Past Makes Future: Role of pFC in Prediction

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Abstract

■ The pFC enables the essential human capacities for predicting future events and preadapting to them. These capacities rest on both the structure and dynamics of the human pFC. Structurally, pFC, together with posterior association cortex, is at the highest hierarchical level of cortical organization, harboring neural networks that represent complex goal-directed actions. Dynamically, pFC is at the highest level of the perception–action cycle, the circular processing loop through the cortex that interfaces the organism with the environment in the pursuit of goals. In its predictive and preadaptive roles, pFC supports cognitive functions that are critical for the temporal organization of future behavior, including planning, attentional set, working memory, decision-making, and error monitoring. These functions have a common future perspective and are dynamically intertwined in goal-directed action. They all utilize the same neural infrastructure: a vast array of widely distributed, overlapping, and interactive cortical networks of personal memory and semantic knowledge, named cognits, which are formed by synaptic reinforcement in learning and memory acquisition. From this cortex-wide reservoir of memory and knowledge, pFC generates purposeful, goal-directed actions that are preadapted to predicted future events. ■

INTRODUCTION

With the extraordinary development of the pFC in evolution, the human brain has gained the capacity to make future predictions far beyond that of any other animal species. pFC provides the brain with the ability not only to adapt the organism reactively to its environment but also to preadapt proactively to it. Thus, pFC makes the human brain self-predictive, enabling it to generate behavioral changes and to preadapt to them. Preadaptation allows the fulfillment of an immense variety of personal purposes that transcend procreation and survival. Each relies on precedent, prediction, and preparation; here the prefix "pre" implies a prospective (future-oriented) temporal connotation. In short, one may state allegorically that evolution of pFC has endowed humans with the sense and command of their future.

The concept of the future orientation of pFC has a long history. After WWI, German and Russian neurologists (Choroschko, 1923; Feuchtwanger, 1923) observed that the most characteristic mental manifestation of substantial war injury to the frontal lobes was a profound difficulty in forming and executing plans of goal-directed action. That symptom has since become pathognomonic of extensive frontal injury (Morris & Ward, 2005; Grafman, Vance, Weingartner, Salazar, & Amin, 1986; Luria, 1966, 1970; Goldstein, 1942; Kleist, 1934); it does not occur after any other form of extensive cortical lesion. Furthermore, it is demonstrably unrelated to depression or apathy, which also often results from some frontal lesions.

In addition to the planning deficit, psychological and clinical reviews of frontal-lobe lesions often mention other manifestations of failed anticipation of future action and its consequences. Expectancy, prospective attention, creative intelligence, error prediction, and motor set are common casualties of frontal disease or trauma (reviewed in Fuster, 2008). From the diverse signs of its failure, the basic prospective functions of pFC can be inferred, including planning, attentional set, working memory, decision-making, and error monitoring. The purpose of this review is to summarize the evidence that the prospective pFC functions are based on a common structural substrate, the cognit, and a common dynamic substrate, the perception–action (PA) cycle.

Because it can be easily time-bracketed, working memory is the frontal function with the clearest operational definition. We have written about it in the past from the perspective of the same network paradigm that we use here (Fuster & Bressler, 2012; Fuster, 2009). However, the prospective, predictive aspect of working memory, which Baddeley (1983) included in its definition, has been largely neglected. This review is an attempt to remedy that neglect and, furthermore, to relate two central concepts, the cognit and the PA cycle, to other prospective prefrontal functions. The overall aim is to contribute understanding to the predictive role of pFC in the temporal organization of novel behavior.

Because of the centrality of those two concepts, the cognit and the PA cycle, we briefly reiterate their previously published descriptions. In a new context presented here, these descriptions confer generality to the principles we are trying to establish about the predictive role

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of the pFC in a way that heretofore ours and other reviews have fallen short of doing.

The human ability to predict the future and to pre-adapt to it requires access to personal memory and semantic knowledge. To forecast novel scenarios and plan new behavioral schemas, pFC must draw upon memory and knowledge resources within itself and other cortical regions. Those resources we have proposed (Fuster & Bressler, 2012) consist of the vast depository of widely distributed, overlapping, and interactive networks of cortical neurons that we call cognits. Some cognits are perceptual, acquired through the senses, and distributed largely in the posterior association cortex of the parietal, temporal, and occipital lobes (PTO cortex). As a concrete example, purely visual cognits are proposed to consist of memory-specific networks extending throughout the visual system. Other cognits are executive, acquired through the motor and proprioceptive systems and distributed largely in the prefrontal association cortex and the BG. Then there are others, perceptual/executive cognits, that span both territories. Cognits are structured by life experience from networks that are, to a large degree, synaptically unstructured from birth until they are self-organized by that experience.

In goal-directed behavior, the attainment of goals requires the continuous readjustment of predictions in accord with the consequences of the actions they precipitate. That readjustment is the basis of the general neural mechanism that we term the PA cycle. The PA cycle is the circular flow of perceptual and executive neural processing underlying the execution of goal-directed sequences of behavior, language or reasoning (Amiri & Haykin, 2014; Gómez & Flores, 2011; Friston, 2009; Fuster, 2004). Although conceptually a general principle, it has received several names. In that cycle, percepts lead to actions, which lead to new percepts, and so on, until a goal is reached. Residing at the top of the cortical perceptual and executive hierarchies, pFC coordinates and directs the PA cycle at its highest levels (Fuster, 2008, 2009). It anticipates percepts and actions, integrates them across time, monitors their consequences, and implements necessary corrections to ensure that behavioral objectives are achieved. Through its crucial role in the PA cycle, pFC temporally organizes novel goal-directed behavioral and linguistic sequences.

THE COGNIT: BEYOND HEBB'S CELL ASSEMBLY

A cognit is a network of neuronal assemblies of the cortex that represents sensory stimuli and/or motor actions that have occurred at the same, or nearly the same, time. It is formed by synaptic modulation according to Hebbian principles (Hebb, 1949) and is subject to modification by subsequent stimuli and/or actions that are associated with it. The cognit is thus a structural unit of memory or knowledge (see Fuster & Bressler, 2012, Fuster, 2009,

and below). In essence, cortical neurons—regardless of the distance between them—are linked into cognits if anatomically connected and simultaneously excited by external or internal stimuli. In sensory and parasensory cortex (e.g., visual and extrastriate cortices), the concept of cognit coincides with that of Hebb's "cell assembly." Beyond these regions, however, neurons of association cortex form large-scale self-organized and widely distributed cognitive networks, or cognits, that deviate from the "Hebbian cell assembly" in three critical ways.

(A) Cognits are hierarchically organized in two tiers of cortical association areas. Hierarchy is here defined anatomically by the synaptic distance from the periphery (sensory receptors in the perceptual systems and musculature in the executive system). The cognitive attributes of abstraction and complexity increase with higher anatomical levels. One tier, caudo-rostral in PTO cortex, contains the perceptual hierarchies of cognits that represent progressively more abstract categories of sensory-based memory and knowledge (Figure 1). The other tier, rostro-caudal in frontal cortex, contains the executive hierarchy of cognits that represent a gradient of progressively more concrete memory and knowledge of action. Not only are these tiers arranged hierarchically, but they are also heterarchical, in that they contain connections linking neurons across multiple levels of the same hierarchy and at the same level between hierarchies. Some large cognits extend between posterior and frontal cortex, linked by myelinated fibers in the longitudinal fasciculi; others extend between the two hemispheres, linked by myelinated fibers in the corpus callosum.

(B) Up the cortical hierarchies, the neural connectivity of cognits is divergent as well as convergent and recurrent as well as feed-forward.

(C) Cognits overlap one another and share network nodes of heavy association at several levels (Figure 2). This is attributable to the hierarchical nesting of lower, smaller, cognits within higher, larger ones and to the heterarchical connectivity between them. It is also because cognits share associated features. Some of these features may constitute nodes of heavy association or shared cognits that represent a particular feature; for example, the color yellow, which is shared by many objects. Again, cognit overlap takes place in the executive hierarchy of the frontal lobe in similar manner as in the perceptual hierarchy of posterior cortex. The general connective framework of unstructured networks that constitutes the anatomical infrastructure for the synaptic modulatory formation and hierarchical organization of cognits has been well substantiated in the human and nonhuman primate (Averbeck, Battaglia-Mayer, Guglielmo, & Caminiti, 2009; Mesulam, 1998; Cavada & Goldman-Rakic, 1989a, 1989b; Pandya & Yeterian, 1985; Van Essen & Maunsell, 1983; Jones & Powell, 1970).

