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The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia

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Abstract

A personality and behavioral disorder is an important and defining feature of frontal lobe dementia (FLD) or frontotemporal degeneration (FTD). The diagnosis usually depends on the progressive development of various behavioral symptoms rather than a set of neuropsychological measures. Quantification of the personality–behavior disorder is important for standardizing the diagnosis. An inventory was constructed to capture the major positive and negative behaviors and personality change, and it was administered prospectively to caregivers of 108 patients in a cognitive neurology clinic, at the time of first diagnostic assessment. The prevalence and extent of behavioral abnormality was quantitated in the clinic population of FLD, vascular dementia (VaD), Alzheimer's disease (AD), primary progressive aphasia (PPA), and depressive disorder (DD) patients. The mean scores of FLD patients were significantly above all other groups. Scores in VaD were also higher than in AD, PPA, and DD. Interrater reliability (Cohen's kappa of .90) and item consistency (a Cronbach alpha of .89) were both high. *Perseveration*, *indifference*, *inattention*, *inappropriateness*, and *loss of insight* rated highest in FLD, significantly different from all other groups. *Apathy*, *aspontaneity*, *inflexibility*, *disorganization*, *impulsivity*, *personal neglect*, and *poor judgment* were also significantly higher in FLD. Discriminant function correctly classified 92.7% *versus* all other patients (NON-FLD) in the study. A total of 18.8% of VaD patients were misclassified as FLD. *Indifference*, *alien hand*, and *inappropriateness* were the highest discriminant functions. *Perseveration* and *verbal apraxia* were important discriminatory items for FLD and PPA, respectively. The FBI is a standardized behavioral inventory useful to diagnose FLD, to differentiate it from other dementias, and to quantify the behavior disorder.
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Keywords: Frontotemporal dementia, Pick's disease, Frontal Behavioral Inventory

INTRODUCTION

Personality and behavioral changes are often the presenting features of Pick's disease (PiD) or frontal lobe dementia (FLD) in contrast to Alzheimer's disease (AD), which begins with memory deficit. Frontotemporal degeneration (FTD) has become a term widely used, since the Lund/Manchester group published consensus criteria (Brun et al., 1994). The abbreviation of FLD will be used here to distinguish the personality–behavior disturbance, even though it is recognized that temporal lobe degeneration is often a feature. The core features of FTD or FLD were defined as disinhibition, loss of insight, apathy, disorganization, aspontaneity, indifference, loss of personal hygiene, mental rigidity, perseveration, hyperorality, and utilization behavior with preserved visuospatial abilities (Lund and Manchester Groups, 1994). A further consensus paper for frontotemporal lobar degeneration (FTLD) provided refinements on the checklist of core features and exclusions (Neary et al., 1998).

Some descriptive studies have utilized noncognitive behavioral changes to differentiate between AD and PiD (Mendez et al., 1993), as well as AD and FLD (Lopez et al., 1996; Mendez et al., 1996; Sjogren et al., 1997). Gustafson and Nilsson attempted to separate FLD and PiD from AD by quantitating the items typical of PiD and those of AD and comparing their relative weight (Gustafson & Nilsson, 1982). They found that early disinhibition, irritability, dysphoria, confabulation, and echolalia distinguished PiD. A retrospective questionnaire was used to correlate diagnostic features with autopsy findings in AD and FLD to verify the diagnostic features by autopsy (Barber et al., 1995). FTD pa-

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tients were distinguished by disinhibition, lack of insight, empathy, social inappropriateness, and mutism. Recent studies were aimed at investigating behavior in FLD and AD using the Neuropsychiatric Inventory (Binetti et al., 1995; Cummings et al., 1994; Levy et al., 1996; Rozzini et al., 1997). Another retrospective study considered any of the five of the core diagnostic features from the Lund/Manchester criteria necessary for the diagnosis of FTD (Gregory & Hodges, 1996). A semistructured interview with caregivers of various dementia patients found overlap, but good discrimination of FTD from AD and VaD based on total ratings of psychiatric symptoms (Lebert, 1996). A caregiver inventory specifically designed to operationalize and quantify the personality and behavior disorder of FLD or PiD was constructed (Kertesz et al., 1997), and further standardization is described here.

Primary progressive aphasia (PPA) is also a recently defined clinical syndrome, characterized by language deficit in the first 2 years of the disease (Mesulam, 1987). Pick's original patient with lobar atrophy was also aphasic (Pick, 1892), and PPA has been shown to have a similar course, eventual outcome, and pathology to FLD (Kertesz et al., 1994). Independent daily living and overall behavior are preserved longer in PPA when compared to AD and FLD but may be affected in the later stages of either disease. Initially, agrammatical, nonfluent, and at times semantic language deficits overshadow minor behavioral and frontal lobe deficits. Eventually the features of FLD and progressive language disorder overlap. In addition, many patients develop extrapyramidal symptoms similar to corticobasal degeneration (CBD) and some motor neuron disease (MND). In various combinations, these disorders form a clinical and pathological spectrum, termed the "Pick complex" (Kertesz & Munoz, 1998). This indicates the relatedness of these entities and avoids the confusion of using FTD for the whole complex as well as for the personality–behavior disorder.

