

The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour

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A common or multiple-demand (MD) pattern of frontal and parietal activity is associated with diverse cognitive demands, and with standard tests of fluid intelligence. In intelligent behaviour, goals are achieved by assembling a series of sub-tasks, creating structured mental programs. Single cell and functional magnetic resonance imaging (fMRI) data indicate a key role for MD cortex in defining and controlling the parts of such programs, with focus on the specific content of a current cognitive operation, rapid reorganization as mental focus is changed, and robust separation of successive task steps. Resembling the structured problem-solving of symbolic artificial intelligence, the mental programs of MD cortex appear central to intelligent thought and action.

Multiple-demand activity in the human brain

Over the past 20 years, functional neuroimaging has identified many individual associations between specific cognitive functions and specific regions of the human cerebral cortex. In parallel, there has been a more unexpected discovery – a common pattern of activity that is a salient part of the brain's response to many different kinds of cognitive challenge. Illustrated in [Figure 1a](#), this multiple-demand (MD) pattern [[1,2](#)] extends over a specific set of regions in prefrontal and parietal cortex, in particular: cortex in and around the posterior part of the inferior frontal sulcus (IFS), in the anterior insula and adjacent frontal operculum (AI/FO), in the pre-supplementary motor area and adjacent dorsal anterior cingulate (pre-SMA/ACC), and in and around the intraparietal sulcus (IPS). A smaller region of accompanying activity is sometimes seen in rostralateral prefrontal cortex (RPF). Highly similar MD patterns are identified by a range of methods, from pooling of activity associated with different kinds of task to analyses of temporal correlations in resting state data, and are variously described as 'task positive' [[3](#)], a 'task-activation ensemble' [[4](#)] or a 'task control' network [[5,6](#)].

A closely similar activity pattern can also be seen by contrasting standard tests of fluid intelligence [[7](#)] – generally, tests of novel problem-solving – with suitable sensorimotor controls ([Figure 1b](#); [[8–10](#)]). Correspondingly, recent lesion data suggest that deficits in fluid intelligence are specifically associated with damage to the MD network (Woolgar *et al.*, unpublished data). In psychometrics, tests

of fluid intelligence are of interest for their broad ability to predict success in many kinds of laboratory and real-world activity. One candidate explanation is that tests of this kind are a good measure of some general or *g* factor [[11](#)], to some extent contributing to effective performance in many different task contexts. Evidently, this suggestion fits well with a brain system showing activity associated with multiple kinds of cognitive demand.

How should we understand the function of this MD system? Undoubtedly, frontoparietal cortex is important in cognitive control, but how should 'control' be conceived? Much current work on control is concerned with isolated operations, such as response inhibition [[12](#)] or control of attentional bias [[13,14](#)]. Beyond these, I suggest, the problem of control is centrally concerned with the structure and requirements of complex, multi-component behaviour.

In all realistic behaviour, from cooking a meal [[15](#)] to solving a problem in formal logic [[16](#)], goals are achieved by assembling a series of sub-tasks, each separately defined and solved. In this respect, human behaviour resembles the sequential activity of conventional computer programs, assembling a series of operations that together achieves the final goal. The problem is well illustrated by artificial intelligence systems, from the earliest days of the General Problem Solver [[17](#)] to systems such as Newell's SOAR [[18](#)] and Anderson's ACT [[19](#)]. In all these systems, as in all complex human behaviour, the problem is not simply to control isolated steps of thought or behaviour, but equally significant, a task must be decomposed into useful parts, with these component sub-tasks addressed in turn.

It has long been noted that, after major frontal lobe damage, the structure of complex behaviour is impaired, with important parts omitted, irrelevant parts introduced, and the whole failing to achieve its ends [[20,21](#)]. Such results indicate an obvious link to the problems of symbolic artificial intelligence [[22,23](#)], and to the sequential programming of goal-directed behaviour [[20,21](#)]. Sequential mental programming has several requirements. Each step requires focus, that is enclosed processing only of the parts of the current sub-task. As sub-tasks are completed, the current cognitive focus must be abandoned and a new focus created. Often, selected results from one sub-task must be passed to the next. Especially in novel tasks, useful sub-parts must be defined and separated. Mental programming of this sort is an indispensable part of all structured mental activity. I suggest that neural activity in MD cortex is well suited to such programming, explaining broad recruitment

