Cell
PRESS

Neural correlates of executive control functions in the monkey

Gijsbert Stoet[1] and Lawrence H. Snyder[2]

[1] Institute of Psychological Sciences, University of Leeds, Leeds, LS2 9JT, UK
[2] Washington University, School of Medicine, Dept of Anatomy & Neurobiology, 660 S Euclid Ave, St. Louis, MO 63110, USA

Executive control functions (ECFs) have become an important topic in the cognitive sciences in the past 40 years. The number of publications has steadily increased, and in the last decade, studies have been conducted in one of the best models of human cognition: the old-world macaque monkey. Here, we review recent studies in the monkey that have contributed to our understanding of the neuronal implementation of ECFs, with a focus on task-switching paradigms. These paradigms have revealed that ECFs are distributed across both the parietal and frontal lobes.

The benefits of animal studies of executive control functions

Executive control functions (ECFs) are responsible for the integration of information from multiple separate cognitive functions to plan and support goal-directed behavior (Box 1). ECFs are studied in various research fields, especially in psychiatry and neuropsychology [1], experimental psychology [2] and human cognitive neuroscience [3]. Various models have been proposed, some purely functional and others addressing anatomical instantiation in detail [4–6]. These models are inspired largely by human research and often highlight the role of the prefrontal cortex (PFC).

Unfortunately, there are limits to what can be gleaned from research using human subjects. We can study behavior, electroencephalograms, neuropathology and regional brain metabolism in humans, but techniques that address neural processing at high spatial and temporal resolution are best suited to animal studies (Box 2). Higher spatial resolution reveals, for example, that the prefrontal and posterior parietal cortical lobules are not unitary structures, but instead comprise multiple regions with diverse functions. These techniques can also reveal the fine details of neuronal computations on the time scale at which cognition takes place, without sacrificing fine spatial resolution.

This review focuses on the unique contributions that monkey research can make to understanding the neurocognitive implementation of ECFs, and in particular on two crucial issues. At the highest level of control, it is necessary to maintain a representation of the task in which one is currently engaged. To switch to a new task, the current task representation must be replaced with a new representation. Several paradigms are commonly used to study task representation and switching between tasks. The Wisconsin card sorting task (WCST) and the task-

switching paradigm were designed to address these issues, and we concentrate on studies that use animal-appropriate variations of these tasks. Behavioral planning, another high level ECF, has been recently reviewed elsewhere [7].

Neuronal correlates of task context

The most frequently used paradigm in the study of human ECF is the WCST (Box 3). It has been successfully adapted for neuropsychological research in monkeys [8–12]. Tanaka's [13] laboratory was among the first to demonstrate that the monkey can learn the adapted WCST. Monkeys were seated behind a touch-sensitive projection screen, and to get a reward they needed to touch one out of three stimuli that matched either the color or the shape of a centrally presented stimulus (Figure 1a). In a subset of trials, 'conflict' was introduced by providing a distractor stimulus that matched the central stimulus according to the incorrect rule. The color or shape rule was maintained for at least 40 trials. A change in the rule was signaled by error feedback (lack of reward).

Single-neuron recordings (Box 2) during this WCST analogue revealed that rule-specific information was maintained in both banks of the principal sulcus (PS) in the dorsolateral prefrontal cortex (DLPFC) [14] (Figure 2). Monkeys could perform the WCST even after bilateral anterior cingulate cortex (ACC) removal, whereas DLPFC removal impaired performance [15]. Lesioning of the ACC did not affect responses in the presence of heightened conflict, whereas lesioning of the PS did [15]. These findings by Tanaka's group contrast with human functional magnetic resonance imaging (fMRI) research: Carter and colleagues and many others [16,17] find that the human ACC is activated by conflict and error monitoring. This demonstrates either that the human and monkey ACC are not functionally homologous, or alternatively, that the ACC in both species receives information related to conflict and error monitoring (and therefore is activated in an fMRI study), but does not have a direct role in mediating the behavior.

Everling and colleagues [18–21] have also studied prefrontal neuronal activity using a WCST analogue (Figure 1b). Monkeys performed either a saccade or an antisaccade task, and were required to switch between these two tasks in uncued blocks of 30 trials. This design helped the researchers, among other things, to study task maintenance. One of the central findings is that the PS and arcuate sulcus (AS) contained neurons that encoded which task was being performed [18–21]. Furthermore, neurons

Corresponding author: Stoet, G. (g.stoet@leeds.ac.uk).

in both the ACC and the DLPFC show different activity levels in the two different tasks (i.e. task encoding). Activity in the ACC was highest at the start of a block, just after a task change, whereas the activity in the DLPFC was constant across trials within the block [21].

