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Olivier Godefroy

Frontal syndrome and disorders of executive functions

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Pr. O. Godefroy (✉)
Service de Neurologie
CHU Nord
80054 Amiens, France
Tel.: +33-3 22/6 68-2 40
Fax: +33-3 22/6 68-2 44
E-Mail: godefroy.olivier@chu-amiens.fr

Abstract The study of executive functions began with the early description of behavioural disorders induced by frontal damage. The development of experimental neuropsychology has led to the description of a large variety of cognitive disorders. Such approach has generated numerous tests that are used in clinical practice. More recently, theoretical approaches have proposed an organisation of executive processes and have documented the diversity of executive functions and related anatomy. These studies have deeply influenced the clinical approach, the assessment and the diagnosis of planning and executive disorders. For clinical practice, these data have favoured specific assessment of some key behavioural and cognitive deficits based on a battery of tests.

Key words executive functions · frontal syndrome · planning · controlled processes

Introduction

Executive functions refer to high-order functions operating in non-routine situations such as novel, conflicting or complex tasks. The term executive functions (and dysexecutive syndrome) is now frequently preferred to frontal functions (and frontal syndrome) because an impairment of these functions has also been observed in patients with non-frontal lesions. A large number of pathologies involving the prefrontal cortex, or deep structures such as the striatum or the thalamus may disrupt executive functions (Table 1), and compromises the patient's autonomy. The complexity of these functions and related disorders is well known and possibly contributes to their underevaluation. Recent studies have shed some light on deficits of executive functions and have contributed to improve clinical assessment.

Table 1 Main pathologies compromising executive functions

Stroke	Arterial Infarct: deep or anterior middle cerebral artery, anterior cerebral artery, thalamus (paramedian infarct), Cerebral venous thrombosis: superior sagittal sinus Ruptured aneurysm: anterior communicating artery, pericallosal artery Haemorrhage: frontal, striatum and thalamus
Other focal lesions	Tumours, abscess: frontal, third ventricle, striatum and thalamus
Dementia	Vascular dementia Subcortical dementia (Progressive supranuclear palsy, Huntington's disease, Parkinson's disease) Fronto-temporal dementia Cortico-basal degeneration Alzheimer's disease
Closed head injury	
Inflammatory	Multiple sclerosis NeuroAIDS Encephalitis
Hydrocephalus	

From behavioural disorders to cognitive approaches

The early descriptions of clinical consequences of frontal damage have documented a large variety of behavioural disturbances such as abulia, apathy, aspontaneity, akinetic mutism, pseudodepressive state, lack of drive, poor motivation, euphoric state, distractibility, impulsivity, disinhibition, irritability, restlessness, moria, pseudopsychopathic state, anosognosia, indifference, confabulation, and perseveration [4, 16, 24, 30]. This area is still evolving and, for example, imitation and utilisation behaviour, psychic akinesia and athymhormia have been reported more recently [23, 26, 29]. A comprehensive review is beyond the scope of this paper [47] which summarises the main behavioural disorders. Some terms refer to similar clinical conditions (e. g. apathy, abulia, aspontaneity and pseudodepressive state are used interchangeably) and have been produced by different approaches of behaviour focusing on alteration of emotion, social interaction or cognition [47]. From a clinical point of view, the recognition of behavioural disturbances is very important because it suggests or allows the diagnosis of frontal syndrome and has important consequences on the patient's autonomy. In order to simplify the clinical assessment, a French cooperative group [22] has proposed a list of the main behavioural changes which separates highly suggestive and supportive disorders (Table 2). The improvement of the diagnosis of behavioural changes would require us to determine the deficits of processes underlying clinical disturbances. Such approach has been produced by neuropsychological studies.