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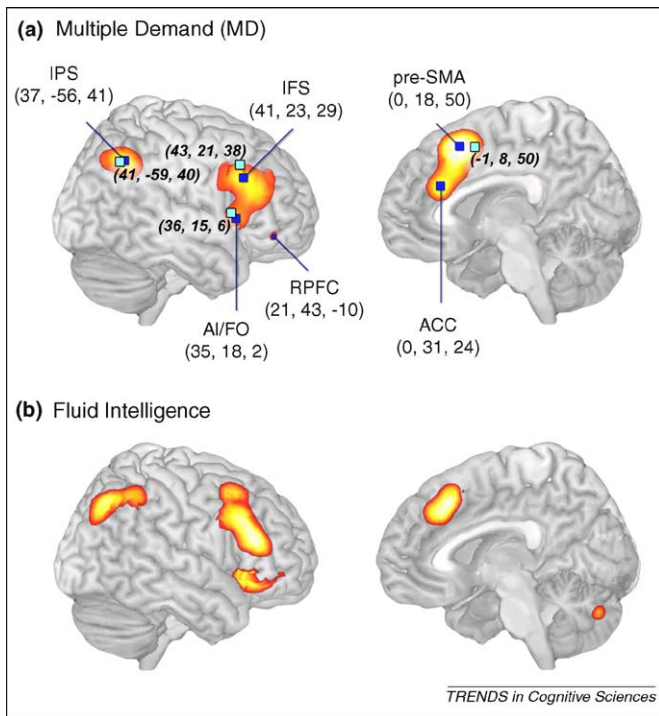


Figure 1. (a) MD pattern. Data are drawn from a previous review of brain activity associated with diverse cognitive demands [1,2]. To produce this figure, peak activity coordinates from the original studies have been smoothed and summed, and the resulting summed map thresholded to show regions of most frequent activity. To combine data from left and right hemispheres, left hemisphere peaks were transposed to the right. Coordinates of local maxima (dark blue) are shown in the IFS, AI/FO, pre-SMA, ACC, RPFC and IPS. Nearby coordinates (pale blue, italics) come from an independent analysis of activity peaks associated with different aspects of task control [64]; the parietal coordinate is the average of more anterior and posterior coordinates from the original report. Coordinates have been transformed as necessary into Montreal Neurological Institute (MNI) space. (b) Right hemisphere activity associated with a standard test of fluid intelligence. Adapted, with permission, from Ref. [10].

across cognitive domains, and a central role in human intelligence.

Neurophysiology of mental programs

Each step of a mental program defines a new cognitive epoch, with different operations, goals, and task-relevant information. In everyday behaviour, such epochs follow in rapid succession, requiring frequent changes of processing context. Both single unit and functional magnetic resonance imaging (fMRI) data show features of MD activity well matched to the construction of focused cognitive epochs, and rapid transition from one to the next.

An example is shown in Figure 2 [24–27]. In these experiments, monkeys were trained to monitor a series of pictures, awaiting a specific target (Figure 2a). The side of the stimulus stream (left or right) varied randomly from one trial to the next. Maintained fixation was required until the target was detected; reward was then given for a saccade to the stimulus location at target offset. In one task variant (fixed target), the same picture served as target throughout training. In a second (cued target), monkeys learned associations between three cue pictures and three corresponding targets. Each trial began with a cue instructing the target for the current trial; in this variant, most nontargets were pictures that had served as targets on other trials.

One key feature of mental programming is selective coding of information relevant to the current decision. In the above tasks, up to 50% of all cells recorded in lateral prefrontal cortex discriminated targets from nontargets [24–26] (see example data in Figure 2b). By contrast, many fewer cells made the task-irrelevant discrimination between one nontarget and another [24]. Many other studies have reported selective coding of task-relevant objects, features and categories in prefrontal neurons [28–30]. Even when neurons are randomly sampled, as in our experiments, large proportions show coding of some kind of task-relevant information [31]. Similar results have also been described in medial frontal, insular and parietal cortex (e.g. [32–34]).

Wide MD coding of attended or task-relevant information is also shown by human fMRI data (Figure 3). In adaptation studies, for example, changes to an attended object [35,36] or feature [37] lead to extensive activity throughout the MD system. Such change-related activity occurs even in passive conditions, with subjects simply instructed to attend to one input stream [35,38]. Similar conclusions are indicated by multivoxel pattern analysis (MVPA) [39], showing extensive MD coding of task-relevant stimuli and cognitive operations [40,41].

A second key feature of mental programming is rapid change of processing focus and content. In the monkey prefrontal cortex, neurons show rapid changes in the information they code, depending on corresponding changes in how stimuli should be interpreted and responses chosen. In the tasks of Figure 2, for example, prefrontal cells show similar patterns of target/nontarget discrimination whether the target is fixed (Figure 2b, left) or cued (Figure 2b, right), although in the latter case, the same stimulus that is to be categorized as target on one trial serves as nontarget on others. Again, many other experiments show the ability of prefrontal cells to follow rapid changes of cognitive context [14], either across [29,42] or even within [43] trials.