The WCST is an excellent paradigm for studying how feedback leads to changes in task strategy. In humans, the subject must not only detect when the task has changed but also must discern the new task rules. Monkeys, by contrast, learn all the task rules before the testing session. This simplifies the task, yet interpretation of neuronal activity is difficult for two reasons. First, multiple high-level cognitive processes are simultaneously active. Animals must represent the current task but also monitor, represent and respond to feedback. These processes can be difficult to separate. Second, the transition from one task to the other can be gradual as the animal slowly recognizes that the rules have changed (Box 3). These issues are ameliorated in a cued task-switching paradigm, in which the task rule is explicitly cued on each trial. Here, we review several such studies.

Wallis and Miller [22] developed a task-switching paradigm using two different rules, a match and a non-match rule (Figure 1c). At the start of each trial, a cue informed monkeys about the rule required for the current trial. This cue consisted of both a specific background color and the presence or absence of a liquid reward. A sample image was presented simultaneously with the cue, followed by a delay and then a second image. In match-rule trials, a match between the two images required a lever-release. In the non-match rule trials, dissimilar images required a lever-release. In this task, rule-related activity (task representation) can be easily discerned from processes

Box 3. Wisconsin Card Sorting Test and task-switching paradigms

The Wisconsin Card Sorting Test (WCST) was developed to measure flexibility of human thought [54]. Today, it is considered the ultimate test of ECFs [1]. Human participants sort a deck of 64 cards into two piles. Each card is marked with one to four instances of one of four symbols in one of four colors. Participants are not given explicit instructions about how to sort the cards. Instead, they receive the feedback 'right' or 'wrong' after placing each card in one of the two piles. The sorting rule is changed every ten trials without an explicit cue. Participants must use the error feedback to determine what rule to use and when to switch to a new rule.

By contrast, participants in a task-switching paradigm are trained in two different tasks, and then explicitly cued to switch between the two tasks.

The WCST taps into various fundamental properties of ECFs: the capacity to 'represent the current sorting rule', the capacity to 'monitor error feedback' and the capacity to 'change the course of action based on internal criteria'. Like the WCST, the task-switching paradigm requires 'representing the current rule', but it does not require that feedback be monitored or that this feedback be used to decide when to switch from one task to another. Instead, the task-switching paradigm directly measures the ability to switch from one task to another on cue. In some implementations, participants are instructed to switch every two trials, which requires more internal control than when there is an explicit cue [36].

In monkey versions of both the WCST and task-switching paradigm, animals respond to visual stimuli according to previously learned task rules (but see Ref. [55]). Each stimulus requires that one of two responses must be made (e.g. one of two buttons must be pressed), depending on a particular feature of the stimulus (e.g. its location, color or shape). A juice reward or lack thereof replaces verbal feedback in the WCST. In the WCST, monkeys typically perform long blocks of each task, making switch trials rare. In the task-switching paradigm, switch and non-switch trials are fully interleaved and equally likely.

Thus, the essential methodologic differences between the animal WCST and task-switching are whether task switches are implicitly or explicitly cued, and whether tasks are performed in blocks or fully interleaved. In the task-switching paradigm, errors made after the explicit switch cue primarily reflect either perseveration or confusion, or more broadly, cognitive inflexibility. In a WCST, a failure to switch rapidly after an error can reflect cognitive inflexibility, but it could also occur because the animal has not yet recognized that a change in the task has occurred.

related to task performance because early in trials using the same sample image the only difference between match and non-match trials is the rule that the animal plans to follow. Rule-encoding neurons were found in the dorsolateral, ventrolateral and orbital PFC.

A subsequent study using the same paradigm found that rule-specific activity was represented earlier and even more strongly in the premotor cortex compared to the PFC [23,24]. Thus, these studies provide the surprising suggestion that executive control originates in (or is functionally closer to) premotor cortex rather than PFC.

One of the accomplishments of the work of Miller's [22–24] laboratory is the sophisticated design that helps to distinguish between contributions of sensory and motor information on the one hand, and different activity levels in the two different tasks (i.e. task encoding) on the other hand. Earlier work using neuronal recording and reversible inactivation studies had shown that concrete task rules are represented in the frontal lobes [25]. Miller and colleagues [22–24] extend this by showing that the frontal lobes also represent abstract task rules.

