Acta neurol. belg., 2005, **105**, 187-196

Functional imaging of executive functions

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Summary

Executive functioning refers to cognitive processes that facilitate our adaptation to new or complex situations when action routines are not efficient. Neuropsychological studies in brain-damaged patients suggested that executive functions were predominantly dependent on prefrontal regions. However, prefrontal lesions frequently occurred in a context of more widespread brain involvement, and a dysexecutive syndrome was described in posterior cortical dementia of the Alzheimer type. Functional imaging can precisely identify brain networks involved in executive functioning. We discuss functional imaging studies that show both frontal and posterior activation during executive tasks and bring information concerning unity and diversity in executive processes.

Key words : executive functions, functional imaging

Introduction

Executive functioning refers to cognitive processes that facilitate our adaptation to new or complex situations when action routines are not efficient. In such situations, the intervention of control processes is required. These control (or executive) processes include a great number of distinct functions, such as inhibition of prepotent responses, initiation of behavior, planning of action, hypothesis generation, cognitive flexibility, judgment and decision making or feed-back management.

The existence of distinct executive functions was initially based on studies of brain-damaged patients. Dissociations were described in patients with intact performances for a conceptual inhibition task (the Hayling test) but impaired abilities for rules detection (Brixton test), while an inverse profile was described in other subjects (Burgess & Shallice, 1994 ; Shallice & Burgess, 1993). Results of group studies were also consistent with the existence of distinct executive processes (Letho *et al.*, 1996 ; Robbins *et al.*, 1998 ; Duncan *et al.*, 1997). For example, distribution of resources during simultaneous realization of two tasks, modification of strategies to retrieve information, selective attention (and particularly inhibition) and activation of information in long term memory were considered as individual executive functions (Baddeley, 1996).

In a recent work, the diversity of executive functions or their unity (in the sense that they would depend on a same basic mechanism) was questioned (Miyake *et al.*, 2000). The authors administered to a large sample of young volunteers a series of tasks that tapped updating (i.e. the modification of working memory content according to new entries), flexibility (the controlled displacement of attention from one stimulus to another, or from one cognitive process to another) and inhibition (preventing non-pertinent information to disturb a current task). Confirmatory factor analyses confirmed that those three executive functions were clearly separable, but that there remained some relationship between them. So, updating, flexibility and inhibition processes could be discriminated one from the other, but they were not totally independent, so that they would share common processes. The authors suggested that those common processes might be related to the need to maintain in working memory information about the goal and the context of the current action, or might correspond to basic inhibition mechanisms.

The brain substrate of executive functions : neuropsychological studies

Neuropsychological studies in brain-damaged patients suggested that executive functions were predominantly dependent on prefrontal regions (Shallice, 1982). Lesions in the frontal lobe were effectively accompanied by deficits in abilities for planning and flexibility, inhibition capacities and rules detection (Burgess & Shallice, 1996 a et b ; Cowey & Green, 1996 ; Milner, 1964 ; Owen *et al.*, 1990 ; Shallice, 1982). However, the exclusive implication of prefrontal regions was questioned. Patients with frontal lesions did not always show impaired performances in executive tasks. So, groups of patients had normal performances in fluency tasks (Ahola *et al*. 1996), dual tasks coordination (Andrès & Van der Linden, 2002), inhibition (Andrès & Van der Linden, 2001, 2002), planning (Andrès & Van der Linden, 2001 ; Cockburn, 1995) and rule detection tasks (Andrès & Van der Linden, 2001). Moreover, prefrontal lesions frequently occurred in a context of more widespread brain involvement (for example in patients with long-standing epilepsy or when lesions passed beyond frontal boundaries). Other data suggested that patients with non-frontal lesions might present executive dysfunction. For example, patients with non-frontal lesions showed important "perseveration" errors at a categorization task such as the Wisconsin card classification test (Mountain et Snow-William, 1993).

The brain substrate of executive functions : functional imaging in control subjects

Functional imaging techniques such as positron emission tomography (PET) activation studies using radiolabeled water and functional magnetic resonance imaging (fMRI) constitute interesting alternatives for studying executive processes. They could precisely identify brain regions involved in executive tasks and bring information concerning unity or diversity in executive processes.