Neuropsychological testing of the dementias has been complex and often yields inconsistent results particularly in FLD (Miller et al., 1991; Moss et al., 1992; Neary et al., 1988). The more sensitive measures of frontal lobe function are difficult to apply to the majority of the patients, and there is relatively poor agreement as to which set of tests should be used under what circumstances. It is rare that a complete and repeatable set of tests can be applied to other than a small segment of this population. Neuropsychological studies in FLD have not shown a uniform pattern, not only because of the variation between patients, but because the patients were examined at different stages of their illness. Early deficits of executive function, such as set shifting (e.g., the Wisconsin Card Sorting Task) or alternative sequencing (the Trail Making Test), are also found in AD and depression. At times, memory, which is relatively spared in FLD initially, is the only complaint of FLD patients themselves, although when relatives are questioned, a large number of personality and behavior disorders may surface. On further enquiry, the memory problems are often the result of disinterest, indifference, and apathy. On testing, these patients may be oriented and their recognition memory is relatively intact. They tend to do poorly on global tests of memory (Snowden et al., 1996). The preservation of copying, drawing, calculation, and visuospatial function were claimed particularly useful in differentiating between FLD and AD (Brun et al., 1994; Mendez et al., 1996; Snowden et al., 1996). There were exceptions, however, in those studies, as well as in our experience. Simple copying, for example, may be spared while complex copying such as the Rey-Osterrieth Figure may be impaired by disorganization and attentional difficulty (Mendez et al., 1996).

Neuropsychological profiles of FLD resemble VaD. The predominance of frontal white matter changes has been reported in VaD (Erkinjuntti et al., 1996; Ischii et al., 1986), and patients with VaD have a "frontal type" of symptomatology and deficits on neuropsychological tests (Cummings et al., 1987; Ishii et al., 1986; Kertesz & Clydesdale, 1994; Perez et al., 1975; Starkstein et al., 1996; Villardita, 1993). Despite the considerable effort however, neuropsychological criteria cannot be used consistently to distinguish FLD from VaD and AD, and quantification of the behavioral and personality changes may provide a more efficient and accurate diagnostic and research tool.

We designed a behavioral inventory specific for the diagnosis of FLD or the behavior and personality component of FLD, choosing items to reflect the symptoms of our first series of patients and the core symptoms of FLD that have appeared in previous publications. The Frontal Behavioral Inventory (FBI; Kertesz et al., 1997) is a 24-item scorable questionnaire. The FBI items consist of deficit behaviors such as *apathy*, *aspontaneity*, *indifference*, *inflexibility*, *concreteness*, *personal neglect*, *disorganization*, *inattention*, *loss of insight*, *logopenia*, *verbal apraxia*, and *alien hand*. The positive group of behaviors contains items of disinhibition such as *perseveration*, *irritability*, *excessive or childish jocularity*, *irresponsibility*, *inappropriateness*, *impulsivity*, *restlessness*, *aggression*, *hyperorality*, *hypersexuality*, *utilization behavior*, and *incontinence*. The rationale for item selections and comparisons with other behavioral inventories has been described in detail in our previous study. The items correspond by and large to the core items of the Lund/Manchester consensus. The actual scripts for the questions are given in the Appendix of Kertesz et al. (1997). In addition to basic interviewing skills, minimal formal training is required for administration. The caregivers are asked about behavioral or personality changes from the patient's premorbid state. The questions are phrased both in a positive and negative fashion, in order to avoid influencing the caregiver. The scoring on a 4-point-scale (*none*, *mild*, *moderate*, or *severe*) for each item is dependent on the severity as gauged by the caregivers. The cut-off score of 30 was found to be effective in differentiating between FLD, AD, and DD patients (Kertesz et al., 1997). The FBI is intended to serve as a quantitative measure determining the severity of the impairment and assessing change and potential therapeutic effect.

In this study we prospectively administered the FBI to caregivers of AD, FLD, PPA, VaD, and DD to do the following:

1. Determine the interrater reliability and item consistency of the FBI.
2. Study the prevalence of personality and behavioral changes in the five clinical groups.
3. Quantify the personality and behavioral changes in FLD.
4. Classify patients based on the behavioral profiles obtained from the FBI.
5. Determine the discriminate power of the FBI items.
6. Determine the diagnostic sensitivity and specificity of the FBI.

