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Prefrontal neurons in networks of executive memory

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ABSTRACT: The neuronal networks of the frontal lobe that represent motor or executive memories are probably the same networks that cooperate with other cerebral structures in the temporal organization of behavior. The prefrontal cortex, at the top of the perception-action cycle, plays a critical role in the mediation of contingencies of action across time, an essential aspect of temporal organization. That role of cross-temporal mediation is based on the interplay of two short-term cognitive functions: one retrospective, of short-term active perceptual memory, and the other prospective, of attentive set (or active motor memory). Both appear represented in the neuronal populations of dorsolateral prefrontal cortex. At least one of the mechanisms for the retention of active memory of either kind seems to be the reentry of excitability through recurrent cortical circuits. With those two complementary and temporally symmetrical cognitive functions of active memory for the sensory past and for the motor future, the prefrontal cortex seems to secure the temporal closure at the top of the perception-action cycle. © 2000 Elsevier Science Inc.

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INTRODUCTION

In the primate, the cortex of the frontal lobe appears devoted in its entirety to the representation and execution of actions. The frontal cortex as a whole can therefore be considered “motor cortex” in the broadest sense of the word. It coordinates actions in practically all the domains of adaptation of the organism to its environment: skeletal and ocular motility, logical reasoning, communication, and the spoken language. Even visceral actions and emotional behavior are regulated by certain orbital and medial areas of the frontal cortex. In this article, I will outline the rationale for the role of the dorsolateral prefrontal cortex in the temporal organization of action, as well as some of the mechanisms that support it.

I will begin with certain basic assumptions about the cortex in general and the frontal cortex in particular. The cognitive functions of the cortex of the frontal lobe, as those of any other part of the neocortex, consist in the activation and processing within and between networks of representation, or memory networks. Those

networks are widely distributed and highly specific, defined by their synaptic structure and connectivity. Thus the memory code is a relational code, and all memory is associative. The cortical networks of memory extend across modules and areas by any anatomical definition. Memory networks overlap and are profusely interconnected with one another. Thus, one neuron or group of neurons anywhere in the cortex can be part of many networks and thus many memories. This is why it is virtually impossible, by any method, to localize a memory.

The networks of executive or motor memory are distributed in the cortex of the frontal lobe, and like the perceptual networks of posterior, post-rolandic, cortex, are hierarchically organized (Fig. 1). The base of the executive hierarchy consists of the motoneurons and anterior roots of the spinal cord. Above that, in ascending order, are the motor nuclei of the mesencephalon, the cerebellum, and portions of the diencephalon, including certain nuclei of the hypothalamus, the thalamus, and the basal ganglia. Above the basal ganglia is the frontal cortex, which itself is hierarchically organized. At the base of the cortical motor hierarchy is the primary motor cortex, for the representation and execution of elementary skeletal movements. Above it is the premotor cortex, serving more complex movements defined by goal and trajectory, including certain premotor areas involved in speech. At the summit is the prefrontal cortex. We can safely infer that this cortex represents—we do not yet know how—the broad schemas or plans of action in the skeletal and speech domains, and in addition is critically involved in the enactment of those schemas or plans. Indeed, one of the most consistent and specific components of the frontal-lobe syndrome is the inability to formulate and to enact programs of behavioral, linguistic or cognitive action, such as logical reasoning.

TEMPORAL STRUCTURING OF ACTION

From those general assumptions, especially from the distributed nature of cortical networks, it follows that we cannot rightfully consider the cognitive functions of the prefrontal cortex in isolation from those of the rest of the frontal cortex or, for that matter, from the totality of the neocortex and the subjacent anatomical stages of the executive hierarchy. Pursuing methodological

