Dysexecutive Syndrome: Diagnostic Criteria and Validation Study

Olivier Godefroy, MD, PhD,[1] Philippe Azouvi, MD, PhD,[2] Philippe Robert, MD, PhD,[3] Martine Roussel, PhD,[1] Didier LeGall, PhD,[4] and Thierry Meulemans, PhD,[5] on Behalf of the Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group

Objective: Disorders of executive functions are among the most frequent cognitive deficits, but they remain poorly defined and are subject to heterogeneous assessment. To address this major issue, the Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives (GREFEX) group has proposed criteria for behavioral and cognitive dysexecutive syndromes and has designed a battery including a specific heteroquestionnaire and 7 cognitive tests. We investigated the frequency of behavioral and cognitive dysexecutive disorders in patients suffering from various diseases and the association of these disorders with loss of autonomy.
Methods: A total of 461 patients aged between 16 and 90 years with severe traumatic brain injury, stroke, mild cognitive impairment, Alzheimer disease, multiple sclerosis, and Parkinson disease were recruited into this prospective cohort study by 21 centers between September 2003 and June 2006. Behavioral and cognitive dysexecutive disorders were examined using the GREFEX battery.
Results: A dysexecutive syndrome was observed in 60% of patients, concerning both behavioral and cognitive domains in 26% and dissociated in 34%. All behavioral and cognitive dysexecutive disorders discriminated ($p = 0.001$, all) patients from controls. The pattern of cognitive syndrome differed ($p = 0.0001$) according to the disease. Finally, behavioral (odds ratio [OR], 4.6; 95% confidence interval [CI], 2. 3–9.1; $p = 0.0001$) and cognitive (OR, 3.36; 95% CI, 1.7–6.6; $p = 0.001$) dysexecutive syndromes and Mini Mental State Examination score (OR, 0.79; 95% CI, 0.68–0.91; $p = 0.002$) were independent predictors of loss of autonomy.
Interpretation: This study provided criteria of dysexecutive syndrome and showed that both behavioral and cognitive syndromes contribute to loss of autonomy. Profiles vary across patients and diseases, and therefore systematic assessment of behavioral and cognitive disorders in reference to diagnostic criteria is needed.

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Disorders of executive functions are among the most frequent cognitive deficits and are observed in many diseases.[1] Although an impressive number of studies have documented the frequency and variability of executive disorders, 3 important and closely interrelated issues still remain unresolved. First, the domain of executive functions has not been clearly delimitated in contrast with other cognitive syndromes such as aphasia, agnosia, or apraxia. Following Luria's approach,[2] the term *executive functions* was coined by Lezak[3] and was initially circumscribed to goal setting, action initiation and inhibition, planning, shifting, and verification. Its domain has been extended to include behavioral changes observed in frontal lesions.[4] Recent aspects of control functions such as social cognition, theory of mind, strategic processes of episodic memory, insight, and metacognition have been variably incorporated into the domain of executive functions. These variable definitions of executive disorders complicate clinical assessment and experimental studies, emphasizing the need for consensual diagnostic criteria. Second, assessment of executive disorders is highly variable, and the relevance of performance indices is poorly defined. Cognitive assessment uses (1) various tests with unspecified accuracy and equivalence, (2) batteries composed of varying numbers of tests with a risk of poor sensitivity (small number of tests) or poor specificity

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Address correspondence to Dr. Godefroy, Service de Neurologie, CHU Nord 80054, Amiens cedex France. E-mail: godefroy.olivier@chu-amiens.fr

From the [1]Department of Neurology, Laboratory of Functional Neurosciences, University Hospital of Amiens, Amiens, France; [2]Department of Rehabilitation, University Hospital of Garches, Garches, France; [3]Academic Memory Clinic, University Hospital of Nice, Nice, France; [4]Departments of Neurology and Psychology, University of Angers, Angers, France; [5]Department of Psychology, University of Liège, Liège, Belgium.

Additional Supporting Information can be found in the online version of this article.

TABLE 1: Criteria for Behavioral and Cognitive Dysexecutive Syndrome[a]

Behavioral Disorders	Cognitive Disorders
Highly suggestive	**Highly suggestive**
Global hypoactivity with apathy and/or abulia	Response inhibition
Global hyperactivity with distractibility and/or psychomotor instability	Rules deduction and generation
Stereotyped and perseverative behavior	Maintenance and shifting of sets
Environmental dependency (imitation and utilization behavior)	Information generation (fluency tasks)
Supportive deficits and developing areas	**Supportive deficits and developing areas**
Disorders of emotional control (apathy, euphoria, moria, emotional lability)	Planning
Disorders of social behavior	Response initiation and sustained alertness
Disorders of sexual, eating, and urinary behavior	Coordination of dual tasks
Spontaneous confabulation, reduplicative paramnesia	Episodic memory strategic processes (retrieval and memory selection)
Anosognosia, anosodiaphoria	Theory of mind and metacognitive processes

Modified from Godefroy 2003.[7]
Highly suggestive = impairment demonstrated in at least 2 studies showing a significant relation between the impairment and the lesion of the frontal subcortical network (typically comparison between anterior and posterior lesions). Supportive deficits and developing areas = impairment demonstrated in a group (or subgroup) of patients compared to healthy controls or controversial results across studies or limited number of studies.
[a]To be considered as dysexecutive, the disorder should not be more readily explained by perceptuomotor, psychiatric (depression, manic state, or obsessive-compulsive disorder), or other cognitive (language, memory, visuospatial) disturbances.