METHODS AND RESEARCH PARTICIPANTS

The FBI was given to caregivers of 108 patients in our cognitive neurology clinic usually at the time of the first diagnostic assessment, 2 to 5 years from onset. The average duration of illness from estimated onset to the FBI for each diagnostic group is included in Table 1. The clinical diagnosis was made independently from the FBI, based on neurological examination, structured clinical interview for dementia, evaluation of neuropsychological reports, and neuroimaging. A different person from the clinician carrying out the interviews, usually another physician, a psychometrician, or a social worker, administered the FBI. Thirty-eight of these patients were diagnosed with AD, as per the NINCDS–ADRDA criteria (McKhan et al., 1984). Twenty-six patients were identified as FLD in accordance with the Lund/Manchester consensus (Brun et al., 1994). Eleven patients were diagnosed as PPA using Mesulam's (1987) suggested criteria. Sixteen patients had VaD as determined by a history, examination, and a modified Ischemic Score of 6 or more. Seventeen patients had DD, based on combined psychiatric and neuropsychological evaluation, and the cut-off points on the Cornell or Beck Depression Scales. None of these patients had a major clinical depression, and their mood disorder represented an elderly population referred by psychiatrists or family doctors for differential diagnosis. The demographics of the patients are presented in Table 1.

The FBI was administered to a caregiver in the absence of the patient. A change in behavior or personality from the patient's pre-morbid state at the beginning of the illness was specifically emphasized during the interview with the caregiver. Each item was scored on a severity scale of 0 to 3 (0 = *never*, 1 = *mild or occasional*, 2 = *moderate*, 3 = *severe or very frequent*).

For interrater reliability, 14 consecutive FBIs were recorded on videotape and then scored by four raters who viewed the tapes independently. The four raters included two trained psychometricians, a neurologist, and a trained medical student. Pearson's correlations and Spearman's correlations were done between raters, and Cohen's kappa mean was used for the final interrater score. For these 14 patients Cronbach alpha was done to determine internal consistency.

We used one-way analysis of variance (ANOVA) with *post-hoc* Tukey's HSD multiple comparisons for the FBI totals and the 24 items of the FBI as dependent variables. A "leave-one-out" cross-validation of the discriminant function analysis between FLDs and each of the other groups was used to cross-validate patients to their clinical diagnosis. Canonical coefficients are reported to explain variances between groups. The Statistical Package for the Social Sciences (SPSS v.8.0 Win95/NT; SPSS Inc., Chicago, IL) was used for all probability testing, including the discriminant analysis, the "leave-one-out" cross-validation method, ANOVA, and parametric and nonparametric correlation testing. All hypotheses were tested at alpha = .05.

RESULTS

Differences Between Groups

Mean total scores, standard deviations, and range of scores per groups on the FBI are shown in Table 1. ANOVA revealed a significant difference in group scores [$F(4,103) = 52.8$, $p < .001$]. *Post-hoc* Tukey's tests showed the FLD group was significantly higher than all other groups ($p < .05$). The VaD group is also significantly higher than the AD, PPA, and DD ($p < .05$). The means of the other AD,

Table 1. Demographics of the patients ($N = 108$)

			Age		Duration in months		FBI scores		
Group	*N*	M/F	*M*	(*SD*)	*M*	(*SD*)	*M*	(*SD*)	Range of scores
Frontotemporal dementia (FLD)	26	16/10	58.2	(9.0)	28.8	(22.0)	39.5	(9.1)	27–61
Vascular dementia (VaD)	16	13/3	68.4	(9.5)	17.6	(13.0)	24.6	(11.0)	7–47
Alzheimer's disease (AD)	38	20/18	68.9	(9.2)	26.6	(13.7)	12.0	(7.6)	0–26
Primary progressive aphasia (PPA)	11	5/6	67.7	(6.0)	39.5	(26.2)	11.5	(5.9)	4–20
Depressive disorder (DD)	17	10/7	55.9	(9.6)	52.7	(66.0)	9.2	(8.7)	0–28

Table 2. Interrater reliability of the Frontal Behavioral Inventory (FBI)

Pearson's *r*	Spearman's *rho*
Rater 1/Rater 2 = .94	Rater 1/Rater 2 = .89
Rater 1/Rater 3 = .92	Rater 1/Rater 3 = .95
Rater 1/Rater 4 = .90	Rater 1/Rater 4 = .93
Rater 2/Rater 3 = .87	Rater 2/Rater 3 = .82
Rater 2/Rater 4 = .86	Rater 2/Rater 4 = .78
Rater 3/Rater 4 = .93	Rater 3/Rater 4 = .97
Cohen's kappa = .89	Cohen's kappa = .90
SD = .08	*SD* = .03

PPA, and DD are not significantly different from each other. The mean age of FLD and DD groups are significantly less than the PPAs, ADs, and VaDs. Male:female ratios were only significant in vascular dementia, where male participants were preponderant.