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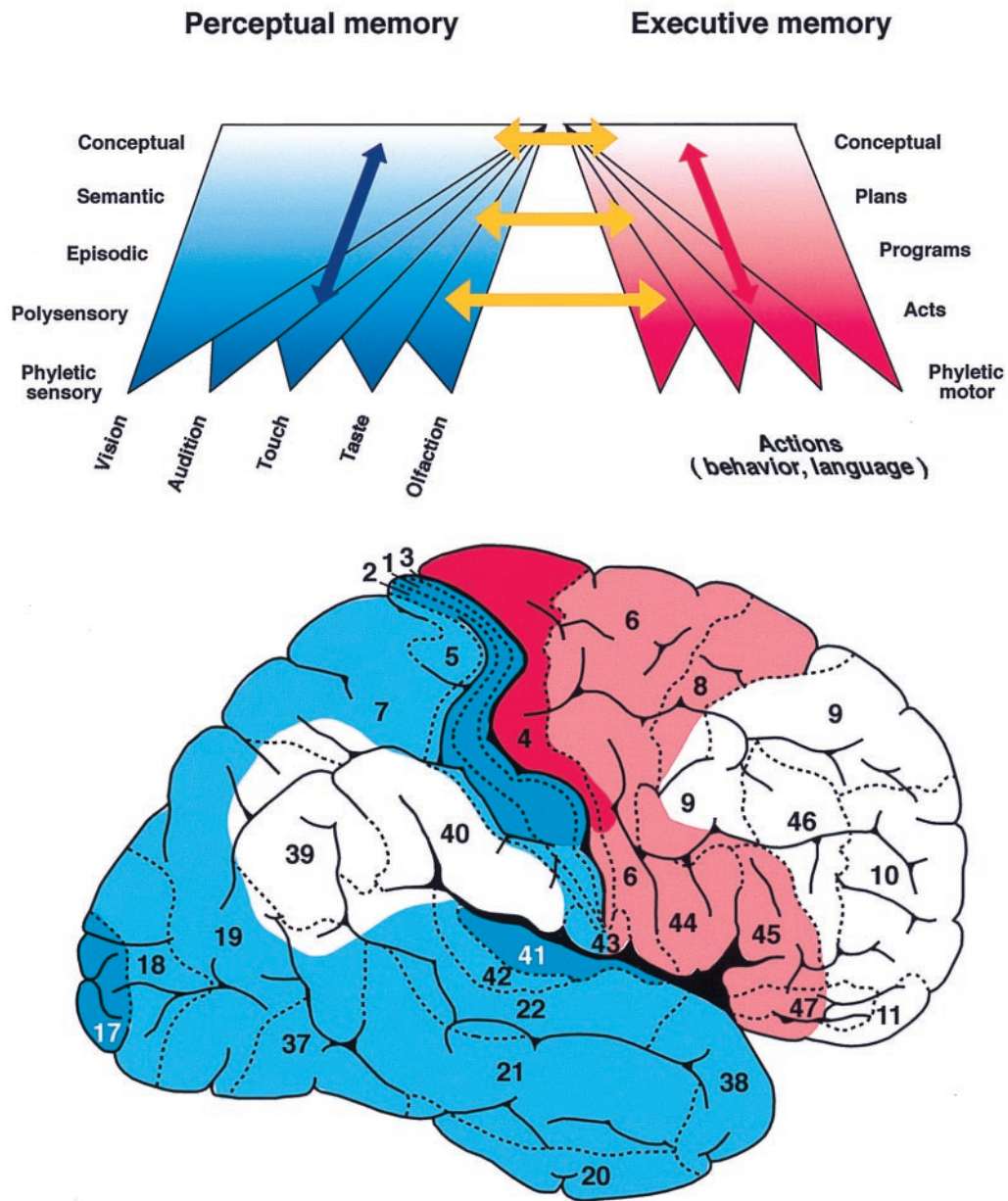


FIG. 1. Hierarchical organization of memory networks in posterior cortex (perceptual memory) and in frontal cortex (executive memory). Arrows represent functional connections and interactions within and between networks. The color codes in the scheme of the hierarchies and in the underlying diagram of the cortex are meant to correspond only roughly to each other. (For more details, see [7]).

neatness, we have often been misled to the localization of cognitive functions that are not localizable. In my opinion, this is true for the so-called working memory, for the so-called “central executive,” for spatial memory and for various forms or aspects of attention. All these are indeed cognitive functions within the physiological purview of the frontal lobe, but none of them is localized there. What appears localized there, to some degree, is the distributed representational substrate, the content of those functions, in other words, the networks of executive memory. It is by transactions within those networks, and between those networks and others elsewhere in the neocortex, that the prefrontal cortex

most probably exerts its role in the temporal organization of behavior, speech, and logical reasoning.

