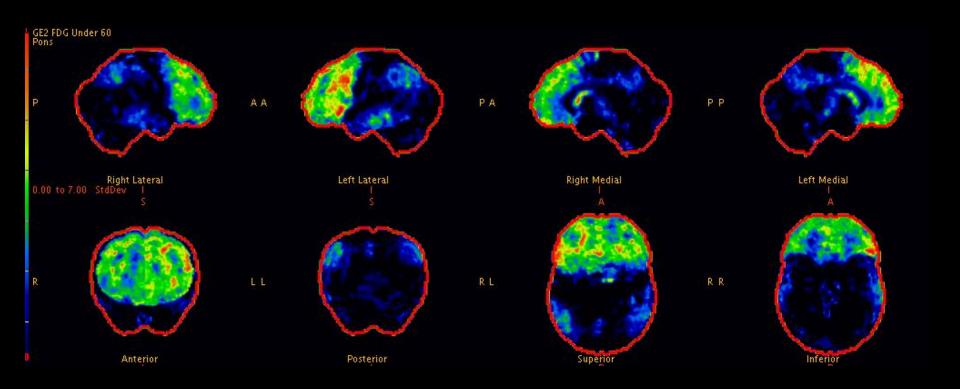
- 1. Critères de vcDFT Possible
- 2. Atteinte significative du fonctionnement
- 3. Imagerie doit montrer 1/2 de
 - a. Atrophie frontale et/ou temporale antérieure au TDM ou IRM
 - b. Hypoperfusion/hypométabolisme frontal au SPECT ou TEP

Variante comportementale





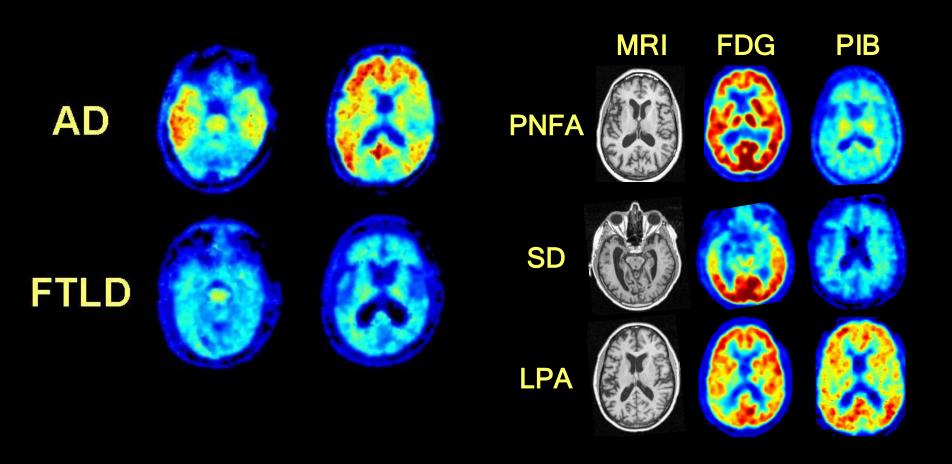
FDG-PET



Critères d'exclusion

- Pattern de déficits compatible avec une autre maladie non-dégénérative du système nerveux ou un trouble médical
- Les changements comportementaux sont explicables par une problématique psychiatrique
- Biomarqueurs fortement suggestifs de la maladie d'Alzheimer ou d'un autre processus dégénératif

L'imagerie amyloïde distingue la MA de la DFT



Rascovsky 2011 vs Neary 1998

- Neary nécessitait la présence des 5 critères
 - Insidious onset and gradual progression, early decline in personal and social interpersonal conduct, emotional blunting and loss of insight
 - 78% pour blunting ad 99% pour insidieux
- Neary avait 11 critères d'exclusion core et 3 relatifs
 - Seulement 19% de l'échantillon de Rascovsky ont ≥ 1
 - Amnésie sév tôt ou désorientation spatiale = prudence!

