The frontal lobe syndrome

Krudop, W.A.

2016

document version
Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)
Krudop, W. A. (2016). *The frontal lobe syndrome: A neuropsychiatric challenge*.

Chapter 2

HISTORICAL EVOLUTION OF THE FRONTAL LOBE SYNDROME

ABSTRACT

The function of the frontal lobes and the related frontal lobe syndrome hasn't been described in detail until relatively late in history. Slowly, the combination of knowledge from animal models, the detailed examination of symptoms after traumatic frontal lobe injuries and the rise and fall of the psychosurgery lead to increasing insight in frontal lobe function. The fronto-subcortical circuits were described and increasingly related to clinical syndromes, confirmed by the latest developments in functional connectivity networks.

A HISTORY OF THE FRONTAL LOBES

Hippocrates (460-377 BC) and his contemporaries were the first known to describe not the heart but the brain as the source of intelligence and thought [1]. Throughout history many efforts to modify the human behavior by skull or brain surgery have taken place and many prehistoric examples of trepanation and subsequent bone healing have been found [2]. Although it is likely that in some of these cases neurological or psychiatric illnesses were the underlying disorders, obviously very little understanding of the underlying physiology was present and the procedures were veiled by mystical or shamanistic rituals [2].

It wasn't until Thomas Willis in the 17th century that someone attributed the higher cognitive functions to the cerebral cortex. Although many scientists throughout the ages described, drew or painted the shape of and the different structures within the brain, little was known about the function of the frontal lobes. The French anatomist Francois Chaussier (1746-1828) was the first to make an adequate description of the frontal lobes and created the division of the brain into the different lobes as we still use it. The philosopher and theologian Emanuel Swedenborg (1688-1772) linked the frontal lobes to a number of functions: imagination, memory, thought and suffering, but his work was overlooked in his time. Franz Joseph Gall (1758-1832) and Johann Kaspar Spurzheim (1776-1832) argued that since animals have smaller frontal lobes compared to humans, this area must harbor the highest human functions [1]. The extraordinary case of the railway worker Phineas Gage mid-19th century, surviving severe damage to his frontal lobe by an iron rod, caused a major step in understanding the frontal lobe function by description of a wide range of character and behavioral changes [3].
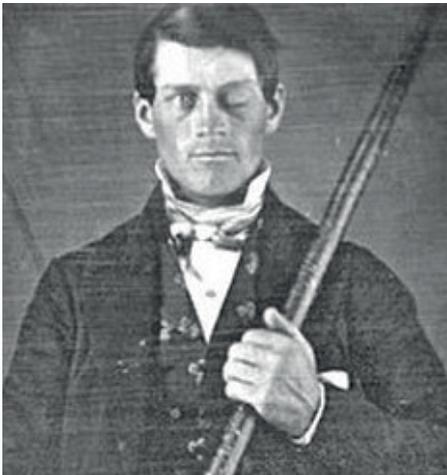

Phineas Gage with iron rod and reconstruction skull

Moses Allan Starr (1884) reviewed the American literature on behavioral changes after tumors, abscesses and traumatic lesions and noted that frontal lobe damage often affected attention, intellect, temperament and personality. Paul Broca described part of the frontal lobes as 'the speaking centre' resulting in an eponym for the phenomena of a motoric aphasia, but he noted the total frontal lobes to be the area for higher intellectual functions as well. Arnold Pick (1851-1924) first described patients with frontal and temporal degeneration who showed indifference, poor judgment and insight, diminished creativity, careless dressing, antisocial behavior and aphasia [4]. Pick's primary interests were the language and behavioral disturbances and he did not claim to have found a new disease. It was Carl Sneider who, among others, introduced the eponym 'Pick's disease' for the frontal lobe degeneration accompanied by behavioral disturbances, followed by focal symptoms and generalized dementia [5]. In the 19th and 20th century multiple scientific papers on altered behavior, poor planning and restlessness in animals after frontal lobe damages were published by Bianchi and others [1;6]. During World War I and II large numbers of soldiers suffered from frontal lobe damage and Poppelreuter (1918), Berger (1920) and Feuchtwanger (1923) described impaired thinking and reasoning, perseveration, reduced attention, euphoria, loss of initiative and emotional changes in these patients [1]. Luria (1902-1977) investigated the frontal lobes by studying soldiers with penetrating head injuries, as well as patients with tumors and other focal lesions. In *Higher cortical Functions in Man (1962)* he described the frontal lobes exerting a controlling function in the hierarchy of the brain and operating the planning, executing and monitoring of mental processes [1].

