International Psychogeriatrics (2004), 16:4, 379–387 © 2004 International Psychogeriatric Association
DOI: 10.1017/S1041610204000081X Printed in the United Kingdom

GUEST EDITORIAL

Cognition, behavior and the frontal lobes

Our knowledge of how the brain functions has markedly improved in recent years, but this improvement has largely been constrained to simpler levels of processing such as those involved in sensory or motor systems. In contrast, the neural bases of higher functions such as consciousness, will, long-term planning, complex problem- solving, etc., are still under investigation, although everyone agrees that the frontal lobes (FL) play an important role in such processes. The importance of understanding these neural bases of higher functions becomes even more evident in the study of aging, since a decrease of frontal lobe perfusion is reported during aging, and because this age-related frontal lobe dysfunction has been proposed to explain part of the cognitive disorders (attention disorders, decreased mental flexibility and abstraction) and behavioral changes (mainly apathy or indifference) associated with aging.

In order to understand the contribution of the FL in cognition and behavior, it may be important to first consider the FL, at a most global level, as one unit dedicated to every aspects of voluntary action, whatever the output (cognitive, behavioral or in the realm of social interactions). All these aspects – that include anticipation of the goal, selection of the appropriate piece of information, monitoring of information within the working memory buffer, execution of the plan, validation of its pertinence – are mainly organized within the prefrontal cortex (PFC) in closed relationships with the premotor and primary motor cortices. Indeed, whereas the latter structures are oriented toward the execution and motor preparation of response, the PFC can be seen as a multimodal associative region that integrates many parameters in order to elaborate and adjust adaptive behaviors (for review, see Goldman-Rakic, 1987; Fuster, 1997). According to Miller and Cohen (2001), the main function of the PFC is to exert a top-down control on other brain areas that allows the most adaptive and integrated response to occur.

In this view, the PFC constitutes an interface between afferent sensory signals (it is the only region of the neocortex that receives messages from both the external word and internal milieu) and the output system. It allows behavioral adaptation by creating the temporal buffer needed for the preparation of the most adequate pattern of responses. By elaborating new patterns of behavior, the PFC *de facto* inhibits the automatic activation of reactive responses triggered by external stimuli. The difficulties encountered by patients with prefrontal lesions to prevent reflexive or purely externally-driven behavior are represented by a tendency to involuntarily grasp objects presented in front of them, to

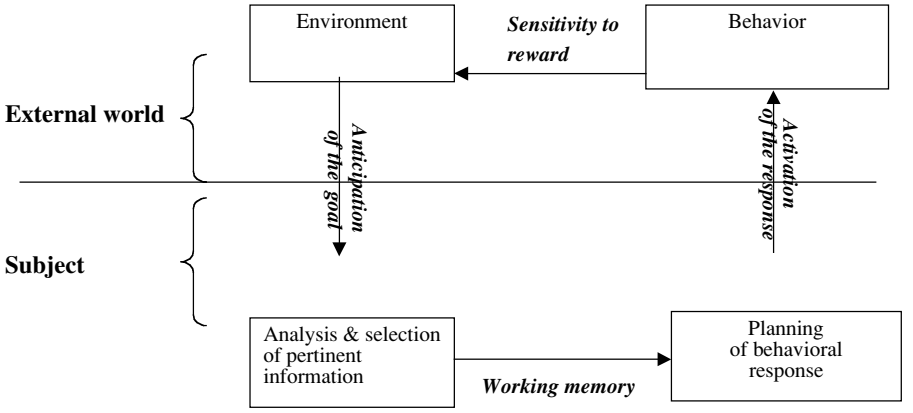

Figure 1. Behavioral adaptation loop
Processes needed for behavioral adaptation:
1) Analysis of the environment with selection of pertinent pieces of information;
2) that are maintained and monitored within working memory; and
3) which trigger a program of response that is executed and controlled;
4) which interacts with the environment; and finally
5) an evaluation of the congruence of the behaviour, with both internal and external contingencies based on reward sensitivity.

spontaneously imitate the gestures of the examiner or to use objects even when they are told not to do so. These so-called prehension, imitation and utilization behaviors, described by Lhermitte and collaborators (1986), are never observed in normal controls in the absence of explicit instructions. In contrast, they are spontaneously expressed by frontal patients, reflecting a loss of the inhibitory control normally exerted by the FL on the automatic activation of patterns of behaviors. In other words, the external world automatically activates behavioral responses when the FL are damaged. The environment drives the patient's behavior even though he or she does not want it to. This means that the FL are needed for the elaboration of new and voluntary patterns of behaviors. The processes required for elaborating goal-directed behaviors are summarized in Figure 1.