Interrater Reliability and Internal Consistency

Cohen's kappa correlation for the interrater reliability was .89 with a standard deviation of .08 for Pearson *r* and .90 and a standard deviation of .03 for Spearman *rho*. Individual interrater correlations are displayed in Table 2. Item scores were correlated with a Cronbach alpha of .89 establishing a high level of internal consistency.

Analysis of Behaviors

Figures 1 and 2 show a bar graph of the mean scores of each of the behaviors assessed with the FBI. The mean scores reflect the frequency of incidence as well as the severity for each group. All items except *hypersexuality* showed an overall significant *F* value in the analysis of variance [$F(4,103) = 1.61$, $p > .18$]. *Post-hoc* Tukey's tests showed the FLD group was significantly higher in mean item scores than all other groups in *indifference*, *concreteness*, *perseveration*, *inattention*, *loss of insight*, *inappropriateness*, *impulsivity*, and *utilization behavior* (Notation *A* on Figures 1 and 2). FLD patients scored significantly higher than AD, PPA, and DD for *apathy*, *aspontaneity*, *inflexibility*, *disorganization*, *irritability*, *jocularity*, *judgement*, *restlessness*, *aggression*, *hyperorality*, and *personal neglect* (Notation *B* on Figures 1 and 2). VaD patients scored high, close to FLD patients on *irritability*, *inflexibility*, *apathy*, and *aspontaneity*. *Verbal apraxia* was significantly higher for PPA patients than for all other groups [$F(4,103) = 18.13$, $p < .05$] (Notation *C* on Figure 1). PPA patients also had higher logopenia scores significantly different from DD and AD patients.

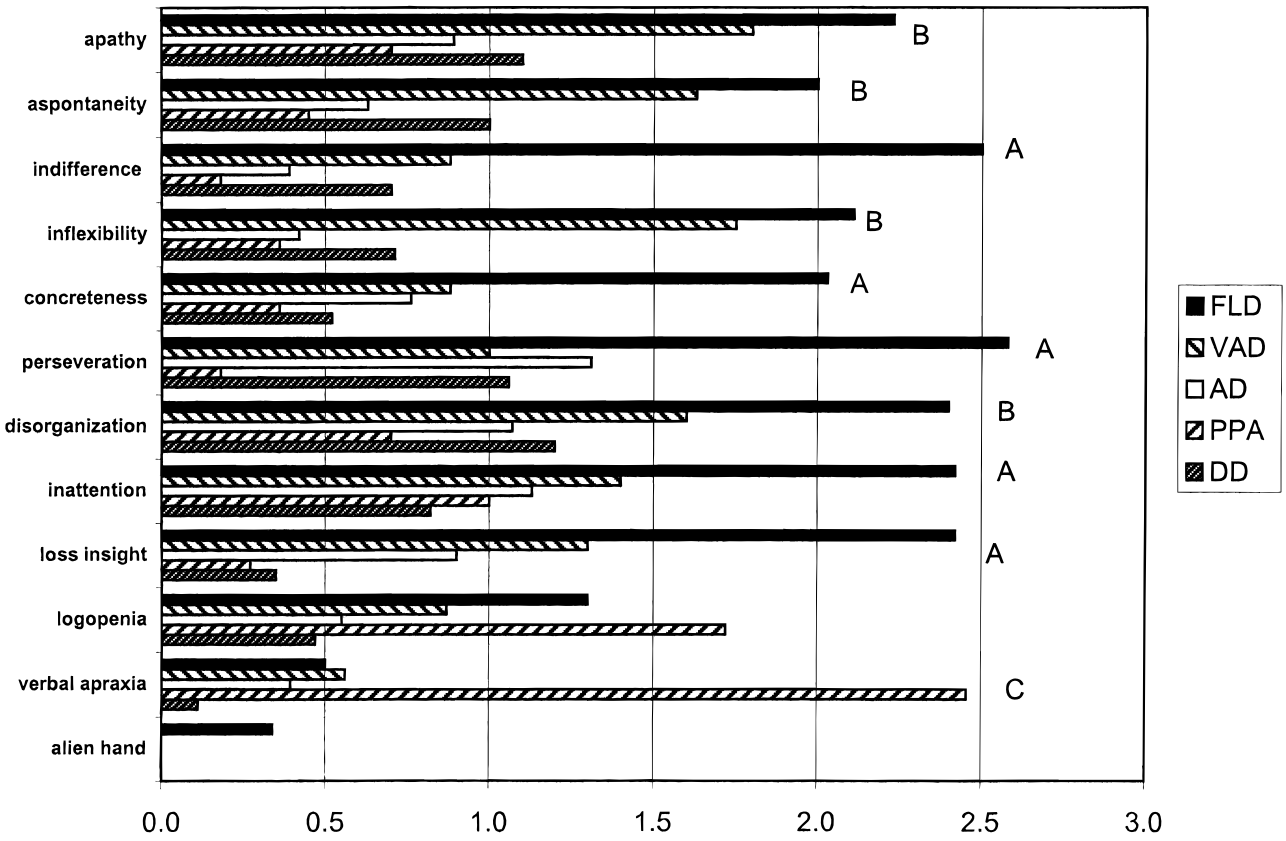

Fig. 1. Mean behavior scores on the FBI.