In organized behaviour, several steps or cognitive epochs follow in sequence. How do prefrontal cells code successive steps? The question can be examined [27] in the context of the same cued-target detection task illustrated in Figure 2a (right). For this analysis, data were analysed from a randomly selected sample of 324 neurons in lateral prefrontal cortex. For each neuron, mean firing rates were calculated for each of 18 separate task events – 6 cues (each possible combination of cue picture x visual field), 6 delay periods (intervals between one stimulus and the next, for each cue x visual field combination) and 6 targets – then converted to relative activity by normalizing for the neuron's mean firing rate across events. For each task event, the analysis thus produced a pattern or vector of activity across the sample of 324 neurons; by correlating these vectors, we asked how similar are frontal codes for different task events. A cluster analysis of the resulting correlation matrix is shown in Figure 2c. Three major clusters are defined by the 3 task phases – cue, delay and target. Each cluster is further divided by hemifield, and then by cue/target identity. For different task phases, activity patterns were approximately orthogonal (correlations close to 0); for different cue/target identities within

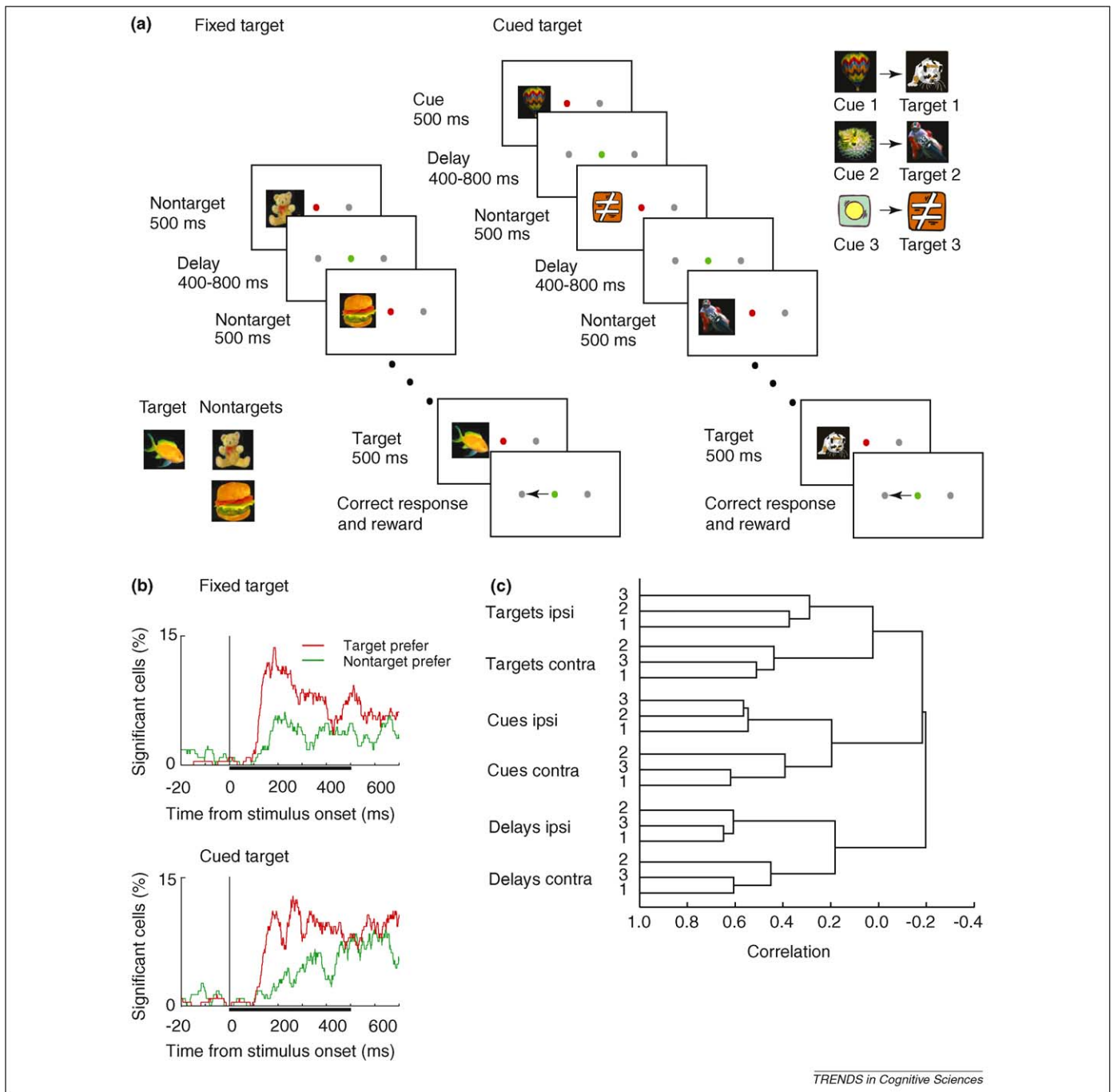


Figure 2. (a) Fixed and cued target detection tasks. Monkeys maintained central fixation (red/green dots) while monitoring a stream of pictures presented either to left or right. When a specified target appeared (unpredictably following 0–3 nontargets), reward was given for a saccade to the position of the stimulus stream, made at target offset. In the fixed target task, nontargets (teddy bear, burger) and target (fish) were fixed throughout training. In the cued target task, pictures changed their status as target or nontarget from one trial to the next; a cue at trial onset indicated the target for this trial. Cue-target associations (upper right) were learned pre-experimentally. (b) Example data showing percentages of cells in lateral prefrontal cortex that discriminated targets from nontargets (red – stronger response to targets; green – stronger response to nontargets). Heavy black line shows time of stimulus presentation; discrimination was tested in sliding windows beginning 200 ms before stimulus onset. Data are similar from the two tasks, with an early peak of target-preferring cells, beginning around 100 ms from stimulus onset. Across stimuli and time periods, up to 50% of all randomly selected cells showed target/nontarget discrimination. (c) Cued target task. Cluster analysis showing similarity of prefrontal activity pattern for 18 different task events (3 trial types [search for target stimuli 1 to 3] × 3 task epochs [cue, interstimulus delay, target; nontargets not analysed] × 2 stimulus sides [ipsi-/contralateral to recording location]). For each task event, mean normalized activity was measured in a sample of 324 cells; similarity was measured by correlation of activity patterns across this cell sample. Correlations were close to zero for different task epochs (cue, delay, target), showing that activity in one epoch was unpredictable of activity in others. By contrast, searching for different targets, especially on the same side, produced strongly correlated activity patterns at each task epoch. Adapted, with permission, from Refs. [24–27].

one phase and hemifield, correlations rose to a median of 0.5. Thus each successive task stage was defined by its own, unique pattern of activity across prefrontal cells whereas stimulus information within each stage was coded by modest modulations of the basic stage pattern. The results indicate that, in complex behaviour, transitions from one

step to the next are managed by corresponding transitions among widely distributed, largely independent patterns of prefrontal activity.

In distributed representations, orthogonal codes are useful to maximize discriminability. This makes sense for the successive stages of complex behaviour, where