(large number of tests), and (3) poorly validated performance indices (eg, completion time of the Trail Making and Stroop tests). Third, dysexecutive behavioral disorders are usually not included in the evaluation of dysexecutive syndrome, although they tend to be prominent and can even correspond to the entire dysexecutive deficit, especially in mediofrontal lesions.[5] The assessment of dysexecutive behavioral disorders is usually based on clinical interview, as illustrated by a survey in French-speaking centers,[6] or uses nonspecific questionnaires incorporating other features. These uncertainties emphasize the need to (1) propose criteria defining the dysexecutive syndrome, (2) clearly define the assessment of dysexecutive disorders, and (3) validate these criteria in a large population with various brain diseases. In addition, this will provide a basis to examine whether patterns of dysexecutive disorders differ across diseases, an assumption that has been partly addressed in small groups with selected diseases.

To address these issues, the Groupe de Réflexion pour l'Evaluation des Fonctions EXécutives (GREFEX) working group has proposed criteria for dysexecutive syndrome.[1,7] Following a comprehensive review of the literature pertaining to behavioral (ie, changes observed clinically or on behavior inventory) and cognitive (ie, deficits observed on tests) changes occurring in major diseases, features of dysexecutive disorders were selected during a consensus conference according to level of evidence.[8] As behavioral disorders may be observed in patients without cognitive deficit,[5] separate criteria for behavioral and cognitive dysexecutive syndromes were proposed (Table 1). In addition, a battery was designed including a new specific informant questionnaire and an adaptation of 7 tests. The battery has been previously standardized and normalized in 718 participants.[1] The objective of this multicenter study was to assess the validity of the proposed criteria for dysexecutive syndrome in a group of patients presenting various diseases representative of clinical practice.

Patients and Methods

Patients

Patients referred for cognitive assessment with target diseases were recruited by 21 memory, stroke, and rehabilitation centers between September 2003 and June 2006. Inclusion criteria were age between 16 and 90 years and Mini Mental State Examination (MMSE)[9] score $\geq$16/30. Exclusion criteria were: (1) sensorimotor deficit, hemineglect, or aphasia precluding

cognitive assessment; (2) illiteracy; (3) alcoholism or severe general comorbidity; (4) previous neurologic and psychiatric diseases except for depression or anxiety; (5) recent introduction of psychoactive or antiepileptic medication; and (6) absence of informed consent. Target diseases were severe traumatic brain injury (initial Glasgow Coma Scale <8), stroke, mild cognitive impairment (MCI),[10] Alzheimer disease,[11] multiple sclerosis,[12,13] Parkinson disease,[14] early stage Huntington disease (diagnosed using genetic testing), and single brain tumor.

This study included 461 patients and 461 age- and education-matched controls selected from the normalization database (Table 2). Although demographic characteristics did not differ between the patient group and controls ($p > 0.05$), differences were observed according to diagnosis (see Table 2): (1) age was younger in traumatic brain injury, multiple sclerosis, and stroke than in MCI, Parkinson disease, and Alzheimer disease; (2) overrepresentation of females was observed in Alzheimer disease and multiple sclerosis and overrepresentation of males in traumatic brain injury and Parkinson disease; and (3) right-handers were less frequent in stroke and traumatic brain injury groups. MMSE differed across groups, due to lower scores in dementia, followed by MCI, Parkinson disease, and others, then traumatic brain injury, stroke, multiple sclerosis, and finally controls. Finally, digit span[15] was lower in the Alzheimer disease group.