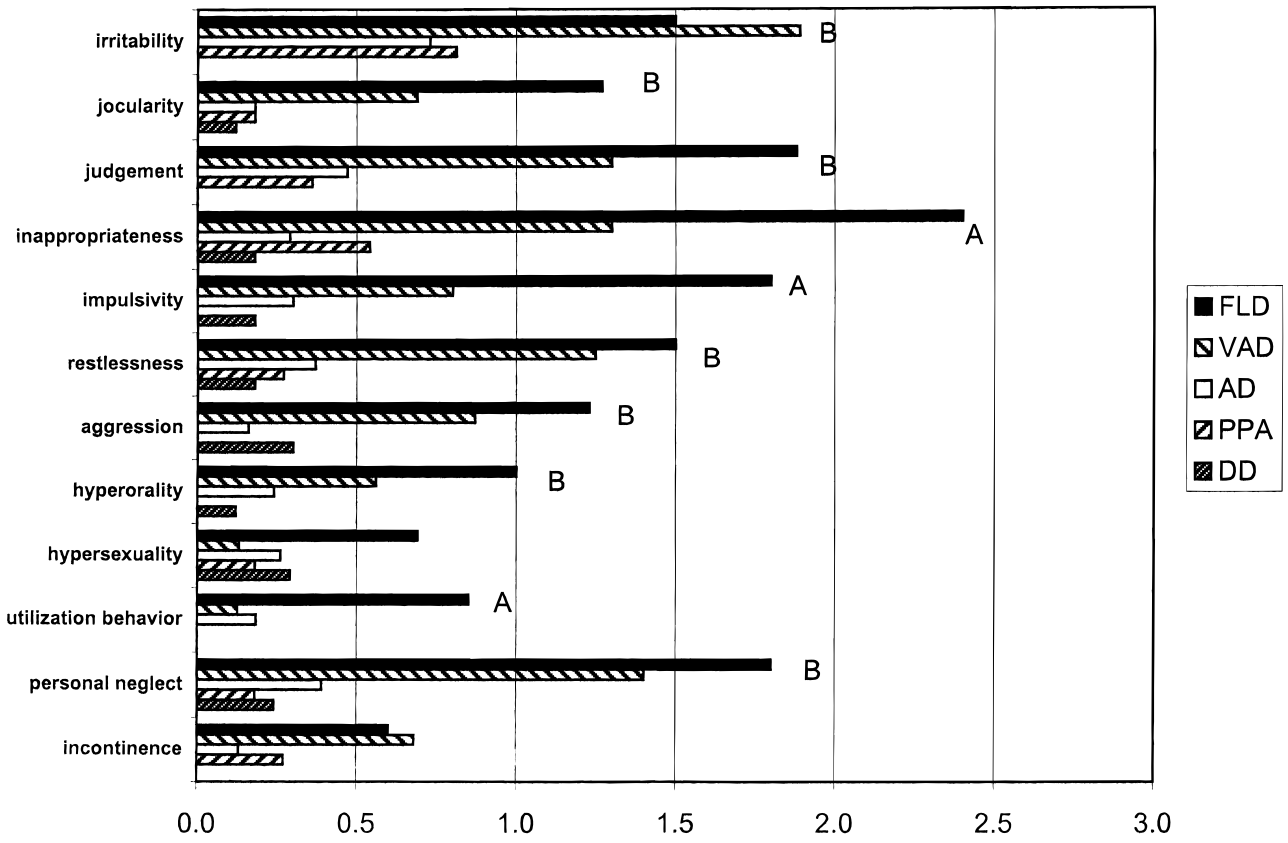

Fig. 2. Mean behavior scores on the FBI.

Discriminant Analysis of FBI

Table 3 shows a summary of the behavior items that entered into the discriminant function analyses between FLD and NON-FLD, FLD and VaD, FLD, and AD groups. The percentage of variance explained for each function is shown as the square of the canonical correlation. The total percentages will be greater than 100% because the analysis is multidimensional. *Indifference* (41%), *alien hand* (25%), *inappropriateness* (18%), *perseveration* (7%), and *impulsivity* (7%) were responsible for the overall separation between the FLD group and the NON-FLD groups. *Indifference* accounted for 65%; *perseveration*, 48%; *alien hand*, 36%; and *concreteness*, 19% of the separation between the FLD and VaD group. Other items that come into the discriminant analysis are *inflexibility* (38%) for the FLD *versus* AD comparison and *personal neglect* (36%) and *hypersexuality* (18%) for the FLD *versus* PPA group.