Rascovsky 2011 vs Neary 1998

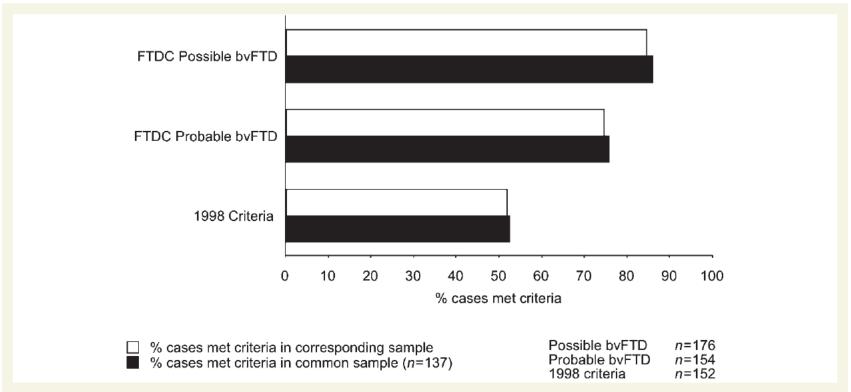


Figure 2 Sensitivity of FTDC and 1998 criteria as per cent of cases that met criteria in the corresponding sample (white bars) or the common sample (black bars). bvFTD = behavioural variant FTD.

Published Ahead of Print on May 1, 2013 as 10.1212/WNL.0b013e318293e368

Interrater reliability of the new criteria for behavioral variant frontotemporal dementia

Amanda K. LaMarre, PhD Katya Rascovsky, PhD Alan Bostrom, PhD Parnian Toofanian, JD, PsyD Sarah Wilkins, BA Sharon J. Sha, MD David C. Perry, MD Zachary A. Miller, MD Georges Naasan, MD Robert Jr Laforce, MD, PhD Jayne Hagen, PhD Leonel T. Takada, MD Maria Carmela Tartaglia, MD Gail Kang, MD Douglas Galasko, MD David P. Salmon, PhD

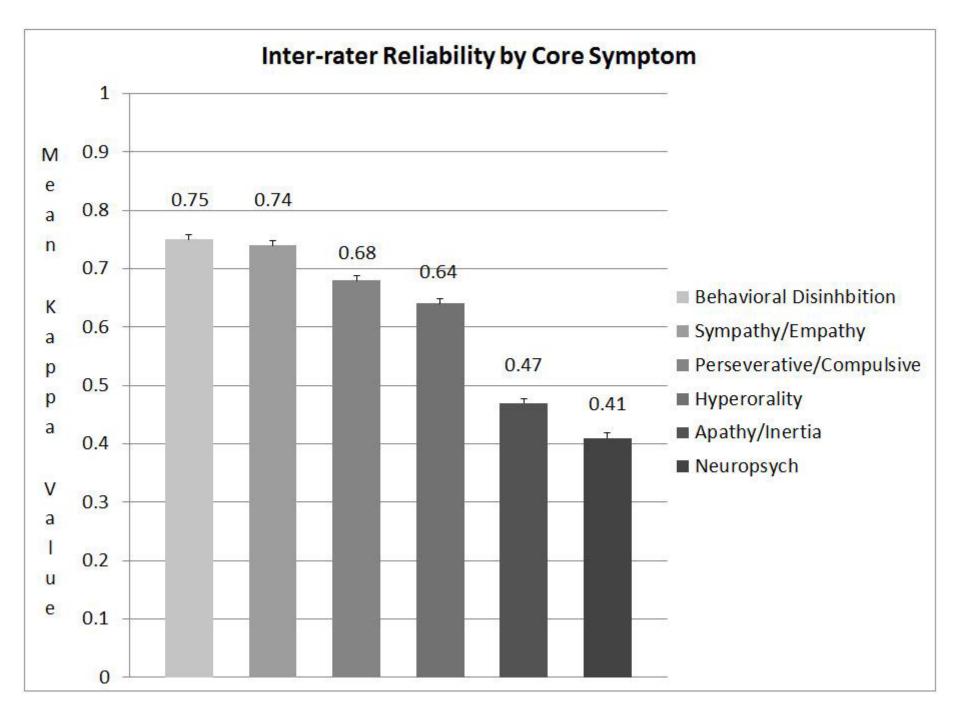
ABSTRACT

Objective: To evaluate the interrater reliability of the new International Behavioural Variant FTD Criteria Consortium (FTDC) criteria for behavioral variant frontotemporal dementia (bvFTD).

