Persistent activity in the prefrontal cortex during working memory

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The dorsolateral prefrontal cortex (DLPFC) plays a crucial role in working memory. Notably, persistent activity in the DLPFC is often observed during the retention interval of delayed response tasks. The code carried by the persistent activity remains unclear, however. We critically evaluate how well recent findings from functional magnetic resonance imaging studies are compatible with current models of the role of the DLFPC in working memory. These new findings suggest that the DLPFC aids in the maintenance of information by directing attention to internal representations of sensory stimuli and motor plans that are stored in more posterior regions.

Working memory refers to the temporary representation of information that was just experienced or just retrieved from long-term memory. These active representations are short-lived, but can be maintained for longer periods of time through active rehearsal strategies, and can be subjected to various operations that manipulate the information in such a way that makes it useful for goal-directed behavior. Most definitions of working memory include both storage and (executive) control components [1]. Cognitive neuroscientists are searching for ways to disassociate the separate components of working memory in attempts to localize and clearly characterize their neural implementation. The prefrontal cortex (PFC) is thought to be the most important substrate for working memory (Fig. 1). Two key findings from studies of monkeys performing delayed response tasks suggest a crucial role for the PFC in working memory. First, experimental lesions of the principal sulcus in the dorsolateral prefrontal cortex (DLPFC) cause delay-dependent impairments [2–4]. That is, forgetting increases not only when a delay is imposed but increases with the length of the delay. Second, neurophysiological unit recordings from the DLPFC often show persistent, sustained levels of neuronal firing during the retention interval of delayed response
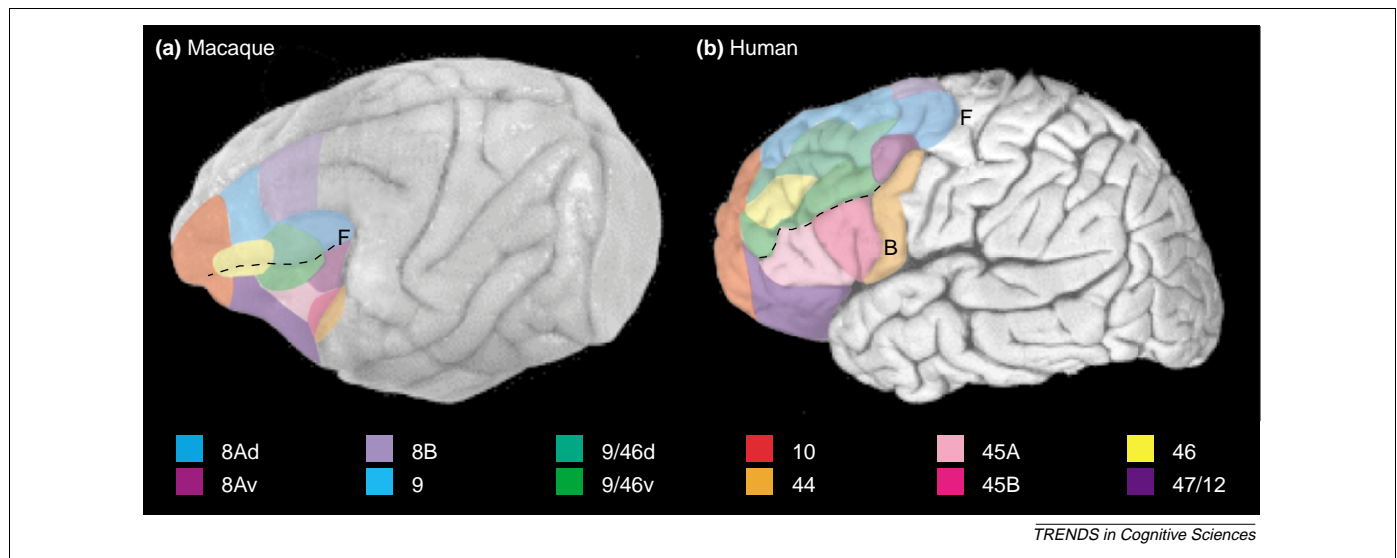

Fig. 1. Lateral surface of (a) macaque and (b) human brain. The PFC is composed of lateral, medial, and orbital sectors that are believed to be functionally distinct given the selective effects of damage and distribution of afferent and efferent projections. The tinted areas correspond to those defined by Petrides and Pandya [71] based on cytoarchitecture and connectivity. Notably, the mid-DLPFC comprises areas 46 and 9/46 and the mid-VLPFC comprises areas 45 and 47/12. Note that much of area 46 lies in the depths of the principle sulcus of the monkey and the intermediate frontal sulcus of the human. Frontal premotor regions are also highlighted. The frontal eye field (F) in the macaque lies in the anterior bank of the arcuate sulcus in area 8A. In the human, F is found in the vicinity of the precentral sulcus and superior frontal sulcus junction (area 6 and maybe the caudal-most portion of 8A). The frontal eye field is a premotor region involved in the control of eye movements. Broca's area (B, area 44) is also a premotor area that is involved in the production of speech. The dotted line represents the principle sulcus in the macaque and the inferior frontal sulcus in the human.