Figure 1. Highly schematic hierarchical structure of perceptual cognits.
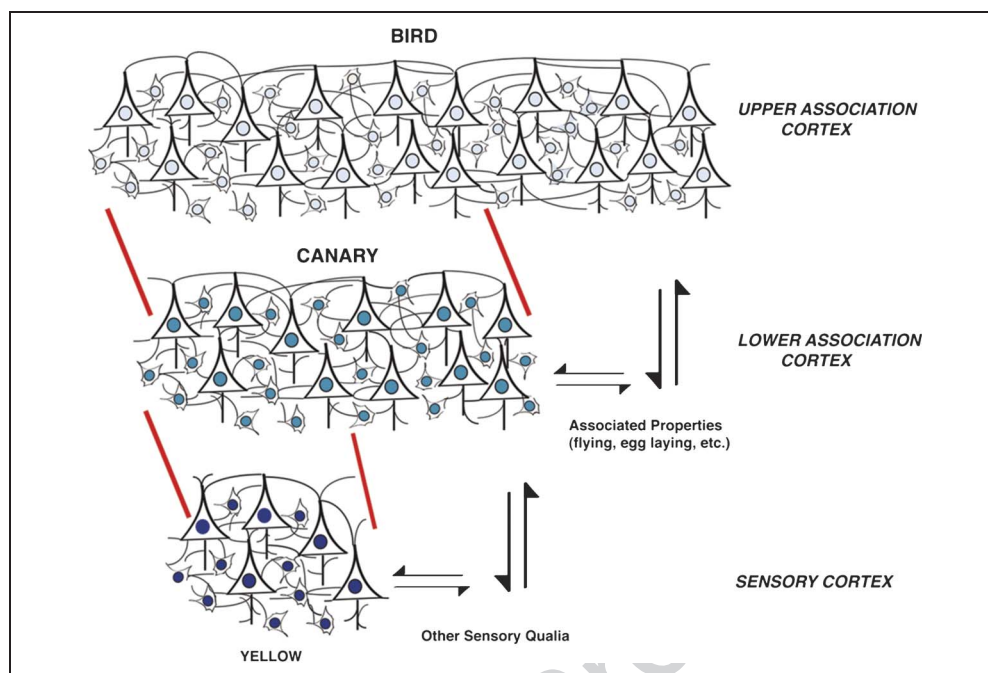
The cognit model incorporates in the cerebral cortex three fundamental principles that, singly or together, are present in connectionist models of cognition (Marcus, 2001; Elman et al., 1996): (1) distributed network structure, (2) relational (i.e., associational) coding, and (3) hierarchical organization. These features are absent in the theoretical Hebbian cell assembly, although even in their higher hierarchical levels, cognits are theoretically self-organized synaptically according to Hebbian principles.

An enormous variety in the size and distribution of cognits can easily be inferred from the anatomical dispersion of their potential neuronal components. Additionally, cognits can be assumed, on neurobiological grounds, to possess an important, but not previously emphasized, property: A cognit does not have sharp borders, but rather is surrounded by a penumbra of weak connections with other cognits. This feature, which stems from the graded nature of associations in learning and memory, may have momentous implications for phenomena like priming, preconscious association, and the retrieval and rehabilitation of memory in a future-directed context.

THE PA CYCLE

In our terminology, the PA cycle is the application to the mammalian brain of a basic principle of biological adaptation of the organism to its environment (Uexküll, 1926). The cycle consists essentially of a feedback-guided flow of information processing: Environmental events change the activity of receptors, which, when transmitted to the brain, lead to adaptive motor action, which induces further changes in the environment, which again through receptors and the brain lead to further adaptive

action. Figure 3 illustrates schematically the cortical organization of the human PA cycle.

The PA cycle runs through PTO and frontal cortex to process incoming sensory information and outgoing executive information, respectively. Thus, the cycle courses through several hierarchical layers, linking at each layer perceptual and executive cognits of comparable abstraction and/or complexity. All connections indicated by arrows in Figure 3 represent well-known anatomical paths in the nonhuman primate, now substantiated in the human by diffusion tensor imaging (Kuhnt, Bauer, Ganslandt, & Nimsky, 2013; Lemaire et al., 2013; Martino et al., 2013; Cheng et al., 2012). Thick arrows indicate the major connectivity of the cycle. Thin arrows represent intracortical feedback. The red arrow from prefrontal to PTO cortex represents the aggregate functions of cognitive control, which include top–down attentional set, working memory, decision-making, and error monitoring (next section).

Jackson (1882) long ago stated what is now a truism: that the motor cortex, which represents movement, is in charge of its coordinated execution. There is no structural distinction between representational and executive substrates, in this case cell populations. In a similar manner, modern neuroscience is coming to the conclusion that the hierarchically higher pFC not only represents complex prospective series of goal directed actions but also enables their execution by predictive cognitive functions under cognitive control (Fuster, 2008; Koechlin, Ody, & Kouneiher, 2003; Miller & Cohen, 2001). Cognitive control by pFC is modulated by inputs from the posterior PTO cortex and also from subcortical sources, as schematically depicted in Figure 4. Inputs from subcortical structures form part of an emotional PA cycle that parallels
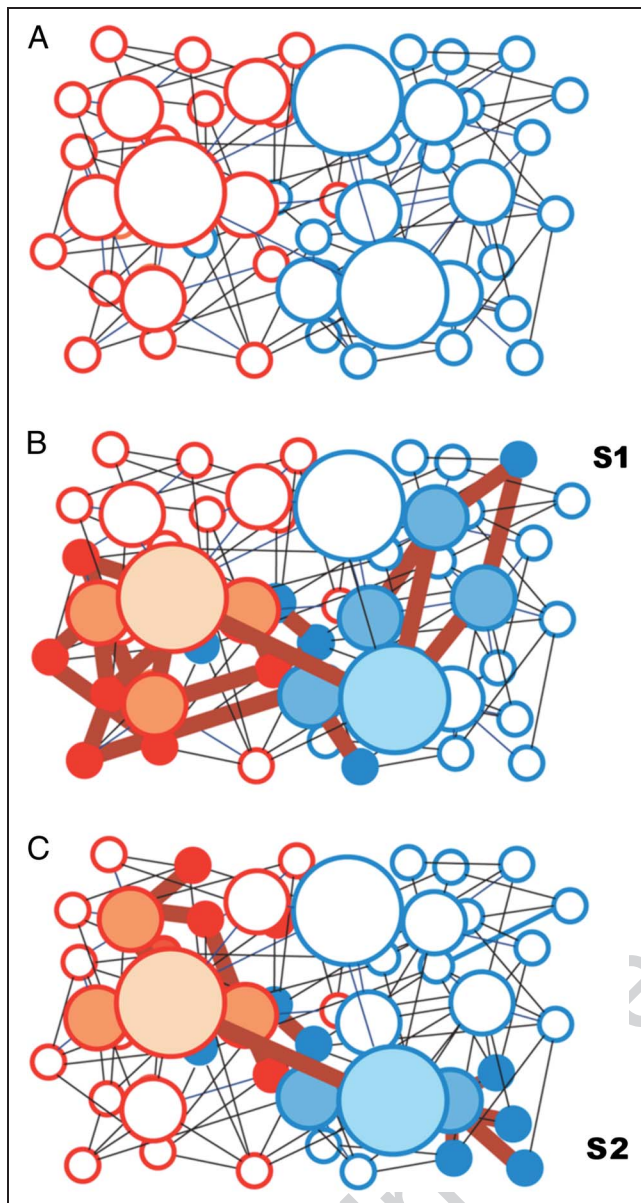
Figure 2. Structural and dynamic properties of cognits. (A) Hierarchies of perceptual (blue) and executive (red) cognits of different sizes and hierarchical levels (three sizes and levels are arbitrarily chosen; thin lines indicate bidirectional connections; blank circles represent cognits of long-term memory in resting state). (B) Stimulus 1 (S1) activates a large distributed cognit made of smaller, more localized cognits connected by excitatory pathways (large maroon lines). (C) Stimulus 2 (S2) activates another large cognit and its nested components. Cognits 1 and 2 are partly heterarchical and share common nodes.

and interacts with the cognitive PA cycle in the orbital and medial pFC.