A related paradigm was used by Stoet and Snyder [26–28] to study task representation (Figure 1d). On each trial, a task cue informed the monkey to perform either a color discrimination task (i.e. is the stimulus red or green?), or a stimulus orientation task (i.e. is the line horizontally or vertically oriented?). Rather than being presented in blocks as in the WCST, the two trial types were randomly interleaved. Although difficult to train, this cued task-switching paradigm had several positive features.

First, a delay separated the cue and the imperative stimulus, so that delay activity could unambiguously be attributed to cue representation. Second, multiple cues were used for each task, allowing visual responses to be distinguished from representations of the rule itself. Finally, each imperative stimulus had both a color and an orientation, so that in each trial animals could plan a response based on either task rule. In half of all trials, applying the incorrect rule would result in an incorrect response. Thus, one can study not only how different tasks are represented but also how conflicts between different potential responses are resolved.

We recorded from isolated neurons in posterior parietal cortex (PPC), especially in the lateral bank of the intraparietal sulcus and on the angular gyrus. A subset of PPC neurons responded selectively to cues for different task rules during the cue-stimulus interval [28]. We demonstrated that these neurons reflect the abstract rule and take part in the decision-making process, rather than merely representing a particular motor command [29]. Under some conditions, the PPC can encode decisions well in advance of a behavioral response [29]. We speculate that factors implemented downstream of the PPC might delay response execution [30].

The shift-stay paradigm of Wise and colleagues [31] is a variant of a cued task-switching paradigm. In this design, the cue explicitly signaled whether the animal should switch to a new rule or reapply the previous rule. This study found that some DLPFC neurons represented only the current task rule, whereas others represented a combination of the task rule along with sensory and motoric aspects of the tasks. This was similar to the results of Stoet and colleagues, and indicates that neurons in DLPFC and PPC have similar properties with regard to task representation.

Neuronal correlates of cognitive flexibility

The previous discussions have focused on task representations. A second important facet of ECF is the ability to switch from one task to another (i.e. flexibility). A special case of this is switching from automatic to controlled behavior. Automatic behavior is routine behavior; controlled behavior is behavior that requires the overruling of a routine response. Exerting control to override automatic behavior is a key feature of ECF (Box 1). Switching between two controlled processes or between controlled and automatic processes can be studied using the WCST and other task-switching variants.