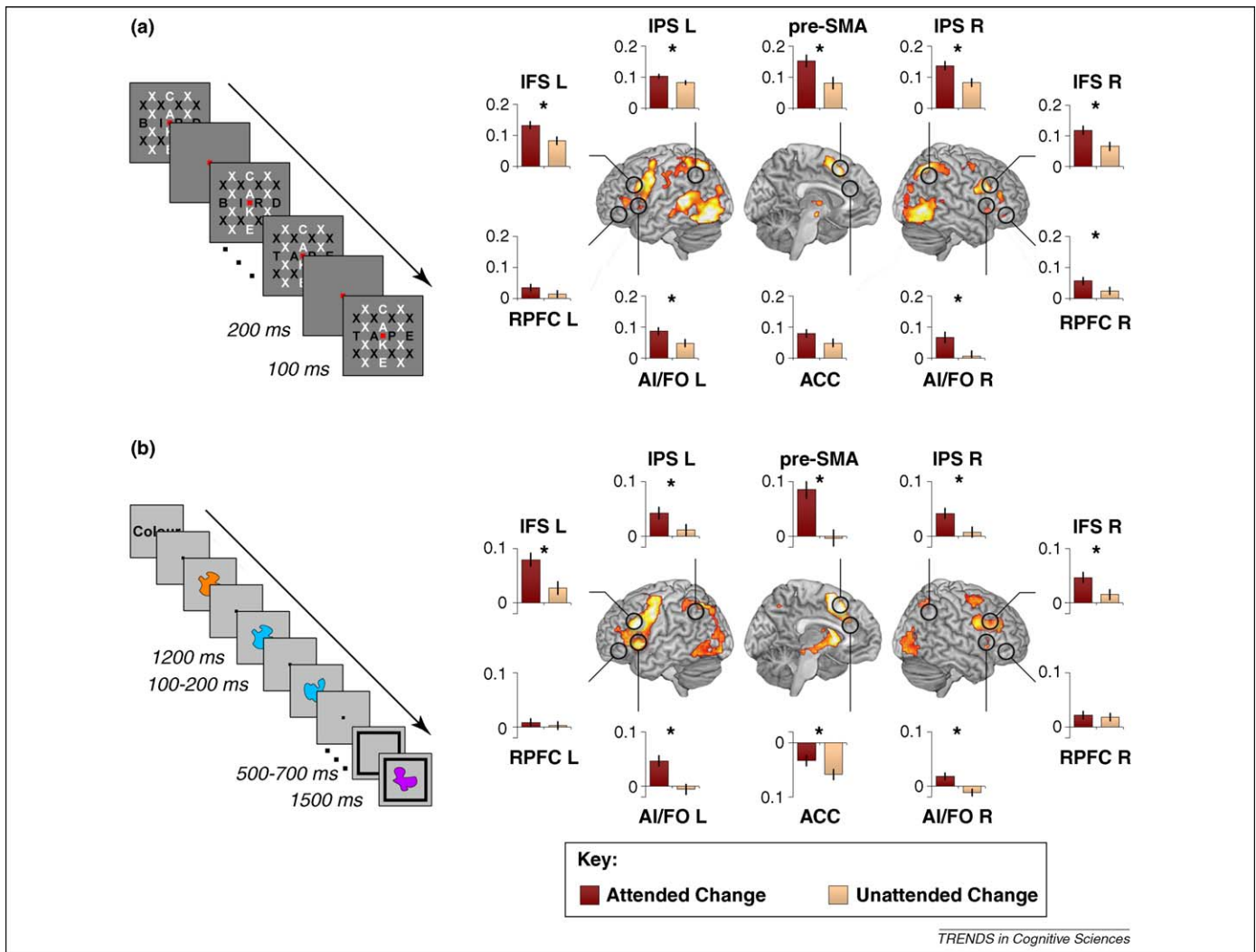


Figure 3. (a) MD response to attended stimulus changes. A series of stimulus frames (left) contained black (horizontal) and white (vertical) words, both centred on fixation, surrounded by distracting Xs. Participants were required to watch either the black or the white word stream, but with no active task to perform. As the series flashed on and off, either attended or unattended words were periodically changed. Images to right show response (per cent signal change) to attended and unattended word changes in spherical ROIs (black circles) centred on peak MD coordinates from Figure 1. Asterisks and whole brain render show activity significantly greater for attended compared to unattended word changes. (b) Similar data for attended vs. unattended stimulus features. A cue at trial onset instructed participants to attend to either colour or shape. A series of stimuli preceded a final test display (black frame); participants indicated whether the test matched the immediately preceding stimulus on the attended feature. Because the occurrence of the test was unpredictable, participants were required to attend to the relevant feature for every stimulus in the series. Each such stimulus matched the preceding one in shape, colour or both features; the analysis (right) contrasts increased response for attended vs. unattended feature change. In both (a) and (b), the trend was for greater response to attended stimulus changes across the MD network, although with stronger and more consistent results in IFS, AI/FO, pre-SMA and IPS than in RPFC and ACC. L = left, R = right. Data adapted, with permission, from Refs. [35,37].

any number of steps, each with arbitrary cognitive content, might need to be assembled. Orthogonal patterns could be valuable in maintaining the separate identity and processing content of each step.

Recent modelling work illustrates the potential of such schemes [44]. To assemble the arbitrary rules of a particular behavioural epoch, for example 'If the context is X and the stimulus is Y, then make response Z', cells selective for specific content (e.g. context X, stimulus Y, response Z) could be linked through a further, large population of cells with random connections. Because these linking cells are connected to random combinations of content-specific cells, they are useful in stabilizing arbitrary combinations of specific cognitive activities. The system has greatest representational power when each randomly connected cell is linked to about half of the specific cells. Under these circumstances, randomly connected cells have properties

strongly reminiscent of those observed in prefrontal cortex, with selective, somewhat independent activity in many different cognitive epochs, and rapid transitions from one epoch to the next [44]. In systems of this sort, randomly connected cells are involved not only in controlling, but also in learning and storing the successive steps of a mental program. In this sense they are reminiscent of both process and representational models of prefrontal functions [45].

Transitions between coalitions of active neurons, each associated with a different task epoch, are also seen in analyses of activity patterns across multiple, simultaneously-recorded cells. Transitions can be reflected not only in changes of mean firing rate for each cell, but in altered patterns of correlation between cells, either between epochs [46,47] or occurring at the moment of switch from one task epoch to the next [48]. Similar data come

Box 1. Integration across successive task events after frontal-temporal disconnection

In the monkey, several methods are available to disconnect prefrontal from inferotemporal cortex. Because most connections between these regions are intrahemispheric, one method is to remove inferotemporal cortex on one side, and prefrontal cortex on the other. The method avoids the very severe performance impairments that follow large, bilateral prefrontal removals. Instead, it asks how performance depends on direct communication between prefrontal cortex and the high-level visual representations of the temporal lobe.