Like cognits, PA cycles are hierarchically organized and executed. Also hierarchically organized in pFC, according to some studies, is the scale of temporally structured executive representations (Harrison, Bestmann, Rosa, Penny, & Green, 2011; Badre, 2008; Botvinick, 2008), with some evidence that the frontal polar region contains the highest cognits, which represent the longest temporal

extension into the future (Okuda et al., 2003). The pursuit of a major goal by a long PA cycle usually involves the parallel or sequential pursuit of several subordinate goals. This implies several subordinate PA cycles concomitantly or sequentially carried out in the service of that higher goal. Accordingly, because of the ability of the human to engage in several PA cycles at the same time ("multitasking"), we assume that a given cycle carries with it the potential to be interrupted and resumed at a later time. Although we do not know the neural mechanisms by which this is accomplished, we speculate that a time-bridging function such as working memory can be stopped and restarted by pFC to provide continuity to the pursuit of goals.

PROSPECTIVE FUNCTIONS OF pFC

We propose here that pFC endows the PA cycle with temporal integration and continuity in the pursuit of goals. We examine how future-oriented aspects of five functions attributed to pFC enable the prospective operations of the cycle. We take the parsimonious position that in the pFC, as in motor and sensory systems, representation and function have the very same substrate; in other words, that the latter is the activation of the former within a given spatiotemporal pattern of neural activity. Therefore, a prefrontal cognitive function results exclusively from the timely activation (elevated neuronal firing) of one or more executive cognits in conjunction with behavioral or linguistic cognits that are appropriate for the function.

Because of the wide distribution and overlap of cognits, no prospective prefrontal function can be easily localized. At best, we can attribute a "preferred cortical domain" to a function, which will depend on the dominant spatiotemporal distribution of cortical activity associated with the function. In this conceptual framework, it seems futile to attempt, for example, a canonical differentiation between attention and working memory, because the latter can be rightfully viewed as attention directed to an internal representation, which we call a cognit (Baddeley, 1993).

Nonetheless, pFC functions can be defined by the computations they employ and by the timing of activation of their cognits in the PA cycle. Sharp anatomical localization of any pFC function is out of the question, as neuropsychological and physiological studies in animals and humans make clear. In light of some of those studies, however, it is appropriate to speak of a preferred cortical focus or domain for a given pFC function (cf. reviews by Bari & Robbins, 2013; Bissonette, Powell, & Roesch, 2013; Coutlee & Huettel, 2012; Katsuki & Constantinidis, 2012; Fuster, 2008). Accordingly, the general domain for working memory is the dorsolateral and polar pFC; for attentive set, it is the same cortex plus inferior pFC and ACC; for error monitoring, it is the medial and ACC; and for decision-making, all of the above.

Any given cognit can be used in several of the five functions, which in behavior as well as language blend into

Figure 3. Cortical circuitry of the PA cycle. Unlabeled rectangles represent cortical areas intermediate between labeled areas or subareas of the latter. The perceptual hierarchies of cognits are depicted on the left, the executive hierarchy on the right of the main diagram. (The top left compartment, PTO, includes both unimodal and multimodal association cortex; Mesulam, 1998). The major connectivity of the cycle runs through thick arrows. Thin arrows mark intracortical feedback connections that play important roles in cognitive control. Bottom left: Uexkull's internal feedback in lower animals (red arrow), which in the human cycle at right is represented by the red arrow from prefrontal to PTO cortex.
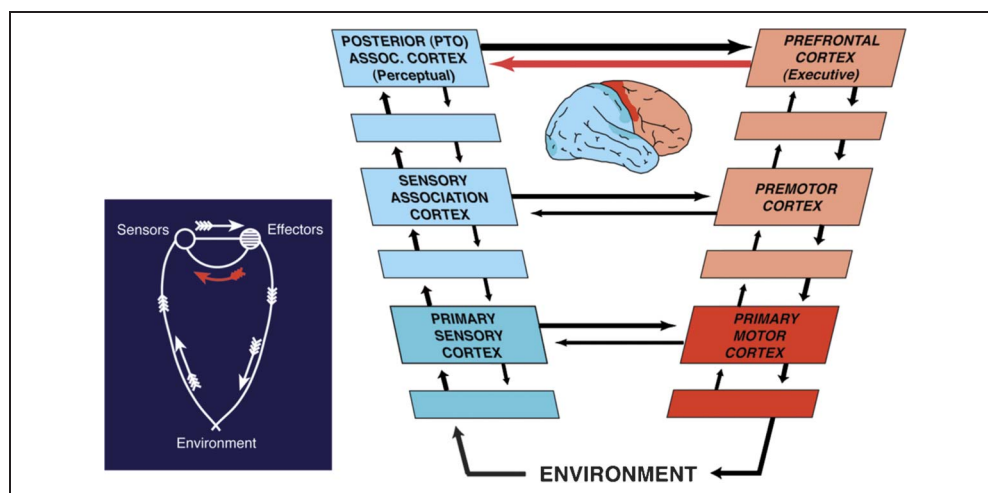
one another in brain space and time. The PA cycle is based on serial processing, but any attempt to computationally model these functions must also take into account the extensive parallel processing that is characteristic of the cortex. Figure 5 depicts, in general outline, the approximate relative timing of these functions in the cycle (at the exception of planning, which transcends the time of the test depicted in the figure).

Planning

Planning is the first cognitive function that was attributed to pFC from extensive frontal injury in the human, yet it is the least localizable in pFC. It is also the latest to be explored by functional neuroimaging. Several studies have been devoted to it, directly or indirectly (Wunderlich,

Dayan, & Dolan, 2012; Harrison et al., 2011; Badre, 2008; Botvinick, 2008; Addis, Wong, & Schacter, 2007; Okuda et al., 2003), but here we focus on the work by Schacter and colleagues, whose research on the topic is the most recent, original, and relevant to our topic and who have recently published a comprehensive review of the subject (Schacter et al., 2012). We focus in particular on their research on the mental simulation (imagination) of plans of action, especially as it bears on prefrontal function (Gerlach, Spreng, Madore, & Schacter, 2014; Gerlach, Spreng, Gilmore, & Schacter, 2011; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010).

That research has led to three important findings. The first (Spreng et al., 2010) is that the same cortical area can be activated by recall of a memory as by imagining it in the context of a future plan. This finding is in line with

Figure 4. Schematic diagram of the principal inputs into (right) and outputs from (left) the lateral pFC at the top of the PA cycle. Prefrontal areas are numerated according to Brodmann's map. Pink arrows represent outputs of top–down cognitive control.
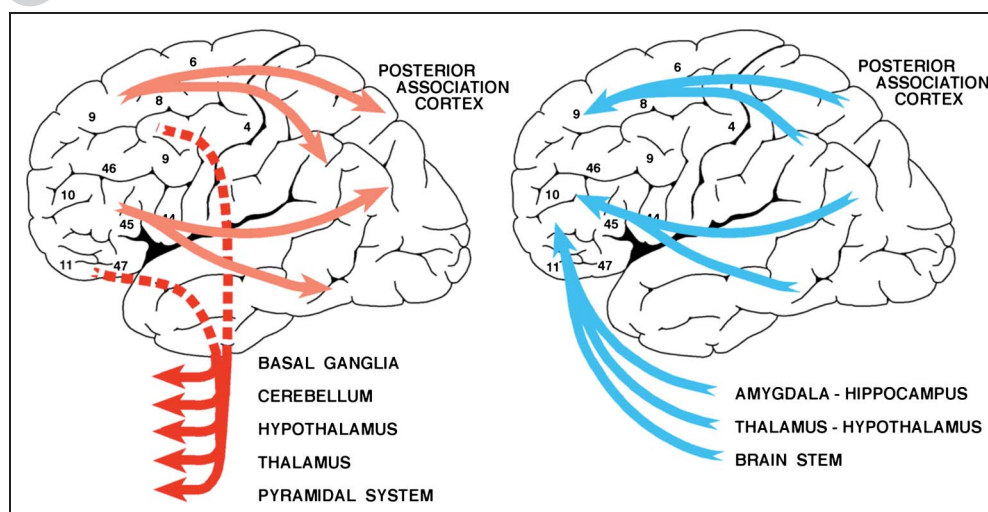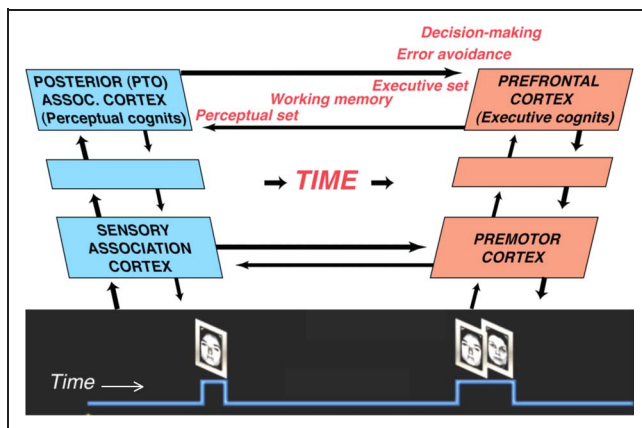
Figure 5. Temporal deployment of future-oriented pFC functions in upper, cortical, levels of the PA cycle during a test of working memory. Each function is predicted and expected from the past, which is made of the context, the instructions from the tester, and the outcome of previous trials. The trial begins with attentional perceptual set to the face presented on the screen (the memorandum). That is followed by the working memory of that face, which smoothly leads to the attentional set (perceptual and executive) for the presentation of two faces, followed by the decision to choose the memorandum. That decision is preceded and accompanied by error avoidance, which includes the suppression (inhibition) of the alternate face. All timing is arbitrary and relative to the events of the test. Just as a cortical cognit is spatially "scale-free," its activation in a cognitive function is also temporally "scale-free" (quotation marks imply the relative nature of congits and their activation, not the strict mathematical definition of the word they enclose).