This behavioral adaptation loop intervenes each time the subject is confronted with a new or changing situation: it is needed for resolving complex cognitive tasks, for current activities of daily living or for social interaction. As the frontal lobes intervene at each level of this loop, it is not surprising that lesions can induce a wide variety of deficits in different domains of action (cognition, behavior, social interaction).

How are these different processes organized within the PFC? Based on dissociations observed in patients and data from functional imaging in humans and from experimental studies in monkeys, it is now well established that PFC is

https://doi.org/10.1017/S104161020400081X Published online by Cambridge University Press

not one homogeneous structure: it can be divided into three main regions whose activity can be combined together to allow integrative and adaptive functions: 1) *the lateral prefrontal cortex* (mostly Brodmann areas 44, 45, 46, lateral 9 and 10), for cognitive aspects of behavior (planning, cognitive control); 2) *the orbital and ventromedial cortex* (mostly Brodmann areas 11, 12, 13, 24, 25, 32 and medial 10), for defining overall goals and adjusting behaviors to the context; and 3) *the dorsomedial PFC* (mostly medial 9, the adjacent anterior cingulate cortex and cortices immediately posterior to them: the medial 6 – preSMA and SMA), for initiating the behavioral response and for managing conflicts between several possible responses. The role of each of these sub-regions is determined by its specific connections. Although this simplified tripartite model should be viewed as a working hypothesis, it provides a framework for understanding the clinical syndromes observed in patients with discrete prefrontal lesions.

The dorsolateral PFC (DLPFC): working memory and planning

Clinical syndromes

Patients with lesions of the DLPFC usually share severe difficulties in complex cognitive tasks that require the patient: to find a rule, to shift mental set, to solve a multiple steps problem (Shallice, 1982; Milner and Petrides, 1984), to resist environmental interferences, to share attentional resources, to maintain and manipulate mental representation for a non-automatic response (Petrides and Milner, 1982; de Fockert *et al.*, 2001), to select information to be processed (Knight, 1994, Ferreira *et al.*, 1998), and to actively retrieve information from memory (Incisadella, *et al.*, 1993; Fletcher *et al.*, 1998; Rapcsak *et al.*, 2001).

Proposed mechanism

Most of these cognitive processes depend on *working memory*, defined here as the ability to maintain and manipulate pertinent information from the outside world during a brief period of time and to use this internal representation to elaborate a goal-directed behavior (Goldman-Rakic, 1987). The role of the DLPFC in working memory and elaboration in goal-directed behaviors is mainly explain by its anatomical connections and by the physiological properties of its neurons.

The DLPFC is located at the interface between sensory associative and motor systems. Connections are reciprocal with posterior *associative sensory areas*, allowing the DLPFC to receive relevant sensory information but also to filter out interfering sensory stimuli via its feedback pathways (Knight, 1994). The DLPFC's connections with the *hippocampal formations* (Goldman-Rakic, 1987) allow the mental representation of the situation to be compared to past experiences that are important for decision-making. Moreover, inputs from

https://doi.org/10.1017/S104161020400081X Published online by Cambridge University Press

other *limbic structures* provide information about affective and motivational states and about the behavioral relevance of sensory events, which are necessary for adapting the cognitive plan to the rewarding value of the ongoing behavior (Watanabe, 1996; Leon and Shadlen, 1999). On the other hand, the DLPFC is strongly connected with the *motor system* and the basal ganglia, indicating that it is involved in response execution and control (Selemon and Goldman-Rakic, 1985; Alexander *et al.*, 1986; Goldman-Rakic, 1987).