In the late 19th century the psychiatrist Gottlieb was the first to perform modern psychosurgery on a patient with intractable psychiatric illness [2]. In 1935 the era of the modern psychosurgery on a large scale began [7]. With the exertion of Moniz and Lima, implementing damaging the neuronal tracts in the frontal lobes in patients with mental illnesses, psychosurgery took a flight [2;7]. Moniz received the Nobel prize for his work (1949), which at the time was considered an important advance in treating seriously ill patients with severe psychotic, aggressive or anxious conditions for whom no effective therapy was available. Watts and Freeman introduced the lobotomy through boreholes, a less invasive procedure evoking comparable features like 'dispassion', indifference or inertia [8]. Freeman recites on the patient's reduced emotional reaction regarding anything that affected the patient him- or herself [8;9]. The widespread availability, performed without anesthesia, led to more than 60.000 lobotomies being done in the US between 1936 and 1956 [10]. The various frontal surgeries were designed to destroy the connections, assumed to account for mental illness, by disrupting frontal-subcortical circuits, the anterior thalamic radiation to the frontal cortex and limbic circuits by means of discrete frontal white matter lesions or in some cases by alcohol injections into the white matter [7;8]. Some patients did improve, but many treatments resulted in seizures, incontinence, severe apathy or death. These complications, as well as the rise of effective antipsychotic medications in

the 1950's, led to frontal surgery being abandoned by the 1970s [1;10]. During the first half of the 20th century the focus considering mental illnesses lay more on psychoanalysis, but Geschwind's paper "*Disconnexion syndromes in animals and man*" restarted the quest for neuro-anatomical connections and their associated syndromes in 1965 [6;11].
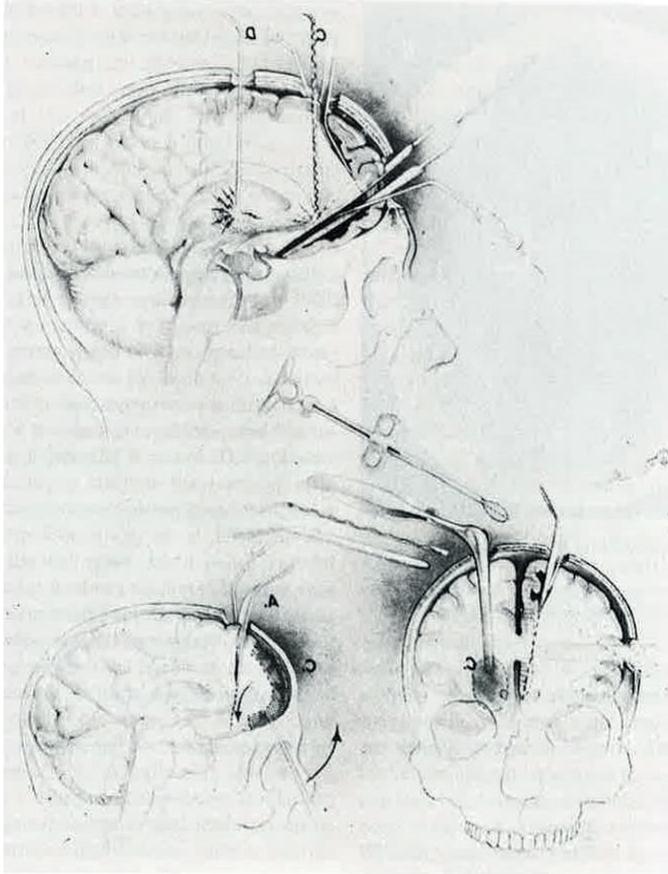
Tools and techniques of leucotomies
(Handbook of clinical neurology, Vinken, Bruyn, Klawans, 1989)

Clinical features of the frontal lobe syndrome

The term 'frontal lobe syndrome' (FLS) has been used in many ways over the years [1]. In some rare cases, the FLS definition includes the symptoms attributed to the more posterior parts of the frontal lobe: impairments in speech, frontal eye movements, control of continence and motor function [6;12]. In most cases though, the FLS refers to a clinical syndrome associated with functional or structural changes in the prefrontal cortex (anterior to the

motor cortex), leading to personality, affective or behavioral changes. Historical scientists like Moniz or Benson already described multiple features still considered to be caused by frontal lobe dysfunction: indifference, distractibility, emotional instability, diminished anxiety, impulsiveness, facetiousness, euphoria, a lack of initiative and impaired integration of behavior over time [7;13]. Added to these symptoms where impairment on executive functioning, deficits on working memory, lack of concern with events in the past or the future, impaired concentration, poor judgment, inappropriate social behavior, hallucinations, utilization behavior, imitation and the 'environmental dependency syndrome' [1;9;10;13-17]. The FLS was summarized by Nauta as an impairment to integrate information from the internal milieu with the environment, provided by neocortical processing [16]. In the 1980's Stuss and Benson collected information on long-term effects of leucotomies and suggested that the prefrontal cortex consisted of three major anatomical regions: the orbitofrontal, anterior cingulate and dorsolateral prefrontal cortex [18]. After this, regional specialization within the frontal lobes was increasingly recognized and these three cortical prefrontal regions repeatedly turned out to be correlated with specific neuropsychiatric features [17].