our view of the cognit as a cortical network that holds long-term memory and when activated can become part of an action plan (what has been called "memory of the future").

The second finding is that three large cortical networks can be identified by BOLD fMRI study of functional coupling in planning (Figure 6A): the default network, a dorsal attention network, and a frontoparietal control network. These networks roughly correspond to those described in other studies (Hellyer et al., 2014; Sadaghiani & D'Esposito, 2014; Raichle et al., 2001). The default network (Figure 6B) is activated (with increased coupling within it) by mentally simulating an autobiographical plan, whereas it is deactivated (decoupled) by a visuospatial plan. In the dorsal attention network (Figure 6C), the reverse occurs. The frontoparietal control network (Figure 6D) is activated in both types of planning. Reciprocal planning-related correlations of the default and dorsal attention networks with the frontoparietal control network were observed (Figure 6E). The differences between network activations and planning types are small and relative. They might be attributed to differences between cortical areas with regard to the assumed involvement of those areas in planning. But we consider it more plausible that those differences are derived from differences in the concentration and coupling of perceptual and executive cognits entering the planning. Note that the three "networks" have a frontal

and a posterior component, and thus, all three straddle the PA cycle at the highest cortical level.

The third finding (Gerlach et al., 2014) is that mental simulation (imagination) of the outcome of a plan, especially if pleasant, activates medial prefrontal areas and limbic structures, such as the amygdala, commonly associated with the evaluation of reward. (Those areas and structures fall within or partly overlap the black area in Figure 6 and thus are not delineated there.) These structures and the orbitomedial pFC are likely functional components of the emotional PA cycle mentioned in the previous section.
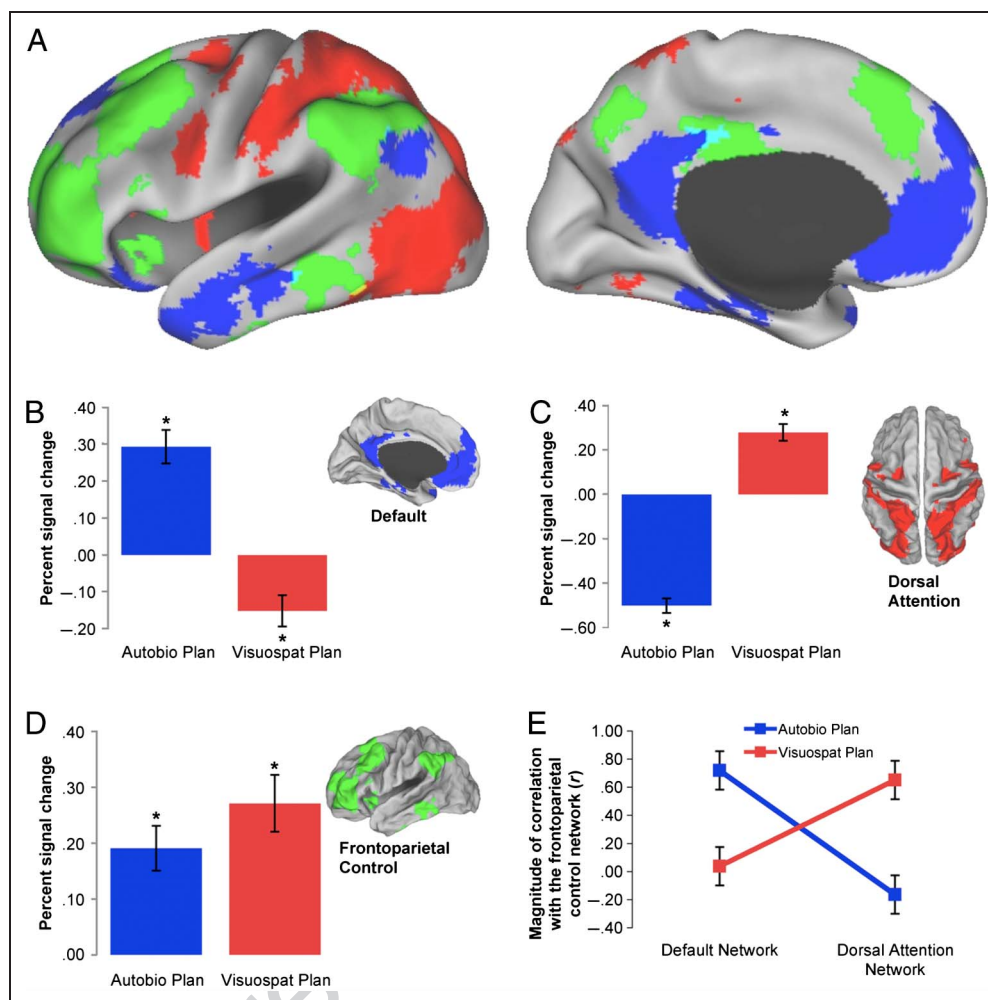
Attentional Set

Attentional set is the selective anticipatory priming of a sector of the sensory or motor apparatus for an expected sensory percept or motor action. It is attention directed to a future-expected event in the environment, whereas working memory (below) is attention directed to "stored" information that will be used in the proximate future to perform an action. With the exception of automatic correction of "prediction error" (Adams, Shipp, & Friston, 2013; Asaad & Eskandar, 2011; Modirrousta & Fellows, 2008), attentional set is the most nimble prospective function of pFC. It differs from sustained attention and working memory by its shorter duration and by immediately preceding an expected sensory stimulus or action. Its neural manifestations can best be recorded before the discrete stimuli and motor acts that take place in a cued attention or working memory task.

Like attention in general, attentional set depends on two complementary brain mechanisms: one facilitatory and inclusionary and the other suppressive and exclusionary. The first is thought to be primarily based in the lateral pFC, the second in the inferior and orbital pFC (Bari & Robbins, 2013). Both act in a top–down manner upon the substrates of perception and action as part of the cognitive control of so-called "biased competition" (Desimone & Duncan, 1995).

The neural manifestations of attentional set can be recorded from pFC by neuroimaging immediately before an anticipated visual stimulus. Anticipatory BOLD activations (Figure 7) are observed in a portion of pFC (FEF) and in the visual cortex when subjects anticipate a visual stimulus (Sylvester et al., 2009). Anticipation of musical sequences can also activate a portion of pFC (rostral pFC; Leaver, Van Lare, Zielinski, Halpern, & Rauschecker, 2009). Expectation of predicted sensory stimuli can improve their working memory, as well as their long-term memory (Bollinger, Rubens, Zanto, & Gazzaley, 2010).