Cognitive subtraction in functional imaging

Most studies of executive processes in control subjects relied on tasks similar to those used with brain-damaged patients, and experimental paradigms frequently rested on "cognitive subtraction". The general principle is to compare brain activity in two conditions, (1) during the realization of the experimental executive task and (2) during a control task comprising similar motor, perceptive and memory components, but no executive processes. Comparing cerebral activation obtained in experimental versus control condition allowed to emphasize brain regions specifically associated to recruitment of executive processes. Several studies explored updating, inhibition (Stroop, go/no-go, Hayling task), categorization (Wisconsin card sorting test), divided attention (dual tasks), planning (Tower of London), random generation and flexibility in fluency tasks. An important heterogeneity was observed in brain regions activated by these executive tasks (Collette & Van der Linden, 2002). As a general process, manipulation of information in updating tasks recruited different frontal regions in both left and right hemisphere, but involvement of the parietal cortex was not always observed. For inhibition, prefrontal regions intervened, but according to the task, temporal areas and (to a lesser extend) parietal cortices were also activated. Parts of the prefrontal cortex were also recruited for planning and random generation, but involvement of some additional temporal or parietal regions was reported. For dual tasks coordination, a specific activation in bilateral prefrontal and anterior cingulate cortex was emphasized in one study (D'Esposito *et al*., 1995). In another publication, however, performance of dual tasks was accompanied by an increase of activity in regions already recruited by simple tasks, so that this executive function was suggested to depend on complex interrelations between systems specialized in processing information related to each simple task (Adcock *et al*., 2000).

In summary, frontal regions play a key role in executive processes, but posterior cortices (such as parietal areas) would also intervene during executive tasks; leading to the conclusion that executive functioning is then subserved by a distributed anterior and posterior cerebral network. In this network, dorsolateral prefrontal cortex and anterior cingulate are frequently activated by different executive tasks and could house very general processes. For example, dorsolateral prefrontal cortex (Brodmann's area 9/46) appears to play a role in monitoring information and responses (Owen, 2000). Anterior cingulate is associated to conflict monitoring (Bush *et al*., 2000). Other regions, such as frontal BA 44, 45 or 47, and parietal BA 7 and 40 are less systematically engaged, and they would subserve more specific executive processes. It is also important to emphasize the existence of heterogeneity in brain activations reported for a same executive task between different studies.

Different theoretical and methodological limitations of subtraction studies may explain discordances between studies in the literature (Burgess, 1997 ; Rabbit, 1997). Firstly, numerous cognitive functions were attributed to the executive system, but the nature of those functions and their possible interrelationships were not always well established. Secondly, most tasks in the literature can hardly be considered as "pure" measures of executive functioning, and the performance of participants would be contaminated by their ability to realize non-executive components of the experimental paradigm. Moreover, each executive function can be evaluated by different tasks. For example, inhibition can be studied using the Stroop test (Stroop, 1935), the Hayling task (Burgess & Shallice, 1996b), or the stop-signal task (Logan, 1994).

From a cognitive viewpoint, there might not exist a systematic relationship between specific executive processes and tasks. For example, the Wisconsin card sorting task (Milner, 1963) was used to assess the brain substrate of inhibitory processes (e.g., Konishi *et al*., 1999), but other authors used it to explore cerebral areas associated to flexibility abilities (Naghama *et al*., 1996). This is due to the multi-determined nature of many executive tasks. So, the choice of an experimental task for a neuroimaging study is quite important. But the choice of a control task is also crucial. So, the Tower of London task (Shallice, 1982) is considered to recruit abilities for action planning, but other processes such as inhibition and updating also intervene. If a control task is matched only for perceptive and motor aspects, it will not be possible to determine which brain regions are devoted to the specific executive component of planning.