Hikosaka and colleagues [32] studied a simple case of switching using a saccade-overriding task. On each trial, monkeys were required to saccade to a peripheral stimulus that matched a central cue. The same central cue and
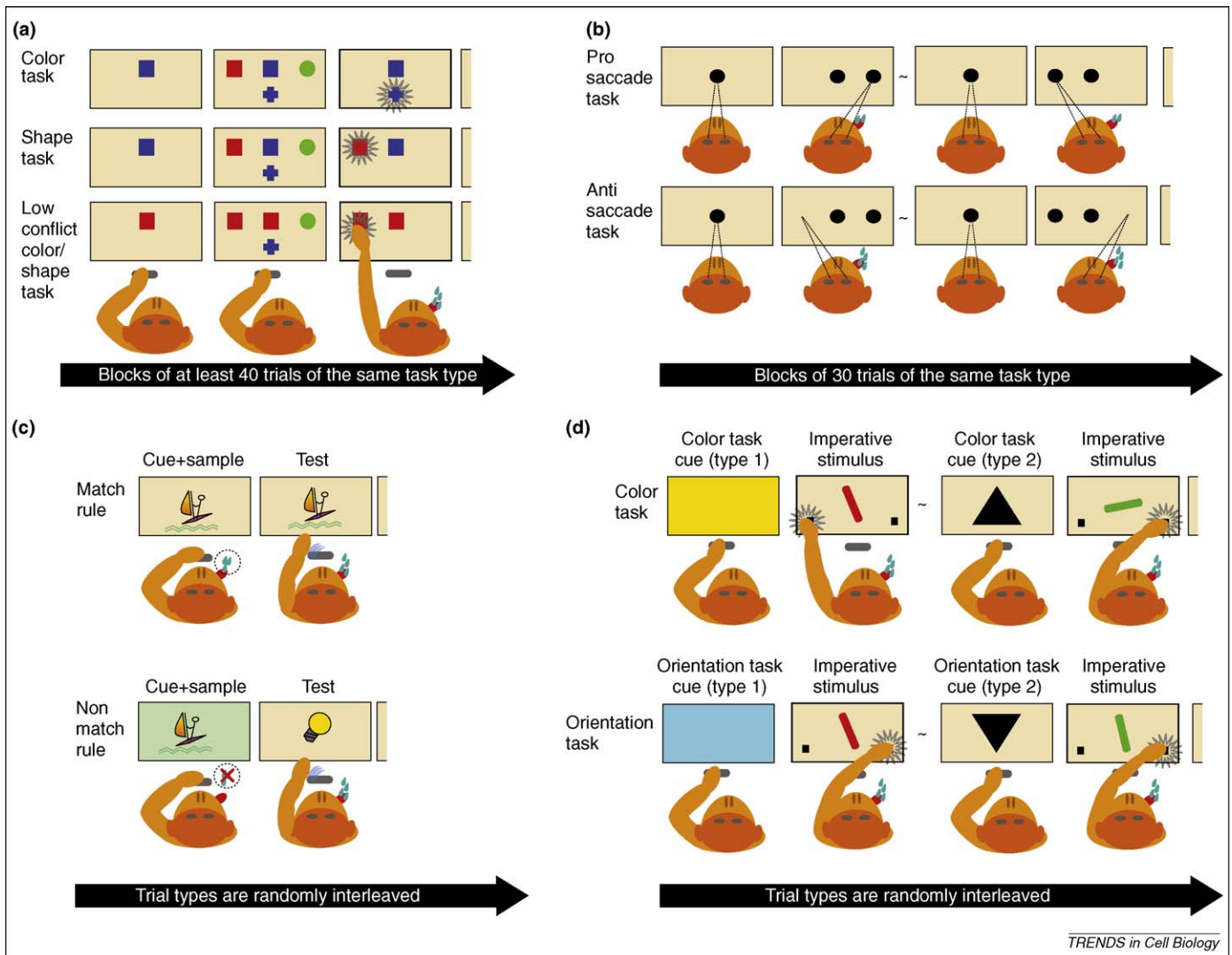
**Figure 1**. Example trials of four paradigms. Panels are read from left to right. Not all events are illustrated, such as error signals, which have an essential role in panels (a) and (b). Screen touches are indicated by a star-burst, liquid rewards with drops and lack thereof with crossed out drops. **(a)** Analogue of WCST [15]. Monkeys alternated between blocks of matching shape and blocks of matching color. Changes in task were not cued; monkeys used error feedback to switch between tasks. In high conflict trials (top two rows), knowledge of the task rule was necessary to perform the task; in low conflict trials either rule resulted in the same answer (bottom row). **(b)** Another WCST analogue [19]. Monkeys alternated between saccade and anti-saccade blocks. The '~' character separates trials [also in panel (d)]. **(c)** A task-switching paradigm analogue [22]. One of two possible matching rules was cued on each trial: respond on match or respond on non-match. The task cue (screen color and presence or absence of a drop of liquid) was presented simultaneously with a sample image. Animals judged whether a second image was a match or non-match, and combined this information with the current rule to release or refrain from releasing a bar. **(d)** Another task-switching paradigm analog [28]. On each trial, the animal first viewed a task-cue, instructing it to respond to the color or orientation of the following stimulus. There were two distinct cues for each task, to distinguish sensory and task related signals. In the color task, red and green stimuli required a left or right button press, respectively; in the orientation task, vertical and horizontal lines required a left or right response, respectively. A delay period between the task cue and imperative stimulus allowed for the measurement of task-specific neuronal signals.

peripheral stimuli were presented for multiple consecutive trials, so that exactly the same saccade was performed many times in a row. At some point, a new cue was presented, requiring a change in the saccade. The saccade reaction time was increased on these switch trials. This increase is presumably the consequence of a switch from performing a repetitive, predictable behavior to a novel movement. One-third of neurons in the pre-supplemental motor area (pre-SMA) responded differently on successful switch trials compared to non-switch trials, and switch-trial performance improved when pre-SMA was microstimulated. These findings indicate that pre-SMA supports behavioral switching from a practiced behavioral response to a new response. Although the saccade-overriding task is designed to measure flexibility in switching between response patterns, it is limited in that one cannot use

the paradigm to investigate the difficulties in (and neural mechanisms of) switching between abstract rules.

Schall and colleagues [33] pioneered another type of saccade-overriding task in monkeys. In the countermanding paradigm, animals were cued to make a saccade to a target, but on some trials were subsequently cued to cancel that saccade. Microstimulation of neurons in the supplementary eye fields (SEF, just lateral to pre-SMA) improved countermanding performance. This research demonstrates that SEF has a role in canceling inappropriate behavior, but because of the specificity of the paradigm we once again cannot generalize to a role in switching from one abstract task or rule representation to another.