Sensitivity and Specificity on Cross-Validation

Results of the discriminant analysis done between the FLD and the other clinical groups (NON-FLD) show that 100/108 (92.6%) patients were classified correctly [χ^2 (5, N = 108) = 126.0, $p < .001$] (Table 4). Of the NON-FLD, 5/82 (6.1%) were classified falsely as FLD and 3/26 (11.5%) of the FLD group were classified as not being NON-FLD, on the "leave-one-out" cross-validation. This indicates a diagnostic specificity of 89.5% and sensitivity of 93.9% for FLD using the FBI in this population.

When the FLD group was compared with the other clinical groups individually, the FLDs and the VaDs were cross-validated correctly at 36/42 (85.7%) [χ^2 (4, $N = 42$) = 49.8, $p < .001$]. Of the FLD, 3/26 (11.5%) were classified as VaD and 3/16 (18.8%) of the VaDs were classified as FLDs. The FLDs were classified as DD 11.8% of the time (2/17)

Table 3. Discriminant functions and canonical correlation values

Comparison	Indifference	Alien hand	Inappropriateness	Perseveration	Impulsivity	Concreteness	Inflexibility
FLD *vs.* NON-FLD	41%*; .64	25%; .50	18%; .43	7%; .26	7%; .26		
FLD *vs.* VaD	66%; .81	35%; .59		48%; .69		19%; .43	
FLD *vs.* AD	48%; .69	36%; .60	43%; .65				38%; .62

*Percentage is the square of the canonical correlation and represents the amount of variance explained by each analysis.

Table 4. Discriminant analysis cross-validation of the FBI

Comparison	Percent classified correctly	Chi-square test	Percent false negatives	Percent false positives
FLD *vs.* NON-FLD	92.7	($\chi^2 = 126.0$, $p < .001$)	11.5	6.1
FLD *vs.* VAD	85.7	($\chi^2 = 49.9$, $p < .001$)	11.5	18.8
FLD *vs.* AD	100	($\chi^2 = 119.8$, $p < .001$)	0	0
FLD *vs.* PPA	100	($\chi^2 = 82.1$, $p < .001$)	0	0
FLD *vs.* DD	90.7	($\chi^2 = 67.0$, $p < .001$)	7.7	11.8

and DDs were classified as FLD 7.7% of the time (2/26). AD and PPA patients correctly classified 100% of the time *versus* FLD patients.

DISCUSSION

The FBI was successful in discriminating between the major groups in our dementia population in a prospective study. The items were designed to explore frontotemporal symptoms, and, as expected, high scores were achieved in the frontotemporal group, but VaD represented an important differential diagnostic issue with high scores on some items. Nevertheless, the mean total scores are significantly different between VaD and FLD, and, although some overlap exists, a conservative cut-off score of 30 or above for FLD suggested by our previous study remains valid as 23/26 (88.5%) of FLD and only 3/16 (18.8%) of VaD patients score above this. In the overlapping group, item analysis and other clinical features such as sudden onset, strokes, and focal deficits may be useful in the differentiation. None of the AD, PPA, or DD score above the cut-off point.

Apathy, *aspontaneity*, and *indifference* overlap, to some extent, and can be expressed by "detachment and disengagement" used in other descriptions (Snowden et al., 1996). Amotivational state or *apathy* can be the earliest or a cardinal manifestation of depression, but in FLD it appears without the characteristic sadness, crying, and expressions of worthlessness and suicidal ideation. *Aspontaneity* or the lack of spontaneous initiation of activity, be it physical or verbal, whether at home or at work, may refer to the lack of motivation or to the failure to carry out routine work such as doing the laundry or taking out the garbage. Our DDs, however, had lower than expected average scores on these items, and they were different from FLD even in this respect. This could be related to the relatively mild depression that characterized the patients referred to us for the differential diagnosis. *Aspontaneity* and *apathy* also overlap with *inattention*, which in this inventory is meant to explore losing track or lack of sustained attention. These behaviors are often interpreted by the family as instances of forgetfulness.