Moreover, when non-executive components are comprised in executive tasks, they may influence brain activation, and be erroneously associated to the experimental executive process. For example, in an updating task, participants saw series of 6 to 10 letters presented one by one on a screen. They did not know the length of each series, and they had to retrieve only the last 6 letters. In such a task, subjects need to continuously update the content of their working memory according to newly presented letters. Serial recall in this task requires the intervention of the phonological loop, while updating recruits central executive resources (Morris et Jones, 1990). A cognitive subtraction between an experimental updating task and a control task tapping the phonological loop could isolate brain regions specifically involved in the executive process. The task was used in a study where participant had to decide if a probe letter was included in the last six items of a series of consonants (Salmon *et al*, 1996). The control task was similar but contained only 6 consonants (no need for updating). Activation was observed in the frontal lobe (left and right middle frontal gyrus and right frontal pole) and in the parietal lobe (right inferior parietal and left supramarginal gyrus). Those data were consistent with a prefrontal involvement in central executive functions, but suggested also that the neural substrate of updating might be distributed between anterior and posterior cortices (D'Esposito & Grossman, 1996 ; Fuster, 1993 ; Morris, 1994 ; Weinberger, 1993). However, a problem with this study was that the initial serial recall used by Morris and Jones was changed in a recognition task. Recognition appeared to induce a preferential recruitment of the visuo-spatial sketchpad for temporary storage of visual information, which could explain activation of the parietal cortex in the experimental task. Moreover, 6 letters correspond to a memory load that is close to the span, so that the central executive might already intervene in the control task.

Consequently, a second study was designed with a load of 4 letters and with a serial recall task to promote the use of the phonological loop. The updating task was accompanied by a left frontopolar activation and an involvement of left middle and inferior frontal cortices. The comparison with the previous task demonstrates that load and response modality do modulate brain activation during the updating process.

CONJUNCTION STUDIES

In conjunction studies, different tasks can be used to explore a common executive process, and the non-executive components are not retained in the analysis if they are different between tasks. Effectively, conjunction is used to emphasize common activation between different experimental paradigms tapping similar processes.

We recently explored the cerebral substrate of three executive processes, updating, flexibility and inhibition, that were clearly dissociated from a cognitive viewpoint (Miyake *et al*., 2000). The cognitive tasks were adapted to the PET procedure, and control paradigms were constructed.

UPDATING

Previous studies of the updating process used either *«running span»* tasks with verbal material (Salmon *et al*., 1996 ; Van der Linden *et al*., 1999), or *«n-back»* tasks using letters, spatial location or visual patterns (Braver *et al*., 1997 ; Jonides *et al*., 1997 ; Schumacher *et al*., 1996 ; Smith *et al*., 1996). Brain activation was observed in prefrontal regions (dorsolateral, inferior prefrontal and anterior cingulate cortices), but also in parietal areas ; a predominant frontopolar involvement was suggested (Van der Linden *et al*., 1999).

Our experimental design comprised three different updating tasks, using consonants, words and sounds (Collette *et al*, 2004). Subjects had to process series of items of unknown length, and the response was a retrieval (or an identification) of a specific number of the last items presented. Control conditions involved temporary storage of items without updating. More precisely, the updating task with consonants was similar to that described for a previous study (Van der Linden *et al*., 1999). For semantic information updating, concrete words were presented on a screen and subjects had to categorize each item. There were three to four categories, and the task consisted in keeping only the last word of each category in working memory. In the control task, only exemplars of a single category had to be memorized. In the last experimental conditions, sounds with different pitches (high, medium, low) were randomly presented and the task was to update the number of presentations to identify the fourth occurrence of each sound. In the control task, subject identified each occurrence of a predetermined sequence of three sounds.

Globally, participants made more errors for the updating tasks than for the temporary storage of information. A conjunction analysis of brain activation for the three studies demonstrated an antero-posterior brain network subserving all updating tasks : left frontopolar cortex, right middle frontal gyrus, right premotor cortex, right inferior parietal, left superior parietal cortex, and cerebellum. Each individual updating task was associated to a preferential activation of a specific set of those regions.

In summary, those results indicate that updating is related to the activation of a cerebral network of precise frontal, parietal and cerebellar regions in both hemispheres, which appears independent of the material used for the task. The updating process is subserved not only by prefrontal, but also by parietal and cerebellar regions. Different regions in the network are more especially activated according to the specific characteristics of the task (material, response modality). This allows to explain different patterns of activation observed in previous reports on updating (Salmon *et al.*, 1996 ; Van der Linden *et al.*, 1999). The number of regions involved in the network would suggest that different cognitive processes intervene when a task requires that information be updated.