In this article, I attempt to outline some of the physiological transactions in cortical memory networks that appear to support the role of the prefrontal cortex in the enactment of temporal structures of action, and thus in establishing temporal order in behavior, in reasoning, and in speech. Basically, at the root of that order is a set of cognitive operations—I should like to argue physiological operations—that implement a fundamental principle: the mediation of cross-temporal contingencies between events, between words, between stimuli, between particular stimuli and

particular acts. That principle can be expressed by two simple and complementary logical statements with a temporal dimension: If now this, then later that action; if earlier that, then now this action. The first proposition is temporally prospective, the second temporally retrospective. The dorsolateral prefrontal cortex plays a critical role in the cortical dynamics that implement the mediation of cross-temporal contingencies. This has now been substantiated in the human and nonhuman primate by several behavioral and functional methods. At the behavioral level there is apparently no better way to study temporal structuring and the mediation of cross-temporal contingencies than the use of delay-task paradigms (e.g., delayed response, delayed matching to sample). The single trial in a delay task is the epitome of the temporal structure or gestalt of behavior. Because it separates by time two events that are mutually contingent, and because these events are for all practical purposes novel inasmuch as they change at random from one trial to the next, the delay task is also the epitome of the cross-temporal contingency. Thus, the delay task is one of the most practical methods to investigate the neuropsychology and the neurophysiology of executive networks.

I will briefly summarize some of our past and current work with delay tasks in support of the following: (1) the critical importance of dorsolateral prefrontal cortex for the mediation of cross-temporal contingencies; (2) the role of prefrontal networks in short-term memory, also called working memory, which constitutes the retrospective aspect of cross-temporal contingencies; (3) the role of prefrontal networks in short-term attentive set, the prospective aspect of cross-temporal contingencies; and (4) the cortical mechanisms of short-term active memory, and the importance of reentry through recurrent circuits as one of those mechanisms.

The cooling of dorsolateral prefrontal cortex—large portions of areas 9 and 46 of Brodmann—in the monkey have been found to induce reversible deficits in the performance of visual, auditory and tactile delay tasks [6]. These are tasks in which motor acts are contingent on prior sensory stimuli that the animal must retain for a few seconds or minutes. The deficit with visual stimuli can be observed whether those stimuli are, for behavioral purposes, spatially defined or not. Ostensibly, the animal with inactivated or depressed dorsolateral prefrontal cortex cannot suitably mediate the cross-temporal contingency between a stimulus of any of those three modalities and the consequent response to it, especially if the time between the two is relatively long (<5 s). If the task is a visual nonspatial delay task (delayed matching to sample), a comparable deficit can be obtained by cooling inferotemporal cortex. The latter procedure does not affect a visuospatial delay task. However, I should emphasize, the evidence of multimodal deficit from cooling a large prefrontal region does not exclude the areal stimulus-specificity within it. In fact, there is abundant evidence from anatomical and functional studies for areal specificity within dorsolateral prefrontal cortex, with regard to stimuli as well as contingency tasks [8,11,15,16]. Here I mention the multimodal prefrontal deficits of the monkey in delay tasks simply to highlight the importance of the dorsolateral prefrontal cortex as a whole for the mediation of cross-temporal contingencies.

To further highlight the cross-temporal role of the prefrontal cortex, I can refer to the numerous functional imaging studies of the human performing delay tasks [1,3,10,13–15,19]. They all demonstrate the activation of various prefrontal areas during one form or another of cross-temporal integration. We contributed to this literature with a PET-fluorodeoxyglucose study of human subjects performing a visual delayed matching-to-sample task [20]. We were able to verify the activation of not only dorsolateral prefrontal cortex but postrolandic cortex—including visual cortex—during the mnemonic retention of abstract visual images. This points to the functional cooperation of frontal and posterior

cortical areas in that temporal process, an issue to which I shall come back later.

The cortical mechanisms behind temporal integration, however, can best be studied in real time at the cellular level. At that level, neuronal phenomena reveal that the translation of perception into action, across time, depends on the cooperation of at least two temporally complementary cognitive functions: (1) active short-term or working memory for sensory stimuli, and (2) short-term attentive set, also conceptually understandable as the activation of prospective motor memory. Further, what neuronal physiology shows is that the integrative work of those two functions depends on the close cooperation between widely separated cortical areas, and that in that coordination the prefrontal cortex plays a fundamental role [7]. Let us briefly examine those two temporally converse but complementary functions on which the structuring of action appears to depend.