Similarly, signals of attentional set can be recorded immediately before an expected motor act. Such signals may serve to encode that motor act in memory and to prepare the motor apparatus for it. An early example of anticipatory motor priming and executive set was obtained by single-cell recording from pFC in a memory

Figure 6. Network coupling (intrinsic connectivity) in the course of autobiographical and visuopatial planning. Default (blue), dorsal attention (red), and frontoparietal control (green) networks. Planning task-related BOLD signal changes within each connectivity network (*significant difference from baseline). In E, frontoparietal control network is coupled with default network and decoupled from dorsal attention network during autobiographical planning. The reverse is true in visuospatial planning. (From Schacter et al., 2012, with permission.)

task (Quintana & Fuster, 1999). Notably, the neuron-firing expression of attentional set depended on the probability with which the animal could predict the required action. The cells seemed to obey a Bayesian rule of probability as they readied the motor system to execute the action (Figure 8).

In a sensorimotor working memory task (Scheidt, Lillis, & Emerson, 2010), human participants adjusted the force of manual movements to a predicted motor "load." Here, in a similar manner as in the monkey experiment, the predictive prefrontal activation, assessed by fMRI neuro-imaging, varied with the "load." In pFC, electrophysiological
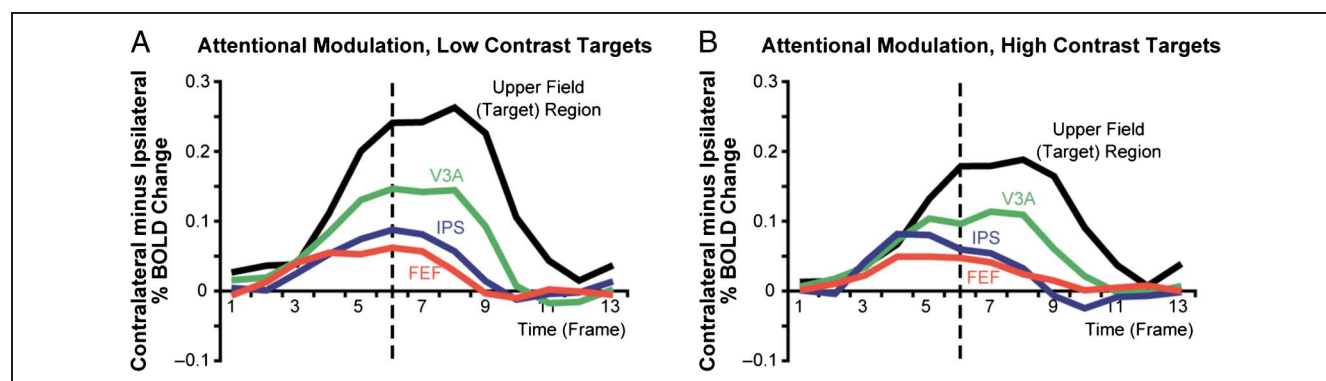

Figure 7. Prestimulus onset increases in BOLD activity in attentional set. Effects of visual set before the onset (dashed vertical line) of a visual target of low (A) and high (B) contrast. On the ordinate, % BOLD change difference between contraleteral and ipsilateral field stimulation. IPS, intraparietal sulcus; V3A, visual area 3A. Upper visual field responses are shown for comparison. (From Sylvester, Shulman, Jack, & Corbetta, 2009, with permission.)
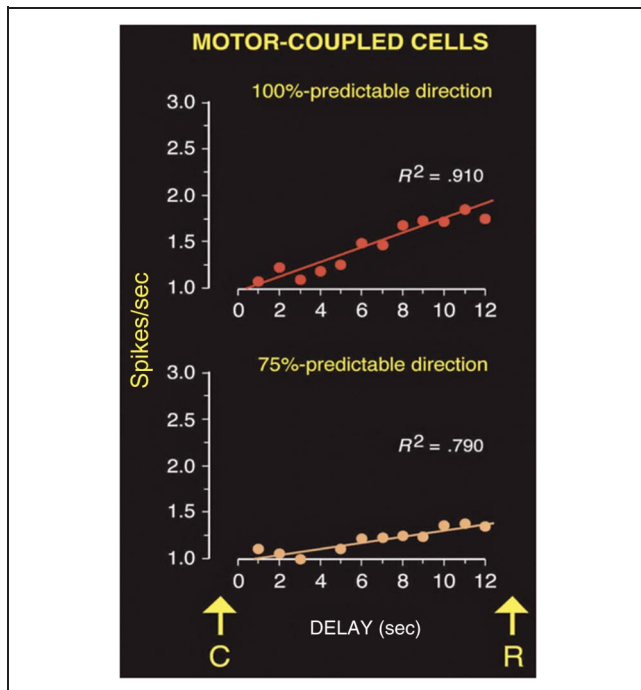
Figure 8. Predictability-tuned cells in pFC during the delay (memory period) between a cuing stimulus (C) and the predicted response (R). Monkeys performed a memory task in which the memorandum (a briefly lit colored disc in the center of the visual field) predicted with variable probabilities the direction of a manual response required after a 12-sec delay. At the start of a trial, cues of some colors predicted with certainty (100% probability) a required manual choice to the right or to the left between two stimuli presented simultaneously side-by-side at delay's end. Cues of certain other colors predicted the required response direction with only 75% probability. Some neurons were attuned to the direction of the motor response (motor-coupled cells), others to the memorandum; during the delay those motor-coupled cells showed a ramping increase of firing as the response of the animal grew near. These cells were presumably involved in priming the motor system for the approaching motor response. Remarkably, their activity was in accord with the predictability of that response: The steepness of the firing ramp during the delay was greater when that predictability was 100% than when it was 75%. R^2, square of correlation coefficient. (From Quintana & Fuster, 1999, with permission.)

(Potts, Martin, Kamp, & Donchin, 2010) and neuroimaging signals (Diekhof, Kaps, Falkai, & Gruber, 2012; Rutledge, Dean, Caplin, & Glimcher, 2010; Kable & Glimcher, 2007) predict expected reward and value in the outcome of approaching action. Especially strong signals arise in the ACC (in the medial pFC) by reward prediction error (the violation of prediction).

Both the inclusionary and exclusionary aspects of top–down predictive cognitive control were demonstrated by another neuroimaging study (Chadick & Gazzaley, 2011). It showed differential coupling of a sensory cortical region (the parahippocampal place area, PPA) with either a fronto-parietal network or the default-mode network, depending on whether a scene stimulus was relevant (enhancing PPA activity) or not (suppressing PPA activity).

A study of visual spatial attention directly demonstrates top–down bias signals from pFC to retinotopic visual cortex in relation to attentional set (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008). Directional influences were measured from fMRI BOLD signals, in both top–down and bottom–up directions between the FEF in pFC and the visual cortex as subjects anticipated a target visual stimulus. Top–down bias was observed in the form of asymmetric directional interaction between FEF and visual cortex. The results of this study indicate that the FEF sends bias signals to visual cortex in top–down attentional set, in accord with a previously cited experiment (Sylvester et al., 2009).

In the aggregate, the research summarized in this section reveals pFC as the source of descending premodulation of sensory and motor cortices in anticipation of percepts or actions expected to occur in the immediate future. By inference, that prefrontal anticipatory modulation of lower cortices plays the role of preadaptive primer for impending perception as well as action in the lower stages of the PA cycle. That modulating top–down influence is similar to the "igniter" in the terminology of Braitenberg (1978).

Working Memory

By definition, working memory is a prospective function: It consists of the temporary retention of information for performing a task or solving a problem (Baddeley, 1983). The purpose, explicit in the definition, distinguishes working memory from all other forms of STM. Neither time nor content defines working memory, but its future-directed purposive quality, which makes it a pFC function. The first step toward understanding the brain mechanisms of working memory was the revelation of "memory cells" in pFC of monkeys (Funahashi, Bruce, & Goldman-Rakic, 1989; Niki, 1974; Fuster, 1973). These are cells that during the retention period of a working memory task exhibit persistently elevated firing rates above the spontaneous baseline. Depending on the sensory modality of the stimulus to be remembered, memory cells are also found in inferotemporal (IT; Fuster & Jervey, 1982) and parietal (Andersen, Bracewell, Barash, Gnadt, & Fogassi, 1990) association cortices in addition to pFC.