Procedures

Examination of dysexecutive disorders included assessment of behavioral changes using the Behavioral Dysexecutive Syndrome Inventory[1] and assessment of cognitive deficits using the Cognitive Dysexecutive Battery, which included an adaptation of 7 tests.[1] The complete battery and normalization study have been previously reported[1] and are briefly presented (see also Supporting Information Methods). The Behavioral Dysexecutive Syndrome Inventory is a structured interview of an informant assessing changes compared to previous behavior in 12 domains: (1) global hypoactivity with apathy-abulia; (2) difficulties for anticipation, planning, and initiation of activities; (3) disinterest and indifference to his own concern and others; (4) hyperactivity-distractibility-psychomotor instability; (5) irritability-impulsivity-aggressiveness; (6) euphoria, emotional lability, and moria; (7) stereotyped and perseverative behavior; (8) environmental dependency; (9) anosognosia-anosodiaphoria; (10) spontaneous confabulations; (11) social behavior disorders; and (12) disorders of sexual, eating, and urinary behavior (see Supporting Information Methods). Using a procedure similar to that of the Neuropsychiatric Inventory,[16] the informant was first given a screening question that provided an overview of the domain. If the informant provided a positive answer, the domain was then explored with 8 questions that provided more detailed information. For each domain with at least 1 positive answer, the informant had to rate its frequency and its severity in everyday life. To be interpreted as dysexecutive, behavioral changes (1) could not be more readily explained by perceptuomotor, psychiatric (especially depression, manic state, or obsessive-compulsive disorder), or other cognitive disorders; (2) had to induce

TABLE 2: Demographic Data

Characteristic	Stroke	Traumatic Brain Injury	Mild Cognitive Impairment	Alzheimer	Parkinson	Multiple Sclerosis	Other[a]	Controls	*p*
No.	152	112	18	73	45	50	11	461	
Age, yr	48 ± 14	30.8 ± 12	72.2 ± 11	76.3 ± 8	61.7 ± 10	44.9 ± 12	56.8 ± 9	50.5 ± 18	0.0001
Male sex, %	51	76	44	35	70	37	45	48	0.0001
Education, % 1/2/3[b]	29/43/28	23/43/34	33/28/39	37/30/33	31/42/27	20/40/40	36/27/36	29/39/32	0.6
Handedness, %, R/other	91/9	87/13	100/0	100/0	98/2	98/2	100/0	93/7	0.01
Loss of autonomy, %	40	83	0	100	72	51	82	0	0.0001
MMSE/30	27.8 ± 2.3[c]	27.1± 2.4[c]	25.8 ± 2.9[c]	23.1 ± 2.7[c]	26.9 ± 2.5[c]	27.9 ± 2[c]	27.1 ± 2.7[c]	28.7± 1.3	0.0001
Digit Span/9	5.47 ± 1.2	5.37 ± 1.2	5.29 ± 0.9	4.83 ± 1[c]	5.2 ± 1	5.15 ± 1	4.82 ± 1	5.58 ± 1.1	0.0001

[a]Other included 5 patients with Huntington disease and 6 with brain tumor involving the frontal lobes (right, n = 3; left, n = 1; bilateral, n = 2).
[b]1 = primary school level usually with schooling <9 years; 2 = to secondary school level usually with schooling <12 years; 3 = to tertiary schooling level usually with schooling ≥12 years.
[c]Different from controls.
R = right.

significant modifications compared to premorbid behavior; and (3) had to induce significant changes in activities of everyday life, social life, or work. Using normative data,[1] participants with $\geq$3 impaired domains (cutoff score corresponding to the 5% level[1]) were considered to suffer from behavioral dysexecutive syndrome (see Supporting Information Methods). To reduce the number of results, and as high correlations were observed between some domains,[1] inventory performance is presented according to 8 domains (the score for global hypoactivity with apathy-abulia was grouped with that of difficulties for anticipation and with that for disinterest; the score for hyperactivity-distractibility-psychomotor instability was grouped with that for irritability-impulsivity and with that for euphoria, emotional lability, and moria) (see Supporting Information Methods).

The Cognitive Dysexecutive Battery used a French adaptation of 7 tests[1]: Trail Making test,[17] Stroop test,[18] Modified Card Sorting test,[19] verbal fluency test (animals and words beginning by letter F in 2 minutes),[20] Six Elements task,[21] Brixton test,[22] and Dual task test.[23] In patients for whom time constraints or fatigability precluded the use of the complete battery, investigators were asked to present tests in the following order: verbal fluency, Stroop, Trail Making test, Modified Card Sorting, Dual task, Brixton test, and Six Elements task. Using normative data,[1] subjects with $\geq$3 impaired performances (cutoff score corresponding to the 5% level[1]) were considered to suffer from cognitive dysexecutive syndrome (see Supporting Information Methods). To reduce the number of results, and as high correlations were observed between some indices,[1] cognitive performance is presented according to 7 executive processes (see Supporting Information Methods) that have been found to be representative of executive deficits reported in the literature[8]: (1) initiation, (2) rule deduction, (3) information generation, (4) action coordination, (5) inhibition, (6) planning, and (7) shifting.