Indifference, emotional flatness, or detachment is explored at the emotional level in this questionnaire, specifically referring to the patient's emotional responsiveness to an event or statement. At a more general cognitive level, when there is a lack of reaction to any kind of stimulus, it is assessed under *apathy*. At a more severe degree this is the well known symptom of abulia or lack of responsiveness while appearing fully conscious and still carrying out some motor and elimination functions. In hospitalized patients with advanced FLD, there may be a complete loss of verbal or purposeful motor responsiveness. Abulia is common at later stages of FLD and like mutism it is not specific, occurring in other psychiatric and neurological conditions. Its progressive development however should alert the clinician to FLD.

Apathy, *aspontaneity*, and *indifference* can be and often are associated with various features of *disinhibition* in FLD. The paradoxical combination of the apathetic patient, who is emotionally and attentionally disengaged with disinhibited, childish jocularity (moria) and restless, compulsive, perseverative, or impulsive behavior is characteristic of FLD, in contrast to depression, although the disinhibition behavior may occur in manic-depressive psychosis. This has to be carefully considered in the differential diagnosis in FLD, as it is a treatable condition. A therapeutic trial for a bipolar disorder is warranted when the diagnosis is in doubt.

Inattention, *disorganization*, and *lack of insight* are common in all dementias, but lack of insight in the early stages is particularly characteristic of FLD. In contrast many AD patients are aware of their memory loss early in their illness. *Perseveration*, *inattention*, *indifference*, and *social inappropriateness* scored high in FLD, but the less frequent *alien hand*, *impulsivity*, *utilization behavior*, and *aggressiveness* separates FLD (who have higher scores on these) from VAD. Some studies emphasize obsessive, compulsive, stereotypical, repetitive behaviors as a distinct variety related to striatal pathology (Tonkonogy et al., 1994; Snowden et al., 1996). These behaviors are captured by our items of *perseveration*, *utilization behaviors*, and *social inappropriateness*. The well known *jocularity* (*Witzelsucht*) and childishness (*moria*) have occurred relatively infrequently, not in sufficient extent to be of discriminatory value, but high scores may be obtained in some of the frontal patients of both degenerative and vascular etiology, adding to the usefulness of the total score.

Verbal apraxia predominated in PPA and is included among the items to detect the early appearance in FLD, even though it tends to be a primary complaint in PPA. *Verbal*

apraxia is an item that includes several motor aspects of speech. The strict technical definition of the term is variable and can be difficult (Darley et al., 1975). For the FBI, the caregiver is asked if the patient is making speech errors or has any difficulty speaking or articulating. The other speech item, called *logopenia* in the inventory, is specifically aimed at detecting decrease in the amount of speech, usually associated with word finding difficulty, which is distinct from the aphasic–dysarthric speech errors in the *verbal apraxia* item. Most early cases of FLD, AD, VaD, and DD have no impairment on the *verbal apraxia* item, but it is useful for the detection of progressive aphasia and for early PPA. Occasionally, it may be positive in FLD and in VaD patients who have had an aphasic or left hemispheric stroke. The language items are not personality or behavioral changes in the strict sense but they were included to detect the frequent early language complaints in many varieties of the Pick complex. Although *verbal apraxia* and *logopenia* may be detected on examination, direct questioning establishes the extent and evolution of the language disturbance. Progressive aphasics have specific language symptoms which are more adequately captured on formal language testing such as the Western Aphasia Battery (WAB; Kertesz, 1982).

Moderately impaired AD and FLD patients have been found to have an overlap of scores for verbal fluency on formal neuropsychological testing (Mendez et al., 1996). Decreased verbal fluency and speech have been noticed in VaD on mental status examination (Cherrier et al., 1997), and in this respect some vascular patients appear to have early frontal language dysfunction. However, verbal fluency or word retrieval in semantic association (naming examples of a category) is a different cognitive process from *logopenia*, which is judged by the number of speech units produced in conversation. Therefore, *logopenia* rating may be more specific than verbal fluency scores for the diagnosis of FLD or PPA patients.

Irritability is high in VaD, and it is seen often in PPA along with *verbal apraxia* and *logopenia*. Patients with increasing language deficit usually recognize their problem and become quite frustrated and at times irritable as a consequence. High scores of irritability in VaD is similar to other findings in the literature (Cummings et al., 1987). Even though this item did not have an objective discriminatory value, it was retained because it is at times a significant problem for the caregiver. Some of the behavioral changes are stage dependent. *Aggression* is an occasional early symptom of FLD and as a rule tends to be late in AD, in our experience.

The items of *concreteness* and *alien hand* are a difficult concept for many caregivers. These are relatively infrequent behaviors. Even though *concreteness* has been observed during examination, caregivers rarely responded to this readily, and it was difficult to cite examples that would apply to the patient. *Alien hand* is not a frequent phenomenon, but the item is included to capture an element of the corticobasal degeneration syndrome (CBDS), also part of the Pick complex (Kertesz & Munoz, 1998). This may or may not be a spontaneous complaint, and a direct question was formulated to elicit it. Most caregivers, however, had difficulty understanding it except in FLD with features of CBDS where they have witnessed the phenomena. Levitation and immobility were secondary features used to elicit the response. Although we had low return on these questions, they were useful in some instances and we continued to use them.