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Box 1. Organization of lateral PFC

A separate but related issue to the topic of this review is the broader interest in characterizing the functional organization of the lateral convexity of the PFC [59]. The middle portion of the lateral PFC, including the dorsal (area 46, 9/46, and 9) and ventral (area 45 and 47/12) lateral aspects, has distinct cytoarchitecture and connectivity [71]. Several models have been proposed to characterize the organization of the mid-lateral PFC. For example, a 'material-specific' model [17] claims that the dorsal and ventral PFC can be functionally segregated by the preferred type of material it supports in working memory. The dorsolateral PFC is engaged in 'on-line' maintenance of spatial memoranda, while the ventrolateral PFC supports non-spatial (e.g. face, objects) memoranda. The material-specific model is essentially an extension of the dorsal 'where' and ventral 'what' segregated pathways for the processing of visual information in posterior portions of the cortex. An alternative 'process-specific' model [20] claims that the functions of the mid-lateral dorsal and ventral PFC are not best described by the type of information but instead by the operations performed upon information in working memory. The process-specific model proposes a hierarchy where the mid-ventrolateral PFC supports simpler processes such as the active encoding and retrieval of information and the mid-dorsolateral PFC supports higher order control functions like the monitoring and manipulation of information in working memory. Models also exist about the functional organization of the lateral PFC that extend beyond working memory [13]. For instance, long-term memory processes might be functionally organized along an anterior–posterior gradient in the PFC, with greater domain specificity in the more posterior areas and higher-level control processes that generalize across domains in the more anterior areas [74].

tasks [5–7]. This sustained activity is thought to provide a bridge between the stimulus cue, for instance, the location of a flash of light, and its contingent response, for instance, a saccade to the remembered location. Such compelling data established a strong link implicating the DLPFC as a crucial node supporting working memory.

Over 30 years has elapsed since these initial observations were reported and the role of the PFC in working memory continues to be an area of intensive investigation and controversy. In the past 10 years, over a hundred functional magnetic resonance imaging (fMRI) studies of working memory in the human brain have been performed, many with the goal of understanding the function of the PFC. Many contemporary models of PFC function (Box 1) and working memory rely on attempts to integrate data from various methods such as single unit recordings in monkeys [5,6,8], neuropsychological performance of human neurological patients with focal lesions [9–11], and more recently transcranical magnetic stimulation [12]. In this review, we critically evaluate how well new fMRI findings are compatible with current models of DLPFC function.

Representations and operations

Understanding PFC functions is likely to hinge on our ability to resolve the nature of stored representations in addition to the types of operations performed on such representations necessary for guiding behavior [13]. Representations are symbolic codes for information stored either transiently or permanently in neuronal networks. Operations are processes or computations performed on representations. Models of working memory [1,14] and models of PFC function [15–21] vary substantially in the relative importance

given to representations and operations [13]. For example, Baddeley's model of working memory [14] proposes that information is represented in various storage buffers depending on the form of the information (e.g. verbal or visuospatial). A central executive, similar to Norman and Shallice's supervisory attentional scheduler [22], is proposed to coordinate operations performed on the contents of information represented in memory. Some models attribute storage functions or representations to posterior cortical areas (e.g. premotor, parietal, and temporal cortex) and reserve the collection of 'executive' operations for the PFC [15,20,23]. The distinction between representations and operations can be made clear in the vernacular of our cognitive models, but as we shall see, it might prove extremely difficult to distinguish between them with our current indirect (e.g. fMRI) and even direct measures (e.g. unit recordings) of neuronal activity.

Models of dorsolateral prefrontal cortical function

Founded on experimental lesion and unit recording data in awake-behaving monkeys, Goldman-Rakic formalized her highly influential theory of PFC function [17]. In this model, lesions of area 46 in the DLPFC impair the ability to maintain on-line sensory representations that are no longer present in the environment but are necessary for adaptive performance. Damage to the DLPFC results in the forgetting of relevant information. Persistent delay-period activity reflects the temporary storage of some stimulus feature like its position or shape [24–26]. Although local operations permit for the feeding of sensory representations to neurons that control effectors, for example, the primary function of the DLPFC is proposed to create and maintain internal representations of relevant sensory information. Miller and Cohen [19] extend this idea by suggesting that in addition to recent sensory information, integrated representations of task contingencies and even abstract rules (e.g. if this object then this later response) are also maintained in the prefrontal cortex. This notion is similar to what Fuster has long emphasized [27], namely, that the PFC is crucially responsible for temporal integration, the mediation of events separated in time but contingent on one another. Sustained delay-period activity might reflect the maintenance of several goal-directed representations including past sensory events (i.e. a 'retrospective' code), but also representations of anticipated action and preparatory set (i.e. 'prospective' codes) [28,29]. All of these models emphasize that the DLPFC plays a prominent storage role in the temporary maintenance of relevant information through persistent neural activity.