The general neuropsychological assessment varied between centers, as the GREFEX study was conducted according to the routine practice in each center. Assessment of anxiety, depression, language, visuospatial abilities, short-term and episodic memory, and general intellectual efficiency had to be performed using validated tests chosen according to the disease. In addition, investigators had to systematically examine whether numbering (counting from 1 to 25), writing, and reading (as examined using the MMSE subtests) abilities were spared for interpretation of the Trail Making and Six Elements tests. Autonomy was assessed when a reliable informant was available. Interview determined whether the disease induced difficulties in activities of daily living that interfered with lifestyle or precluded independent functioning. Disability assessment was based on the use of 4 well-validated scales selected according to the diagnosis: modified Rankin scale,[24] Instrumental Activities of Daily Living,[25] Patient Competency Rating Scale,[26] and Reintegration to Normal Living Index.[27] Scores on 4 items (telephone, treatment, transportation, financial affairs) of the Instrumental Activities of Daily Living scale have been found to predict loss of autonomy and dementia.[28] The Patient Competency Rating Scale[26] used both a self-administered and informant questionnaire with an informant assessing abilities in 30 activities of daily living. The Reintegration to Normal Living Index[27] required the patient to indicate on a visual analog scale the ability to perform 11 activities of daily living. Loss of autonomy was defined as difficulties in activities of daily living that precluded independent functioning in structured interview, the Reintegration to Normal Living Index,[27] or the informant score on the Patient Competency Rating Scale,[26] and this corresponded to a modified Rankin score >1 or significant difficulties on the Instrumental Activities of Daily Living.[28]

Statistics

The validity of the criteria of dysexecutive syndrome was examined by their ability (1) to discriminate between patients and controls and (2) to predict loss of autonomy. In domains without an established well-validated gold standard, validity studies are usually restricted to performance comparison with a reference group. This demonstration of impaired means in the pathological group is an important step, but for clinical purpose, 2 other criteria should be examined. First, the frequency of impairment determined using norms available in clinical practice should also discriminate patients from the reference group. This demonstration is important for clinical purposes, because differences in group mean do not necessarily imply that impairment is reliably detectable at the individual level.[29] Second, impaired performance should be associated with significant difficulties as judged using an external assessment in everyday life activities. This is especially needed in domains where high inter- and intraindividual variability of abilities/behavior is observed (like the executive functions), to ensure that the impaired performance does index a clinically significant deficit. This is even more important with the multiplication of tests and indices, which artificially increases the probability of finding 1 impaired performance.

The first analysis compared mean performance (12 behavioral domain indices and 16 cognitive indices) of patients and controls using a multivariate analysis (Wilk lambda test) followed by univariate tests (t test with correction for variance inequality). To control for the contribution of other cognitive deficits, the group comparison analysis was repeated using MMSE score as covariate. Second, the frequency of disorders (see Supporting Information Methods) in the 8 behavioral domains (global hypoactivity with apathy-abulia; hyperactivity-distractibility-psychomotor instability; stereotyped and perseverative behavior; environmental dependency; anosognosia; confabulations; social behavior disorders; disorders of sexual, eating, and urinary behavior) and 7 cognitive processes (deduction, planning, initiation, generation, shifting, inhibition, coordination) were compared using chi-square test with continuity correction. To ensure that the use of matched controls from the normalization database did not bias this result, the analysis was repeated in 2 subsets of controls, and this is detailed in the Supporting Information Results. Third, the relation with loss of autonomy was determined by comparing the frequency of behavioral (8 domains) and cognitive (7 processes) disorders and of dysexecutive syndrome according to autonomy. This bivariate analysis was followed by a logistic stepwise regression analysis used to

determine whether the criteria of dysexecutive syndrome were related to loss of autonomy. The dependent variable was the loss of autonomy (present, absent), and the independent variables submitted to analysis were age (years), level of education (primary school, secondary school, tertiary schooling), MMSE score, forward digit span, behavioral dysexecutive syndrome (present, absent), and cognitive dysexecutive syndrome (present, absent). Fourth, the hypothesis that dysexecutive patterns differed across diseases was examined by comparing the frequency of behavioral (8 domains) and cognitive (7 processes) disorders and of dysexecutive syndrome between the 6 pathological groups (the Other Diseases group was omitted, as it included heterogeneous pathologies, and Mild Cognitive Impairment was not considered for analysis of behavioral disorders due to small number of data). The analysis was repeated after stratification for loss of autonomy, which differed between pathological groups and presumably influenced results. Analyses were performed using SPSS (SPSS Inc., Chicago, IL), and p values <0.05 were considered as significant.

Results

The Cognitive Dysexecutive Battery was performed for 461 patients (all test performances available in 422), the Behavioral Inventory was performed for 280 patients, and the autonomy status was available for 383 patients. The subgroup of 280 patients with behavioral assessment did not differ from the total sample except for a tendency ($p = 0.056$) regarding pathological group due to more frequent assessment in stroke (Supporting Information Table 2) (age, $p = 0.7$; sex, $p = 0.9$; education, $p = 0.6$). The subgroup of 383 patients with autonomy assessment (Supporting Information Table 2) did not differ from the total sample (age, $p = 0.5$; sex, $p = 0.5$; education level, $p = 0.9$; pathological group, $p = 0.5$).