The cycling of activity in reentrant circuits has been advanced as a mechanism to explain the persistent neuronal firing observed when working memory is maintained for prospective action. All plausible computational models of working memory assume some form of reentry (Wang et al., 2013; Liang, Wang, & Zhang, 2010; Tang, Li, & Yan, 2010; Durstewitz, 2009; Verduzco-Flores, Bodner, Ermentrout, Fuster, & Zhou, 2009; Compte, Brunel, Goldman-Rakic, & Wang, 2000). Both local (within-region) and cross-cortical (interregional) reentry have been proposed. They are not only compatible with one another but also are likely to cooperate in working memory maintenance at all levels of the cortical hierarchy. They are also compatible with our cognit model, in which working memory is maintained across time in the PA cycle by both local and cross-cortical reentry between cognits (Fuster & Bressler, 2012).

The concept of cross-cortical reentry in working memory is supported by converging evidence from a number of different recording types. First are studies showing that, for two areas involved in working memory, the functional depression of one induces a functional depression of the other. It is also observed that, if the inferred reentrant circuit between the two is interrupted, working memory performance deteriorates. This has been shown in visual working memory by cooling either lateral prefrontal or IT cortex and recording single-cell activity from the other cortex (Fuster, Bauer, & Jervey, 1985). Similar results have been obtained using the same procedure on prefrontal and parietal cortex (Chafee & Goldman-Rakic, 2000; Quintana, Fuster, & Yajeya, 1989).

The cross-modal and cross-temporal integrative properties of pFC neurons in support of prospective choices were convincingly demonstrated by a study on behaving monkeys (Fuster, Bodner, & Kroger, 2000). Animals were trained to match colors with tones: red with a high-pitch tone and green with a low-pitch tone (Figure 9). A trial began with a brief tone, high-pitch or low-pitch. After a delay, the monkey was presented with two colored discs and had to choose the one that matched the tone. Hence, the task was a working memory task with delayed audio-visual ("synesthetic") matching. Prefrontal cells discriminated tones and colors according to the task rule: Some cells preferred the high tone and red, others the low tone and green. No cells were found. During the memory period before the prospective choice, the cells showed sustained differential discharge, with the preponderance of cells favoring the preferred audio-visual association of the approaching choice. We conclude that some prefrontal neurons belong to large cognits that integrate pFC with visual and auditory cortical areas. Furthermore, when those cognits are activated in working memory, we postulate that the maintained selective firing of their cells directs the motor system to execute the appropriate prospective cross-temporal and cross-modal matching response.

The concept of cross-cortical reentry in working memory was further strengthened by a recent electrophysiological study of behaving monkeys (Salazar, Dotson, Bressler, & Gray, 2012). Interaction between prefrontal and posterior parietal cortical areas was observed in the form of elevated synchrony in the beta frequency range during the memory period of a delayed match-to-sample visuospatial working memory task. Moreover, frontoparietal synchrony was found to be content specific, with the magnitude of beta synchrony coding for the identity of the sample visual item held in working memory.

Cross-cortical co-operation by reentry in working memory has also received considerable recent support from human functional neuroimaging. Some imaging studies focus on the temporal correlations between prefrontal and posterior association cortices during working memory. Others, by changing the characteristics of the tasks and memoranda, attempt to define the precise aspects of working memory processing in which pFC is involved. One basic question is this: Does that cortex serve the maintenance or the processing ("manipulation") of

Figure 9. Cross-temporal and cross-modal integration by cells of pFC. (A) Audio-visual delayed-matching task. Trial sequence: (1) 2-sec tone, high-pitch (3000 cps) or low-pitch (240 cps); (2) 10-sec delay; (3) two colors presented simultaneously, red and green; (4) monkey chooses red if tone was high pitch, green if it was low pitch. (B) Diagram of monkey's brain, with numbers indicating Brodmann's areas; in blue, frontal region from which tone and color discriminating cells were recorded. (C and D) Firing frequency histograms of two cells at the times of the tone and of the matching color-choice, one cell (C) preferring the high-tone–red association and the other cell (D) the low-tone–green association. The histograms are time-locked (0) with the tone-onset and the manual color choice. Note the correlation of selective cell reactions to tones and colors in accord with the task rule. (E) Firing frequency histograms of three cells selective for low-tone–green. Note that, after a low tone, the cells maintain that selective firing throughout the memory period (10 sec) in anticipation of the choice of green. (From Fuster et al., 2000, with permission.)
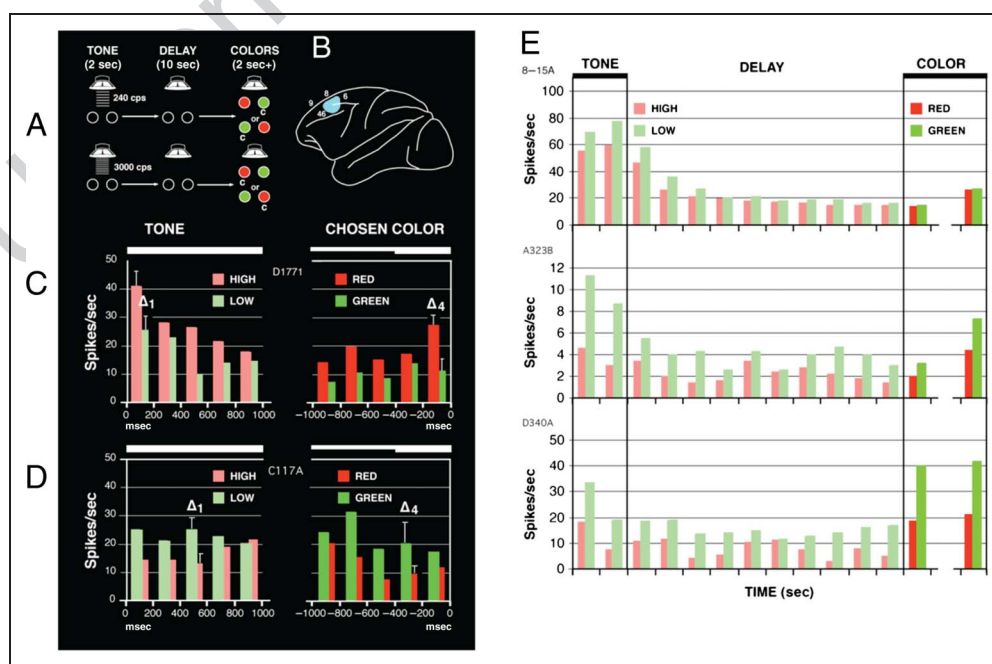
working memory? Because each hypothesis implies a prospective role for pFC, we will briefly treat them together next.

A graphical meta-analysis of a large number of studies (reviewed in Fuster, 2008) revealed that, during working memory, there is a consistent activation of a prefrontal region in addition to one or several regions of posterior cortex. The specific area activated in working memory, in addition to pFC, depends on the nature of the memory task and its memorandum. In addition to an area of lateral pFC, IT and occipital areas are activated if the memorandum is visual, as in Figure 10 (Linden, Oosterhof, Klein, & Downing, 2012; Yee, Roe, & Courtney, 2010; Rajah & D'Esposito, 2005; Crottaz-Herbette, Anagnoson, & Menon, 2004; Wager & Smith, 2003; Cabeza & Nyberg, 2000; D'Esposito, Postle, & Rypma, 2000; Duncan & Owen, 2000; Mecklinger, Bosch, Gruenewald, Bentin, & Von Cramon, 2000), posterior parietal if it is spatial (Jerde & Curtis, 2013; Silver & Kastner, 2009; Klingberg, 2006; Wager & Smith, 2003; Cabeza & Nyberg, 2000; Pollmann & Von Cramon, 2000; Casey et al., 1998), and temporo-parietal if it is auditory (Goldstein et al., 2005; Crottaz-Herbette et al., 2004; Wager & Smith, 2003; Cabeza & Nyberg, 2000; Buchsbaum et al., 1982).

In all cases, a reentrant loop of activity flow is presumed to underlie the activation of areas that bridge the memory period of the task. Those areas supposedly harbor the perceptual and executive cognits that the task activates in the PA cycle for a successful choice. The role of selective reentry in working memory is further suggested by neuroimaging (Lowe, Dzemidzic, Lurito, Mathews, & Phillips, 2000) and MEG (Baldauf & Desimone, 2014) studies that reveal functional coupling between frontal and posterior-sensory cortical areas in the context of sustained selective attention or working memory. It is further suggested by a study of effective cortical connectivity in verbal working memory (Honey et al., 2002). Regardless of the memory task utilized, OFC is activated after the choice (Figure 10), reflecting the reward value of the choice's outcome (Sescousse, Barbalat, Domenech, & Dreher, 2013; Levy & Glimcher, 2012; Schoenbaum, Roesch, Stalnaker, & Takahashi, 2011).