The administration of the FBI usually takes 15 to 30 min. During the interview, the caregiver may have a tendency to discuss behaviors that are not related to the questions asked. Although flexibility is desirable, and extra information may be useful, caregivers should be reoriented towards the item by saying, for example, “We were discussing apathy” and then repeating the scripted question. It is advisable to encourage the caregiver to describe behaviors, and only if the caregiver does not seem to understand the question should the interviewer provide an example, as this may be disadvantageous should the caregiver be suggestible; while deviation from the scripted questions may be necessary, it should be avoided in general, as it leads to a great deal of extraneous material being discussed.

The scoring is intended to capture severity rather than the frequency of behavioral abnormalities, although the two are interdependent, of course. Asking the caregiver how often a certain behavior occurred in a week or a day may provide an illusion of quantitation, but it is notoriously difficult to answer and interpret and often elicits unreliable guessing. The accuracy and reliability of the answers are, to a large extent, dependent on the caregiver. Some caregivers are not as perceptive as others, and a few are very protective, minimizing the symptoms. We used a second caregiver in several instances when reliability was an issue.

Progression of illness may introduce new behaviors but also lead to the disappearance of others. Stage dependent profiles and information pertaining to long-term follow-up with the FBI are being collected, as part of our continuing effort to explore the usefulness of the questionnaire. Some late-stage FLD patients lose the characteristic disinhibition symptoms, but may develop others such as *hypersexuality* or *utilization behavior*. Some caregivers may feel uncomfortable when asked about *hypersexuality*, and often the negative answer reflects absent activity. It should be explained that the question relates to increased interest, verbal or physical, not necessarily to performance.

The inventory appears to have high specificity for FLD with the exception of some cases of VaD and manic-depressive psychosis, which may produce similar scores. A few items such as *perseveration* and *utilization behavior* may if present be unique for FLD. In the few questionable instances, possibly in mixed dementia, the diagnosis is influenced by associated features such as vascular phenomenon, a high ischemic score, or the vegetative symptoms of depression. At times, patients need to be followed longitudinally to solve the diagnostic dilemma. Neuroradiological investigation is also helpful for the differential diagnosis, although at times no atrophy or hypometabolism appears in early cases. In other cases, white matter changes may be

interpreted as ischemic, influencing the diagnosis in the wrong direction. Neurological examination is usually normal with the appearance of primitive reflexes as an inconsistent, nonspecific, and late phenomenon. Echolalia, echopraxia, grasp reflex, and similar classical frontal lobe signs may be present in late stage hospitalized patients and were not included in the inventory, although they may be detected on examination. The diagnosis of FLD in this population is based on symptoms similar to those quantitated on the FBI, accounting for the high specificity. This introduces a degree of circularity that is common to all diagnostic inventories based on the symptomatology of an illness (i.e., a depression inventory for depression). Nevertheless, the use of a standard inventory and quantitation has many additional advantages to symptoms obtained on history alone.

The questionnaire has a wide applicability, as it is free of cultural and gender bias. Some of the behavioral abnormalities may be treated with more tolerance or even denial in some cultures and by some individuals, but this has not been a major factor in our study. There are several other applications of the questionnaire apart from this population. Traumatic brain injury, a common cause of disability in our society, often produces a similar personality and behavior alteration, which could be effectively quantitated by the FBI. Telephone application and questionnaires filled out and scored in the waiting room while the patient is being examined have been tried, but were found to be not as satisfactory as a face-to-face interview, although the information can be useful, even diagnostic. These applications however have not been standardized and were used only occasionally in our clinic. Retrospective application for early diagnosis at the time of examination of more advanced cases or in autopsy material requires the questions to be presented so the caregiver understands that they pertain to the beginning of the illness or to the presenting symptoms. This will give a different result from a score obtained at a later stage. Validation of the FBI against independent markers of the disease, such as autopsy or a biochemical abnormality, would be desirable in the future.

In summary, the FBI discriminates FLD from AD, PPA, and DD. The total score above a conservative cut-off point of 30 is suggestive of FLD. VaD may also score high, but *indifference*, *perseveration*, and *utilization behavior*, when present, are useful to discriminate FLD. In the low-scoring groups (below the cut-off point of 27) the PPA patients can be discriminated by *verbal apraxia*, and *logopenia*. Others require cognitive testing or longitudinal psychiatric observation and pharmacological treatment for diagnosis. The test is most useful for early diagnosis and follow-up. Application in later stages is less specific, although it can still be used as a measure of deterioration. It has high interrater reliability and content validity and it is easy to administer.

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