Methods: Twenty standardized clinical case modules were developed for patients with a range of neurodegenerative diagnoses, including bvFTD, primary progressive aphasia (nonfluent, semantic, and logopenic variant), Alzheimer disease, and Lewy body dementia. Eighteen blinded raters reviewed the modules and 1) rated the presence or absence of core diagnostic features for the FTDC criteria, and 2) provided an overall diagnostic rating. Interrater reliability was determined by κ statistics for multiple raters with categorical ratings.

Results: The mean κ value for diagnostic agreement was 0.81 for possible bvFTD and 0.82 for probable bvFTD ("almost perfect agreement"). Interrater reliability for 4 of the 6 core features had "substantial" agreement (behavioral disinhibition, perseverative/compulsive, sympathy/empathy, hyperorality; $\kappa=0.61$ –0.80), whereas 2 had "moderate" agreement (apathy/inertia, neuropsychological; $\kappa=0.41$ –0.6). Clinician years of experience did not significantly influence rater accuracy.

Conclusions: The FTDC criteria show promise for improving the diagnostic accuracy and reliability of clinicians and researchers. As disease-altering therapies are developed, accurate differential diagnosis between bvFTD and other neurodegenerative diseases will become increasingly important. **Neurology® 2013;80:1-5**



Le dîner de Noël

Le gars qui se lève

Tapper des pieds

Le gars du chien

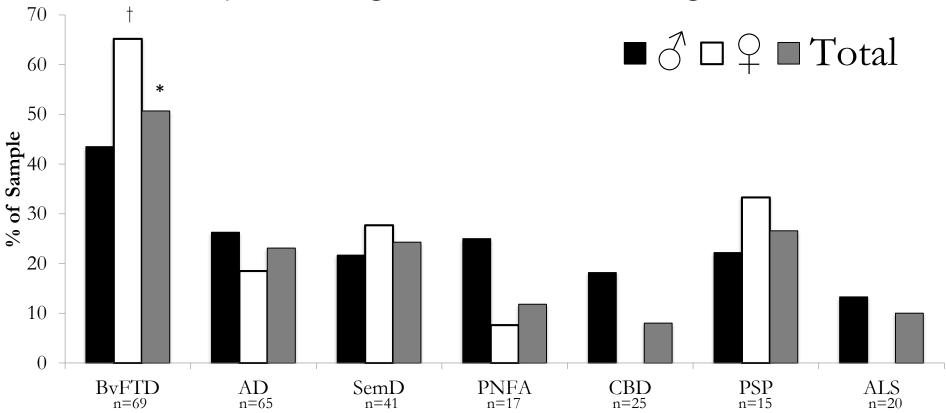
Bob et les fourmis...

La dame espagnole...

Beware of misdiagnosis

1/3 have a Psych Dx early in the disease

Rates of Psychiatric Diagnosis within each Neurodegenerative Disease



Woolley J Clin Psychiatry 2011
Blinded chart review of 252 pts

Characterization of the Psychiatric Diagnoses

bvFTD		
Diagnosis	₹	우
Depression	13 (65%)*	8 (50%)*
Bipolar affective	4 (20%)*	4 (25%)*
Schizophrenia	1 (5%)	1 (6%)
Anxiety		1 (6%)
Adj. Disorder		

p<0.01; (–) denotes a value of zero; percent listed is in comparison to ND group

FTD OU MALADIE PSYCHIATRIQUE?

IL FAUT VÉRIFIER!...