Intriguingly, the disconnection has no effect on some demanding visual tasks [69,70]; an example is concurrent object discrimination learning. On each trial of this task, the monkey sees a pair of objects; touching the correct one brings reward. Importantly, trials with different pairs (e.g. AB, CD, EF...) are interleaved, so that multiple pairs are learned concurrently. Evidently, frontal-temporal communication is unnecessary for simple association of a visual object with reward.

Instead, the disconnection produces deficits in several task variants, which in the normal animal allow radical improvements in performance. In one such variant, object pairs are not interleaved, but learned one at a time. In experienced normal animals, this task is much easier than the concurrent version, probably reflecting a win-stay lose-shift strategy. In this strategy, information is combined

across successive trials: if the initially chosen object is rewarded then the monkey chooses it again, otherwise switching to the alternative. Following frontal-temporal disconnection this strategy is apparently lost and performance returns to a level comparable to concurrent-pair learning [69]. A second task variant similarly emphasizes integration of information across successive task episodes. Now, each object choice is followed by presentation of a second object, uniquely associated with the particular object chosen. For example, choice of object A is followed by W and then reward; choice of B by X and no reward; in another concurrently-learned pair, C is followed by Y and reward, D by Z and no reward and so on. As compared to a version with an empty delay between choice and reward, the opportunity to associate each possible choice with a unique following object ('A leads to W') substantially improves performance in control animals. Again, this improvement is absent following frontal-temporal disconnection [70].

Evidently, the need for frontal involvement in visual tasks is not predicted by simple task difficulty. Instead, frontal involvement is crucial when visual information must be combined across successive task epochs, or passed from one stage to the next of a sequential mental program [69–71].

from lateral and medial frontal cortex of the rat. Again, the activity of single cells is strongly modulated by task epoch [49]. As in the monkey data, a given cell can be active in one or more task epochs, and transitions between epochs result

not only in changed patterns of mean activity across cells, but in changed correlation between cell pairs [50].

Across MD regions, these physiological results show neural properties suitable for the needs of sequential,