However, other models place less emphasis on a storage role for the DLPFC and instead (or additionally) emphasize its role in providing top-down control over more posterior regions where information is actually stored [10,15,19,20,23]. Thus, the sustained activity in the DLPFC does not reflect the storage of representations, *per se*; it reflects some maintenance operation or top-down process that influences which aspects of our external or internal milieu is actively maintained by other posterior areas. Studies showing the enhancement of task performance
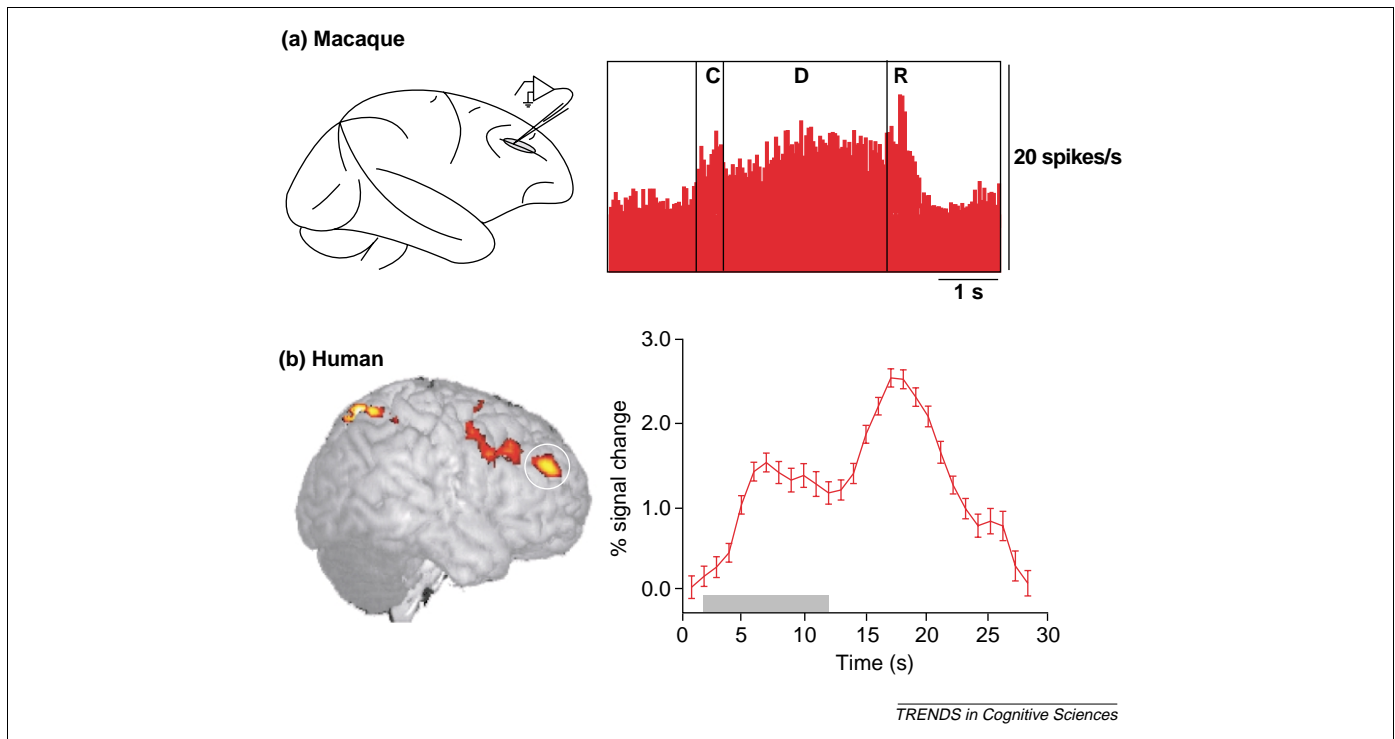
Fig. 2. Activity in the monkey and human DLPFC during the retention interval of a spatial oculomotor delayed response (ODR) task. **(a)** Average of single-unit recordings from 46 neurons with delay period activity from the monkey DLPFC (area 46) (Adapted from Ref. [76]. C = cue; D = delay; R = response. **(b)** Significant maintenance-related activity (left) and average (±SE) fMRI signal (right) from right DLFPC (area 46; circled) in a human performing the ODR task depicted in Box 2, Fig. Ia. The grey bar represents the length of the delay interval. Notice how in both cases the level of DLPFC activity persists throughout the delay, seconds after the stimulus cue has disappeared. (Data presented is for illustrative purposes, to show persistent prefrontal activity in humans; C.E. Curtis and M. D'Esposito, unpublished results)

and changes in the properties of extrastriate cortex attributable to the focusing of visual attention have been influential in developing this viewpoint [30,31].

Evidence from fMRI studies

To test whether the DLPFC supports maintained representations and/or control operations, fMRI has been used to detect and characterize persistent delay period activity during delayed response type tasks. We will now review key studies that address the role of the DLPFC in working memory. We exclusively focus on recent fMRI studies that employed event-related designs because blocked designs cannot isolate the component processes (e.g. maintenance) of working memory [32] (see Box 2).

