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# Frontotemporal dementia to Alzheimer's disease

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*Behavioral manifestations may dominate the clinical picture of the frontal variant of frontotemporal dementia (fv-FTD) for a long time before the appearance of true cognitive deficits. On the other hand, a deficit in the episodic memory domain represents the main manifestation of Alzheimer's disease (AD). Many behavioral disorders have been described in the clinical course of both FTD and AD; however, apathy and personality changes characterize frontal dementias, while depression dominates in AD, at least in the earlier stages. Depending on the distribution of neural damage, different patterns of noncognitive manifestations may be expected in different subtypes of FTD. Recent research on the social cognition deficit in FTD has offered new insights into the relationship between cognition and behavior, suggesting that some aspects of the behavioral changes in dementia may be generated by impairment in this domain.*

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The term frontotemporal dementia (FTD)[1-3] refers to a complex of behavioral-cognitive symptoms produced by progressive degeneration of the frontal and/or temporal regions.

The syndrome originally described by Pick,[4] and thus termed Pick's disease in the following decades, was characterized by atrophy and argentophilic intraneuronal inclusions (Pick's bodies). Indeed, the histopathological features of the frontal dementias are not distinctive, and a continuum towards other neurological conditions, such as the tauopathies or motor neuron diseases, has now been documented,[5,6] suggesting extensive pathological and etiological heterogeneity.

In spite of this, there is quite a large consensus that the clinical presentations of FTD should be restricted to three main subtypes principally reflecting the distribution of neuronal loss, ie, of atrophy, in the brain: (i) the behavioral or frontal variant (fv-FTD) due to prevalent prefrontal damage, dominated by behavioral symptoms and dysexecutive disorders; (ii) primary progressive aphasia (PPA),[7] characterized by a progressive nonfluent linguistic impairment associated with left perisylvian atrophy;[8] and (iii) semantic dementia (SD), in which a progressive agnosia for words and objects follows left anterior temporal lobe degeneration.[9]

Well-identified patterns of cognitive disorders, largely confined to the linguistic domain, characterize the onset of both PPA and SD, which are both generally complicated by the emergence of behavioral manifestations only at later stages.[10,11] On the other hand, the early manifestation of the frontal variant frequently involves noncognitive behavioral domains and personality changes that may dominate the clinical picture for a long time before true cognitive decline appears.[12] FTD is considered to be the second most frequent type of degenerative dementia.[13] However, it should be taken into con-

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## Selected abbreviations and acronyms

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| *AD* | *Alzheimer's disease* |
| *DLB* | *dementia with Lewy bodies* |
| *FTD* | *frontotemporal dementia* |
| *fv-FTD* | *frontal variant of frontotemporal dementia* |
| *SD* | *semantic dementia* |
| *TofM* | *theory of mind* |

sideration that the noncognitive nature of the onset manifestations in the frontal variant probably contributes to an underestimation of its true prevalence.[14,15] Regarding the most frequent degenerative dementia, Alzheimer's disease (AD), a cognitive deficit, principally in the episodic memory domain, represents its typical onset and remains the core feature of the syndrome for the entire clinical course; noncognitive disorders are only occasionally early symptoms, but become more frequent and stable as the disease progresses.[16]

In the past, the cognitive disorder has by far been the main focus of clinical studies on AD. Only in the last two decades has systematic investigation of the noncognitive manifestations of this type of dementia become possible, thanks to the publication of structured scales for their assessment.[17,18]

One could say that clinical research on cognitive-behavioral disorders in dementia has followed different routes in AD and FTD. Although behavioral manifestations have been reported in AD since its original description, it has been considered to be a disease involving primarily the cognitive systems, and thus "dementia" by definition. Interest in the behavioral disorders is more recent. FTD was initially mistaken for AD and for psychiatric diseases. It has only recently been rediscovered,[19,20] and because of the presence of a clear noncognitive component in the symptomatology (at least in the frontal variant) it has been, since the earliest reports, considered to be a behavioral-cognitive syndrome.

Noncognitive disorders in AD have been diffusely investigated, and a large number of descriptions have become available in the past decade. However, most reports on the behavioral disturbances in FTD have not specifically focused on this type of dementia; they are, in fact, comparative studies between AD and FTD. In addition, since the scales for assessing the behavioral deficit were originally devised for AD, it is likely that disorders more specific to FTD were not sufficiently identified until diagnostic tools were devised explicitly for FTD.