- ENTREVUE AVEC LE PATIENT **ET** AUSSI AVEC LES PROCHES
 - ANTÉCÉDENTS MÉDICAUX ET PSYCHIATRIQUES PERSONNELS ET FAMILIAUX
 - PERSONNALITÉ ET FONCTIONNEMENT PRÉMORBIDE
 - UTILISATION DE SUBSTANCES, MÉDICAMENTS...
 - DÉBUT ET PROGRESSION DES SYMPTÔMES PHYSIQUE, COMPORTEMENTAUX, PSYCHIATRIQUES ET COGNITIFS, STRESSEURS RÉCENTS
 - INTENSITÉ, ATTEINTE DU FONCTIONNEMENT
 - EXAMEN MENTAL

Et si c'était l'Alzheimer?

doi:10.1093/brain/awv191 BRAIN 2015: Page 1 of 18 / I

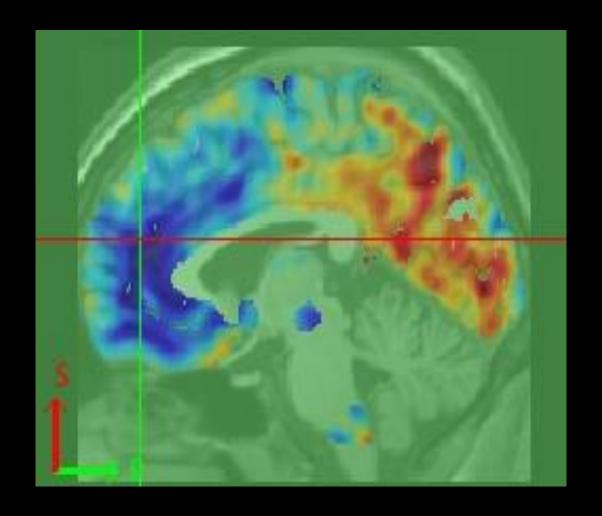


The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features

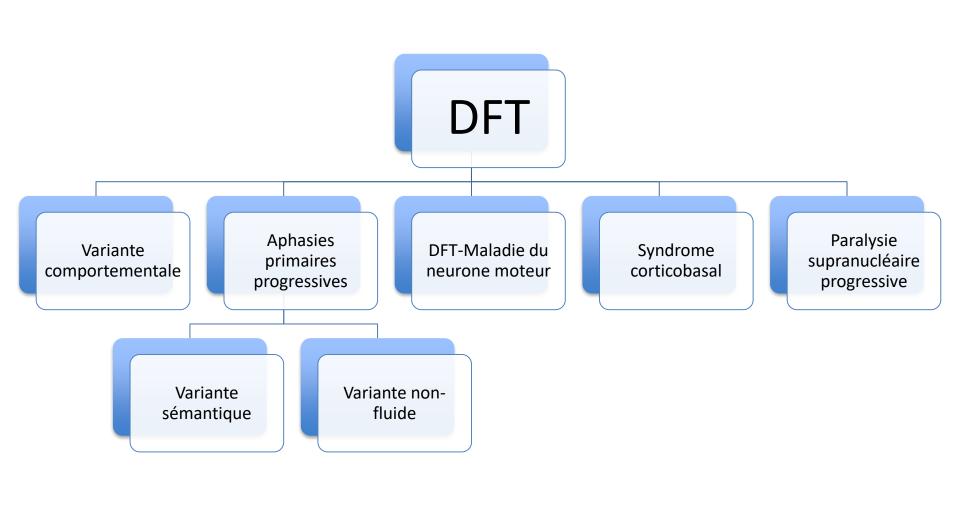
Rik Ossenkoppele, ^{1,2,3,4} Yolande A. L. Pijnenburg, David C. Perry, ¹ Brendan I. Cohn-Sheehy, ¹ Nienke M. E. Scheltens, Jacob W. Vogel, Joel H. Kramer, Annelies E. van der Vlies, Renaud La Joie, Howard J. Rosen, Wiesje M. van der Flier, Lea T. Grinberg, Annemieke J. Rozemuller, Eric J. Huang, Bart N. M. van Berckel, Bruce L. Miller, Frederik Barkhof, William J. Jagust, Philip Scheltens, William W. Seeley, and Gil D. Rabinovici, Philip Scheltens, William W. Seeley, and Gil D. Rabinovici, Philip Scheltens, Philip Scheltens,