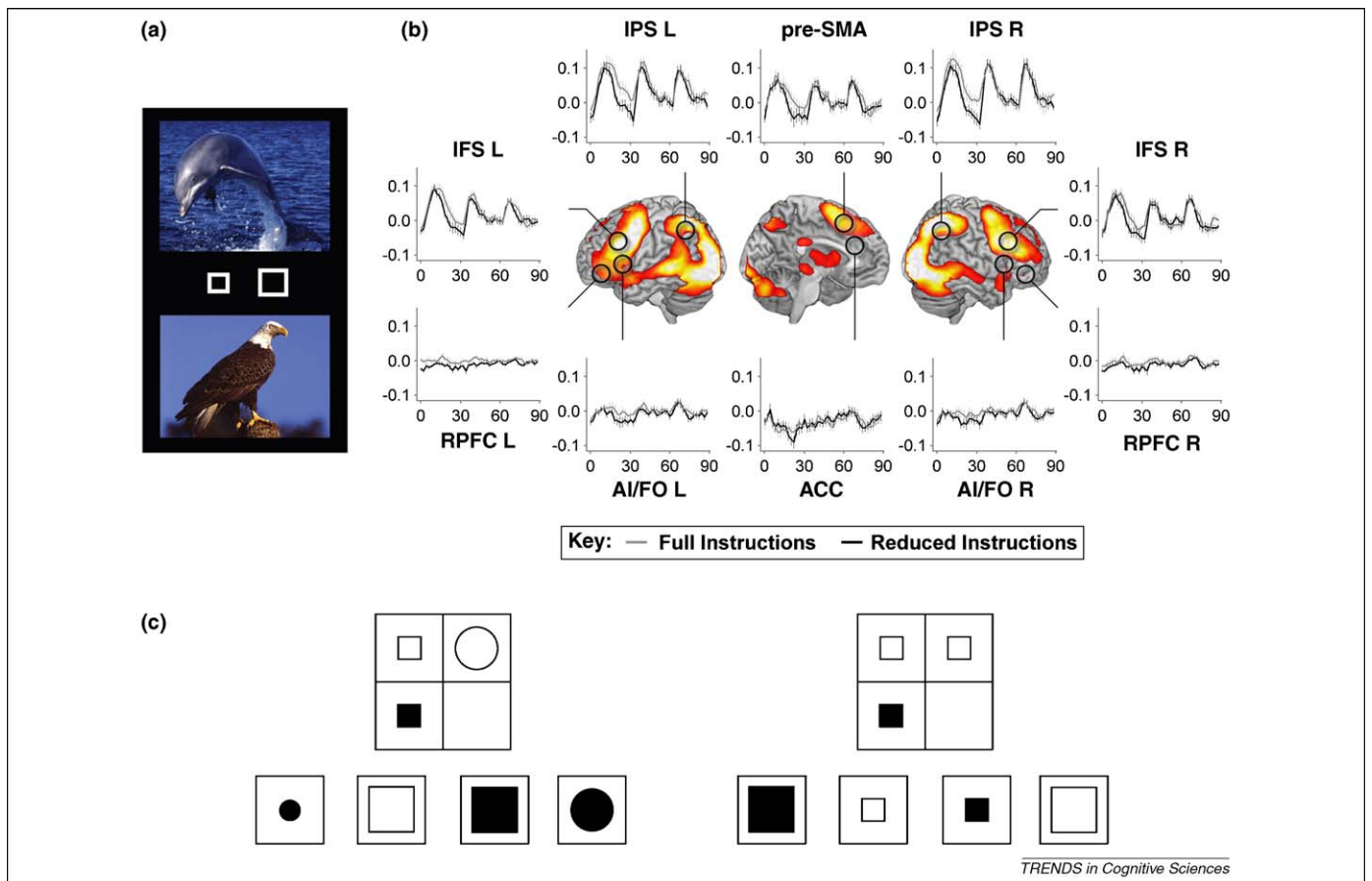


Figure 4. (a) Example stimulus for 1 of 8 tasks used in Ref. [54]. For each task, instructions could define up to 5 rules (e.g. if upper and lower pictures are identical, press left key; if 1 picture depicts a bird, press key on side of larger square). (b) Phasic activity linked to instruction screens (20 s on, 10 s delay between screens) for each new rule. Whole brain render shows regions with stronger activity during instruction screens than intervening delays; surrounding panels show signal strength (finite impulse response parameter estimate) as a function of time (s) for 3 successive instruction screens (onsets at 0, 30 and 60 s) in MD ROIs (black circles). Data are for the final 3 rules of each task, presented either following instructions for 2 previous rules (pale grey, full instructions), or without preceding rules (dark grey, reduced instructions). Phasic activity linked to each new rule presentation was strong in IFS, IPS and pre-SMA, with significant but weaker activity in left AI/FO and right RPFC. L = left, R = right. (c) Example matrix problem (left), with variation in 3 stimulus features (shape, size, colour), and equivalent problem (right) with only 1 varying feature. In each case, the task is to complete the matrix (top) with 1 of 4 response alternatives (bottom).

multi-step behaviour, with selective focus on many kinds of task-relevant information, and rapid transitions between different, largely independent processing states as successive task steps unfold. Complementing these conclusions are recent lesion studies in the monkey (Box 1), showing that, when prefrontal and temporal cortex are disconnected, deficits are predicted not only by task difficulty, but by a requirement to integrate visual information across successive task epochs.

MD activity in new task assembly