The physiological properties of DLPFC neurons are also interesting to consider with regard to this area's role in working memory and planning. Microelectrode recordings in primates have shown sustained activation of prefrontal neurons between the presentation of the cue and the response in delayed response tasks, i.e. during a period of time where nothing happens from a behavioral point of view (Fuster and Alexander, 1971; Kubota and Niki, 1971). Therefore, the firing of the DLPFC neurons fills the gap between the stimulus and the response and allows the relevant information to be maintained and monitored before a response is carried out. Indeed, different patterns of neuronal activities can be observed in the DLPFC during the delay period: some are associated with the pure maintenance of sensory information; other activities are mostly associated with the control of the response, such as inhibition of the reflexive response, preparation of the forthcoming actions, decision-making or temporal ordering of the sequence of actions to come (Funahashi *et al.*,1993; Kim and Shadlen, 1999). This suggests that planning functions can be subserved by the local combination of these different neuronal activities within the DLPFC. This also indicates that the working memory function of the DLPFC is not only restricted to the maintenance of information but is mostly concerned with the use of information for the forthcoming action (Rowe *et al.*, 2000). These hypotheses are corroborated by the result of a recent fMRI study that we have performed in normal subjects (Pochon *et al.*, 2001). The study was aimed at comparing brain activation during two different delayed response tasks – a matching and a reproduction task – based on the same principle: (1) the presentation of sensory information, (2) a delay and (3) the response. The sensory information consisted of a spatial pattern presented on a screen that was followed by an 8 second delay during which brain activation was recorded. The nature of the response was the only difference between the two tasks: in the matching task, the subject had to decide, after the delay, whether a new sequence appearing on the screen was similar or different from the one presented before. In this condition, the subject could not prepare his response during the delay and fMRI recording showed significant bilateral activation only in posterior parietal and premotor areas. There was no activation in the DLPFC even though sensory information has to be stored in short-term memory. In the reproduction task, the subject used a mouse to reproduce the sequence presented before. In this condition, the subject had to

both maintain the information and prepare his response during the delay: fMRI recording showed an additional activation in the DLPFC which underlines the role of this area when one must use prior information to program the behavioral response. The DLPFC should, therefore, be considered as a region involved in the executive aspects of the behavioral response rather than a structure only involved in the maintenance of information within working memory.

The orbital and ventromedial PFC: reward anticipation and feedback sensitivity

Clinical syndromes

Other patients with FL lesions, such as the patient E.V.R., described by Eslinger and Damasio (1985), may have no cognitive deficit even on the Wisconsin Card Sorting Test. In contrast, such patients may present a severe impairment in complex social behavior that is related to a deficit in decision-making, which Damasio and colleagues referred to as acquired sociopathy (Bechara *et al*. 1996). After lesion has occurred, the patients are no longer able to evaluate, in real-life situations, the future consequences of their actions. In these cases, damage mainly concerned the orbital and ventromedial parts of the PFC, areas normally involved in reward anticipation and sensitivity to the affective value of behaviors (Rolls, 1990).

Proposed mechanism

Behavioral adaptation is based on *reward anticipation*, and the PFC is involved in these motivational aspects together with the ventral striatum and limbic structures. In primates, cell recordings showed the presence of anticipatory neurons in the orbital ventral part of the PFC that are specifically activated during task instruction, indicating the nature of the reward associated with the forthcoming response (Tremblay and Schultz, 1999). Moreover, orbital ventral neurons are differentially activated as a function of the expected reward. These anticipatory neurons create the emotional state needed for the activation of mental processes required for the successful execution of the behavioral response. Consequently, orbital ventral lesions may induce an inability to anticipate the consequences of the forthcoming action. This can be evidenced in humans with the gambling task (Bechara *et al*., 1996), in which the subject is asked to choose cards from different packets. Some of these packets provide high gains but occasionally very important losses: they are disadvantageous in the long run. In contrast, other packets provide small gains but very few losses: these packets are advantageous. Normal controls implicitly learn to choose cards in the latter packets whereas patients with ventral-medial lesions do not change

https://doi.org/10.1017/S104161020400081X Published online by Cambridge University Press

their behavior and continue to choose disadvantageous packets with high gains. These patients did not show significant changes of skin conductance responses, a peripheral marker of emotional state, before their decision-making. This emotional bluntness may explain the inability to anticipate the consequences of the forthcoming action.

We have seen that two main functions can already be allocated to the PFC, each relying on a specific neural network: one is involved in the processing of response programming and relies on a parietal-premotor-dorsolateral network; the other is involved in the processing of the emotional valence of the context and relies on an orbital-ventral-medial network. How do these networks interact? To answer this question, we designed an fMRI study using a working memory task, in which the load of information and a monetary reward could vary from one trial to another (Pochon *et al.*, 2002). Trials with monetary reward induced an increased activation of voxels of the DLPFC already activated by working memory, leading to the conclusion that the promise of reward enhanced the level of activation in those frontal areas involved with cognitive processing. Alternatively, a deactivation was observed in the orbito-ventral PFC as a function of the complexity of the task and of the intensity of the expected reward, suggesting the existence of "an emotional gating" that filters counterproductive emotional messages that may decrease attentional resources.