52% of pts with behavioural AD met Dx criteria for possible bvFTD

Atrophie DFT vs MA



Voxel-based morphometry (VBM) DFT & MA versus normaux

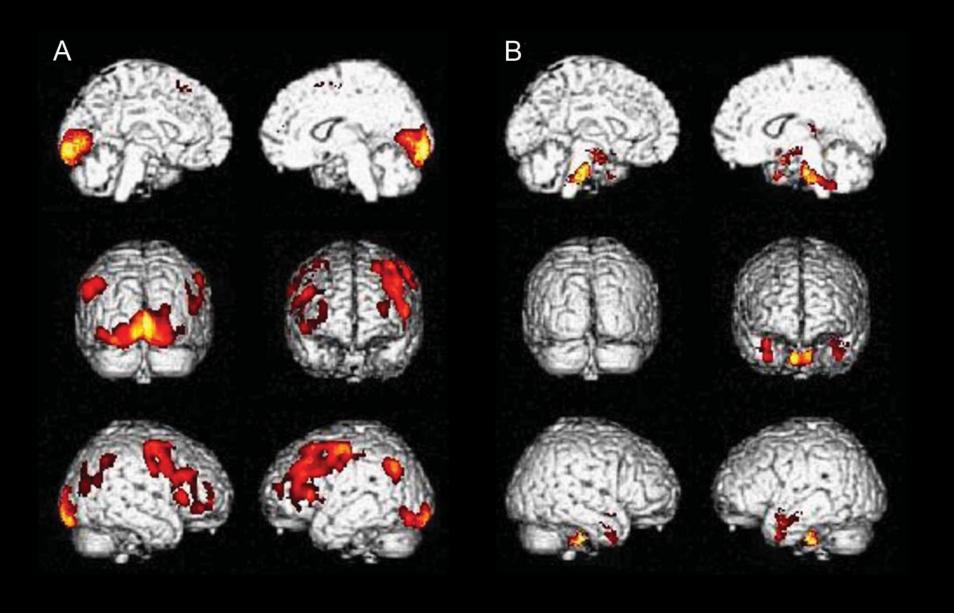


Review

Lancet Neurol 2013

Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment

Laura H Goldstein, Sharon Abrahams



Pagani et al., Neurology 2014



GENFI I – Brain volumes (C9orf72)

p<0.05	p<0.01	p<0.001		



	-25	-20	-15	-10	-5	0	5	10
Frontal								
Temporal								
Parietal								
Occipital								
Insula								
Cingulate								
Hippocampus								
Amygdala								
Striatum								
Thalamus								



REVIEW

Cognitive and behavioral features of c9FTD/ALS

Bradley F Boeve*1 and Neill R Graff-Radford2

Earlier age at onset, longer survival, more thalamic atrophy

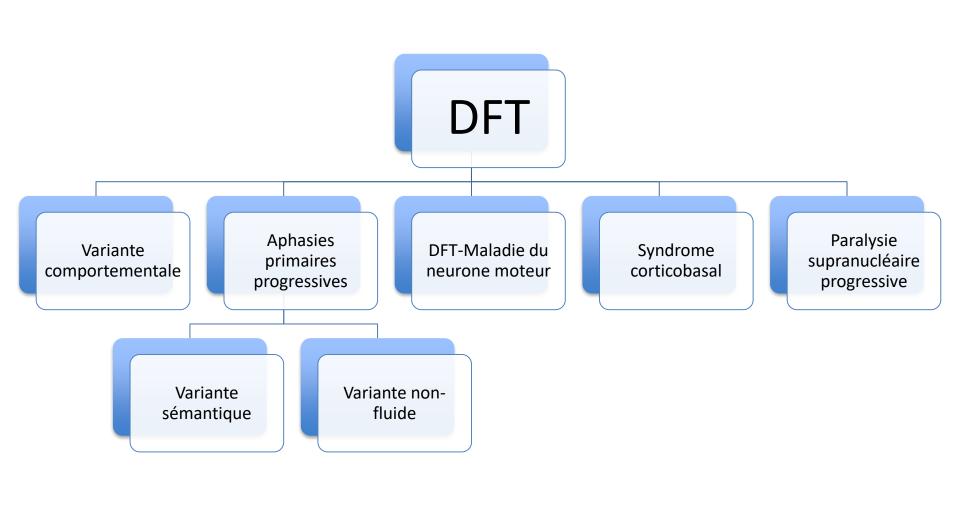
Frontotemporal dementia due to *C9ORF72* mutations