Flexibility

There are two different aspects of cognitive flexibility, i.e. reactive and spontaneous flexibility (Eslinger & Grattan, 1993). Reactive flexibility is the ability to displace attentional focus from one stimulus to another or from one cognitive operation to another. Spontaneous flexibility is the capacity to produce a flux of ideas or responses following a single question.

Functional imaging studies indicate that reactive flexibility is related to activation in prefrontal, parietal and subcortical regions (Fink *et al.*, 1997 ; Gurd *et al.*, 2002 ; Konishi *et al.*, 1998 ; Rogers *et al.*, 2000 ; Sohn *et al.*, 2000 ; Wilkinson *et al.*, 2001). Those studies explored flexibility between different dimensions of a stimulus (e.g. Konishi *et al.*, 1998), between different cognitive tasks (Sohn *et al.*, 2000) and between different processing levels (Fink *et al.*, 1997). Spontaneous flexibility was investigated with fluency tasks. When both semantic and phonemic fluency tasks are compared to resting state, common activation is observed in the inferior frontal gyrus (BA 45) and in left dorsomedial thalamic nucleus (Paulesu *et al.*, 1997). Phonemic fluency is characterized by a specific activation of the posterior part of the inferior frontal gyrus (BA 44/6) and of the left insula, while semantic fluency is accompanied by a left retrosplenial activation (BA 30/31).

We used a conjunction analysis to determine the neural substrate of reactive flexibility. Flexibility tasks consisted in alternating between cognitive processes or between different aspects of the stimuli. Three conditions were administered : arithmetic, verbal categorization and visual categorization.

In the arithmetic condition, one of the control tasks consisted in adding 3 to a number displayed on a screen. The second control task required subjects to subtract three from the presented number. In the experimental task, participants had to alternate between adding and subtracting three to each presented number.
For verbal categorization, subjects viewed pairs of number and letter (for example 7G). In one of the control tasks, the pairs were displayed in the upper half of the screen and participants had to classify the number as even or odd. In the other control task, the pairs were presented in the lower half of the screen and the letter had to be categorized as consonant or vowel. The flexibility task consisted in alternating between number and letter processing according to the upper or lower location of the pairs.

For visual categorisation, hierarchical geometrical figures were used : for example, a global figure such as a large triangle was composed of local figures consisting in little squares (Navon, 1977). In one of the control tasks, subjects had to count the number of sides in the large figure drawn with continuous lines. In the second control task, the drawing consisted in dotted lines and participants had to identify the number of sides in the local figure. The experimental task necessitated to determine the number of sides of the global figure when lines were continuous, and the number of sides of the local figure when there were dotted lines.

Behavioural data showed that performances were lower in flexibility than in control tasks. The conjunction analysis of brain images demonstrated an activation of bilateral parietal regions, predominant in the right intraparietal sulcus. Moreover, subtraction analysis (functional imaging in experimental compared to both control tasks) demonstrated right middle frontal activation for the flexible arithmetical task, and a predominant left parietal involvement with a supplementary temporo-occipital recruitment for shifting between visual categorizations.

Those results suggest that parietal regions can be considered as the neural substrate of reactive flexibility, independently of the material to process. Even if parietal regions were frequently associated to the realization of executive tasks, their role was rarely discussed in terms of genuine executive processes. However, parietal areas were often involved in attentional functions (Cabeza & Nyberg, 2000). In this context, there are two interpretations for the results of conjunction analysis : (1) parietal regions are directly involved in executive functioning and would subserve specific executive (sub)-processes; (2) the single common aspects for all three flexibility tasks are attentional (not executive) processes. In keeping with this idea, its important to highlight the close overlap between the concepts of executive and attentional functions. Similar tasks can be classified as executive or attentional according to the general theoretical framework in which they are used.