For many reasons, studies of behavioral disturbances in dementia are often difficult to compare. First of all, reports largely reflect the tool adopted for assessing the syndrome. In addition, groups in which studies have been conducted may be heterogeneous, either for disease severity and clinical expression, or the selection criteria adopted to group the patients. Misdiagnoses seriously hinder achieving a reliable description and a quantification of the behavioral manifestation. The use of standard diagnostic criteria for patient selection does not in fact guarantee a correct diagnosis,[21,22] and autopsy confirmation should be obtained. However, only in a minority of reports is the diagnosis supported by pathology. For example, inclusion of patients with dementia with Lewy bodies (DLB) in AD groups is likely to produce an overestimation of the frequency of hallucinations in this form of dementia.

Finally, studies not corroborated by pathological data are necessarily tautological to some extent. For example, since the presence of behavioral disorders constitutes a diagnostic criterion for FTD,[3] only FTD patients with behavioral disorders are selected for inclusion, and this could artificially increase their true frequency. At the same time, symptoms not specifically mentioned in the diagnostic criteria adopted are misidentified, and their occurrence is thus underestimated.

The assessment of behavioral disturbances also suffers from other limitations compared with the assessment of cognitive disorders. Symptom detection and quantification are not based on direct observation of patients and mostly rely on caregivers' reports, and the influence caregivers' variables may have on symptom description and quantification is not always adequately taken into account.

## Noncognitive disorders in AD and FTD: a brief review

### AD

Many behavioral disorders have been reported in AD patients, ranging from mood changes to psychoses and to modification in social conduct.[18,23,24] There may be several explanations for this heterogeneity. First, the disease itself is heterogeneous in its noncognitive manifestations. Occasionally, noncognitive disorders may characterize the onset.[25] The behavioral manifestation, however, may emerge at any stage of the disease, and it tends to worsen

over time; fluctuations have also been reported.[26] Thus, presence and severity of symptoms largely depend on the stage at which the patient has been observed. Second, methodological reasons may also contribute to heterogeneity. Only in the last decade have symptom detection and quantification been evaluated by means of structured or semistructured scales, validated in large groups of patients. This has allowed for more objective descriptions of symptoms, as well as attempts to compare different reports. Nevertheless, the prevalence rate seems to be still largely influenced by the clinical diagnostic criteria used for evaluation.[27] Finally, since a few reports are corroborated by postmortem pathological confirmation, misdiagnoses should be considered as a potential cause of heterogeneity. For example, if the temporal variant of FTD is erroneously included in AD dementia groups (differential diagnosis may not be easy at earlier stages) manifestations of this type of dementia might, indeed, be considered proper to AD.

There is some agreement in considering major depression and, in general, the affective disorders, as common symptoms either at the onset[28] and throughout the entire clinical course of AD.[29-34] Pathological anxiety is also reported.[35] The average frequency of depression is approximately 40% (see ref 36 for a review) even if its prevalence seems to decrease over time.[37] Apathetic behavior, which is significantly correlated with but distinct from depression,[38,39] also seems to be widely represented in AD[40] and is considered as a factor predicting more aggressive dementia.[41] Psychotic symptoms, and specifically delusions and hallucinations, are also described as frequent manifestations in the clinical course of AD,[42-45] mostly in later stages.[46] Paranoid misidentifications, such as in Capgras' syndrome, have also been occasionally reported.[47]

The emergence of psychotic symptoms is currently considered to predict faster cognitive and functional decline[48-53] as well as increased risk of mortality,[54] even if some studies lead to different conclusions.[55] A relationship between psychotic symptoms, age at onset, and disease duration has also been pointed out by some authors (see ref 56 for a review). Currently, there are descriptions of other noncognitive symptoms, primarily pathological conduct, which merge into a large variety of syndromes.[57] Agitation, aggression,[58-60] aberrant motor behavior and wandering,[57] sleep and eating disorders,[61,62] and impaired insight[63] are frequently described in association with depression or psychoses.