Clinical and imaging features

Sharon J. Sha, MD, MS*

Neurology 2012

More delusions, greater impairment in wm and milder eating dysregulation



Treatment

- Non-pharmacological
 - www.theaftd.org
 - www.memory.ucsf.edu
 - http://lifeandminds.ca/whendementiaisinthehouse/
 - www.cliniquedememoire.ca
- Pharmacological
 - Sx oriented, no approved molecule
 - SSRI, atypical NLP, Trazodone (Kerchner et al., 2011; Manoocherhi et al., 2012; Seltman et al., 2012)
 - CheI, memantine = **NOT INDICATED**

Les ressources

- www.theaftd.org
 - Support & Resources
 - Canadian Regions
 - Quebec
 - 2 pdf
- www.memory.ucsf.edu





Les Société Alzheimer

Y a-t-il une place pour les IAChe?

- Rarement
 - Système cholinergique intact (contrairrement à 5-HT et dopaminergique) (*Huey 2006*)
- Malgré cela, prescrit chez 40 % des patients...
- Études
 - Rivastigmine (*Moretti 2004*)
 - 12 mois, ouverte, n=20, amélioration au NPI mais pas cog
 - Donepezil (*Mendez 2007*)
 - 6 mois, non random, ouverte, n=24, peut ↑ Sx cpt (désinhibition, compulsivité)
 - Galantamine (*Kertesz 2008*)
 - 18 sem, ouverte puis random/insu/placebo 8 sem, n=36, aucun effet
- Donc, non recommandé et peuvent même ↑ risque d'étouffement...

Et la mémantine?

- Maintenant un total de 7 études!
- Études ouvertes non contrôlées
 - Swanberg (2007): 3 mois, n=3, améliore apathie, anxiété, agitation
 - Diel-Schmind (2008): 6 mois, n=16, déclin cog
 - Boxer (2009): 26 sem, n=21, amélioration transitoire au NPI
 - Chow (2011, 2012): ↑ métabolisme FDG-PET
- Études randomisées/insu/placebo
 - Vercelletto (2011): 12 mois, n=49, 3 échelles (CIPIC-PLUS, NPI, FBI), aucun effet cognitif ou comportemental
 - Boxer (2012): 26 sem, n=64, aucun effet au CGIC ou NPI, tendance non-significative vers détérioration cognitive
- Non indiquée...mais encore très utilisée...

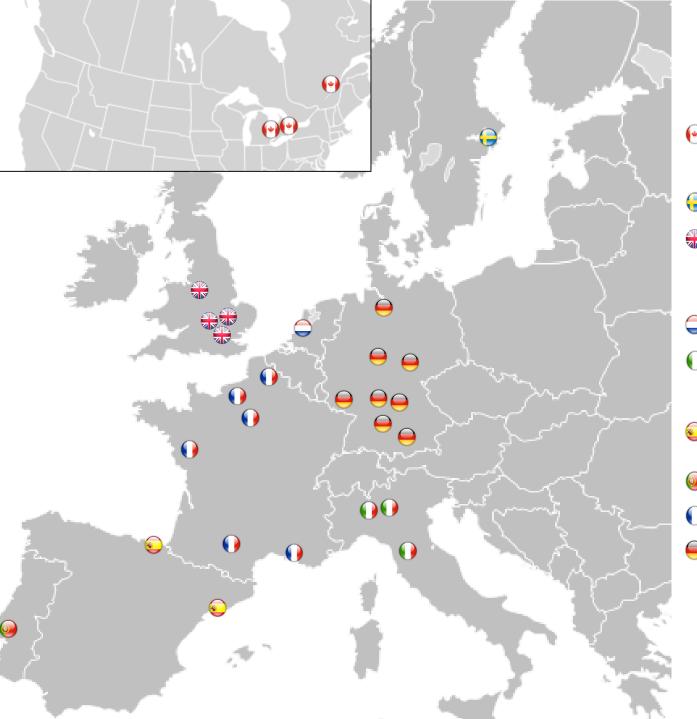
doi:10.1093/brain/awr171 Brain 2011: 134; 2493–2501 2493