Comparisons between Patients and Controls

Raw scores of patients differed from controls on the multivariate analysis (Behavioral Inventory, $p = 0.0001$; cognitive battery, $p = 0.0001$) (Table 3). All subsequent univariate analyses were significant except for confabulations, disorders of social behavior, and error on the Stroop reading subtest. The covariance analysis using MMSE score as covariate showed that all comparisons achieved significance (see Table 3).

Frequencies of behavioral and cognitive disorders were usually >20% and were more frequent in patients ($p = 0.001$, all) (Fig 1). Regarding dysexecutive syndrome, both behavioral (patients, 42.1%; controls, 4.8%) and cognitive (patients, 45.8%; controls, 6%) syndromes were more frequent in patients ($p = 0.0001$, both). In addition, we examined the combination of cognitive and behavioral disorders in the 280 patients in whom both cognitive and behavioral indices were available: 113 (40.4%) had no dysexecutive syndrome, 72 (25.7%) presented a combined behavioral and cognitive dysexecutive syndrome, 46 (16.4%) a pure behavioral syndrome, and 49 (17.5%) a pure cognitive behavioral syndrome.

This indicates that (1) all behavioral and cognitive disorders discriminated patients from controls; (2) dysexecutive syndrome discriminated patients from controls; and (3) dysexecutive syndrome was more frequently dissociated with an equal proportion of pure cognitive and pure behavioral syndromes.

Relation between Dysexecutive Syndrome and Loss of Autonomy

Loss of autonomy was observed in 238 patients (62%). All disorders except coordination were more frequent in patients with loss of autonomy (planning, $p = 0.03$; others, $p = 0.0001$) (see Fig 1). Both behavioral and cognitive dysexecutive syndromes were more frequent ($p = 0.0001$, both) in patients with loss of autonomy (behavioral syndrome, 58%; cognitive syndrome, 58%) than without (behavioral syndrome, 16%; cognitive syndrome, 19%). Logistic regression analysis selected the following variables to predict loss of autonomy: (1) behavioral dysexecutive syndrome (odds ratio [OR], 4.6; 95% confidence interval [CI], 2.3–9.1; $p = 0.0001$), (2) cognitive dysexecutive syndrome (OR, 3.36; 95% CI, 1.7–6.6; $p = 0.001$), and (3) MMSE score (OR, 0.79; 95% CI, 0.68–0.91; $p = 0.002$). This indicates that both behavioral and cognitive dysexecutive syndromes are independently related to disability.

Pattern of Dysexecutive Disorders according to the Pathology

The frequency of behavioral dysexecutive syndrome differed according to the diagnosis ($p = 0.0001$); it was more frequent in Alzheimer disease (65%) and traumatic brain injury (57%) (Parkinson disease, 42%; multiple sclerosis, 38%; stroke, 25%). The pattern of behavioral changes was relatively similar according to the diagnosis, with a high frequency of anosognosia and hypoactivity with apathy-abulia (Fig 2). In the subgroup of patients with loss of autonomy, frequencies of behavioral disorders did not differ according to the diagnosis ($p > 0.3$, all; data not shown), except for stereotyped and perseverative behavior ($p = 0.006$), due to higher frequency in Alzheimer disease.

The frequency of cognitive dysexecutive syndrome differed according to the diagnosis ($p = 0.0001$) and was more frequent in Alzheimer disease (73%) and traumatic brain injury (54%) (Parkinson disease, 39%; stroke, 29%; multiple sclerosis, 28%). The pattern differed according to the diagnosis (see Fig 2): (1) generation was predominantly affected in Alzheimer disease, (2) planning was predominantly affected in Alzheimer disease and MCI, (3) shifting was predominantly affected in