## FTD

As previously mentioned, most research on noncognitive disorders in FTD consists of comparative studies between the two most frequent forms of dementia, AD and FTD. Only in more recent years have comparisons been made with vascular dementia,[64,65] DLB, or Parkinson's disease.[66]

From the time of the first reports on FTD,[68] alteration of social conduct, reduced insight, personality changes, and apathy have been described as core features of the disease and have been included in the diagnostic criteria.[3] Behavioral alterations seem generally more severe in FTD than in AD[69-71] and a relationship with patient's gender and age has been hypothesized.[72] Descriptions are quite consistent throughout the literature, in spite of the use of different scales for symptom detection.

Not only severity, but also symptom patterns, seem to differentiate the two dementias. Both "negative" symptoms such as apathy, loss of insight, indifference, and personal neglect, and "positive" symptoms such as disinhibition, impulsivity, euphoria, and aberrant motor behavior prevail in FTD,[14,15,64,72-74] while depression is confirmed to be more characteristic of AD.[72] Reports of apathy are especially consistent in FTD[74-77] and are documented throughout the disease course.[78] Repetitive behavior, ranging from motor stereotypes to complex obsessive-compulsive disorders, is also reported as a dominant manifestation,[10,71,74] and, according to some authors, as the presenting symptom.[79] Eating disorders are also considered typical in this dementia[78] and more common than in AD.[64,65,76,80] Changes in food preferences towards sweet foods and an increase in appetite[10,64,81,82] have been reported in studies providing more detailed descriptions.

### Frontal vs temporal variant and right vs left atrophy in FTD

From the onset, pathological processes may be distributed asymmetrically in the frontal region,[83] determining variability in the clinical manifestation. Behavioral disorders do not seem significantly different in the frontal vs temporal variant (semantic dementia)[10,71,84] or PPA,[11] even if they tend to manifest earlier in the frontal variant.[10,11] However, some differences have been pointed out. For example, apathy[74,84] and stereotypes[74] are described as being more frequent in the frontal compared with the temporal variant, while sleep disorders[84]

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and a complex disorder such as the Kluver-Bucy syndrome, dominated by oral exploratory behavior, hyperphagia, and hypersexuality,[80] are more likely to manifest in the temporal variant.[80]

Studies on FTD do not generally take into consideration the issue regarding left vs right asymmetry of atrophy distribution. Indirect evidence about the characteristics of the behavioral syndrome in asymmetric-left atrophy can be obtained by observing patients with SD and PPA in which linguistic disorders suggest left-sided involvement. Similarly, a few papers are also available on FTD patients in whom cognitive symptoms suggest a prevalent right pathology. In general, although the pattern of cognitive impairment is largely consistent with the distribution of atrophy,[69,85] mostly when the diagnosis of PPA or semantic dementia (temporal variant) is made,[10] the influence of left-right asymmetry is less predictable in the behavioral domain. Only a few studies have specifically compared the behavioral syndrome of patients with prevalent left or right hemispheric atrophy. Disinhibition,[69,84] but also anxiety, depression, and eating disorders[84] have been associated with right-asymmetric frontotemporal atrophy. Greater attention has been given to patients with right frontotemporal pathology in studies investigating "high-level" activities that might be located at the interface between cognition and behavior, such as activities related to social cognition.[86,87] This issue will be discussed later.

## Impairment of different cortical subcortical prefrontal circuits: different cognitive-behavioral syndromes?

Three cortical subcortical circuits are supposed to underlie cognition and behavior in the prefrontal lobe. While the dorsolateral prefrontal circuit is postulated to be involved in cognitive activities proper, primarily planning and attention, the orbitofrontal and anterior cingulate (dorsomedial) circuits are likely involved in behavior. In particular, social cognition and empathy require the integrity of the orbitofrontal circuit, while motivation is accomplished by the anterior cingulate circuit. It is plausible that degeneration involves these neural subsystems in disease evolution differently, giving rise to different cognitive-behavioral patterns. Indeed, this is confirmed by clinical evidence. For example, it is well known that the behavioral manifestations greatly precede the cognitive deficits in some patients, and this is to some extent consistent with the relative preservation, in early stages,

of the dorsolateral circuit. Functional studies conducted in fv-FTD are also consistent with this view. Metabolic involvement of separate brain clusters has recently been demonstrated.[88] The metabolic involvement of the lateral and medial prefrontal cortex has been related to impaired cognitive abilities (memory and executive ability),[88] while an orbitofrontal dysfunction has been correlated to behavioral disorders such as disinhibition and apathy.[89]

## Relationship between cognitive and noncognitive symptoms in dementia

The relationship between cognitive and behavioral disorders is a central issue in all types of dementia. However, while studies on AD are mostly descriptive and focused on clinical aspects, recent studies on FTD are more speculative.