The effects of oxytocin on social cognition and behaviour in frontotemporal dementia

Sarah Jesso, Darlyne Morlog, Sarah Ross, Marc D. Pell, Stephen H. Pasternak, Andrew G. V. Mitchell, Andrew Kertesz, and Elizabeth C. Finger, Andrew Kertesz, and Elizabeth C. Finger, Sarah Ross, Marc D. Pell, Stephen H. Pasternak, Sarah Ross, Sara

- 1 Cognitive Neurology and Alzheimer Research Centre, St Joseph's Hospital, London, Ontario, Canada, N6A 4V2
- 2 School of Communication Disorders and Sciences, McGill University, Montreal, Quebec, Canada, H3G 1A8
- 3 Department of Clinical Neurological Sciences, Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada, N6A 5A5
- 4 Molecular Brain Research Group, Robarts Research Institute, University of Western Ontario, London, Ontario, Canada, N6A 5K8
- 5 Department of Psychology, University of Western Ontario, London, Ontario, Canada, N6A 5C2
- 6 Department of Psychiatry, Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada, N6A 5A5
- 7 Department of Anatomy and Cell Biology, Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada, N6A 5C1
- 8 Centre for Brain and Mind, University of Western Ontario, London, Ontario, Canada, N6A 5B7
- Suberoylanilide hydroxamic acid (SAHA) ↑ PGRN
- Anti-interleukin-6 ou Ac des rct IL-6
- Ferulic acid et yokukansan (herbal) améliore cpt
- Anti-tau: Davunetide (NAP) stabiliserait les microtubules et neuroprotection; GSK-3 inhibitors (comme le lithium) préviendrait l'hyperphosphorylation