As a new task is learned, its components must be identified, separated and assembled. The ability to learn and use the multiple rules of novel, complex behaviour is strongly correlated with fluid intelligence [51,52]. In extreme cases, failure is manifest in 'goal neglect' [51]; although the subject might correctly describe the different task components, one component is lost in actual behaviour. Similar mismatch between knowledge and behaviour has long been described in frontal lobe patients [20,53]. Goal neglect is closely linked to task complexity; as the instructions for a new task are received, and the number of task components increases, the probability of success in adding each new component declines. The results indicate limits on some process of differentiating and maintaining separate, functionally effective parts of a novel task plan.

A recent fMRI study [54] shows what happens in the brain as new task instructions are received. In this experiment, each task rule (Figure 4a) was described in a separate instruction screen, presented for 20 s with a delay of 10 s between each instruction and the next. Time-course analysis asked which brain regions show phasic activity as each new instruction is processed. In line with the visual and linguistic demands of written instructions, extensive activity was seen in occipital cortex, extending especially on the left into the temporal lobe (Figure 4b). Strong phasic activity was also seen, however, in parts of the MD network, in particular the IFS, IPS and pre-SMA. Accompanying this phasic activity was a broader pattern of shift in the return to baseline that followed each instruction: across most or all regions of the MD network, baseline activity increased with increasing task complexity, approaching an asymptote following the second or third rule. Reflecting this asymptotic increase, baseline activity was higher for rules specified after several other rules (Figure 4b, full instructions) than for the same rules specified alone (Figure 4b, reduced instructions). One hypothesis is that, across the MD system, sustained activity reflects the total complexity of the currently maintained task plan. Smaller activity changes for later rules might reflect the weaker impact or representation of these rules. Whether or not this is so, the results show strong MD involvement in new task assembly.