The development of experimental neuropsychology has documented numerous cognitive deficits observed on specific tasks. For example Milner [32] has shown that damage of the dorsolateral prefrontal cortex results in a specific pattern of impairment on the Wisconsin Card Sorting test. Luria [30] has suggested that behind the clinical diversity of frontal syndromes, patients were more specifically impaired in situations that require goal formulation, planning, carrying out goal-directed plans, and verification. This approach has been very influential and implicitly assumes that the unity of frontal functions lies in the domain of control functions operating in non-routine situations. Experimental neuropsychology has generated a large number of tests that are still used in clinical practice. Although these studies have provided essential contributions to clinical neuropsychology and theoretical approaches, several limitations have become apparent. First, most tests involve several executive and non-executive processes. This leads to complicated interpretations in clinical practice (several factors have to be controlled before interpretation) and from a heuristic point of view, it hinders the determination of the underlying cognitive deficit. Test complexity may also contribute to the impairment of some patients with posterior damage. Secondly the ecological validity, i. e., the relations between test performances and disability, has been poorly addressed.

These considerations suggest that future advances depend on a better characterisation of executive processes, using conceptual framework integrating various processes, and on the examination of ecological validity. Such objectives have been developed in a large number of recent studies focusing on supervisory processes [43, 45], working memory [1, 2, 8, 21], attention [39] and emotion [10] (for review: [27, 42]). From a clinical perspective, the present paper will review some recent results focusing on supervisory and planning processes.

Table 2 Main behavioural disorders suggestive of dysexecutive syndrome (adapted from [22])

Highly suggestive
Global hypoactivity with abulia-apathy-aspontaneity
Global hyperactivity with distractibility-impulsivity-disinhibition
Perseveration and stereotyped behaviour
Syndrome of environmental dependency (imitation and utilisation behaviour)
Other supportive features
Confabulation and reduplicative paramnesia
Anosognosia and anosodiaphoria
Disturbances of emotion and social behaviour
Disorders of sexual behaviour and control of micturition

Cognitive deficits: disorders of planning and related processes

Following Luria's approach, Norman and Shallice [33] have proposed a model where action is regulated at different levels and where the control of non-routine actions depends on a specific system, the supervisory system. The supervisory system is supported by the prefrontal cortex and is assumed to operate in novel, conflicting or complex situations, when the previously learned schemas are not able to cope with the situation. The model predicts several empirical observations in patients with frontal lobe damage (in whom the supervisory system is impaired), such as the prevalence of disorders in nonfamiliar situations, the inability to inhibit prepotent schemas, the inappropriate use of routine procedures, and utilisation behaviour, i. e., the tendency to pick up and use objects when they are presented incidentally [43]. Shallice et al. [43] have suggested that one key function of the supervisory system consists of planning. They have designed a problem-solving test, the Tower of London, which requires to use advance planning of sequences of moves. It uses coloured balls which

have to be moved into a new configuration in a minimum number of moves. The task difficulty is indexed by the number of moves needed to achieve the new configuration. Patients with frontal damage solved fewer problems and took more moves to solve problems than posterior-damaged patients [34, 43]. In addition, PET studies have shown that the difficult conditions of the test are associated to higher prefrontal activation [3]. These results provide evidence for the role of the frontal lobes in planning. However, this task engages multiple processes such as mental imagery and working memory and further studies were carried out to characterise executive processes.

Response initiation and suppression

These deficits are frequently observed during clinical examination when the patient is slow to answer or to initiate action and when he provides a wrong answer indicating that he is unable to suppress an automatic response. Early neuropsychological studies have shown that frontal lesions can cause deficits in both response initiation (assessed by verbal fluency tests) and response suppression (assessed by Go/No-go or Stroop tests) [13, 30, 37]. Both deficits seem to arise from opposite disorders: deficit of response initiation suggests a disorder of fast activation of routine response, and deficit of response suppression, a disorder of inhibition of fast, prepotent response. The origin of such conflicting findings has been examined in recent studies.

Burgess and Shallice [5] have designed the Hayling test. Subjects were given a sentence with its final highly significant constrained word removed: in part A, they had to complete the sentence as quickly as possible (e. g.: 'he mailed the letter without a . . . stamp'), and in part B, to complete with any word that makes no sense (e. g.: 'most cats see very well at . . . talk'). Frontal damage resulted in slower responses on part A suggesting a deficit of response initiation, and higher error rate on part B, suggesting a deficit of response suppression. Additional analyses showed that normal subjects generated strategies to avoid the production of automatic responses in part B (mainly the use of a name related to the previous sentence or to an object in the room) and that these strategies were less frequently used by frontal-damaged patients. This result suggests that the deficit of response suppression is due to the persisting use of the routine naming schema and a decreased strategy use. Finally, double dissociation was evidenced indicating that some patients had only an impairment of response initiation and others, of response suppression.