Although there is little evidence suggesting that the cognitive and behavioral manifestations in AD are independent of each other,[90] many studies report data in support of a relationship (at least quantitative) between the severity of cognitive and behavioral syndromes. For example, the severity of the behavioral disorders is predicted by the severity of the cognitive deficit.[91] Further, the presence of delusions and hallucinations has been considered predictive of a more severe cognitive disorder, and in general of a faster dementia evolution.[26,42,44,53,54,92] On the other hand, there is some evidence that in more severe dementia depression is less severe.[57] However, research primarily reports quantitative data, and only occasionally have hypotheses been advanced on a possible causal relationship between specific cognitive deficits and specific patterns of behavioral manifestations. Reduced ability on cognitive tasks sensitive to frontal lobe damage seems to be associated with a higher risk of psychotic symptoms in AD,[43,48] supporting the hypothesis that symptoms such as hallucinations and delusions could be produced by pathological frontal circuitry. Correlation between "frontal" tasks and psychotic symptoms has also been demonstrated in patients with FTD,[93] confirming that, independently of the type of dementia, frontal lobe involvement is the main requisite for the appearance of behavioral manifestations. Generally, however, studies do not explicitly take into account the potential cause-effect relationship between the two types of manifestations. Namely, although hypothesized, it has never been specifically explored

whether cognitive and noncognitive disorders can both be traced back to the same neural damage, or whether behavioral disorders might to some extent represent a "reaction" to the cognitive deficit. Indeed, it is likely that any limitation of cognitive resources could reduce a patient's ability to efficiently react to environmental stimulation in order to generate adequate behavioral responses. The memory disorder, to mention the most common example, typical of AD but also frequent in other types of dementia, might produce such severe functional limitation as to generate reactive depression in amnesic subjects with good insight.

**Theory of mind and behavior in FTD**

The hypothesis of a direct relationship between cognition and behavior in FTD is now currently proposed in the neuropsychological literature. In particular, it has been proposed that the impairment of "high-level" competences of the frontal lobe might generate behavioral changes, mostly in personality and social conduct. Particular attention has been devoted to the theory of mind (TofM). TofM is the ability to make inferences about others' mental states, thoughts, and feelings in order to predict and understand their behavior. TofM is strictly related to the concept of "empathy," that is, the ability to spread emotions to other people and to understand other people's emotions. A deficit in TofM, originally proposed to account for developmental disorders in social cognition of subjects affected by pathologies such as autism or Asperger's syndrome,[94,95] could also explain some aspects of the pathological behavior typical of patients with FTD. The effects of frontal lobe damage on behavior, and in particular of damage in the orbital and ventral regions, have long been known.[96] The neurocircuitry of TofM has been delineated by both lesional and functional studies. There is basic agreement in considering the amygdala[97] and the orbitofrontal cortex,[95] and also the medial prefrontal cortex[98] as the anatomical base for TofM (see also ref 99). A few reports have specifically taken into consideration the relationship between impaired TofM and behavioral disorders in patients with FTD. Gregory et al[100] demonstrated a significant negative correlation between the score obtained on the more sophisticated TofM tasks and the Neuropsychiatric Inventory (NPI) in FTD (but not in AD). They interpreted this finding as supporting the hypothesis that some aspects of the changes in interper-

sonal behavior typical of this pathology might be caused by impaired TofM. Interestingly, confirming a previous report,[101] performance on TofM tasks was largely independent of performance on tasks measuring "conventional" cognitive frontal abilities, first of all, executive tasks. Correlation between TofM and NPI, as well as dissociation between TofM and executive functions (see also ref 97), suggests that TofM tasks should not be considered simply as a measure of the cognitive skill of the frontal lobe, namely of executive function. Rather, they should be considered as reflecting the ability to understand mental states, crucial for generating normal interpersonal behavior. It has also been demonstrated that the reduced competence shown by FTD patients in understanding emotions (empathy) and social transgressions is not fully accounted for by the documented impairment in executive tasks, confirming the independence of social and cognitive abilities.[102] The recently formulated hypothesis on the existence of dissociable emotional and cognitive components of TofM[103] could also contribute to a better interpretation of the relationship between cognition and behavior in FTD.