Persistent delay-period activity

Neurophysiological studies of monkeys [5,6,8,25,28] and more recently event-related fMRI studies of humans [33–37] have recorded persistent activity during retention intervals of delayed response tasks from the DLPFC (Fig. 2). In addition, when this activity is reduced performance has been shown to suffer [26,35,38]. This could suggest that the activity reflects the maintained or more specifically stored representation of the remembered stimulus. However, to establish unequivocally that the DLPFC is involved in the storage of representations, there needs to be clear evidence that activity during the delay is in fact related to storage and not some other related process involved in maintenance.

Put simply, we have a striking observation – sustained activity in the DLPFC during a retention interval – and a

reasonable interpretation: this activity is mnemonic in nature and reflects the active storage of past sensory representations. How do we evaluate whether this interpretation is in fact correct? This may prove difficult. One method used has been to systematically manipulate factors that affect maintenance and evaluate whether or not delay activity is similarly affected. This idea has been explored by increasing the memory load by lengthening the delay interval or by increasing the number items to represent in memory.

Memory load effects

Durability

If the delay period activity reflects the stored representation, then one might expect that the activity should endure throughout the entire length of the retention interval until it can be used to guide a response. This is exactly what has been reported now several times in unit recordings in the PFC of monkeys [5–7,28,33,39]. A few event-related fMRI studies have varied the length of the retention delay up to 24 s and have reported that the DLPFC activity does indeed span the entire delay [34–37]. These results are consistent with the hypothesis that the DLPFC is a site where active representations are stored long enough to guide appropriate responses. As discussed below, they are also consistent with the idea that the sustained activity results from the process of focusing attention on relevant representations stored elsewhere.

Number of items

As with durability, maintenance demands should increase with the number of items to be remembered.

Box 2. Delayed-response task and modeling within trial components of event-related fMRI data

A prototypical oculomotor delayed-response task, like all delayed-response tasks, has three main epochs, a sample cue period where stimuli to-be-remembered are presented, an unfilled delay period where stimuli are retained in memory, and finally a response period where a memory-guided response (i.e. saccade) is required (Fig. Ia). Block designs that attempt to subtract blocks of trials with and without memory requirements cannot be used to assess maintenance related activity because of the untenable assumption of pure insertion [34,75]; that a cognitive process can be added to a pre-existing set of cognitive processes without affecting them. Specifically, the insertion of a maintenance requirement most certainly affects other encoding and retrieval/response processes (e.g. visual encoding; why encode the cue if it will not be used to guide the response made after the delay?). Event-related designs for fMRI have the ability to statistically disambiguate the haemodynamic signals specifically related to encoding the cue stimuli and generating memory-guided responses from the maintenance-related activity present in the retention interval.

When multiple sequential neural events occur within a trial, the resulting fMRI response is a mixture of signals emanating from more than one time and more than one trial component. The gradient under the curve in Fig. Ib schematically represents the mixing or temporal overlap of the various signal components. For example, the white region at the peak of the first hump is almost exclusively evoked from neural processing during the cue phase of the task. However, just a few seconds later, in the darker portion just to the right, the signal is a mixture of processing at the cue phase and the beginning of the delay period. To resolve the individual components of the mixed fMRI signal, separate regressors can be used to independently model the cue, delay, and response phases of the trial (Fig. Ic). The magnitudes of the regressors scale with the degree to which they account for variance in the observed time series data (Fig. Id). The magnitude of the delay regressor can be used as an index for maintenance-related activity.
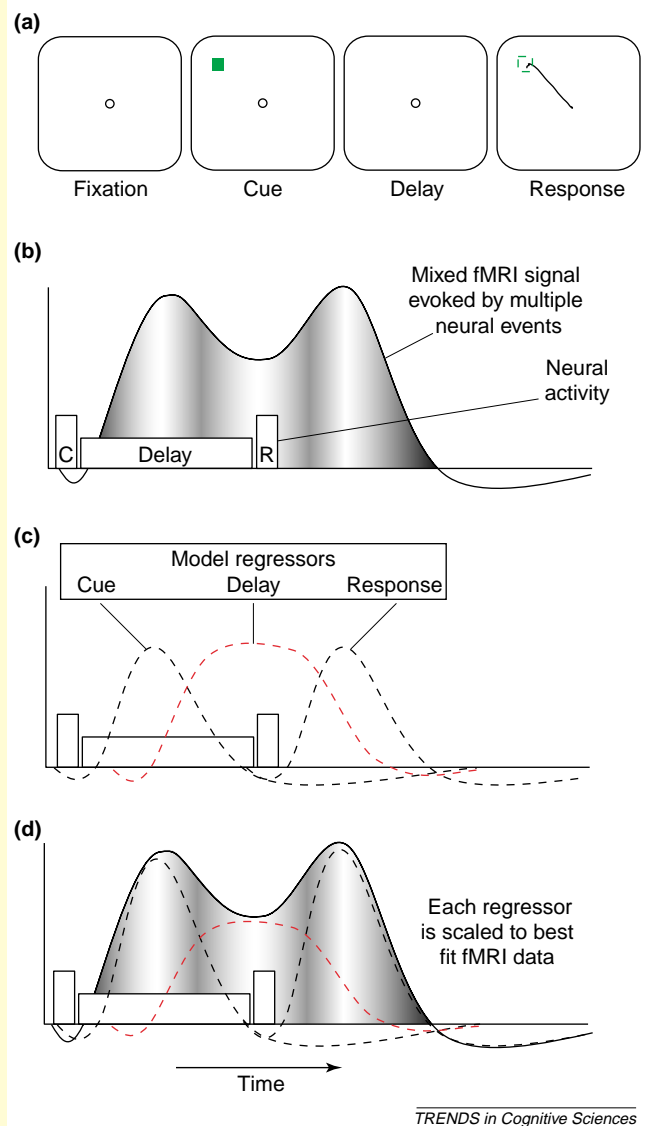