A very similar pattern of performance was observed by Godefroy et al. [18] using simple reaction time (SRT) and Go/No-go tests in patients with post-aneurysmal frontal damage. Tests used mixed auditory and visual stimuli. In the SRT test, subjects had to respond as fast as possible to all stimuli, and in Go/No-go tests, to respond only to stimuli of one modality. Frontal damage resulted in slower SRT and higher error rate on Go/No-go tests. Additional analyses showed [1] that slower SRT was due to a lower proportion of fast responses indicating that the basic deficit concerned the ability to repeatedly initiate fast responses [20], and [2] that errors on Go/No-go tests were associated with excessive sensitivity to variation of stimulus modality (as in the SRT test), suggesting that the deficit of response suppression was due to the persisting use of the SRT schema. Finally, double dissociation was evident.

The two studies performed in different populations and using different tests show striking similarities between the patterns of performances of frontal patients. They provide consistent evidence for deficit of response initiation and suppression in frontal-damaged patients, and suggest that the disorder of response suppression may be secondary to the persisting use of inappropriate routine schemas, and to the decreased use of strategy. The observation of selective deficits strongly suggests that both processes, response initiation and suppression, are separable and presumably are supported by distinct frontal areas.

Problem-solving, rule deduction, cognitive flexibility and strategy

These deficits are frequently noticed in frontal-damaged patients when they make perseverations (especially if they repeatedly use the same rules), they are unable to cope with a simple problem, and they use inappropriate rules. These deficits are well known in patients with frontal damage [31, 32] and are mainly assessed in clinical practice using the Wisconsin Card Sorting test. This test has been found to be more frequently impaired in frontal damage but may be also impaired in patients with non-frontal damage [22]. The nature of impairment on such complex tasks remains unclear and may involve the failure to identify rules, inability to use feedback and inflexibility in switching cognitive sets (responsible for perseveration). Delis et al. [12] have proposed a new sorting task with several conditions ('spontaneous' sorting, naming rules for sorts performed by the examiner, and sorting cards according to cues provided by the examiner) which enabled the examination of each component. They showed that impairment of frontal-damaged patients was mainly due to the deficit of generation of abstract principles, and to a lesser extent, to deficit of cognitive flexibility and inability to use knowledge to regulate behaviour. The presence of multiple deficits was also suggested in a study of Burgess and Shallice [5] using the Brixton test. Subjects were presented with successive pages representing 10

circles, one of them being filled. The position of the filled circle differed from one page to the next according to rules that had to be discovered. Nine rules were used that change in unsystematic fashion. The impairment of frontal-damaged patients was mainly attributed to premature abandon of a correct rule and a greater tendency to guess. Accordingly, Partiot et al. [35] have reported the presence of premature abandon of correct rules in patients with fronto-striatal disease.

To investigate executive functions, one promising possibility is to examine the subject's strategy. Deficit of strategy use has already been mentioned in the Hayling and Brixton tests [5, 7]. Using a spatial working memory task [34, 38] the consistency of search strategy was found to be impaired in frontal-damaged patients. In a study of Levine et al. [28], a deficit of strategy use was observed in some patients with frontal damage or traumatic brain injury. It used an adaptation of the Six Elements task [44] which required the patient to perform three simple tasks within five minutes. Since there were more items than could be completed within five minutes, subjects had to apply a strategy of selective completion of items which provided the maximum number of points.

These results support the notion that problem solving tests engage multiple and coordinated executive processes such as generation of abstract principles and strategy, rule deduction, maintenance and shifting of sets, and verification. For clinical practice, these results indicate that the patient impairment on a test such as the Wisconsin Card Sorting test cannot be attributed to a single deficit (e. g., cognitive shifting) and the level of the underlying deficit may differ according to the lesion location.