The dorsal medial PFC: behavioral activation

Clinical syndromes

A third type of deficit observed in patients with prefrontal lesion is inertia (i.e. apathy or aboulia). It can be included in a more global difficulty to control internally-generated behaviors (self-activation and monitoring potential conflicts among forthcoming actions) in relation to a dysfunction of the anterior cingulate cortex. Indeed, anterior cingulate experimental excision (associated or not with a medial superior frontal gyrus lesion) significantly decreases the number of self-generated behaviors, but spares those triggered by the external milieu (Thaler *et al.*, 1995). This was noticed several years ago by Tow and Whitty (1953) in patients with cingulotomy who became less active after surgery: "One has given up his carpentry, gardening and reading entirely. Both he and another have lost all interest in sport and now never go to football matches as they used to." Therefore, the syndrome of apathy may be related to a medial prefrontal dysfunction (Drevets, 2000).

Proposed mechanism

The mechanism by which behavioral responses are activated remains under debate but different hypotheses can be proposed according the anatomo-functional

https://doi.org/10.1017/S104161020400081X Published online by Cambridge University Press

system to which they refer. One of these models relies on the description in monkeys of discrete parallel striato-frontal loops (Alexander *et al.*, 1986), each linking a specific prefrontal cortical area to a discrete zone in the striatum. According to this model, it is obvious that the pathway linking the frontal striatum to the anterior cingulate cortex is candidate for psychic auto-activation (Laplane and Dubois, 2001). Moreover, several studies suggest that the anterior cingulate cortex is involved in the self-evaluation of internal states and the monitoring of affective and neurovegetative states to control their impact on behavior (Devinsky *et al.*, 1995). In depressed patients, as compared to controls, functional abnormalities have been observed in the rostral portion of the anterior cingulate cortex (Bush *et al.*, 2000; Drevets, 2000). Several studies also indicate its involvement in managing conflicts and monitoring errors between opposite or counterproductive programs (Pardo *et al.*, 1999).

Conclusion

The FL allow behavioral adaptation by inhibiting automatic activation of over-learned procedures and by elaborating new schemas of response based on two integrated processes: the programming of the response, whatever its output (cognitive, behavioral, social) and the evaluation of the affective valence that the response will have for the subject. What could the clinical relevance of this organization be? Patients with frontal lesions may have difficulty in planning, programming and executing a response. They also may have apathy and/or disinhibition resulting from impaired motivation or impaired behavioral adaptation due to a lack of sensitivity to reinforcement.

Therefore, to the classic right /left (visuo-verbal) hemispheric dissociation, we would like to propose a new one, the anterior/posterior dissociation according to which: (1) *the retro-rolandic areas* are mainly involved in the processing of sensory information (tactile, spatial, visual, visuo-gestural, auditory and linguistic) in order to give a meaning to what is perceived; and (2) *the pre-rolandic regions*, i.e. the frontal lobes, constitute the neural system for action. This system for action is composed of i) the PFC which is implicated in the preparation of the forthcoming response according to external/internal contingences and will and ii) the premotor and motor cortices which are involved in the executive aspects and control of the response.

Bruno Dubois and Richard Levy
Department of Neurology and Inserm Unit U610,
Hôpital de la Salpêtrière,
Paris, France
Email:chouippe@chups.jussieu.fr

https://doi.org/10.1017/S104161020400081X Published online by Cambridge University Press

References

Alexander, G. E., Delong, M. R. and Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neurosciences*, 9, 357–381.

Bechara, A., Tranel, D., Damasio, H. and Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cerebral Cortex*, 6, 215–225.

Bush, G., Luu, P. and Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Science*, 4, 215–222.

de Fockert, J. W., Rees, G., Frith, C. D. and Lavie, N. (2001). The role of working memory in visual selective attention. *Science*, 291, 1803–1806.

Devinsky, O., Morrell, M. J. and Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, 118, 279–306.

Drevets, W. C. (2000). Neuroimaging of mood disorders. *Biolological Psychiatry*, 48, 813–829.

Eslinger, P. J. and Damasio, A. R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology*, 35, 1731–1741.

Ferreira, C. T., Verin, M., Pillon, B., Levy, R., Dubois, B. and Agid, Y. (1998). Spatio-temporal working memory and frontal lesions in man. *Cortex*, 34, 83–98.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S. and Dolan, R. (1998). The functional roles of prefrontal cortex in episodic memory. II. Retrieval. *Brain*, 121, 1249–1256.