Anatomical frontal-subcortical circuits

The regional specializations became increasingly known, but it seemed that damage in connected areas could result in similar symptoms. Wernicke, Pavlov and Luria were some of the first considering specific locations to be part of a large-scale network [1]. Alexander et al. published a detailed description of the anatomy of multiple segregated 'loops' running from cortical areas to the subcortical grey matter within the frontal lobes creating a first basis for a more network-based approach [19]. By then, it was already clearly stated by Damasio and Geschwind that the effects of damaging a circumscribed locus could only be understood by taking into account that the healthy brain tissue that has been destroyed was a component of a neural network [20]. According to Geschwind, only very simple cognitive functions could be assigned to defined areas, but higher order cognitive processes must be the achievement of the fiber tracts connecting the different regions [6]. The anatomically distinguishable parallel but separated fronto-subcortical circuits suggested by Alexander et al. are now generally accepted [19;21]. The frontal-subcortical circuits described by Alexander were elaborated in more detail by Cummings [1;19;22]. These consist of subcortical loops, beginning in prefrontal cortex and proceeding to the striatum, globus pallidus, thalamus and back to the cortex [22]. Each frontal-subcortical circuit has both a direct pathway, projecting from globus pallidus interna to medial thalamic regions, and an indirect pathway, projecting from globus pallidus externa to the subthalamic nucleus and back to the globus pallidus interna before connecting to thalamic nuclei [12]. These circuits include a motor circuit that originates in the supplementary motor area, an oculomotor circuit originating in the frontal eye fields and three 'behavioral' circuits [19;21]. The main cortical areas within these circuits correspond with the areas earlier described by Stuss and

Benson: disturbances within the *dorsolateral prefrontal* circuit are associated with impaired organization, generation of ideas and planning, inflexibility, poor abstraction skills and distractibility [12;21;22]. Disturbances of the *orbitofrontal circuit* are associated with restlessness, impulsiveness, disinhibition, perseveration, aggression, euphoria, imitation, utilization, compulsive or ritualistic behavior, inappropriate social behavior, impaired empathy and impaired theory of mind (the ability to attribute mental states to others and to oneself) [12;21;22]. Disturbances of the *medial frontal circuit* are associated with apathy and loss of initiative, diminished motor activity, general and emotional indifference, reduced social interest, impaired problem solving, poor maintenance of implemented activities, hyperorality and loss of insight [12;21;22]. It was also acknowledged that regional damage at different localizations anywhere within one circuit could give rise to the same syndrome, confirming the clinical relevance of these circuits [22].

Differential diagnosis

In case of the occurrence of a frontal lobe syndrome, a broad differential diagnostic spectrum may be considered. Cerebral infarction, hemorrhage, intracerebral or intracranial extracerebral tumors, multiple sclerosis, hydrocephalus and traumatic brain injuries may, among other causes, damage the brain tissue causing a combination of different frontal lobe syndrome features [12;23;24]. Among the neurodegenerative disorders (many in their turn associated with a heterogeneous range of pathologies) behavioral variant frontotemporal dementia (bvFTD) most specifically affects the frontal and temporal lobes [25]. Mild cognitive impairment (MCI) or dementia due to Alzheimer's disease (AD) can present with a clinically apparent frontal lobe syndrome [26-28]. Also, dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Parkinson's disease, vascular dementia (VaD) and myotonic dystrophy type 2 can all result in similar symptoms [29-35]. Especially apathy is apparent frequently in especially VaD and Parkinson's disease [29;36]. Cerebral vasculitides, infectious disorders or inflammatory brain diseases may also give rise to a clinical FLS [37]. Among the toxic etiologies of an FLS, excessive alcohol use (and its associated withdrawal or deficiency syndromes) is probably the most common cause [37].

Furthermore, a number of psychiatric disorders can result in functional defects of the same fronto-subcortical circuits [22;38]. Emotional blunting, apathy, economy of thought and speech are frequently presenting symptoms of a psychiatric syndrome. The negative symptoms in schizophrenia, depression, dysthymic disorder or autism spectrum disorders can involve the same fronto-subcortical circuits resulting in apathy and lack of initiative. Similarly, in manic episodes, bipolar disorder, anxiety disorders, obsessive-compulsive disorder or tic syndromes (e.g. Tourette's) other behavioral disturbances like stereotypical language, motor or disinhibition occur [39-44]. Many of the differential diagnoses show great clinical overlap, especially bvFTD and psychiatric disorders, like schizophrenia [45-47].

The use of biomarkers in differentiating between FLS causes

After taking a detailed history and a physical exam, more discriminating instruments might be needed to differentiate between frontal lobe syndrome causes. Measuring CSF levels of Amyloid-beta, total Tau and phosphorylated Tau (p-tau) is mainly helpful to distinguish FTD from Alzheimer's disease (AD), but no specific pattern is found in other causes of FLS [48-53].

In psychiatric disorders like depression and schizophrenia CSF biomarker results have been found to vary between normal to slightly elevated tau and p-tau levels compared to healthy controls but significantly lower than seen in AD, which could possibly be explained by co-occurrence of AD pathology in elderly populations [54-56] .