Diversity and unity of executive functions

The diversity of clinical presentation of frontal syndromes is well known. For example, some frontal-damaged patients may mainly exhibit behavioural disturbances whereas their performances on neuropsychological tests is not so much impaired [15]. Within the cognitive domain, clinical practice and some studies have shown that performances on various tests assessing executive functions may be dissociated, a deficit being observed on some tests and not on others [14]. For example, in a study using decision tasks subjects were trained to a basic version and three modifications requiring different control processes (use of novel response-stimuli associations, temporary inhibition of response, and coordination of sequential tasks) were introduced that left the basic requirement unchanged [17, 19]. Taking into account reliability of the tests, novel decision, inhibition and tasks coordination were selectively impaired suggesting that they depend on different executive processes. Series of experiments in animals, normal and brain-damaged subjects [36, 40, 41] have documented dissociations between executive processes and their anatomy.

The interpretation of dissociated deficits differs according to conceptions of executive functions. The recent version of Shallice's model [45] assumes that executive functions depend on several processes such as strategy generation, implementation of new schema and verification which have been documented in several studies. According to this model, the diversity of deficit is related to the nature of the impaired processes. Within the framework of working memory, dissociated deficits are interpreted in terms of the nature of stored informations [25]. Briefly, working memory is a system required for temporary storage and cognitive manipulation of information. According to Baddeley's model [1], working memory depends on a central system (the central executive) and on slave modality-specific systems which are responsible for the temporary storage of information. Impairment of storage capacity, assessed using forward spans, has been mainly observed in parieto-insular lesions [11, 46]. Conversely, processes accounting for the manipulation of information and coordination of simultaneous tasks were found to depend on the prefrontal cortex [2, 8, 9] with a location varying according to the nature of information [21, 49]. The somatic marker hypothesis [10] accounts for the presence of some behavioural disturbances in patients with otherwise spared cognitive abilities on neuropsychological tests. This approach assumes that behaviour is regulated partly by somatic markers which include emotions and feelings. Ventromedial prefrontal lesions would disrupt the use of somatic markers and this results in choices that are not personally advantageous or socially adequate.

These approaches suggest that the clinical diversity is due to the functional heterogeneity of the frontal lobes and that the lesion location determines the impairment of cognitive or emotional processes, or of stored information. These conceptions are not exclusive and they will probably allow a fragmentation of the frontal syndrome into several subsyndromes. For clinical practice, these data indicate that it is preferable to assess several cognitive processes using a systematic strategy.

Relationships between behavioural abnormalities and cognitive deficits

The relationships between clinical abnormalities of behaviour and cognitive deficits observed on formal testing have been examined in a few studies. Some clinical disorders such as distractibility and impulsivity were found to be related to attentional deficits as measured on neuropsychological tests [2, 18]. In a large series of brain

damaged patients of varying aetiologies, Burgess et al. [6] showed multiple correlations between neuropsychological tests (Modified Card Sorting test, Trail Making test, Verbal fluency, and Six Elements Test) and behavioural abnormalities assessed by a questionnaire covering common symptoms of frontal syndrome. These data are consistent with the hypothesis that some behavioural abnormalities such as distractibility are the external manifestations, clinically assessable, of disorders of attention and executive functions. However, other behavioural disorders have not been linked to cognitive deficits and may be due to disorders of emotional processes [10].

Table 3 Main cognitive disorders suggestive of dysexecutive syndrome (adapted from [22])

Highly suggestive
Response initiation; response suppression and focused attention Rule deduction; maintenance and shifting of set Problem-solving and planning Information generation
Supportive deficits and developing areas
Tasks coordination and divided attention; sustained attention Strategic mnemonic processes 'Theory of mind' [48]

Conclusions for the clinical practice

The observation of dissociated cognitive and behavioural disorders in frontal-damaged patients should lead to the use of systematic assessment of some key behavioural and cognitive disorders. Although clinical assessment is essential for the diagnosis and identification of behavioural abnormalities, it may underestimate the presence of cognitive deficits, and a formal assessment based on tests should be performed when possible. The use of questionnaire may be very useful for the assessment and the follow-up of behavioural disorders. Since cognitive impairment may differ according to the pathology, the recommendation is to use a battery of tests assessing different executive processes such as those listed in Table 3. The choice of tests remains open and is beyond the scope of this study. A combination of tests assessing response inhibition, rules deduction, set maintenance and shifting, planning and information generation has been proposed [22]. Future studies documenting the patterns of associations and dissociations of executive disorders across pathologies will further improve clinical assessment.

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