Two recent studies have used the WCST to determine which neurons are involved in switching from one abstract task to another. As described earlier, Everling's [21] group
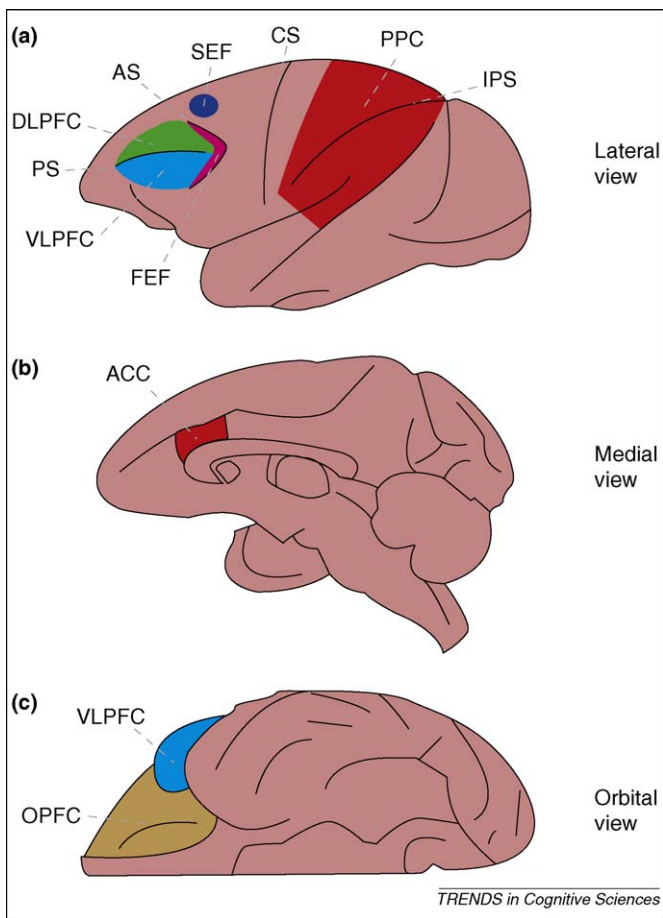
Figure 2. Schematic view of monkey brain with relevant parts labeled. (a) Lateral view. AS, Arcuate; CS, Central; IPS, Intraparietal sulcus; PS, Principal. Areas and regions on the lateral cortical surface: DLPFC and VLPFC, Dorsolateral and Ventrolateral prefrontal cortex; FEF, Frontal eye fields; PPC, Posterior parietal cortex; SEF, supplemental eye fields. (b) Medial view with a portion of the anterior cingulate cortex (ACC) indicated. (c) Orbital (bottom) view. OPFC, Orbital and ventrolateral prefrontal cortex are indicated.

Box 4. Outstanding questions

Task-switching anomaly

Monkeys are better at task-switching paradigms than humans. If cognitive flexibility depends on frontal cortex, why would animals with a small frontal cortex be more flexible than humans? Perhaps large switch costs in humans compared to monkeys are a feature rather than a bug. Humans are somewhat resistant to distraction. Switch costs could represent the other side of this coin: a resistance to rapidly switching from one task to another [37].

Distributed nature of ECFs

Task-rule representing cells have been found in multiple areas, even in areas typically not associated with ECFs. What does this tell us about the distributed nature of ECFs?

Contrasting findings

Some of the findings in monkey ECFs are inconsistent with each other or with human brain imaging results. In particular, what is the role of the ACC? Bilateral removal does not disrupt monkey performance of the WCST [15] and does not appear in monkey imaging [34], yet the activity in the region does correlate with the timing of task switching [21].

Development of task-representations

Neurons that represent the current task-rule are abundant in PFC, PMC and PPC. What are the roles of these populations when a new task is being learned? Long-term recording studies could answer these questions (e.g. with chronically implanted electrode arrays).

contrast, the task-switching paradigm was specifically designed to measure task-switching and therefore employs an explicit task-switching cue [36]. Switch costs are measured by contrasting performance on trials in which subjects switch with trials in which subjects repeat the task of the preceding trial.

Using a task-switching paradigm, we found that monkeys, like humans, prepare tasks in advance [27]. Surprisingly, monkeys were more flexible than humans in their task-switching ability [26] (Box 4). Many studies have shown that switch costs occur in humans no matter how slowly the trials are paced. One might expect that, given enough time to prepare, switch costs would disappear. This is true in the monkey – switch costs appear with fast-paced trials, but go to zero at moderate pacing – but not in the human, where costs persist even with one second of preparation time [36]. Thus, monkeys, unlike humans, are capable of fully preparing a task switch in advance.