SHORT-TERM MEMORY

There is now conclusive evidence, from several methodologies, that the frontal cortex as a whole, especially the dorsolateral prefrontal cortex, is critically involved in all forms of active (“working”) memory toward a goal, in other words, toward the completion of a gestalt of action, whether that is in the domain of behavior, reasoning or speech [6]. Some of that evidence has been cited above in the context of temporal organization. What defines frontal memory in the active state is precisely the teleological quality of a memory that has been mobilized in the construction of future action. From that teleological quality of frontal memory derive all the apparent physiological attributes of individual areas and cell groups in the dorsolateral frontal cortex. The sensory cell groupings and sensory memory subdivisions of that cortex are probably the stepping stones or pathways of access to that executive, teleological memory, and thus the paths to the action. Consequently, sensory working memory is probably a servant of the so-called central executive, rather than the other way around. Furthermore, certain areas of medial or orbital prefrontal cortex are the recipients of visceral input and of information related to reward or emotion. These areas have also prominent inputs from the amygdala and other regions of the limbic system. They may be in the pathways to emotional behavior or visceral action, or both.

The participation of prefrontal neurons in short-term memory has been amply documented by numerous descriptions of single units that respond with activation of firing frequency to the presence of a memorandum for prospective action (e.g., [4,5]). Many such units have two characteristics that unmistakably define them as so-called “memory cells”: (a) the specific response to one or more memoranda, and (b) the temporal decay of their firing in the course of the memorization period; this phenomenon is most conspicuous in manual memory tasks with long delays (10 s or longer). These cells are probably the constituents of motor memory networks that are activated by the recall or retrieval of a memorandum for the retention of that memorandum toward the correct action. Indeed their discharge has been related not only to the memorandum but to the efficiency of performance of the task. In any event, different sensory memoranda seem to have different prefrontal distributions in accord with the provenance of fibers from different parts of posterior, perceptual cortex, that arrive to the prefrontal cortex. Recently, we have been studying the distribution of auditory memory cells in monkeys that perform a cross-modal audio-visual task [2].

Using a task with variable probabilities of association between a visual stimulus and a later manual response, we were able to examine the temporal characteristics of memory cells in the dorsolateral prefrontal cortex of the monkey [17]. The task combines

delayed matching-to-sample with delayed conditional discrimination. A color is the initial cue at the beginning of each trial. After a delay of 12 s, a second visual cue is given, and the animal is required then to perform a manual choice that depends on both cues, the first and the second, thus on the combination of two visual stimuli separated by time. Each combination of the two stimuli—double contingency—determines whether the response after the delay will be to the left or to the right. That combination changes at random between trials. However, two of the trial-initiating cue colors, blue and yellow, are always followed by white (second cue) and require response respectively to the left (after blue) and right (after yellow). The other two, red and green, are followed by either white or a side-by-side display of green and red (relative position of the two colors changing at random between left and right). If after red or green the second cue is white, the monkey must choose left or right response, respectively; if the second cue is red-green or green-red the monkey must choose the color that matches the first cue, which may be on the left or the right. Because of the randomness with which the stimulus combinations are presented, and because of the above design of contingencies, blue and yellow at the start of a trial predict the response side with 100% probability, whereas red and green do it with only 75% probability.

The exploration of the prefrontal cortex during performance of that double-contingency task revealed two broad categories of “memory cells,” that is, cells with elevated discharge during the delay period. Some cells responded with a different level of activation depending on the color of the initial cue, in other words, they seemed to prefer certain colors, and their discharge in the course of the delay tended to descend toward baseline level. They appeared to distinguish and remember the colors and, during the delay period, to “look back” to the color of the first cue. Their discharge during that period seemed to reflect the temporal decline of short-term memory.

The second category of cells in dorsal prefrontal cortex behaved in the opposite way. Their discharge during the delay reflected the direction of the manual response before that response was prompted by the second cue, as if anticipating that response and preparing for it. These cells seemed to “look forward in time.” Their discharge accelerated as the second cue and the motor response approached. Furthermore, the degree of acceleration varied in proportion to the certainty with which the animal could predict the direction of that response. Most probably the neurons of this second type were involved in the setting of the neuromotor apparatus for the response. This is why we attributed these cells to the attentive set or active motor memory, the second of the two temporally integrative prefrontal functions postulated (next section).