Funahashi, S., Chafee, M. V. and Goldman-Rakic, P. S. (1993). Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature*, 365, 753–756.

Fuster, J. M. (1997). *The Prefrontal Cortex* (3rd ed.) New York: Raven Press.

Fuster, J. M. and Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science*, 173, 652–654.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behaviour by representational memory. In F. Plum and V. Mountcastle. (Eds.) *Handbook of Physiology*, Vol. 5, 373–517. Washington, D.C: The American Physiological Society.

Incisadella Rochetta, A. and Milner, B. (1993). Strategic search and retrieval inhibition: the role of the frontal lobes. *Neuropsychologia*, 31, 503–524.

Kim, J. N. and Shadlen, M. N. (1999). Neural correlates of a decision in the dorsolateral prefrontal cortex of the macaque. *Nature Neuroscience*, 2, 176–185.

Knight, R. T. (1994). Attention regulation and human prefrontal cortex. In: A. M. Thierry, P. S. Goldman-Rakic and Y. Christen. *Motor and Cognitive Functions of the Prefrontal Cortex*. Heidelberg: Springer-Verlag.

Kubota, K. and Niki, H. (1971). Prefrontal cortical unit activity and delayed cortical unit activity and delayed alternation performance in monkeys. *Journal of Neurophysiology*, 34, 337–347.

Laplane, D. and Dubois, B. (2001). Auto-activation deficit: a basal ganglia related syndrome. *Movement Disorders*, 16, 810–814.

Leon, M. I. and Shadlen, M. N. (1999). Effect of expected reward magnitude on the response of neurons in the dorsolateral prefrontal cortex of the macaque. *Neuron*, 24, 415–425.

Lhermitte, F., Pillon, B. and Serdaru, M. (1986). Human anatomy and the frontal lobes. Part I. Imitation and utilisation behaviors: a neuropsychological study of 75 patients. *Annals of Neurology*, 19, 326–334.

Miller, E. K. and Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neurosciences*, 24, 167–202.

Milner, B. and Petrides, M. (1984). Behavioural effects on frontal-lobe lesions in man. *Trends in Neurosciences*, 7, 403–407.

Pardo, J. V., Pardo, P. J., Janer, K. W. and Raichle, M. E. (1999). The anterior cingulate cortex mediates processing selection in the Stroop attentionnal conflict paradigm. *Proceedings of the National Academy of Sciences, U.S.A.*, 87, 256–259.

Petrides, M. and Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia*, 20, 249–62.

Pochon, J. B., *et al.* (2001). The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: an fMRI study. *Cerebral Cortex*, 11, 260–266.

Pochon, J. B., *et al.* (2002). The neural system that bridges reward and cognition in humans: an fMRI study. *Proceedings of the National Academy of Science U.S.A.*, 99, 5669–5674.

Rapcsak, S. Z., Nielsen, L., Littrell, L. D., Glisky, E. L., Kaszniak, A. W. and Laguna, J. F. (2001). Face memory impairments in patients with frontal lobe damage. *Neurology*, 57, 1168–1175.

Rolls, E. T. (1990). A theory of emotion, and its application to understanding the neuronal basis of emotion. *Cognition and Emotion*, 4, 161–190.

Rowe, J. B., Toni, I., Josephs, O., Frackowiak, R. S. and Passingham, R. E. (2000). The prefrontal cortex: response selection or maintenance within working memory? *Science*, 288, 1656–1660.

Selemon, L. D. and Goldman-Rakic, P. S. (1985). Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkeys. *Journal of Neurosciences*, 5, 776–794.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society: Biological Sciences*, 298, 199–209.

Thaler, D., Chen, Y. C., Nixon, P. D., Stern, C. E. and Passingham, R. E. (1995). The functions of the medial premotor cortex. I. Simple learned movements. *Experimental Brain Research*, 102, 445–460.

Tow, P. and Whitty, C. W. (1953). Personality changes after operations on the cingulate gyrus in man. *Journal of Neurology, Neurosurgery and Psychiatry*, 16, 186–193.

Tremblay, L. and Schultz, W. (1999). Relative reward preference in primate orbitofrontal cortex. *Nature*, 398, 704–708.

Watanabe, M. (1996). Reward expectancy in primate prefrontal neurons. *Nature*, 382, 629–632.