The increased flexibility of monkeys compared to humans is not a function of training. Even after tens of thousands of practice trials, adult humans still show switch costs [37]. Performance in the task-switching paradigm is disturbed by systemic injections of a N-methyl-D-aspartate (NMDA) antagonist. Ketamine administration results in a reduced ability to focus on the task at hand, along with a modest increase in switch costs [38]. This pattern resembles what is observed with some neurological diseases such as schizophrenia [39].

To summarize, monkeys do not show switch costs when task changes occur with high probability and are explicitly cued (task-switching paradigm). Under these conditions, we found representations of the current task but no correlates of task switching in the PPC. By contrast, when changes in the task are infrequent and must be recognized by monitoring the pattern of errors (WCST), switch costs are often present and switch-related activity is found in

found that neurons in ACC represent rules most strongly immediately following a task switch, demonstrating that the ACC is specifically involved in switching. Nakahara and colleagues [34] also used the WCST in a monkey functional imaging study. They found switch-related activity in PFC, especially in the bilateral inferior sulcus, and concluded that this reflects an inhibitory process that suppresses the previous task representation. Switch related activity was also found in the inferior parietal lobule and the anterior insula. This study was of great interest because of the comparison of monkeys and humans performing a similar paradigm. Ventrolateral PFC seemed to be particularly relevant to cognitive switching in both species. Much of the work on task switching in humans focuses on the inferior frontal junction [35] and it seems that the same region subserves the same function in monkeys. The most important contrast in findings between the single unit recordings of Everling's group [21] and the brain imaging study of Nakahara and colleagues [34] was that the latter reported no switch-specific activity in the ACC in the monkey.

In the WCST, recognizing that a task switch has occurred is complex, and as a result, the moment at which a switch occurs is not always well-defined (Box 3). By

both the parietal and prefrontal cortices [21,32,34]. It is likely that the switch related-activity seen in the WCST reflects the executive processes of monitoring error feedback and recognizing that a task switch has occurred. These processes are likely to be distributed across at least PPC and PFC.

Conclusions

We are just starting to understand the neurophysiology of ECF in the monkey. There is a strong emphasis on the frontal lobes in both modeling [40] and primate recording studies. For example, there are no single unit recordings from parietal areas using WCST analogues. Yet, both human and animal studies have shown that ECF as a group are not confined to the frontal lobe, but also occur in other parts of the brain, including the parietal cortex [28,29,34,41–45]). The next experimental challenge is to determine how ECF are subdivided, and which component functions are computed in PFC, which are computed in PPC and which are truly distributed across areas.

Currently, the relationship between neurons that represent task context, including task rules, in frontal and parietal areas is unknown. Certainly, the frontal lobes are important for executive functions, and it is possible that the frontal lobes cause the PPC to represent task context. Alternatively, cells that represent the current task in PPC might be driven directly by bottom-up (sensory) signals or from a combination of sensory signals and feedback from the frontal lobes. To address how these representations evolve during a trial, we must record single-unit activity during the performance of a rule-representation paradigm (e.g. a task-switching paradigm) in both the prefrontal and parietal lobes. This can be done using simultaneous recording, or by recording serially from one lobe at the time, but using exactly the same paradigm for both lobes. Simultaneous recording ensures that all variables, including the strategies of the animal, are held constant across areas. More importantly, simultaneous recording can reveal intra-areal timing relationships, which are crucial for understanding information flow.

Few monkey studies have addressed the role of neurotransmitters and neuromodulators in ECF. Many cases of disordered ECF (e.g. schizophrenia) are associated with disturbances of these systems [46]. There have been some studies using systemic injections of dopaminergic and glutaminergic neurotransmitters and one study of localized serotonin depletion [38,47–52] along with some neurocognitive modeling [5], but this is clearly an area for future exploration.

We expect the greatest improvements in our understanding of the interplay between frontal and parietal areas from simultaneous recording in multiple areas [53], and from recording from multiple areas using the same paradigm. Reversible inactivation of frontal [25] or parietal areas, especially in conjunction with simultaneous recording, could also help to map out the specific contributions of these areas. These techniques are all well developed, but the time required for animal training greatly constrains progress. Despite this constraint, we are optimistic that in the near future some of the most pressing questions regarding ECF will be answered (Box 4).