A remarkable finding is that the cells of the two types, sensory-coupled or motor-coupled cells, appear anatomically intermixed with each other. It is not possible to discern a separate topography for them, overlapping as they do with each other in the prefrontal cortex around the sulcus principalis. It would appear from this fact alone that, during the delay, there is a direct transfer of information from sensory memory cells to motor set cells. More probable, however, is the temporal transfer from one prefrontal network to another, both with ties to the visual networks of posterior origin (inferotemporal) and the motor networks downstream in the executive hierarchy.

SHORT-TERM ATTENTIVE SET

The second class of prefrontal neurons, those that seem to anticipate the action and to prime the motor apparatus for it, may in fact be the substrate for the short-term activation of motor

memory, in other words, the converse of sensory short-term memory. Motor memory, in this context, would be the so-called “memory of the future” [12]. Thus, in principle, there seems to be a sensory and a motor short-term memory, one retrospective and the other prospective, the two complementing each other at the service of the “frontal executive” in the mediation of cross-temporal contingencies.

That function of active prospective memory can also be viewed as the motor counterpart of sensory attention; we may call it motor attention or attentive set. Its cellular manifestations, of course, acquire special significance in light of the well-known neuropsychological significance of the dorsolateral prefrontal cortex in the formulation and execution of action plans. The motor-set cells would be the microcosm of the planning functions of the frontal lobe.

In general, the sustained reactions of prefrontal cells in delay tasks are probably related to the well-known field potentials that can be observed on the human frontal cortex between mutually contingent but temporally separate events, notably the “contingent negative variation.” The accelerating cell reactions of “set cells” are especially reminiscent of the “Bereitschaftspotential,” or “readiness potential,” which is another negative potential that takes place as a continuation of the central nervous system, right before a pre-instructed motor act. Those surface negative potentials, which appear over frontal cortex after a sensory stimulus and before an action contingent on it, most probably reflect the underlying activation of large neuronal populations engaged in active short-term memory and attentive set.

In conclusion, the ramping-up cells and the surface negative field potentials, especially the “readiness potential,” seem to be the electrophysiological manifestations of attentive set, or motor attention. This is the prospective function of the dorsolateral prefrontal cortex. It is attention directed to the action in preparation. This kind of attention is focused in the representation of the action and, at the same time, in the components of long-term motor memory, which are activated ad hoc for the execution of every part of the sequence of behavior in progress, from its initiation to its goal. Those cells that seem to predict future actions—albeit only for the short term—indicate that there are mechanisms in the dorsolateral prefrontal cortex not only for evoking the prospective motor act but for preparing the motor apparatus for it. Perhaps those mechanisms include the priming of structures in lower stages of the motor hierarchy for the impending movement (e.g., premotor cortex, basal ganglia, pyramidal system).

CORTICAL DYNAMICS OF THE PERCEPTION-ACTION CYCLE

Given that the dorsolateral prefrontal cortex mediates cross-temporal contingencies between perception and movement, and given that this mediation is apparently the result of the coordination of two cognitive functions of that cortex, active memory and attentive set, now the question is, what are the neural mechanisms of that functional coordination. How does the prefrontal cortex mediate the transfer of information from the past to the future, from the perception to the action? Clearly, these mechanisms must involve both, local processes, as suggested by our two types of neighboring cells (memory and set cells), and remote or transcortical processes as some of our other cellular evidence and some of the imaging literature suggests. We postulate that in both these kinds of processes, local and remote, reentry or reverberation through recurrent circuits plays an important role.

In our effort to test the reentry hypothesis, we used several analytical methods. The first was to develop an artificial network with an architecture that was essentially recurrent [21]. We trained

that model network to “sample” an external input, to retain it in short-term memory, and to produce an output that was a specified function of that input. One of our purposes was to find out if the “cells” of such a recurrent model would behave like real cortical cells in active short-term memory. To train our model we used a variation of the backpropagation method [18]. That is an error-reducing procedure that allows the network, through many iterations, to adjust synaptic weights to keep a stable relationship between input and output despite variations of the input. After training, those weights stay fixed.

When the network has been fully trained, a memory trial can be simulated by loading an input, i.e., the memorandum, and by holding a gate open through the memory period or delay until the recall, when another load signal closes the gate and emits the output. Some of the units in the network, under these conditions, behave like real cortical cells in a delay task. The output cells behave unremarkably, since they simply reflect the input-to-output function that is defined by the modeler. What is remarkable is the behavior of the internal or “hidden” units of the model, which with adequate scaling behave like real cells in the memory task. We see cells ramping up, cells ramping down, and cells that appear to be a mixture of the two. I should note that those patterns of network unit discharge, which so much resemble the discharge patterns of real cells, are part of a repertoire of many patterns obtained by multiple repetitions of the sample-and-hold function of the model, and are a product of the internal architecture of the model.