Thus, parietal regions are involved in executive processes. Surprisingly, the conjunction analysis did not show any prefrontal area common to the three reactive flexibility tasks. Noteworthy, previous neuroimaging studies showed more systematic activation of parietal than prefrontal regions in different tasks recruiting flexibility capacities (Collette & Van der Linden, 2002; Wager *et al*., 2004). Moreover, neuropsychological reports also indicate that patients with frontal lesions do not necessarily suffer from a decrease of flexibility capacities. On the contrary, a patient with parietal lesion showed low performances at flexibility tasks (Gehring & Knight, 2002).

Besides a common activation, they are different brain areas recruited according to the precise requirement of each task. The results indicate that flexibility capacities depend on two types of processes : (1) a general process, highlighted by the conjunction analysis, depending on parietal regions; (2) individual flexibility processes specific for each task, involving peculiar brain areas. The hypothesis of distinct flexibility processes was confirmed by neuropsychological studies, showing, for example, that a part of the switch deficit in focal right inferior frontal lesions could be accounted for by impaired inhibition of appropriate response or task-sets, while weak top-down control in shifting tasks was related to left middle frontal gyrus lesions (Aron, 2004).

INHIBITION

Inhibition is the third type of executive process isolated by Miyake *et al*. (2000). Inhibitory control is generally viewed as one of the most important executive function, and inhibitory impairment is one of the most frequent consequence of brain lesions (Baddeley, 1986 ; Norman & Shallice, 1986). Different types of inhibitory control can be distinguished, and particularly those (1) preventing access of non-pertinent information for the current task, (2) preventing the production of predominant but inadequate responses and (3) suppressing information when it becomes irrelevant (Hasher, Zacks & May, 1999). Most neuroimaging studies that explored inhibition processes have used variants of the Stroop paradigm and showed increased brain activity during the interference (or inhibition) condition in the anterior cingulate and right orbitofrontal regions (Bench *et al*., 1991 ; Larrue *et al*., 1994 ; Pardo *et al*., 1990). Moreover, some studies demonstrated an activation in left inferior frontal regions (Bush *et al*., 1998 ; Georges *et al*., 1994, Taylor *et al*., 1997), and in temporal and parietal cortices (Bush *et al*., 1998 ; Taylor *et al*., 1997). In other reports using different paradigms implicating semantic or motor inhibition, different cingulate, frontal and parietal areas were involved (Collette *et al*., 2001 ; Chee *et al*., 2000 ; Garavan & Stein., 1996).

To determine the neural substrates of different inhibition tasks, we performed a conjunction analysis of brain activation obtained during three tasks : the Stroop paradigm, the stop-signal and an antisaccades task (Collette *et al*., in press). Effectively, an adequate performance in those tasks implies that the subject avoids to produce predominant but nonpertinent responses. Control tasks were administered, that mobilised cognitive processes similar to those involved in the experimental tasks, but the inhibitory component.

The first inhibitory condition was the Stroop interference task. In this task, colour names are visually presented. They are written in different colour inks (for example, the word “blue” can be written in red). The subject is required to name as quickly as possible the colour of the ink in which each item is presented, while inhibiting the predominant, automatic word reading. The control task consisted in naming the colour in which concrete words (without any association to colours) were displayed.

The stop-signal task consisted in viewing concrete words and in making, as quickly as possible, a living/not living judgment on each word, by key press. In some trials (the inhibitory trials, accounting for 25% of the total trials in the task), a sound signal occurred after the item presentation, and subjects had to refrain from giving a response. For those trials, subjects had to inhibit a motor response initiated by item presentation. In the control task, the same word categorisation was required. A sound signal was again presented in 25% of the trials, but before word presentation, so that the subject knew early enough that he could not initiate the response.

Finally, in the antisaccade condition, subjects had to indicate the orientation of an arrow briefly presented on the left or the right side of a screen. A visual cue (a black square) was presented before the target item. In inhibitory condition, the cue appeared on the side opposite to the target. The subject had to inhibit the reflex tendency to orient attention (and gaze) to the visual cue in order to correctly process the target arrow that appeared on the contralateral side. In the control condition, the visual cue and the target item were displayed on the same side of the screen.