Fig. I. **(a)** Schema for a prototypical oculomotor delayed-response task. **(b)–(d)** Modeling the fMRI response from a trial (see text for explanation).

Three event-related fMRI studies that manipulated memory load have failed to find that the delay period activity was affected by load [37,40,41]. For example, Jha and McCarthy [37] reported that remembering three faces did not evoke greater delay period activity in the DLPFC than remembering one face at any point during 15 or 24 s memory delays. These findings, thus, are contrary to the view that the DLPFC simply maintains task relevant representations. However, Leung, Gore and Goldman-Rakic [36] recently demonstrated that the DLPFC does not sustain a significant level of activity throughout a 18 s delay when maintaining three faces in memory, but does so if five faces are required to be remembered. Two recent studies from our laboratory have also detected significant effects of memory load on delay period DLPFC activity during a face [42] and letter [43] working memory task.

Interpretation of load effects
Even during long delays in which items must be retained in working memory we can often detect sustained DLPFC activation. Although mixed, some studies find that DLPFC activity increases when the number of items to be maintained increases. This would seem to support the conclusion that the DLPFC plays an important role in memory storage. But, does it? On the one hand, increasing the demands of storage should be expected to increase BOLD signal in a region where representations are being actively stored. On the other hand, there are equally plausible explanations that need to be investigated. First, if DLPFC activity reflects top-down signals to more posterior regions where the representations are stored, maintaining higher loads of information might require increased DLPFC input in order for relevant
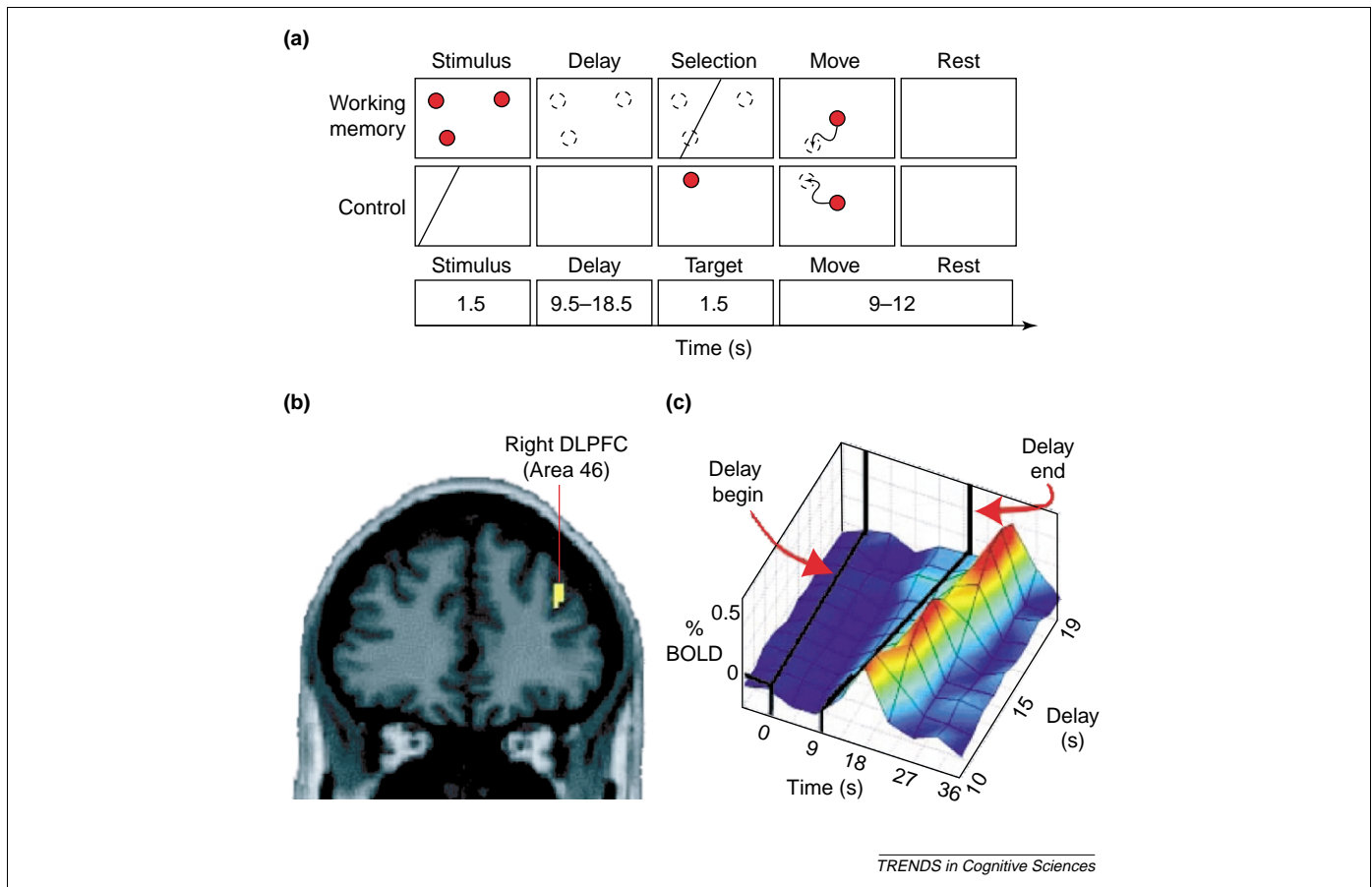
Fig. 3. The selection of a response dependent on working memory activates the DLPFC in humans. **(a)** Task design. Three locations were remembered over an 8.5–18.5 s delay. In one study [46], a line was briefly presented after the delay that crossed one of three locations, marking it for response. In another study ([47], not depicted here), the three locations were presented serially and after the delay a number was presented marking that location in the sequence for response. During the 1.5 s of the selection interval, a response was prepared that moved a central cursor with a joystick to the remembered location. In control trials, subjects simply moved the cursor to a target that was presented after a non-memory delay. **(b)** The right DLPFC (MNI coordinates 42, 38, 28) was active when the subject had to select from memory which response was appropriate given the three locations in memory. In both studies, the DLPFC was active when the appropriate location being maintained was selected for response, but not during the memory delay interval. **(c)** Time series from right DLPFC showing increased BOLD response only after the delay had ended. Maintenance of the locations did not result in significant signal increases in area 46 of the DLPFC. (Adapted from [46]).