Structural magnetic resonance imaging (MRI) scanning of the brain reveals many of the above mentioned causes of the FLS. Posterior cortical or medial temporal lobe atrophy in Alzheimer's disease or disproportional lobar atrophy in 50-70% of the bvFTD patients for instance [57;58]. Nonetheless, some neurodegenerative or psychiatric do not show structural brain changes or, if they do so, these show overlap with other disorder [57;59]. If AD or DLB pathology is suspected a brain PET Pittsburgh compound B (PIB) or Dopamine Transporter (DaT) SPECT respectively may help to differentiate [37]. Fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) with visual rating may detect hypometabolism in the frontal lobes at a stage structural damage is not yet notable[37]. In bvFTD sensitivity rises to a range from 70% (MRI) to 81% up till 90% when [^{18}F]FDG-PET is added [57;60]. Alternatively, it has been suggested that MR perfusion scanning gives similar information as an FDG-PET, without the exposure to radiation and therefore might be the preferred imaging modality [37].

Functional networks and their clinical correlates

In the recent years several large-scale functional connectivity patterns have been identified by functional neuroimaging techniques. Spatially distinct brain regions with co-varying resting state fMRI signals are considered to be functionally connected and this way fMRI reveals functional networks [61]. Overall, functional and structural connectivity in the human brain is believed to be strongly correlated and several studies have shown a direct association between functional and structural connectivity [62]. Connectivity studies have provided confirmation of the frontal networks that were already suspected on the bases of the anatomically described fronto-subcortical circuits [45]. Two specific resting state functional networks have confirmed the link between the frontal cortex and the subcortical grey matter and are relevant when considering FLS [19;22;63]. The *salience network* is made out by linked structures in the anterior cingulate, the orbital frontoinsular cortex, paralimbic and subcortical structures (i.a. thalamus, hypothalamus, putamen, substantia nigra) [63;64]. The *executive control network* links the dorsolateral prefrontal cortex to subcortical regions (i.a. thalamus, nucleus caudatus) as well as the parietal neocortex

[63;64]. These two networks are involved in stressor-associated anxiety and behavior, integrating sensory data with internal stimuli, emotional homeostatic regulation, directing attention and controlling oneself within a context [63]. Disruption of the salience network activity has been demonstrated in various disorders like bvFTD, schizophrenia or autism spectrum disorders [64;65].

Instruments to measure frontal lobe dysfunction

Many test have been developed to evaluate executive functioning and other frontal lobe functions. Within a neuropsychological test battery a selection of specific executive function tests can be made, like the Trail making tests (TMT-A and TMT-B), letter (and category) fluency list generation, the Rey complex figure test or the Wisconsin Card Sorting Test [37]. Some test focus more specifically on inhibitory functioning, like the Iowa Gambling Test, the Stroop test or the Hayling test of sentence completion [37;66]. Reduced abstraction can be measured with the similarities subtest of the Wechsler Adult Intelligence Scale or the rule shift cards of the Behavioural Assessment of the Dysexecutive Syndrome [37;67]. To evaluate social cognition and emotion recognition tests like the Faux-Pas, Reading the Mind in the Eyes test or the Ekman faces have been developed [68;69]. Alternatively, short bedside tests, like the Frontal Assessment Battery, are widely spread used [70]. New alternatives are developed that aim to replicate daily life activities to enhance ecological validity like the Virtual Kitchen Test [71]. And, since in many patients disease insight is lacking due to frontal dysfunction, the behavior changes can be quantified using informant based questionnaires like the Frontal Behavioral Inventory or the Stereotypy Rating Inventory [72;73].

DISCUSSION

The function of the frontal lobes and the related frontal lobe syndrome has been described in detail relatively late in history. The fronto-subcortical circuits were examined carefully and have repeatedly shown to correlate to clinical syndromes: i.e. the *dorsolateral prefrontal,* the *orbitofrontal circuit* and the *anterior cingulate circuit.* Damage to these circuits is associated with three distinct frontal behavioral syndromes: a dysexecutive, a disinhibited and an apathetic syndrome, respectively [18;19;21;22]. The symptoms associated with these behavioral syndromes (in short, resulting in the lost ability to integrate internal and external stimuli and direct attention into appropriate and adequate behavior) and their anatomical correlated have been confirmed in functional connectivity studies [63]. The salience and the executive control network are important for maintaining a homeostatic affective and behavioral status. The frontal cortical and subcortical structures, forming functional networks, are essential for deciding what to do (or not to do) next [63;64].

After it became increasingly clear that not all FLS symptoms are caused by dysfunction in the frontal cortex itself, it has been proposed to use the term 'executive dysfunction syndrome' instead [24;67]. The notification that the frontal lobe syndrome can be caused by damage to the basal ganglia or white matter as well is valid and the term FLS has its limitations. Nonetheless, the term 'executive dysfunction syndrome' seems to narrow to cover the full spectrum of symptoms. Executive functioning incorporates planning, organizing, making judgment in difficult situations as well as a supervisory system weighing previously gained information in novel situations. Some authors try to incorporate many frontal behavioral symptoms within the dysexecutive syndrome [6;19;24;74;75]. Nevertheless, the frontal lobes not only integrate internal and external stimuli into adequate choices, attention and behavior, but also have a major impact on mood, motivation, the ability to feel empathy and (the lack of) insight [21;22]. Furthermore, the dysexecutive symptoms seem to correlate specifically with only the dorsolateral prefrontal circuit, so it seems logical to reserve this term for this specific sub-syndrome [22;75].