Behavioural results demonstrate slowing of reaction times for Stroop inhibition and antisaccade task. However, reaction times are similar for the stop-signal and its reference condition, suggesting that patients installed motor inhibitory processes and did not slow their response times for the entire condition. Surprisingly, the conjunction analysis did not highlight any common activation for the three inhibitory tasks. This does not mean that inhibition did not induce brain activation in individual experiments. Inhibition linked to the Stroop task was related to blood flow increase in the right middle occipital gyrus and the left inferior temporal gyrus. The stop-signal task recruited left postcentral and middle frontal cortices. Inhibition of saccades was associated to right middle and inferior frontal activation.

Thus, we did not observe a neural substrate common to our three inhibitory conditions. This is consistent with the hypothesis that diverse inhibitory processes can be dissociated. For example, Dempster et Corkill (1999 a & b) proposed a distinction between perceptive, motor and linguistic inhibition. Arbuthnott (1995) made a distinction between lateral inhibition and self-inhibition. Lateral inhibition would intervene when a target information needs to be retrieved in an ensemble of related stimuli that must be inhibited. Self-inhibition corresponds to explicit suppression of a representation or a cognitive operation on a target information. Recently, Nigg (2000) suggested that controlled and automatic inhibitory processes could be distinguished. However, those proposals were based on literature reviews, and their validity was never tested. Currently, one can conclude that a better knowledge of the brain areas subserving inhibitory functions will depend on a better cognitive characterisation of the different processes involved in multiple tasks used for evaluation of inhibitory abilities in control subjects and in patients.

Is there a common neural substrate for updating, flexibility and inhibitory processes ?

Looking for brain activation common to updating, flexibility and inhibition, we performed a conjunction analysis on the individual tasks described above (Collette *et al.*, 2004b). The result showed that the right intraparietal sulcus and the left superior parietal cortex were commonly activated for all experimental tasks compared to their reference condition. Those two regions appear to subserve general executive processes, involved in the realization of multiple and distinct executive tasks. At a lower statistical threshold, there is also a common activation for all executive tasks in middle and inferior prefrontal regions, but this activation is less important than in parietal areas.

Those data confirm the importance of parietal regions in executive functioning. Several authors suggest that parietal areas are involved in attentional processes, but they do not necessarily agree on the exact role attributed to those regions in attentional function (e.g. Corbetta *et al.*, 2000 ; Coull *et al.*, 1996 ; Rushworth *et al.*, 1997 ; Yantis *et al.*, 2002). In keeping with Miyake *et al.* (2000), we suggested that the right intraparietal sulcus is recruited for selective attention to pertinent current information and suppression of distractive information. The left superior parietal area would implement an “attentional set” to maintain and suppress active representations in working memory during executive tasks (Wojciulick & Kanwisher, 1999).

Critical conclusion on conjunction analyses

The experiments presented above allowed to highlight brain regions activated for three distinct executive processes (updating, flexibility, inhibition). The use of conjunction analyses allows to consider that the activated brain areas should reflect the neural substrate of each executive process, independently from the peculiar characteristics of each task. The activated patterns are different for each executive process. Updating is related to a network of bilateral regions comprising prefrontal, parietal and cerebellar cortices. Different updating tasks would recruit those regions in different proportions. Reactive flexibility appears to be mainly associated to right intraparietal sulcus activity, but the recruitment of other cerebral regions would depend on the requirement of each task. Finally, we did not observe (at high statistical level) any common activation for the inhibitory tasks, which is consistent with the hypothesis of multiple inhibitory functions.

They are limits to the methodology used in our studies. On the one hand, our tasks were based on previous cognitive analyses that distinguished three executive processes (Miyake *et al*, 2000), and those data might critically depend on the cognitive tests initially selected. On the other hand, we are not sure that there should be a strict correspondence between the recruitment of cognitive processes and an increase in cerebral blood flow. For example, a particular cognitive function might more particularly depend on synchronisation between different brain areas, without increased activity in a single of those regions. To better specify the role of different regions in executive functioning, different experimental paradigms need to be compared. Conjunction analyses are interesting to highlight common regions of activation, but the results should also be confronted to interaction and correlational analyses (Price *et al.*, 1997).