TORONTO
LONDON ONTARIO
QUEBEC CITY

STOCKHOLM

LONDON (UCL)
CAMBRIDGE
MANCHESTER
OXFORD

ROTTERDAM

MILANO (UNIMI/INCB)
BRESCIA (UNIBS/FBF)
FIRENZE

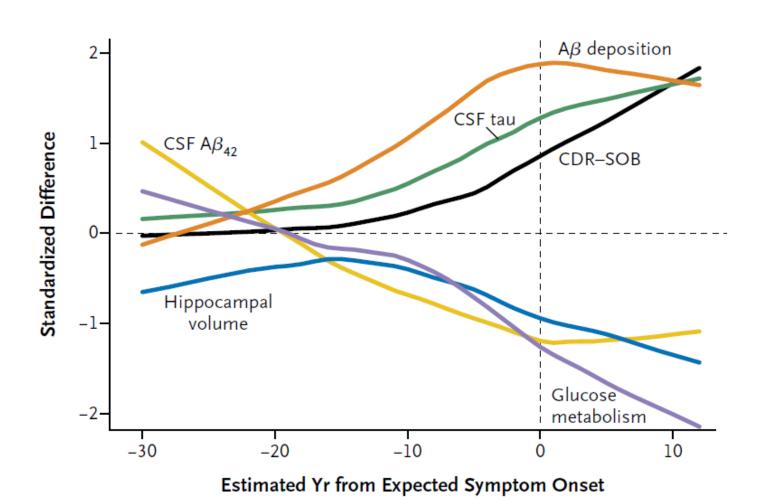
SAN SEBASTIAN

LISBOA

FRENCH FTD NETWORK

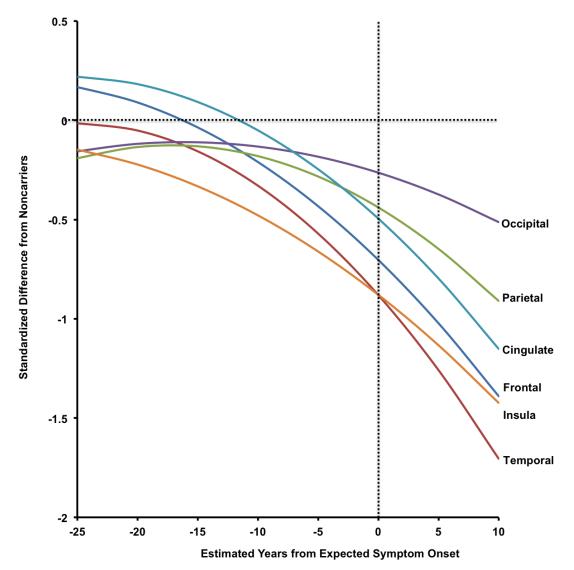
GERMAN FTD NETWORK

DIAN - Bateman NEJM 2012



GENFI I results: predicted grey matter volumes





Earliest significant difference from noncarriers in insula volume around ten years before expected symptom onset

Articles

Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis







Jonathan D Rohrer, Jennifer M Nicholas, David M Cash, John van Swieten, Elise Dopper, Lize Jiskoot, Rick van Minkelen, Serge A Rombouts, M Jorge Cardoso, Shona Clegg, Miklos Espak, Simon Mead, David L Thomas, Enrico De Vita, Mario Masellis, Sandra E Black, Morris Freedman, Ron Keren, Bradley J MacIntosh, Ekaterina Rogaeva, David Tang-Wai, Maria Carmela Tartaglia, Robert Laforce Jr, Fabrizio Tagliavini, Pietro Tiraboschi, Veronica Redaelli, Sara Prioni, Marina Grisoli, Barbara Borroni, Alessandro Padovani, Daniela Galimberti, Elio Scarpini, Andrea Ariqhi, Giorgio Fumagalli, James B Rowe, Ian Coyle-Gilchrist, Caroline Graff, Marie Fallström, Vesna Jelic, Anne Kinhult Ståhlbom, Christin Andersson, Håkan Thonberg, Lena Lilius, Giovanni B Frisoni, Michela Pievani, Martina Bocchetta, Luisa Benussi, Roberta Ghidoni, Elizabeth Finger, Sandro Sorbi, Benedetta Nacmias, Gemma Lombardi, Cristina Polito, Jason D Warren, Sebastien Ourselin, Nick C Fox, Martin N Rossor



Conclusion

- Pas rare... hétérogène
- Nouveaux critères Dx avec une meilleure sensibilité
- Biomarqueurs sont utiles dans les cas complexes
- Traitements sont multidisciplinaires
- GENFI = l'avenir!

Références

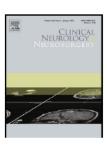
- Miller
- Hodges
- Rohrer
- Rabinovici
- Rankin
- Knopman
- Neary
- Patho: Neumann, Seeley, Mackenzie



Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro



Review

Behavioral and language variants of frontotemporal dementia: A review of key symptoms



Robert Laforce Jr. a,b,*

^a Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, Québec, Canada

^b Faculté de Médecine, Université Laval, CHU de Québec, Québec, Canada

Imaging in Neurodegenerative Disorders

Edited by Luca Saba



OXFORD

CHAPTER 5

Symptoms of neurodegenerative diseases

Robert Laforce Jr, Manja Lehmann, Joël Macoir, Stéphane Poulin, Martin Roy, Jean-Paul Soucy, Louis Verret, Bruce L. Miller, and Rémi W. Bouchard

http://ukcatalogue.oup.com/pr oduct/9780199671618.do#

January 2015



Alzheimer's & Dementia (2018) 1-31

Review Article

Molecular imaging in dementia: Past, present, and future

Robert Laforce, Jr.^{a,*}, Jean-Paul Soucy^b, Leila Sellami^a, Caroline Dallaire-Théroux^a, Francis Brunet^a, David Bergeron^a, Bruce L. Miller^c, Rik Ossenkoppele^d

^aClinique Interdisciplinaire de Mémoire, CHU de Québec, QC, Canada ^bMcConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, QC, Canada ^cMemory and Aging Center and Department of Neurology, University of California San Francisco, CA, USA ^dDepartment of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands



www.cliniquedememoire.ca

Fellowship in Behavioral Neurology and Neuropsychiatry





_ma Faculté pour la vie fmed.ulaval.ca