to-be-remembered features to survive delay and distraction. Second, the studies that do show a load effect during the maintenance period used loads that might have been beyond the capacity of working memory. Increasing storage demands beyond capacity limits might invoke strategic changes in the way information is represented [44]. Rypma *et al.* have argued [41,43] that the increased signal changes with increased load in the DLPFC are the consequence of the strategic process of data compression (e.g. chunking) because these effects are most prominent during the cue period when encoding takes place. Strategic organization of memoranda is a control process that is distinct from raw storage of representations. Indeed, even when memory load decreases, DLPFC activity can increase if encoding strategies are invoked that chunk the memoranda into easier to remember sets [45].

The mere detection of sustained delay period activity in the DLPFC, which under some circumstances shows a memory load sensitivity, is broadly consistent with a storage role for the DLPFC (i.e. the active representation of an item in the DLPFC). The inconsistency and several alternative interpretations of the load effects, however, leave unresolved whether the DLPFC is the site of active representations or is instead involved more generally in control operations. It seems clear that the DLPFC facilitates the maintenance of information, but what is not clear is if it is the site where the representations are stored. Maintenance and storage are not synonymous. Storage, in the context of working memory, is the representation of memoranda through neuronal activity (i.e. an activity based definition [19]). The term maintenance is used more broadly to describe both the active representation and any processes that influences which items survive passive decay and distraction. We now discuss two important processes that aid in the maintenance of information: selection and rehearsal.

Processes that support maintenance
Selection processes
Recently, in a series of fMRI studies, Rowe and Passingham have begun to challenge the notion that the DLPFC represents or stores information in memory [46–48]. Instead, they have emphasized its role in selection, the process of choosing among the most task-relevant internal representations. In these studies, area 46 of the DLPFC was active when the appropriate location being maintained was selected for response, but not during a memory delay interval (Fig. 3). Null effects with fMRI, just like

with any methodology, must be carefully considered. Yet, other areas including the dorsal premotor regions in the superior frontal sulcus and posterior parietal regions were active during the delay, congruent with arguably the most consistent finding among neuroimaging studies of working memory (e.g. [23,49,50]). The authors concluded that the DLPFC does not store active representations of the items; it selects the appropriate memory-guided response. This would suggest an integrative role for the DLPFC where short-term memory representations are linked to goal-directed motor behavior.

There are a few limitations with the Rowe *et al.* studies that must be carefully considered and addressed in future studies. These studies were designed to disassociate mnemonic delay period activity from activity evoked by the process of selecting a memory-guided response. It is clear that they found no activity in the DLPFC during the delay period of memory trials versus the delay period of control trials that did not require memory, even when thresholds were lowered. Given the experimental design and analytic methods, however, the DLPFC activation could be related to response selection processes, as the authors claim, or to motor planning and production processes (i.e. a joystick movement to the target location). Because the response selection interval occurred just 1.5 s before the motor response and functional images were acquired every 4.5 s, it remains uncertain how much of the DLPFC activation was contaminated with motor processes. This uncertainty applies to all event-related delayed-response studies, which consistently show robust DLPFC activation when subjects make a memory-guided motor response.