Conclusions

A number of neuroimaging studies explored the neural substrate of executive functioning. But executive functions are highly integrated, and the executive tasks are frequently complex and multi-determined, so that results may be difficult to interpret in terms of pure executive processes. Most studies confirmed the predominant role of prefrontal regions for performing executive tasks. Such an involvement of the frontal cortex in executive functions had previously been established in brain-damaged patients (Seron, Van der Linden, & Andrès, 1999). However, functional imaging in control subjects allowed to interpret contradictory data obtained in patients. Effectively, some studies did not demonstrate executive dysfunction in patients with frontal lesions (Ahola, Vilkki, & Servo, 1996 ;

Cowey & Green, 1996), while impairment in executive tasks were reported with posterior brain damage (Mountain & Snow-William, 1993). Those data are easier to interpret if neuroimaging data are taken into account, since both frontal and posterior (predominantly parietal) regions were activated for executive tasks in control subjects. This allows to understand the occurrence of executive dysfunction with non-frontal lesions. Moreover, functional imaging demonstrated that the different executive processes do not depend on frontal cortex as a whole, but that precise prefrontal area may subserve specific executive functions. This would explain why executive dysfunction might not be observed with some frontal lesions. If a limited number of neuropsychological tests assessing one or two executive processes were administered to brain-damaged patients, the performance on these tasks might not have been associated to the precise frontal lesions observed in the patients. This could also explain why executive dysfunction is more frequently reported in diffuse than in focal lesions (Andrès & Van der Linden, 2000, 2001 ; Cowey & Green, 1996 ; Simkins-Bullock, Brown, Greiffenstein, Malik, & McGillicuddy, 1994 ; Vilkki, Virtanen, Surma-Aho, & Servo, 1996). Effectively, the extension of the lesion increases the probability that frontal regions involved in the neuropsychological task of interest be impaired.

Functional imaging in normal populations brings also important information about cognitive functioning. It is effectively possible to categorize brain areas according to their involvement in different cognitive processes. In a recent review (Collette & Van der Linden, 2002), dorsolateral prefrontal regions were shown to be involved in information manipulation (Collette *et al*., 1999 ; D'Esposito *et al*., 1999 ; Postle *et al*., 1999), updating (Salmon *et al*., 1996 ; Van der Linden *et al*., 1999), dual task coordination (D'Esposito *et al*., 1995), inhibition (Chee *et al*., 2000 ; Collette *et al*., 2001) and flexibility (Rogers *et al*., 2000). Owen (2000) considered that those dorsolateral prefrontal regions play a role in information monitoring. The intraparietal sulcus that is commonly activated for three executive processes (updating, flexibility and inhibition) would house basic attentional processes (Collette *et al*., 2004b). However, other brain regions appear to play a specific role in executive tasks, and they might be engaged only for one type of executive process (for example, the anterior prefrontal cortex recruited for updating; Van der Linden *et al*., 2003).

Consequently, different processing levels (from very specific to more general) might be considered for executive functioning. General processes would recruit brain regions such as the dorsolateral prefrontal cortex and the intraparietal sulcus for very diverse executive tasks. Specific regions would subserve a precise executive function (such as updating) and would be recruited for different tasks that share this executive function.

Finally, the neural substrate of executive functions probably corresponds to dynamic interrelationships in networks of brain areas. To explore those interactions, other statistical methods will be required, such as functional and effective connectivity (Friston *et al*., 1996 ; Friston & Price, 2001). Effective connectivity (i.e. demonstrating the specific influence of one brain region on an other region) remains limited by a priori knowledge of the precise anatomical relationships between the regions. However, a psycho-physiological interaction is frequently used to highlight the specific functional relationships between one region and cerebral networks recruited during a given cognitive process contrasted to an other one. A better understanding of the neural correlates of executive function will also depend on the integration of data from cognitive psychology and neuropsychology. Cognitive psychology should provide a better characterisation of the different processes involved in executive tasks (for example a specification of different processing levels). Brain activation in control subjects means that a cerebral network is engaged during the task, but does not tell if all cerebral regions is the network are mandatory to perform the task. Studies of brain activation in patients with focal lesions when they perform executive tasks might allow to determine which cerebral areas are essential to engage a specific cognitive process.

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