References

1 Royall, D.R. *et al.* (2002) Executive control function: a review of its promise and challenges for clinical research. a report from the Committee on Research of the American Neuropsychiatric Association. *J. Neuropsychiatry Clin. Neurosci.* 14, 377–405

2 Logan, G. (1985) Executive control of thought and action. *Acta Psychol (Amst.)* 60, 193–210

3 Funahashi, S. (2001) Neuronal mechanisms of executive control by the prefrontal cortex. *Neurosci. Res.* 39, 147–165

4 Cooper, R. and Shallice, T. (2000) Contention scheduling and the control of routine activities. *Cogn. Neuropsychol.* 17, 297–338

5 Hazy, T.E. *et al.* (2006) Banishing the homunculus: Making working memory work. *Neuroscience* 139, 105–118

6 Norman, D. A and Shallice, T. (1980) *Attention to Action* (*Willed and Automatic Control of Behavior* (Technical Report 8006), Center for Human Information Processing

7 Tanji, J. *et al.* (2007) Concept-based behavioral planning and the lateral prefrontal cortex. *Trends Cogn. Sci.* 11, 528–534

8 Dias, R. *et al.* (1996) Primate analogue of the Wisconsin Card Sorting Test: effects of excitotoxic lesions of the prefrontal cortex in the marmoset. *Behav. Neurosci.* 110, 872–886

9 Moore, T.L. *et al.* (2003) Impairment in abstraction and set shifting in aged rhesus monkeys. *Neurobiol. Aging* 24, 125–134

10 Moore, T.L. *et al.* (2005) A nonhuman primate test of abstraction and set shifting: an automated adaptation of the Wisconsin Card Sorting Test. *J. Neurosci. Methods* 146, 165–173

11 Moore, T.L. *et al.* (2005) Executive system dysfunction occurs as early as middle-age in the rhesus monkey. *Neurobiol. Aging* 27, 1484–1493

12 Passingham, R.E. (1972) Non-reversal shifts after selective prefrontal ablations in monkeys (Macaca mulatta). *Neuropsychologia* 10, 41–46

13 Mansouri, F.A. and Tanaka, K. (2002) Behavioral evidence for working memory of sensory dimensions in macaque monkeys. *Behav. Brain Res.* 136, 415–426

14 Mansouri, F.A. *et al.* (2006) Prefrontal cell activities related to monkeys' success and failure in adapting to rule changes in a Wisconsin Card Sorting Test analog. *J. Neurosci.* 26, 2745–2756

15 Mansouri, F.A. *et al.* (2007) Mnemonic function of lateral prefrontal cortex in conflict-induced behavioral adjustment. *Science* 318, 987–990

16 Botvinick, M.M. *et al.* (2004) Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn. Sci.* 8, 539–546

17 Carter, C.S. *et al.* (1998) Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280, 747–749

18 Everling, S. and Munoz, D.P. (2000) Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. *J. Neurosci.* 20, 387–400

19 Everling, S. and DeSouza, J.F.X. (2005) Rule-dependent activity for prosaccades and antisaccades in the primate prefrontal cortex. *J. Cogn. Neurosci.* 17, 1483–1496

20 Johnston, K. and Everling, S. (2006) Neural activity in monkey prefrontal cortex is modulated by task context and behavioural instruction during delayed-match-to-sample and conditional pro-saccade/anti-saccade tasks. *J. Cogn. Neurosci.* 18, 749–765

21 Johnston, K. *et al.* (2007) Top-down control-signal dynamics in anterior cingulate and prefrontal cortex neurons following task switching. *Neuron* 53, 453–462

22 Wallis, J.D. *et al.* (2001) Single neurons in prefrontal cortex encode abstract rules. *Nature* 411, 953–956

23 Muhammad, R. *et al.* (2006) A comparison of abstract rules in the prefrontal cortex, premotor cortex, inferior temporal cortex, and striatum. *J. Cogn. Neurosci.* 18, 974–989

24 Wallis, J.D. and Miller, E.K. (2003) From rule to response: neuronal processes in the premotor and prefrontal cortex. *J. Neurophysiol.* 90, 1790–1806

25 Hoshi, E. *et al.* (2000) Neuronal activity in the primate prefrontal cortex in the process of motor selection based on two behavioral rules. *J. Neurophysiol.* 83, 2355–2373

26 Stoet, G. and Snyder, L.H. (2003) Executive control and task-switching in monkeys. *Neuropsychologia* 41, 1357–1364

27 Stoet, G. and Snyder, L.H. (2003) Task preparation in macaque monkeys (Macaca mulatta). *Anim. Cogn.* 6, 121–130

28 Stoet, G. and Snyder, L.H. (2004) Single neurons in posterior parietal cortex (PPC) of monkeys encode cognitive set. *Neuron* 42, 1003–1012