The imaging data examined thus far are consistent with a maintenance role for pFC in working memory. That role is presumably to maintain temporary storage for goal-directed behavior by selective cross-cortical reentry, modulated over time by the gradual transition of activation of perceptual cognits to that of executive cognits. In a recent review, Sreenivasan, Curtis, and D'Esposito (2014) come to conclusions very similar to ours, though without the emphasis on the future aspects of working memory. As we have proposed above and elsewhere for a long time (e.g., Fuster, 1995), and those authors essentially corroborate, working memory is a widely distributed activation of cognits, in posterior cortex as well as frontal cortex. Both regions are coupled by reentry in the maintenance of the memorandum. Posterior cognits
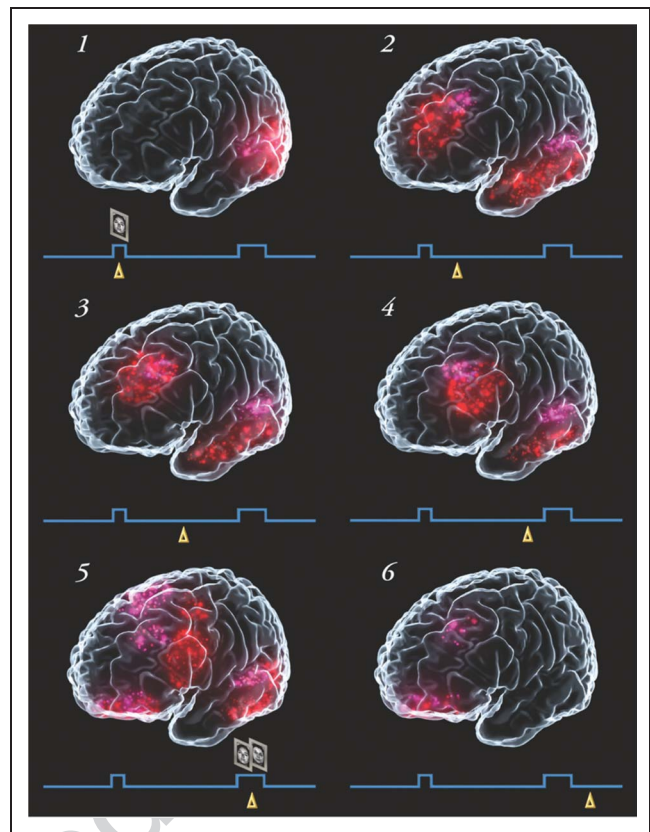

Figure 10. Relative (above baseline) cortical activation at six moments (marked by yellow triangles) in the course of visual memory tasks such as that depicted in Figure 5 (delayed matching-to-sample with faces). The activations above baseline, in red, derive from a graphic analysis of the findings of several functional imaging studies of human participants performing visual working memory tasks with various delay periods. Here a uniform 20-sec delay is assumed. The temporal evolution of activations is inferred from studies of neuronal firing in approximately homologous cortical areas in monkeys performing visual working memory tasks. During the delay or memory period, note the concomitant activation of prefrontal and IT areas, the executive and perceptual poles, respectively, of presumptive reentrant circuits of the PA cycle in the retention of visual information for the forthcoming choice.

are precisely tuned to the sensory qualities of memoranda, whereas prefrontal cognits are tuned to their executive qualities.[1] Together, those qualities are encoded in the dynamics of large-scale neuronal populations operating across the PA cycle.

Decision-making

Making a decision is a cardinal prospective function of pFC. The rules of behavior are represented in pFC as high-ranking executive cognits. The decision to choose a behavioral response at the end of a working memory trial, like other decisions in novel, uncertain, or ambiguous situations, is preceded and accompanied by the activation of a portion of the lateral convexity of pFC (Figure 10), in

one or both hemispheres. pFC's role in making decisions depends on its critical involvement in the PA cycle, and the many factors that affect decision-making are derived from the manifold influences, from both cortical and subcortical structures, that affect pFC. Important sources of influence on decision-making by pFC in working memory are the posterior cortical regions that interact with pFC in the retention of sensory memory for a prospective action. Significant influences also come, through orbital pFC, from thalamic and limbic structures underpinning the biological drive and expectation of reward (Diekhof et al., 2012; Wunderlich et al., 2012; Asaad & Eskandar, 2011; Kennerley, Behrens, & Wallis, 2011; Rolls & Grabenhorst, 2008; Rushworth & Behrens, 2008; Kable & Glimcher, 2007; Schultz, 2006); they critically affect decision-making.

In some situations, the sensory stimulus that unleashes goal-directed series of actions may serve as a single determinant of decision (Eiselt & Nieder, 2013; Nee et al., 2013; Buschman, Denovellis, Diogo, Bullock, & Miller, 2012; Reverberi, Gorgen, & Haynes, 2012; Durstewitz, Vittoz, Floresco, & Seamans, 2010; Montojo & Courtney, 2008; Bunge, 2004). In most circumstances, however, the decision and pFC involvement in it are multifactorial, because of the confluence of many signals upon pFC. The signals may be simple and discrete, as those derived from a short single sensory stimulus, or complex, as those dependent on the associated context in which the stimulus appears. Such complex cues may be mixed and encode what Rigotti et al. (2013), on the basis of primate data, call "mixed selectivity." In any case, a decision may be (a) determined by just one factor, such as that critical stimulus; (b) vectorial, the result of several synergistic factors (e.g., active cognits) with different weights (salience or motivation); (c) "winner-takes-all," when one of the factors decisively outweighs the others; or (d) Bayesian, probabilistically based on the updating of prior memory. In all cases, an executive cognit is activated by prediction based on experience.

In their recent review, Sreenivasan et al. (2014) point to the difference in the discriminating properties of the neuronal populations of posterior (sensory) cortex and pFC in working memory. They postulate that working memory is maintained with high fidelity in sensory cortex, whereas pFC maintains "representations of multiple goal-directed variables," which bias (top–down) stimulus-specific activity in sensory cortex. Transposing their argument to decision-making, which uses largely the same cognits as working memory, we postulate that pFC, informed by sensory cortex and high-level cognits within itself (e.g., for rules), contributes to the making of decisions (choices) by the orderly activation of lower, more concrete goal-directed actions within the framework of the PA cycle.

The complexity of those neural transactions and the multivariate context in which they take place make the computational modeling of prefrontal decision challenging. Nonetheless, several successful attempts at modeling prefrontal cell populations in decision-making have been made by assuming the deciding role of various factors, one of them context (Sigala, Kusunoki, Nimmo-Smith, Gaffan, & Duncan, 2008; Rowe, Stephan, Friston, Frackowiak, & Passingham, 2005; Wang, 2002). Figure 11 illustrates the essential aspects of a recent empirical model of context-determined decision (Mante et al., 2013). Here, monkeys were trained to select noisy visual stimuli to make a choice. Depending on a discrete, context-signaling stimulus, the choice had to be made between motion and color, both embedded in input noise. In records of pFC cell populations during that task, as well as in the behavior of a recurrent-network model performing an analogous task, context was seen to sway the entire population or network of units to discriminate one parameter or the other (motion or color). The authors conclude that the same network (a prefrontal cognit) can direct both the sensory input selection and the integration of the appropriate behavioral response.