Schumacher *et al.* [51,52] have addressed this issue directly with studies designed to identify selection processes by parametrically manipulating factors that affect response selection (e.g. compatibility of stimulus–response associations). Even when subjects are not required to maintain information over delays, the DLPFC is highly sensitive to factors that make response selection more difficult. Thus, it is not necessary that information is being maintained to evoke DLPFC activation, but increasing response selection demands is sufficient to evoke DLPFC activation. Together, with other similar results [53,54], this suggests that the DLPFC is involved in the rule-based selection of responses, whether or not the rule requires the use of mnemonic material presented earlier in the trial or some previously learned stimulus-response mapping.

Rehearsal processes
The observed persistent delay-period activity could reflect active rehearsal mechanisms. Active rehearsal is hypothesized to consist of the repetitive selection of relevant representations or recurrent direction of attention to those items. Subvocal articulations mediate the rehearsal of verbalizable memoranda [14]. Articulatory suppression (e.g. by uttering 'the…the…the' during a retention interval) interferes with rehearsal and degrades memory performance [55]. In addition, the ventrolateral frontal cortex (i.e. Broca's area) is often activated in working memory tasks where subvocal rehearsal is the main

strategy for maintenance [56,57]. Rehearsal of non-verbalizable material like spatial locations has been more difficult to resolve, but is likely to involve a similar motor process [58]. Positional information might be represented in oculomotor coordinates, where the memorized location is maintained in terms of a saccade vector that acquires the target. Therefore, rehearsal of locations could simply be reactivations of oculomotor programs without actually making overt eye movements and can account for consistent activation of the frontal eye-fields (FEF) during spatial working memory tasks [33]. Clear segregations by the type of rehearsal strategy exist in the frontal cortex [59]. Frontal premotor areas like Broca's area and the FEF mediate rehearsal of specific types of information, whereas the DLPFC could influence all types of rehearsal, perhaps by selecting and managing (e.g. updating) the information to be rehearsed. Rehearsal, which is distinct from storage, is an operation that supports working memory by reactivating or refreshing transiently stored representations [60]. If rehearsal processes are what is mediating delay period activity, then this is a prime target for future studies because rehearsal is within our conscious awareness and therefore can be easily experimentally manipulated.

Atop the motor hierarchy
One possible way to reconcile many of the findings that we have discussed thus far is a greater and renewed appreciation that the prefrontal cortex is a *motor* area; it sits at the apex of the motor hierarchy and most probably evolved from more posterior motor areas that are phylogenetically older. Fuster, and others, argue that the PFC is especially important for the selection, planning, and execution of motor behavior [21,27]. All delayed response tasks in monkey and human, require an action to be taken based on some aspect of the maintained information. Therefore, studies so far have not resolved independent mnemonic and motor contributions made by the various regions of the frontal lobe. An important factor might be the requirement to perform an action based on an internal representation. We argue that understanding the motor aspects of working memory tasks will be essential to understanding PFC function. Nevertheless, most studies to date have focused on the input or sensory effects on working memory. For instance, stimulus factors, not motor behavior, are almost exclusively experimentally manipulated and inferences drawn are too almost exclusively framed in terms of memory for past perceptual events. Newer studies are beginning to emphasize processes further down stream in the perception-action cycle, such as response selection, motor preparatory set, and memory-guided actions [61–65]. For example, Pochon *et al.* [66] reported DLPFC activation during the delay only when subjects mentally prepared for an upcoming memory-guided sequence of actions and not when they simply maintained the visuospatial information. This result suggests that the sustained delay period activity often imaged cannot be interpreted solely as a signature of actively stored representations. It might be better accounted for by motor preparation and selection processes that arise during the transition of perceptual

mnemonic information into motor plans. Indeed, an intermixing of neurons with sensory and motor coupled delay period activity is found in some areas of the DLPFC [28].

Comparability of monkey and human studies

Passingham suggests that the reason monkeys with DLPFC lesions fail on delayed-response tasks is not because they forget the cue stimulus, but because they are impaired in the operation of selecting among the correct out of all possible responses [67]. In most delayed response tasks used with monkeys, the monkey knows the forthcoming response during the delay (i.e. the response has already been selected before the delay begins). In human fMRI studies, a delayed recognition task is typically used as an analogue of traditional delayed-response tasks. In a delayed recognition task, the subject simply confirms or denies that a probe item presented after the delay matches one of the sample items presented before the delay. A subject, in that case, cannot prepare the response and the selection happens only after the delay. In one case, the representation of a motor response must persist and in the other case a representation of a sensory cue must persist through the retention interval. Trying to assimilate human and monkey findings from different tasks might be misleading because these two types of mnemonic representations most likely have different neural implementations. Therefore, future research should be devoted to resolving the effects of response selection on delay period activity in addition to isolating their separate effects.
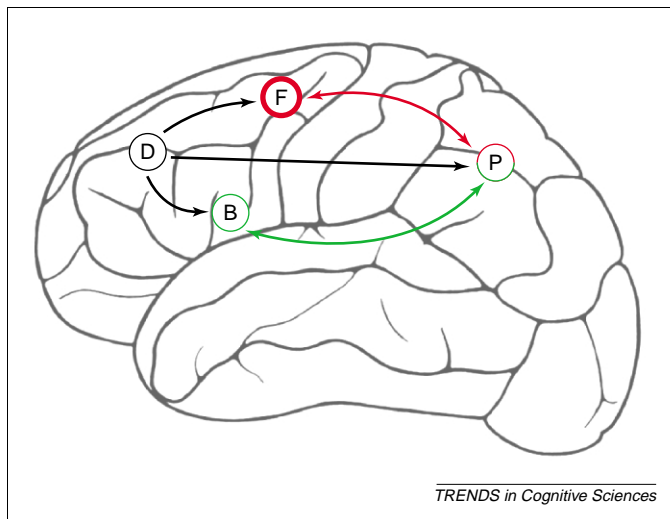