TABLE 3: Group Means on the Behavioral Inventory and Cognitive Battery

No.	Patients, n = 461	Controls, n = 461	Group Comparison, *p*	MMSE as Covariate, *p*
Behavioral inventory				
Global hypoactivity/12	3.2 ± 3.6	0.1 ± 0.7	0.0001	0.0001
Difficulties for anticipation/12	2.9 ± 3.6	0.3 ± 1.5	0.0001	0.0001
Disinterest and indifference/12	2.3 ± 3.6	0.4 ± 1.8	0.004	0.0001
Hyperactivity/12	1.5 ± 2.9	0.1 ± 0.4	0.0001	0.0001
Irritability-impulsivity/12	2.0 ± 3.0	0.5 ± 1.6	0.001	0.0001
Euphoria/12	1.2 ± 2.6	0.1 ± 0.4	0.0001	0.0001
Stereotyped behavior/12	1.8 ± 3.0	0.2 ± 0.7	0.001	0.0001
Environmental dependency/12	0.3 ± 1.3	0.0 ± 0.0	0.02	0.02
Anosognosia/12	1.6 ± 3.0	0.3 ± 1.6	0.04	0.0001
Confabulations/12	0.4 ± 1.5	0.0 ± 0.0	0.053	0.0001
Social behavior/12	0.8 ± 2.1	0.2 ± 1.5	0.2	0.005
Sexual behavior/12	0.9 ± 2.6	0.1 ± 0.3	0.01	0.005
Cognitive battery				
Stroop				
Naming, time, s	79 ± 25	64 ± 16	0.0001	0.0001
Reading, time, s	56 ± 16	45 ± 9	0.0001	0.0001
Interference, time, s	161 ± 78	121 ± 46	0.0001	0.0001
Naming, error, %	0.4 ± 0.8	0.2 ± 0.5	0.03	0.0001
Reading, error, %	0.1 ± 0.6	0.0 ± 0.2	0.15	0.0001
Interference, error, %	2.8 ± 7.3	0.6 ± 1.3	0.009	0.0001
Trail Making test				
Part A, time, s	58 ± 33	43 ± 31	0.004	0.0001
Part B, time, s	166 ± 140	101 ± 61	0.0001	0.0001
Perseveration (n)			0.03	0.0001
Fluency				
Literal	17.4 ± 7.7	21.2 ± 7.1	0.0001	0.0001
Animal	24.5 ± 10.2	30.6 ± 8.6	0.0001	0.0001
Modified Card Sorting test				
Category/6	5.1 ± 1.3	5.6 ± 0.9	0.0001	0.0001
Perseveration, No.	3.4 ± 4.1	1.4 ± 2.5	0.0001	0.0001
Dual task, Mu	87.5 ± 14.8	91.6 ± 13.7	0.02	0.0001
Six Element test, rank	4.4 ± 1.7	5.3 ± 1.1	0.0001	0.0001
Brixton, error, No.	18.4 ± 8.4	14.9 ± 7.1	0.005	0.0001

Mu = 100 × [1 − (decrement of digit series recall on dual task + decrement of tracking on dual task)/2]; where dual task decrement of series = proportion of series correctly recalled on single condition − proportion of series correctly recalled on dual condition; dual task decrement of tracking = (number of marked boxes on single condition − number of marked boxes on dual condition)/number of marked boxes on single condition. MMSE = Mini Mental State Examination.

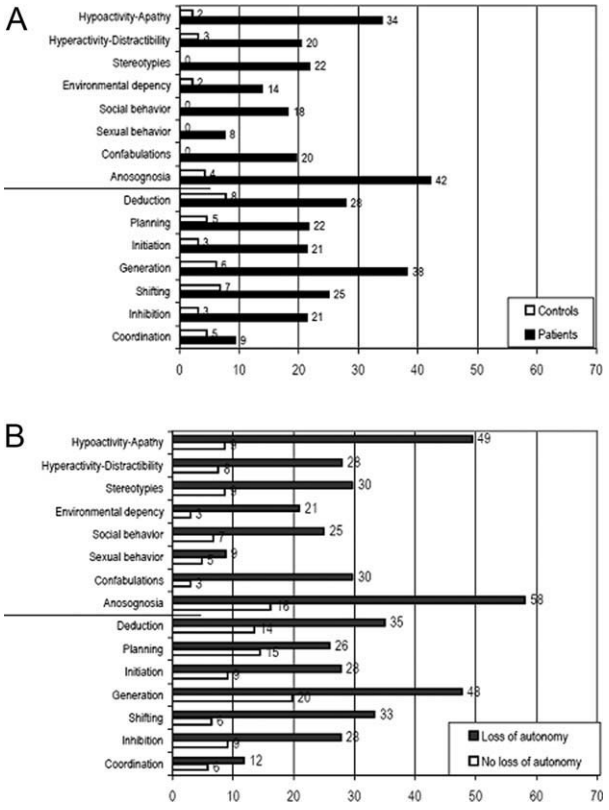

FIGURE 1: Frequency (%) of behavioral (upper part) and cognitive (lower part) dysexecutive disorders in patients and controls (A) and in patients (B) according to the presence of loss of autonomy.

Alzheimer and Parkinson diseases, (4) initiation was predominantly affected in traumatic brain injury and multiple sclerosis, and (5) deduction was predominantly affected in stroke and traumatic brain injury. The differences persisted ($p < 0.03$, all) in the subgroup with loss of autonomy for initiation, generation, and planning (data not shown). This indicates that the pattern of cognitive but not behavioral dysexecutive syndrome was influenced by the underlying disease.

Discussion

This study proposed criteria for dysexecutive syndrome, gave an operational definition based on easily administered tests and questionnaires, and showed that they discriminated between patients and controls, with a higher frequency in patients with loss of autonomy, and that both behavioral and cognitive dysexecutive syndromes were independent predictors of loss of autonomy. In addition, it provided evidence for differing patterns of cognitive disorders according to the underlying disease.