We can conclude from these findings that the firing patterns of cortical cells are understandable as a result of the sustained activation of fully trained recurrent networks with preestablished synaptic weights. Backpropagation, which is the training mechanism that was used by us to train the network and to establish its weights, is irrelevant to that conclusion. The most important point is that, after the weights have been established, the short-term activation of the artificial, recurrent memory network, elicits in some of its units patterns of firing that are practically identical to those of real cortical cells in short-term memory. Thus, the role of reentry in the cortical dynamics of short-term memory receives support from the behavior of the units in a network model in which recurrence is an essential feature of the functional architecture.

Here it is appropriate to refer to some experiments in which the reentry between cortical areas in short-term memory was tested more directly [9]. We first trained monkeys to perform a visual delayed matching task with colors. Then we implanted cooling probes and microelectrode carriers, bilaterally, on two cortical areas that we know from both cooling and single-unit studies are involved in that task, in other words, areas that contain components of the cortical networks activated in visual short-term memory: the dorsolateral prefrontal cortex and the inferotemporal cortex. Then, while the animal performed the task, we proceeded to cool one cortex, prefrontal or temporal, while at the same time we recorded units from the other.

Cooling either cortex to 20°C impairs reversibly the monkey’s performance of the task, while modifying in various ways the spontaneous and memory—delay period—discharge of the cells in the other cortex. In a small but distinct contingent of prefrontal and inferotemporal cells, the discharge during memory is subtly but characteristically modified. These are cells that are differentially activated during the memorization of the sample color: they seem to prefer one color in short-term memory over the others. Under cooling of the distant cortex, inferotemporal or prefrontal, these cells show lesser differences in their memory discharge; they differentiate colors less than while that cortex is at normal temperature. In no case have we observed the opposite effect, that is, increased color differentiation by cooling. It would appear therefore that, in the absence of input from the remote cortex under

cooling, some cells in both prefrontal and inferotemporal cortex become less active in the memorization of their preferred color. Concomitantly, the monkey’s capacity to retain colors diminishes. These data would support the notion that short-term visual memory is maintained by tonic reentrant, i.e., reverberating, excitability between inferotemporal and prefrontal cortices.

That presumptive mechanism of recurrent excitation between the prefrontal—executive—cortex and the sensory association cortex can be conceptualized as a mechanism of temporal closure at the summit of the perception-action cycle. This cycle is a basic principle of biological cybernetics. It is the circular flow of neural information that links an organism to its environment. The neuroanatomy of the cycle essentially consists of two parallel hierarchies of neural structures, one sensory and the other motor, that extend through the entire length of the nerve axis, from the spinal cord to the highest cortex of association and the prefrontal cortex. All structures are interlinked at all levels by reciprocal connections; feedforward and feedback operate between stages and between sensory and motor structures at all levels.

During the performance of new or recently acquired behavior, sensory information is processed along the sensory hierarchy. That information is thus translated into action, which is processed down the motor hierarchy to produce changes in the environment. These changes lead to sensory changes, which are processed in the sensory hierarchy and then modulate further action, and so on and so forth. The posterior cortex of association and the dorsolateral prefrontal cortex are part of the cycle if the behavior contains novelty or uncertainty, and has to bridge time spans with short-term memory and attentive set, in other words, while it has to mediate cross-temporal contingencies. When those requirements disappear and the behavior becomes automatic (as in walking or performance of learned routines), the actions are integrated in lower structures of the cycle (e.g., premotor cortex, basal ganglia) and the processing of sensory inputs is shunted at lower levels of the cycle.

Thus, the so-called central executive, the dorsolateral prefrontal cortex, at the top of the motor hierarchy and the perception-action cycle, integrates actions with perceptions, especially in the presence of novelty and complexity. It does so in close cooperation with remote areas of the neocortex and with structures lower in the executive hierarchy. There is topographic specificity within the prefrontal cortex with regard to the nature or modality of sensory input as well as the nature of the action that the input calls for at any point in time and in any given context. This topographic specificity, however, should not obscure the overarching role of that cortex as a whole in bridging temporal gaps and organizing new actions in all domains of behavior, reasoning, and language.

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