Fig. 4. **Simplified model of the cortical substrate for spatial and verbal working memory.** During the maintenance of a spatial location, top-down signals from the DLPFC (D) would enhance parietal (P) representations of the location to-be-remembered by repeatedly selecting that location for relevance (horizontal black arrow). Top-down DLPFC signals can also bias FEF (F) neurons that represent eye movements to relevant targets. FEF mediated spatial rehearsal could involve the reactivation of saccade goals that would shift gaze to the target location if the eye movement were allowed (red arrow). Similarly, during the maintenance of verbal material, top-down signals from the DLPFC select the relevant verbal representations in the inferior portion of the parietal cortex and Broca's area (B), thus enhancing those representations (curved black arrows). Verbal rehearsal involving Broca's area might be mediated through sub-vocalizations of to-be-remembered items (green arrow).

Focusing on selection

Persistent neural activity has been observed in many cortical and subcortical regions of the brain, notably in the PFC, during the retention intervals of delayed response tasks. Such activity might reflect the active representation of some past item, future motor plan, or abstract rule that one is actively remembering. As of yet, we have not been able to identify what this persistent activity represents and the nature of the code is likely to differ across different brain regions. Regardless, the traditional inference made concerning persistent delay period activity in the PFC has been that it reflects representations of stored memoranda. That inference is not well supported by recent fMRI findings, which have used superior design and statistical analytic techniques compared with the first generation fMRI and PET studies and thus should be given greater weight when trying to assess the role of the PFC in working memory.

We have described here an alternative account of the role of the PFC in working memory that is parsimonious with its organizational position at the apex of the motor hierarchy. First, consistent and sustained delay period activations are not only observed in the DLPFC; they are frequently observed in the dorsal premotor cortex (i.e. FEF) during spatial working memory tasks, the ventral premotor cortex (i.e. Broca's area) during non-spatial working memory tasks, and the posterior parietal and inferior temporal cortices during a variety of working memory tasks. These activations might reflect the rehearsal of relevant information through covert (i.e. not acted upon) motor articulations. Interactions between DLPFC and premotor cortex are a plausible means by which prospective motor intentions, for instance, are maintained. Similarly, reverberatory activity between DLPFC and parietal or temporal cortex might be a means by which retrospective sensory codes are maintained [68]. Second, accumulating new data indicate a crucial role for the DLPFC in a variety of control processes. Although several control processes have been tied to the DLPFC, we have highlighted here the process of selection. This is the operation by which information in short-term storage becomes the focus of attention such that it can be maintained and eventually used to choose an appropriate motor response. The DLPFC, in this view, does not store representations of past sensory events or future motor responses. Instead, its activation is an extra-mnemonic source of top-down biasing control over posterior regions that actually store the representations (Fig. 4). By the repetitive focusing of attention on the items to-be-remembered, the stored representations in more posterior regions are rehearsed and refreshed, bolstering them against degradation and distraction [35]. This idea is very similar to that advocated by Petrides [20], where the DLPFC is regarded as crucially involved in the monitoring of internal representations, such that relevant representations can be effectively used to guide behavior.

Conclusions

The role of the DLPFC in cognition seems at first glance to involve a varied collection of processes [69]. Many

behaviors are impacted by damage [70] and a variety of tasks activate it. However, the key to a more unified role of the DLPFC in cognition could lie in its connectivity with other regions [71]. The exact same top-down signal from the DLPFC could have very different behavioral expressions depending on the recipients of the signal. In that sense, the DLPFC is performing the same function – control. Top-down signals from the DLPFC might enhance internal representations of relevant sensory stimuli in extrastriate cortex or anticipated motor plans in premotor cortex. They might also control when and which representations are rehearsed. All of these scenarios, although different in kind, could lead to the persistent activity that has been observed during retention intervals of working memory tasks.

Importantly, fMRI has the unique ability to image multiple regions of the brain simultaneously. Thus, it has the often-touted potential, which is only currently being realized [72,73], to characterize interactions between the nodes in neural networks, including the network that supports working memory. Undoubtedly, the ability to characterize network interactions will lead to the ability to be more specific in our models and to test them with greater specificity (see also Box 3). In any event, fMRI studies have identified a network of brain regions that implement working memory. Although different nodes probably have different roles, together this network temporarily sustains the most relevant internal representations such that they can be used to select adaptive behaviors.

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