This cooperative study has several limitations. It was a clinical study involving a large number of patients; the complete battery of tests and questionnaires therefore cannot be administered to all patients. A reliable informant was not available in all cases, precluding assessment of behavioral disorders and disability. However, the subgroups did not differ from the complete sample, and the reduction of sample size due to unavailable data did not result in type II error. This study deliberately included patients suffering from various diseases to be representative of clinical populations referred for cognitive assessment. In addition, this transnosological study overcomes numerous biases related to the study of a single disease, such as effects related to associated perceptuomotor deficits (eg, stroke), associated cognitive deficits (eg, memory deficit in Alzheimer disease), or the prominence of one site or type of lesions within the network subserving executive functions. The transnosological study design led us to adopt a common criterion for loss of autonomy based on several severity scales. The loss of autonomy criterion was simple and was assisted by well-validated disability scales.

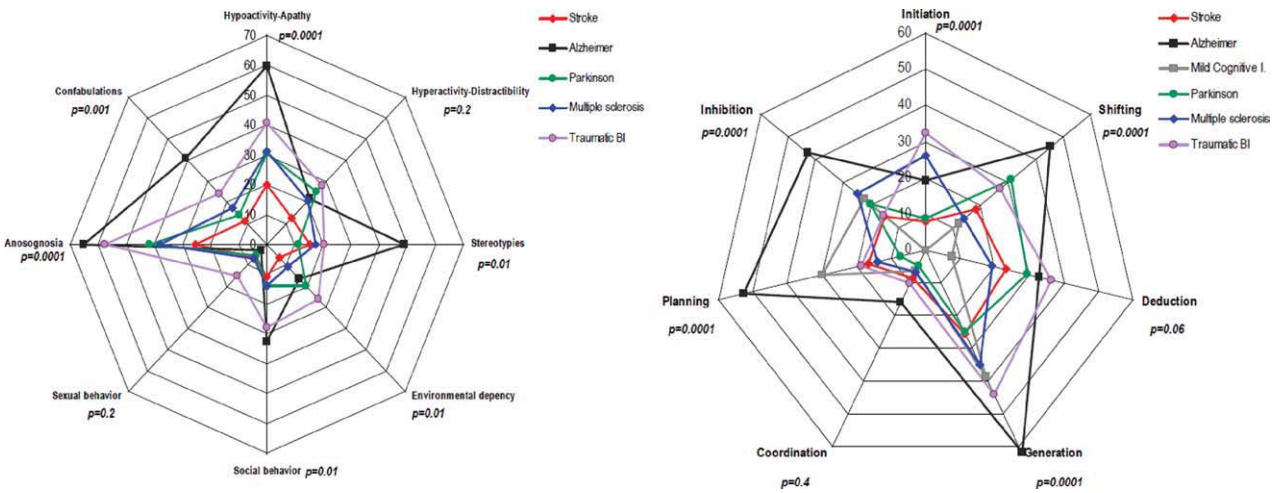

FIGURE 2: Pattern (frequency %) of behavioral (left) and cognitive (right) disorders according to the disease. BI = brain injury; I = impairment.

Our approach provides separate criteria in the behavioral and cognitive domains. This was based on previous reports of dissociated disorders, usually presenting with behavioral disorders unaccompanied by cognitive disorders.[5,7] The present results, obtained in a large group of unselected patients with multiple diseases, support this position, and even revealed that a dissociated disorder was more frequent than the combined behavioral and cognitive syndrome. This is consistent with experimental neuropsychological studies showing prominent impairment of working memory in dorsolateral lesions and prominent impairment of behavioral processes in mediofrontal lesions.[5,7,30] On clinical grounds, the prominence of behavioral impairment has already been reported in mediofrontal damage,[5,7,30] but the reverse pattern remains rarely documented to our knowledge.[31] This indicates that both behavioral and cognitive domains must be examined in clinical practice whenever possible.

The present criteria were strictly defined and operationalized using definite performance indices that have been previously normalized. In addition, the cutoff scores of dysexecutive syndrome were adjusted for the number of indices, and this provides a good specificity (<5% false positive). The validation method was strictly determined and required demonstration that dysexecutive disorders and syndromes (1) discriminate patients from controls and (2) are associated with difficulties in everyday life activities. Both were matched, as dysexecutive disorders and syndromes discriminated patients from controls, and they were related to loss of autonomy. The patient impairment was shown using both raw indices and impaired performance determined with routine norms. Most validation studies are restricted to a unique analysis of frequency of deficits, which provides an indication of the sensitivity of criteria. However, this approach does not provide any indication of the relationship between criteria and difficulties in daily living, which constitute the major outcome in brain diseases. The finding that both behavioral and cognitive dysexecutive syndromes are independently related to loss of autonomy therefore indicates that the present criteria are related to functional outcome. Other factors also contributed to loss of autonomy, such as general cognitive decline indexed by the MMSE and other cognitive and perceptuomotor factors, but this aspect was beyond the scope of the present study. Finally, the effect of anterior versus posterior hemispheric lesions, a traditional design to assess the validity of dysexecutive disorders, was not used, as deficits on executive tests are also observed in posterior lesions,[32] including stroke,[33,34] even when elementary tests are used.[35]