The term 'frontal lobe syndrome' seems more suited for describing the broad spectrum of behavioral and executive impairments associated with fronto-subcortical dysfunction, provided that the term is not just reserved for cortical dysfunction, but may be used for all structural disruptions and functional hypo-activity within the fronto-subcortical circuits, leading to a frontal behavioral or dysexecutive syndrome.

The clinical approach of diseases causing a frontal lobe syndrome has made some progress in the recent years. Imaging techniques like MRI have improved the diagnostic process and made the identification of neurological diseases easier and more precise. Alzheimer's disease, the most common neurodegenerative disease, and it's accompanying amyloid-deposition can be identified by CSF or imaging examination. Nonetheless, especially the distinction between bvFTD on the one hand and psychiatric diagnoses (e.g. depression, schizophrenia and many others) on the other, remains challenging since these groups show great clinical overlap, but both lack structural imaging abnormalities or specific disease biomarkers [46;76]. Moreover, most instruments measuring frontal lobe functions in bvFTD have been tested against dementia patients or healthy controls as a control group, instead of the clinically more relevant psychiatric diagnosis [45;76].

The hypothesized overlap in functional localization of bvFTD and psychiatric disorders has increasingly been confirmed by changes in network activity. The results are also indicative of clinical frontal syndrome severity correlating with loss of connectivity in the salience network [65]. These new developments are exciting and give insight in the pathophysiology of the frontal lobe syndrome. For instance, specific genetic subtypes of bvFTD have shown to express specific fMRI patterns and presymptomatic mutation carriers showed worsening of the salience network connectivity with advancing age [77]. How genetic and epigenetic factors influence the large-scale brain connectivity and how they increase or decrease specific psychiatric and neurological disorders needs to be further investigated.

Given the heterogeneity of the FLS, future treatment research will probably focus on specific etiologic subtypes, identified by biological measures and genetic testing, but it remains interesting to involve the large scale networks in order to maintain a disease transcending overview. Apart from a clear autosomal dominant pathogenic mutation in some FLS causes, there might be a shared susceptibility for some of the differential diagnosis disorders [47]. Another focus of future research will be the improvement of pharmacological treatment options. For the neurodegenerative disorders no disease course changing treatment exists yet, so the focus of present pharmacological therapy is mainly symptomatic relief. Psychiatric disorders are treated according to their categorized treatment protocols, but in some cases antidepressants or antipsychotics have an off-label effect in other disorders. Some studies have shown a positive effect of serotonin selective reuptake inhibitors or Trazodone on the symptoms in bvFTD [37]. Cholinesterase inhibitors might be effective in AD, but no acetylcholine deficiency has been demonstrated in bvFTD [45]. Antipsychotics may be helpful in patients with disinhibition or compulsive behavior, but it must be noted that especially patients with a underlying neurodegenerative disease might be predisposed towards harmful side effects [45].

Since these pharmacological interventions are limited and no disease-modifying treatment is currently available, non-pharmacological interventions may provide a mean to decrease symptom severity as well as caregiver burden [78;79]. On the one hand, patients can be learned compensatory behavior. Depending on the affected cognitive domains, especially memory function, methods focusing on adaptation of the patients reaction to certain environmental cues have shown be effective [78;79]. On the other hand, since many patients with frontal dysfunction develop utilization behavior up till some extend or even an excessive dependence upon environmental cues (sometimes referred to as an 'environmental dependency syndrome'), modifying the environment may be of substantial benefit [79]. Nonetheless, well-designed large-scale research to examine the effects of non-pharmacological interventions on behavioral symptoms of FTD are needed [80].

CONCLUSION

The term frontal lobe syndrome (FLS) has evolved over the last two centuries. Specific clinical features, integrating internal and external stimuli and directing attention with appropriate and adequate behavior as a result, have been repeatedly associated with the fronto-subcortical circuits. Dysfunction within those circuits result in the failure to adjust ones behavior appropriately in response to external contingencies. Structural and functional imaging have provided substantial evidence for these clinico-functional anatomical correlations.

REFERENCE LIST

1. Filley CM. Chapter 35: the frontal lobes. *Handb Clin Neurol* 2010;95:557-70.

2. Robison RA, Taghva A, Liu CY, Apuzzo ML. Surgery of the mind, mood, and conscious state: an idea in evolution. *World Neurosurg* 2012;77:662-86.

3. Macmillan MB. A wonderful journey through skull and brains: the travels of Mr. Gage's tamping iron. *Brain Cogn* 1986;5:67-107.