**Metacognition and behavior in FTD**

Metacognition refers to high-level processing that consists of planning, self-evaluation, and self-monitoring of cognitive activities. Deficits in self-regulatory behavior, deriving from a lack of metacognitive control on executive abilities, have been related to prefrontal lesions. Recently, this aspect was investigated in patients with FTD, and mostly patients with the frontal variant showed poor self-awareness and self-knowledge, not only in cognitive but also in emotional and social domains.[87]

## Conclusion

FTD and AD are both characterized by a wide range of behavioral disorders. However, in contrast to AD, in FTD they may manifest when cognition is still relatively preserved. This allows for their observation without the "noisy" effects of the cognitive impairment. The neural correlates of noncognitive manifestations are more identifiable in FTD, and refer to specific cortical subcortical circuits in the prefrontal regions. Thus, "frontal" behavioral syndromes might be viewed as "system" pathologies and might offer information complementary to that derived from subjects with focal lesions. For these rea-

sons, studies on FTD can make an important contribution to defining the neural basis of human behavior, and also offer a model for studying behavioral disorders in other forms of dementia.

From the clinical point of view, the possibility of identifying specific patterns of cognitive-behavioral symptoms would be very relevant in the differential diagnoses of dementia, mostly in the absence of reliable biological markers.

Newly proposed investigations in the social cognition domain such as TofM, but also metacognition[87] or decision-making,[104] may offer further opportunities for interpreting the nature of the behavioral manifestations and their relationship to cognitive disorders. The correlation some authors have found between tasks exploring social cognition, primarily TofM, and standardized measures of behavioral impairment, has a potentially useful clinical application. Until now, detection and quantification of behavioral changes have relied almost exclusively on caregivers' reports in structured questionnaires aimed toward defining specific symptoms or syndromes. Quantifying the severity of the social cognition disorder could provide a direct measure of the severity of the behavioral manifestation in dementia. This perspective should encourage the development of specific test batteries for investigating this area. ❑

### Desde la demencia frontotemporal a la Enfermedad de Alzheimer

*Previo a la aparición de los verdaderos déficits cognitivos, las manifestaciones conductuales pueden dominar por un largo tiempo el cuadro clínico de la variante frontal de la demencia frontotemporal (DFT-vf). Por otra parte, un déficit en el área de la memoria episódica representa la principal manifestación de la Enfermedad de Alzheimer (EA). Se han descrito muchos trastornos conductuales durante el curso clínico tanto de la DFT como de la EA; sin embargo, la apatía y los cambios de personalidad caracterizan a las demencias frontales, mientras que la depresión domina en la EA, al menos en las primeras etapas. Dependiendo de la distribución del daño neural, se pueden esperar diferentes patrones de manifestaciones no cognitivas en los diferentes subtipos de DFT. Investigación reciente sobre el déficit cognitivo social en las DFT ha entregado nuevos conocimientos acerca de la relación entre cognición y conducta, lo que sugiere que algunos aspectos de los cambios conductuales en la demencia pueden ser generados por deterioro en esta área.*

### De la démence frontotemporale à la maladie d'Alzheimer

*Des signes comportementaux peuvent dominer le tableau clinique de la variante frontale de la démence frontotemporale (vf-DFT) longtemps avant l'apparition des véritables déficits cognitifs. Par ailleurs, un déficit au niveau de la mémoire épisodique constitue le symptôme principal de la maladie d'Alzheimer (MA). L'évolution clinique de la DFT et de la MA comporte de nombreux troubles comportementaux ; l'apathie et les changements de personnalité caractérisent les démences frontales, alors que la dépression prévaut dans la MA, au moins aux stades précoces. Différents schémas de troubles non cognitifs peuvent se manifester dans des sous-types multiples de DFT, selon la localisation des lésions nerveuses. Une nouvelle réflexion sur le lien entre la cognition et le comportement, grâce à une recherche récente sur le déficit en cognition sociale dans la DFT, suggère que certains aspects des transformations comportementales au cours de la démence pourraient être provoqués par des détériorations dans ce domaine.*

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