Although the pattern of behavioral disorders differs according to the underlying disease, this difference was no longer observed after controlling for loss of autonomy except for stereotyped behavior. This indicates that the frequency and pattern of behavioral disorders are mainly influenced by the severity of the disease. Accordingly, anosognosia and hypoactivity with apathy-abulia were the most frequent disorders in all diseases. The high frequency of stereotyped behavior in Alzheimer disease is probably related to memory deficit, and this will be examined in a specific study. The pattern of cognitive disorders varied according to the disease, except for dual task coordination and deduction. After controlling for loss of autonomy, differences of pattern were still observed for initiation, generation, planning, and inhibition. This provides an opportunity to determine the subtype of cognitive dysexecutive syndrome and to select sensitive tests according to the disease.

The criteria of dysexecutive syndrome may be improved using 2 recent findings. First, the prediction of frontal stroke was improved when the impairment of strategic processes of episodic memory (defined by false recognitions and efficiency of cued recall) was included, as compared with the sole use of tests of executive functions.[36] This suggests that strategic memory impairment should be an additional criterion of dysexecutive syndrome.[7] Second, the initiation of action is assessed more specifically using a reaction time index derived from the individual distribution.[37] This index differentiates action slowing due to impaired initiation from that due to perceptuomotor slowing.[37] Using such a reaction time test, action initiation depends mainly on mediofrontal regions, as shown by functional magnetic resonance imaging[38] and lesion studies.[39,40] It is impaired in pathologies known to induce attention deficit, such as mediofrontal stroke,[39] multiple sclerosis,[41] and Lewy body dementia.[42]

In conclusion, for the first time, this study provides criteria of dysexecutive syndrome with operationalized performance indices, providing a way to delimitate this poorly defined syndrome and a basis for future clinical and experimental studies. Although the variability of dysexecutive disorders[43] is supported, it is nevertheless possible to group together these disorders into a clinically meaningful syndrome. These findings indicate that both behavioral and cognitive domains must be examined in clinical practice, that their impairment is frequent, with patterns of cognitive deficits differing according to the disease, and that behavioral and cognitive dysexecutive syndromes are related to loss of autonomy.

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Authorship

O.G. and M.R. designed the study and prepared the statistical analysis plan. O.G. wrote the manuscript with assistance from P.A., P.R., M.R., T.M., and D.L.G. M.R. contributed to data analysis. O.G., M.R., P.A., P.R., M.R., T.M., and D.L.G. identified patients or controls. All authors reviewed the manuscript and approved the final draft.

Potential Conflicts of Interest

Nothing to report.

Appendix

The following centers and investigators participated in the GREFEX cooperative study (n number of patients included at each center; investigators): Amiens University Hospital (France) (n 183; O. Godefroy and M. Roussel), Angers University Hospital (France) (n 19; D. Le Gall), Heliomarin Rehabilitation Center Berck (France) (n 15; C. Bertola), Bordeaux University Hospital (France) (n 28; J. M. Giroire and P. A. Joseph), Saint Luc University Hospital Brussels (Belgium) (n 6; X. Seron, F. Coyette), Cholet General Hospital (France) (n 8; E. Bretault and I. Bernard), Ottignies William Lennox Center (Belgium) (n 3; M. Leclercq), Garches University Hospital (France) (n 9; P. Azouvi and C. Vallat-Azouvi), Grenoble University Hospital (France) (n 24; P. Pollack and C. Mosca), Lausanne University Hospital (Switzerland) (n 9; C. Bindschadler), Lay St. Christophe Rehabilitation Center (France) (n 3; M. Krier), Liège Department of Cognitive Sciences (Belgium) (n 19; T. Meulemans and V. Marquet), Lille Stroke Center University Hospital (France) (n 26; D. Leys and M. Roussel), Nantes University Hospital (France) (n 8; P. Renou and M. Vercelletto), Nice University Hospital (France) (n 6; E. Michel and P. Robert), Nîmes University Hospital (France) (n 15; P. Labauge and C. Franconie), Paris-La Salpétrière University Hospital Neurology Department (France) (n 18; B. Pillon and B. Dubois), Paris-La Salpétrière University Hospital Geriatrics Department (France) (n 13; B. Dieudonnée and M. Verny), Paris-Broca University Hospital (France) (n 5; H. Lenoir and J. De Rotrou), Rouen University Hospital (France) (n 56; D. Hannequin and S. Bioux), Sion Rehabilitation Clinic (Switzerland) (n 12; J. Fuchs, A. Bellmann, and P. Vuadens).

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