4. Pick A, Girling DM, Berrios GE. On the symptomatology of left-sided temporal lobe atrophy. Classic Text No. 29. (Translated and annotated by D.M. Girling and G.E. Berrios.). *Hist Psychiatry* 1997;8:149-59.

5. Hodges. *Frontotemporal dementia syndromes*. Cambridge University Press, 2007.

6. Meyer A. The frontal lobe syndrome, the aphasias and related conditions. A contribution to the history of cortical localization. *Brain* 1974;97:565-600.

7. Tierney AJ. Egas Moniz and the origins of psychosurgery: a review commemorating the 50th anniversary of Moniz's Nobel Prize. *J Hist Neurosci* 2000;9:22-36.

8. Freeman W, Watts JW. Prefrontal Lobotomy: The Surgical Relief of Mental Pain. *Bull N Y Acad Med* 1942;18:794-812.

9. Freeman W. Prefrontal lobotomy: final report of 500 Freeman and Watts patients followed for 10 to 20 years. *South Med J* 1958;51:739-45.

10. Feldman RP, Goodrich JT. Psychosurgery: a historical overview. *Neurosurgery* 2001;48:647-57.

11. Catani M, ffytche DH. The rises and falls of disconnection syndromes. *Brain* 2005;128:2224-39.

12. Miller B, Cummings J. *The human frontal lobes*. The Guilford Press, 2007:3-666.

13. Benton AL. Differential behavioral effects in frontal lobe disease. *Psychologia* 1967;6:53-60.

14. Lhermitte F, Pillon B, Serdaru M. Human autonomy and the frontal lobes. Part I: Imitation and utilization behavior: a neuropsychological study of 75 patients. *Ann Neurol* 1986;19:326-34.

15. Lhermitte F. Human autonomy and the frontal lobes. Part II: Patient behavior in complex and social situations: the "environmental dependency syndrome". *Ann Neurol* 1986;19:335-43.

16. Nauta WJ. The problem of the frontal lobe: a reinterpretation. *J Psychiatr Res* 1971;8:167-87.

17. Cummings JL. Behavioral disorders associated with frontal lobe injury. In: *Clinical neuropsychiatry*. 1985:57-67.

18. Stuss DT, Kaplan EF, Benson DF, Weir WS, Naeser MA, Levine HL. Long-term effects of prefrontal leucotomy--an overview of neuropsychologic residuals. *J Clin Neuropsychol* 1981;3:13-32.

19. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986;9:357-81.

20. Damasio, Geschwind. Anatomical localisation in clinical neuropsychology. In: *Handbook of clinical neurology*. Elsevier science 1985.

21. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. *Dialogues Clin Neurosci* 2007;9:141-51.

22. Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol* 1993;50:873-80.

23. Godefroy O. Frontal syndrome and disorders of executive functions. *J Neurol* 2003;250:1-6.

24. Godefroy O, Azouvi P, Robert P, Roussel M, LeGall D, Meulemans T. Dysexecutive syndrome: diagnostic criteria and validation study. *Ann Neurol* 2010;68:855-64.

25. Mackenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday G, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJM, Kumar-Singh S, Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ, Mann DMA. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol* 2010;119:1-4.

26. Balasa M, Gelpi E, Antonell A, Rey MJ, Sanchez-Valle R, Molinuevo JL, Llado A. Clinical features and APOE genotype of pathologically proven early-onset Alzheimer disease. *Neurology* 2011;76:1720-5.

27. Woodward M, Jacova C, Black SE, Kertesz A, Mackenzie IR, Feldman H. Differentiating the frontal variant of Alzheimer's disease. *Int J Geriatr Psychiatry* 2010;25:732-8.

28. Johnson DK, Watts AS, Chapin BA, Anderson R, Burns JM. Neuropsychiatric profiles in dementia. *Alzheimer Dis Assoc Disord* 2011;25:326-32.

29. Staekenborg SS, Su T, van Straaten EC, Lane R, Scheltens P, Barkhof F, van der Flier WM. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. *J Neurol Neurosurg Psychiatry* 2010;81:547-51.

30. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *J Neurol Neurosurg Psychiatry* 2003;74:1206-9.

31. McMurtray A, Clark DG, Christine D, Mendez MF. Early-onset dementia: frequency and causes compared to late-onset dementia. *Dement Geriatr Cogn Disord* 2006;21:59-64.

32. Gislason TB, Sjogren M, Larsson L, Skoog I. The prevalence of frontal variant frontotemporal dementia and the frontal lobe syndrome in a population based sample of 85 year olds. *J Neurol Neurosurg Psychiatry* 2003;74:867-71.

33. Donker KL, Boon AJ, Kamphorst W, Ravid R, Duivenvoorden HJ, Van Swieten JC. Frontal presentation in progressive supranuclear palsy. *Neurology* 2007;69:723-9.

34. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA, Kertesz A, Lee SE, Miller BL, Reich SG, Riley DE, Tolosa E, Troster AI, Vidailhet M, Weiner WJ. Criteria for the diagnosis of corticobasal degeneration. *Neurology* 2013;80:496-503.