Figure 11. Network model of input selection and integration by a pFC cell population. With synaptic strengths originally randomized, the fully recurrent network was trained by back-propagation (Rumelhart, Hinton, & Williams, 1986) to make binary choices on ambiguous visual information in accord with an independent contextual input (two values, 0 or 1). Each unit in the network receives motion and color inputs as well as input on context. The contextual input

instructs the network to discriminate motion or color. The network thus generates one output at the end of the stimulus presentation if the relevant evidence point toward Choice 1 or another if it points toward Choice 2. The network is "read out" by a single linear read-out of the weighted sum of the response of all units (red arrows). MT, V4, and IT: three areas of extrastriate visual cortex (From Mante, Sussillo, Shenoy, & Newsome, 2013, with permission).
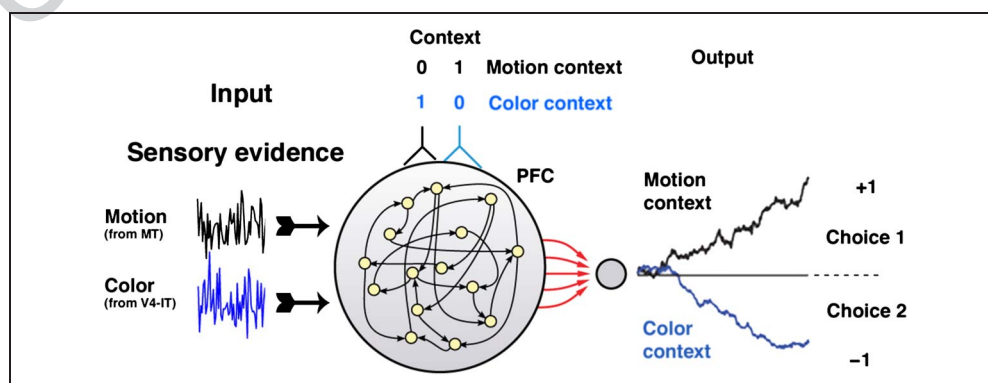
In another study of prefrontal cell population dynamics, Stokes et al. (2013) also investigate the role of context on the patterns of neural response related to decision-making. In this study the subject, a monkey, is presented with a visual cue that signals the rule that governs a subsequent visual discrimination. Despite differences in the format of the tasks, the test is similar to that of the previous study. Both studies use a "context-cue" to bias a behavioral choice and its correlated pattern of cell discharge. In the second study, however, that cue precedes the choice by some time, during which the baseline cell discharge adjusts to a level attuned to the approaching choice. Here is evidence, therefore, of prefrontal predictive discharge tuned to the rule of the task that will govern the choice. In our view both studies provide evidence of the activation of a higher prefrontal cognit (representing the rule, or "context") predicting and modulating the response of lower executive cognits, some possibly reaching into sensory cortex.

The available evidence indicates that every action in a goal-directed sequence is processed in the cortex rostro-caudally, down the executive hierarchy (Figure 3, right side) in cascade fashion, from its upper layers of cognitive representation toward the appropriate motor effectors in M1 (Azuar et al., 2014; Badre, Hoffman, Cooney, & D'Esposito, 2009; Koechlin & Hyafil, 2007). Therefore, the enactment of a series of goal-directed actions seems to follow a generally downward trend (Koechlin's "temporal abstraction gradient"), which is the reverse to that followed by the original formation of executive cognits by memory acquisition and experience. In addition, other imaging evidence indicates that different goal-directed actions may be concomitantly processed in different frontal areas (Charron & Koechlin, 2010), possibly in parallel PA cycles.

Error Monitoring and Avoidance

At the termination of a goal-directed action, information flowing back into pFC signals whether or not the action has led to the goal and, if not, by how much the goal was missed. That information allows pFC to prepare sensory and motor systems for the next action in the sequence toward the goal. On the basis of prior experience, every action in a goal-directed sequence carries with it the implicit prediction that it will succeed. The failure to attain an expected goal or reward has been called prediction error; the minimization of that error has emerged as one of the chief preadaptive, future-oriented functions of pFC.

Rosenkilde, Bauer, and Fuster (1981) were probably the first to detect prediction error signals in the monkey's pFC. They and others later (Asaad & Eskandar, 2011; Kennerley et al., 2011; Hikosaka & Watanabe, 2000; Schultz, Dayan, & Montague, 1997) found cells in orbital pFC that during the performance of behavioral tasks showed marked activation in the absence of an expected reward, whether by error or by experimental design. Cell populations in orbital pFC are part of the dopamine system and are known to be tuned to reward and reward value (reviews by Niv & Schoenbaum, 2008, and Schultz, 2006). A question is then whether they are tuned to prediction error because of its negative reward value. In any case, human neuroimaging (Dreher, 2013) shows the activation of OFC by negative reward, that is, by prediction error, as well as by positive reward.

Whereas a number of brain structures, including the orbital and medial (anterior cingulate) pFC, the amygdala, and the striatum, receive prediction error signals as part of PA cycle feedback, it is not clear through which structures and by what mechanism the error is corrected in subsequent actions. Are the same structures that detect prediction error in charge of error correction? There is no simple answer to this question. The reason is because, as is true for most of the structures in the PA cycle, most methods do not separate input from output signals. This is a problem for the theoretical as well as the empirical analysis of error in the nervous system. Methods that infer directional influences between cortical areas from BOLD time series predictability (Bressler & Seth, 2011) offer a potential solution to this problem.

On the basis of characteristics of the fine structure of the pyramidal motor system and the role of sensory feedback in perception, Friston and colleagues (Adams et al., 2013; Shipp, Adams, & Friston, 2013; Friston, 2003) theorize that the descending output to the musculature in a motor act essentially conveys a "predictive code," anticipating proprioceptive feedback from movement and thus in effect minimizing prediction error. In a similar vein, Clark (2013) argues that the brain is essentially an adaptive "machine" that through its motor apparatus conveys to the periphery "action-oriented predictive coding." Both Friston and Clark place the narrow concept of prediction error at the core of their thinking to implement their theories; this narrow approach, however, poses problems for the generalization of their hypotheses (Niv & Schoenbaum, 2008). In any case, both investigators assume the general concept of the hierarchical organization of action, as we have in this review, and both their theories are compatible with the principles of the PA cycle. Both also espouse the idea that action processing takes place in cascade fashion down an executive hierarchy, as proposed above.

In their review of cingulate functions, Shackman and colleagues (2011) come to the conclusion that the cognitive and emotional contributions of ACC to goal-directed behavior cannot be dissociated. Both are intimately interrelated, anatomically, and physiologically. This agrees well with a recent model (Alexander & Brown, 2011) and with our concept of medial pFC as an integrative hub for both a cognitive and an emotional PA cycle. Both cycles would serve the coordination of preadaptive actions to minimize error and secure reward. Nonetheless, there is some evidence that parts of the anterior cingulate, centered on areas 32 and 24, are more involved in the avoidance of error than in the detection of error itself

or its cognitive and emotional consequences (Magno, Foxe, Molholm, Robertson, & Garavan, 2006). To sum up in the context of the other prospective functions of pFC discussed above, error monitoring may be plausibly viewed as another servant of pFC in its role of guiding the PA cycle toward the adaptation of the organism to future changes in itself and in the world that surrounds it.

CONCLUSIONS

pFC, the latest cortex to develop in evolution and in ontogeny, confers to the organism purpose and goal. This makes pFC a proactive and preadaptive brain structure. Purpose and goal, however, are anchored in memory and knowledge, that is, in a cortex-wide array of overlapping, interactive, and hierarchically self-organized networks of widely differing size and content that we name cognits. Cognits are the cortical "scale-free" units of memory/knowledge. They are formed by the synaptic modulation of cortical connections between simultaneously excited sensory and/or motor neuron assemblies. Perceptual cognits are distributed and organized chiefly in posterior cortex, executive cognits in frontal cortex. In the pursuit of goal-directed actions, perceptual and executive cognits engage in an adaptive biocybernetic cycle called the PA cycle.

This review presents recent evidence on the physiological manifestations as well as their underlying mechanisms of prospective pFC functions: planning, attentional set, working memory, decision-making, and error monitoring and avoidance. Although much remains unknown about their mechanisms, each of those functions elicits neural signals that anticipate stimuli and actions essential to the temporal integration of future goal-directed behavior. Those prospective pFC functions, which in the aggregate could rightfully be considered to manage the cognitive control of the future, recruit a series of cognits that, by their orderly and timely activation, regulate the pursuit of a given objective. Cross-cortical reentry appears to be a mechanism shared by several of those functions, notably working memory. In the preparation and subsequent execution of a plan of action, whether in everyday life or an experimental task, pFC, at the dynamic summit of the PA cycle, coordinates the activity of cortical cognits and subcortical formations to organize predicted actions in the temporal domain, especially if those actions are novel and complex.

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Note

1. In the present context, we have advisedly used the Latin gerundive "memorandum" (a note or record made for future use) to emphasize the prospective essence of working memory.

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