29 Stoet, G. and Snyder, L.H. (2007) Correlates of stimulus-response congruence in posterior parietal cortex (PPC). *J. Cogn. Neurosci.* 19, 194–203

30 Stoet, G. *et al.* (2008) Modification of response time variability in a decision-making task. *Neuroreport* 19, 1321–1324

31 Genovesio, A. *et al.* (2005) Prefrontal cortex activity related to abstract response strategies. *Neuron* 47, 307–320

32 Isoda, M. and Hikosaka, O. (2007) Switching from automatic to controlled action by monkey medial frontal cortex. *Nat. Neurosci.* 10, 240–248

33 Stuphorn, V. and Schall, J.D. (2006) Executive control of countermanding saccades by the supplementary eye field. *Nat. Neurosci.* 9, 925–931

34 Nakahara, K. *et al.* (2002) Functional MRI of macaque monkeys performing a cognitive set-shifting task. *Science* 295, 1532–1536

35 Derfuss, J. *et al.* (2005) Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. *Hum. Brain Mapp.* 25, 22–34

36 Monsell, S. (2003) Task switching. *Trends Cogn. Sci.* 7, 134–140

37 Stoet, G. and Snyder, L.H. (2007) Extensive practice does not eliminate human switch costs. *Cogn. Affect. Behav. Neurosci.* 7, 192–197

38 Stoet, G. and Snyder, L.H. (2006) Effects of the NMDA antagonist ketamine on taskswitching performance: evidence for specific impairments of executive control. *Neuropsychopharmacology* 31, 1675–1681

39 Rowland, L.M. *et al.* (2005) Selective cognitive impairments associated with NMDA receptor blockade in humans. *Neuropsychopharmacology* 30, 633–639

40 Miller, E.K. and Cohen, J.D. (2001) An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24, 167–202

41 Le, T.H. *et al.* (1998) 4 T-fMRI study of nonspatial shifting of selective attention: Cerebellar and parietal contributions. *J. Neurophysiol.* 79, 1535–1548

42 Dove, A. *et al.* (2000) Prefrontal cortex activation in task shifting: an event-related fMRI study. *Brain Res. Cogn. Brain Res.* 9, 103–109

43 Sohn, M.H. *et al.* (2000) The role of prefrontal cortex and posterior parietal cortex in task switching. *Proc. Natl. Acad. Sci. U. S. A.* 97, 13448–13453

44 Dosenbach, N.U.F. *et al.* (2007) Distinct brain networks for adaptive and stable task control in humans. *Proc. Natl. Acad. Sci. U. S. A.* 104, 11073–11078

45 Rossi, A.F. *et al.* (2009) The prefrontal cortex and the executive control of attention. *Exp. Brain Res.* 192, 489–497

46 Carlsson, A. and Lindqvist, M. (1963) Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol. Toxicol. (Copenh.)* 20, 140–144

47 Shiigi, Y. and Casey, D.E. (1999) Behavioral effects of ketamine, an NMDA glutamatergic antagonist, in non-human primates. *Psychopharmacology (Berl.)* 146, 67–72

48 Shiigi, Y. and Casey, D.E. (2001) Effects of benztropine on ketamine-induced behaviors in cebus monkeys. *Behav. Pharmacol.* 12, 293–298

49 Taffe, M.A. *et al.* (2002) Ketamine impairs multiple cognitive domains in rhesus monkeys. *Drug Alcohol Depend.* 68, 175–187

50 Taffe, M.A. *et al.* (2002) Differential muscarinic and NMDA contributions to visuo-spatial paired-associate learning in rhesus monkeys. *Psychopharmacology (Berl)* 160, 253–262

51 Condy, C. *et al.* (2005) Ketamine-induced distractibility: an oculomotor study in monkeys. *Biol. Psychiatry* 57, 366–372

52 Clarke, H.F. *et al.* (2005) Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. *J. Neurosci.* 25, 532–538

53 Buschman, T.J. and Miller, E.K. (2007) Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science* 315, 1860–1862

54 Berg, E.A. (1948) A simple objective technique for measuring flexibility in thinking. *J. Gen. Psychol.* 39, 15–22

55 Chen, L.L. and Wise, S.P. (1995) Neuronal activity in the supplementary eye field during acquisition of conditional oculomotor associations. *J. Neurophysiol.* 73, 1101–1121

56 Churchland, P.S. and Sejnowski, T.J. (1988) Perspectives on cognitive neuroscience. *Science* 242, 741–745