35. Peric S, Mandic-Stojmenovic G, Stefanova E, Savic-Pavicevic D, Pesovic J, Ilic V, Dobricic V, Basta I, Lavrnic D, Rakocevic-Stojanovic V. Frontostriatal dysexecutive syndrome: a core cognitive feature of myotonic dystrophy type 2. *J Neurol* 2015;262:142-8.

36. Grossi D, Santangelo G, Barbarulo AM, Vitale C, Castaldo G, Proto MG, Siano P, Barone P, Trojano L. Apathy and related executive syndromes in dementia associated with Parkinson's disease and in Alzheimer's disease. *Behav Neurol* 2013;27:515-22.

37. Hoffmann M. The human frontal lobes and frontal network systems: an evolutionary, clinical, and treatment perspective. *ISRN Neurol* 2013;2013:892459.

38. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res* 2002;53:647-54.

39. Mendez MF, Perryman KM, Miller BL, Swartz JR, Cummings JL. Compulsive behaviors as presenting symptoms of frontotemporal dementia. *J Geriatr Psychiatry Neurol* 1997;10:154-7.

40. Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2006;77:4-7.

41. Hill K, Mann L, Laws KR, Stephenson CM, Nimmo-Smith I, McKenna PJ. Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. *Acta Psychiatr Scand* 2004;110:243-56.

42. Mayberg H. Depression, II: localization of pathophysiology. *Am J Psychiatry* 2002;159:1979.

43. Saxena S, Brody AL, Maidment KM, Smith EC, Zohrabi N, Katz E, Baker SK, Baxter LR, Jr. Cerebral glucose metabolism in obsessive-compulsive hoarding. *Am J Psychiatry* 2004;161:1038-48.

44. Kremen WS, Seidman LJ, Faraone SV, Toomey R, Tsuang MT. Heterogeneity of schizophrenia: a study of individual neuropsychological profiles. *Schizophr Res* 2004;71:307-21.

45. Pressman PS, Miller BL. Diagnosis and management of behavioral variant frontotemporal dementia. *Biol Psychiatry* 2014;75:574-81.

46. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry* 2011;72:126-33.

47. Harciarek M, Malaspina D, Sun T, Goldberg E. Schizophrenia and frontotemporal dementia: shared causation? *Int Rev Psychiatry* 2013;25:168-77.

48. Mulder C, Verwey NA, van der Flier WM, Bouwman FH, Kok A, van Elk EJ, Scheltens P, Blankenstein MA. Amyloid-beta(1-42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. *Clin Chem* 2010;56:248-53.

49. van Harten AC, Kester MI, Visser PJ, Blankenstein MA, Pijnenburg YAL, Van der Flier WM, Scheltens P. Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. *Clin Chem Lab Med* 2011;49:353-66.

50. Verwey NA, Kester MI, Van der Flier WM, Veerhuis R, Berkhof H, Twaalfhoven H, Blankenstein MA, Scheltens And P, Pijnenburg YAL. Additional value of CSF amyloid-beta 40 levels in the differentiation between FTLD and control subjects. *J Alzheimers Dis* 2010;20:445-52.

51. Bian H, Van Swieten JC, Leight S, Massimo L, Wood E, Forman M, Moore P, de Koning I, Clark CM, Rosso S, Trojanowski J, Lee VMY, Grossman M. CSF biomarkers in frontotemporal lobar degeneration with known pathology. *Neurology* 2008;70:1827-35.

52. Pijnenburg YAL, Schoonenboom NSM, Rosso SM, Mulder C, Van Kamp GJ, Van Swieten JC, Scheltens P. CSF tau and Abeta42 are not useful in the diagnosis of frontotemporal lobar degeneration. *Neurology* 2004;62:1649.

53. Pijnenburg YAL, Schoonenboom SNM, Barkhof F, Knol DL, Mulder C, Van Kamp GJ, Van Swieten JC, Scheltens P. CSF biomarkers in frontotemporal lobar degeneration: relations with clinical characteristics, apolipoprotein E genotype, and neuroimaging. *J Neurol Neurosurg Psychiatry* 2006;77:246-8.

54. Blennow K, Wallin A, Agren H, Spenger C, Siegfried J, Vanmechelen E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? *Mol Chem Neuropathol* 1995;26:231-45.

55. Buerger K, Zinkowski R, Teipel SJ, Arai H, DeBernardis J, Kerkman D, McCulloch C, Padberg F, Faltraco F, Goernitz A, Tapiola T, Rapoport SI, Pirttila T, Moller HJ, Hampel H. Differentiation of geriatric major depression from Alzheimer's disease with CSF tau protein phosphorylated at threonine 231. *Am J Psychiatry* 2003;160:376-9.

56. Schonknecht P, Hempel A, Hunt A, Seidl U, Volkmann M, Pantel J, Schroder J. Cerebrospinal fluid tau protein levels in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2003;253:100-2.

57. Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol* 2007;64:830-5.

58. Knopman DS, Jack CR, Jr., Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Mercaldo ND. Brain and ventricular volumetric changes in frontotemporal lobar degeneration over 1 year. *Neurology* 2009;72:1843-9.

59. Davidson LL, Heinrichs RW. Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis. *Psychiatry Res* 2003;122:69-87.

60. Poljansky S, Ibach B, Hirschberger B, Manner P, Klunemann H, Hajak G, Marienhagen J. A visual [18F]FDG-PET rating scale for the differential diagnosis of frontotemporal lobar degeneration. *Eur Arch Psychiatry Clin Neurosci* 2011;261:433-46.

61. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, Beckmann CF, Adelstein JS, Buckner RL, Colcombe S, Dogonowski AM, Ernst M, Fair D, Hampson M, Hoptman MJ, Hyde JS, Kiviniemi VJ, Kotter R, Li SJ, Lin CP, Lowe MJ, Mackay C, Madden DJ, Madsen KH, Margulies DS, Mayberg HS, McMahon K, Monk CS, Mostofsky SH, Nagel BJ, Pekar JJ, Peltier SJ, Petersen SE, Riedl V, Rombouts SA, Rypma B, Schlaggar BL, Schmidt S, Seidler RD, Siegle GJ, Sorg C, Teng GJ, Veijola J, Villringer A, Walter M, Wang L, Weng XC, Whitfield-Gabrieli S, Williamson P, Windischberger C, Zang YF, Zhang HY, Castellanos FX, Milham MP. Toward discovery science of human brain function. *Proc Natl Acad Sci U S A* 2010;107:4734-9.

62. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol* 2010;20:519-34.

63. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 2007;27:2349-56.

64. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci* 2011;15:483-506.

65. Zhou J, Seeley WW. Network Dysfunction in Alzheimer's Disease and Frontotemporal Dementia: Implications for Psychiatry. *Biol Psychiatry* 2014;75:565-73.

66. Nathaniel-James DA, Fletcher P, Frith CD. The functional anatomy of verbal initiation and suppression using the Hayling Test. *Neuropsychologia* 1997;35:559-66.

67. Hanna-Pladdy B. Dysexecutive syndromes in neurologic disease. *J Neurol Phys Ther* 2007;31:119-27.

68. Diehl-Schmid J, Pohl C, Ruprecht C, Wagenpfeil S, Foerstl H, Kurz A. The Ekman 60 Faces Test as a diagnostic instrument in frontotemporal dementia. *Arch Clin Neuropsychol* 2007;22:459-64.

69. Gregory C, Lough S, Stone V, Erzinclioglu S, Martin L, Baron-Cohen S, Hodges JR. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain* 2002;125:752-64.

70. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000;55:1621-6.

71. Gamito P, Oliveira J, Caires C, Morais D, Brito R, Lopes P, Saraiva T, Soares F, Sottomayor C, Barata F, Picareli F, Prates M, Santos C. Virtual Kitchen Test. Assessing Frontal Lobe Functions in Patients with Alcohol Dependence Syndrome. *Methods Inf Med* 2014;53.

72. Milan G, Lamenza F, Iavarone A, Galeone F, Lore E, de Falco C, Sorrentino P, Postiglione A. Frontal Behavioural Inventory in the differential diagnosis of dementia. *Acta Neurol Scand* 2008;117:260-5.

73. Shigenobu K, Ikeda M, Fukuhara R, Maki N, Hokoishi K, Nebu A, Yasuoka T, Komori K, Tanabe H. The Stereotypy Rating Inventory for frontotemporal lobar degeneration. *Psychiatry Res* 2002;110:175-87.

74. Gilbert SJ, Burgess PW. Executive function. *Curr Biol* 2008;18:R110-R114.

75. Stuss DT, Alexander MP. Is there a dysexecutive syndrome? *Philos Trans R Soc Lond B Biol Sci* 2007;362:901-15.

76. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EGP, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, ehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134:2456-77.

77. Dopper EG, Rombouts SA, Jiskoot LC, den HT, de G, Jr., de K, I, Hammerschlag AR, Seelaar H, Seeley WW, Veer IM, van Buchem MA, Rizzu P, Van Swieten JC. Structural and functional brain connectivity in presymptomatic familial frontotemporal dementia. *Neurology* 2014;83:e19-e26.

78. Kortte KB, Rogalski EJ. Behavioural interventions for enhancing life participation in behavioural variant frontotemporal dementia and primary progressive aphasia. *Int Rev Psychiatry* 2013;25:237-45.

79. Lough S, Hodges JR. Measuring and modifying abnormal social cognition in frontal variant frontotemporal dementia. *J Psychosom Res* 2002;53:639-46.

80. Shinagawa S, Nakajima S, Plitman E, Graff-Guerrero A, Mimura M, Nakayama K, Miller BL. Non-pharmacological management for patients with frontotemporal dementia: a systematic review. *J Alzheimers Dis* 2015;45:283-93.