In many ways, the problems of standard fluid intelligence tests resemble novel task instructions. The matrix problem of Figure 4c (left), for example, instructs several separate task components or cognitive operations, calling for separate processing of object shape, colour and size. Problems with only one such component (Figure 4c, right) seem trivial by comparison [55], implying, as in the goal

neglect experiments, a similar limit in separating and assembling multiple task parts. In problems of this sort, frontal and parietal activity is sensitive to the number of varying dimensions [56]. As noted earlier, useful division of a task into independently soluble sub-parts is perhaps the central challenge of all problem-solving systems [18,57], and MD activity is strong when problem materials are organized into novel sub-units or chunks [58]. In large part, the role of MD regions in separation and assembly of task parts might explain their importance in fluid intelligence.

Conclusions and open questions

The importance of frontal lobe processes in complex, sequential activity has long been recognized [20,21]. Symbolic artificial intelligence has shown how complex, goal-directed behaviour is achieved through sequential mental programming, or dividing complex problems into component sub-problems. With the ascendancy of parallel, neural network models, interest in sequential mental programming has been somewhat in abeyance. Much work has addressed isolated acts of cognitive control, such as attentional bias or response inhibition [12,13]. Less work has considered processes required to build complex, multi-step behaviour.

Questions of sequential mental programming, however, could be central to understanding of MD function, and its role in fluid intelligence. The MD system is defined by common brain activity in tasks of many different kinds. In all tasks, the goal is achieved by a series of focused stages or sub-tasks. In lateral prefrontal cortex, neural properties are well adapted for construction and control of such sub-tasks, with focus on the specific content of a current cognitive operation, rapid reorganization with changing context, and robust separation of successive task stages. When a new, complex task is learned, its different parts must be separated and assembled; this process engages strong MD activity, and is closely linked to fluid intelligence.

These ideas, of course, provide only a beginning, and many open questions remain. In large part, the single cell data I have reviewed come from recordings in the posterior part of the lateral prefrontal cortex. Although plausibly there is some homology with MD activity in the posterolateral frontal cortex of the human brain, more detailed comparisons are needed across species. Similarly, there is a relative lack of single cell data from possible homologues of other MD regions. Work is needed to identify these regions in the monkey, and to study their neural properties in more depth.

As outlined earlier, several different methods define very similar MD patterns (Figure 1). As illustrated in Figures 3 and 4, data from many different kinds of experiment can be effectively analysed using simple, spherical regions of interest (ROIs) defined around a fixed set of peak coordinates. At the same time, there is clear evidence that the definition of MD regions can be improved. In Figure 3, for example, whole brain data indicate peak parietal activity that curves above and around the spherical IPS ROI. On the lateral frontal surface, whole brain analyses often show activity spreading both anterior and posterior to the IFS ROI. Although there are obvious attractions to

using fixed, *a priori* ROIs, it seems probable that, for this purpose, ROIs can be improved over those currently available.

In fMRI, the different components of the MD system are commonly activated together. Usually, the parts of the system appear to work together in assembly and use of a mental program. Their very different connectivity, however, indicates a strong likelihood of different processing roles. The fMRI literature contains a variety of interesting suggestions concerning specialization of function within the MD network. One influential proposal concerns different roles for anterior cingulate and lateral prefrontal cortex, the former serving to detect cognitive conflict, and the latter responding with increased cognitive control [59]. Sometimes, the anterior cingulate indeed shows a phasic response to increased conflict, whereas lateral prefrontal cortex shows tonically increased activity in anticipation of a demanding decision [60]; at the same time, phasic responses during demanding trials can certainly be seen in the lateral prefrontal cortex [61,62], and tonic responses in the anterior cingulate [5,63]. Dosenbach *et al.* [5,64] have recently proposed a rather different separation with RPF, AI/FO and pre-SMA/ACC linked to tonic maintenance of task set, and IFS/IPS more associated with on-line processing of specific task events. Again, the distinction finds some supporting data, in particular the association of RPF with more sustained aspects of task preparation and performance ([65,66]; see also weak phasic responses in Figures 3 and 4). In different task contexts, however, most MD regions can show either strong phasic or strong tonic activity (see e.g. [54]).

On theoretical grounds we can distinguish several requirements in assembly and use of a mental program. One is construction of the current task step, with focus on only those operations that this step requires. To achieve such focus, MD systems must interface with the many separate brain systems executing specific cognitive operations, for example identification of a specific visual object, or retrieval of specific facts from memory. A second requirement is a signal for successful completion of the current step and transition to the next; reminiscent of the 'test' component in the TOTE architecture of Miller *et al.* [67]. Such a success signal might be built upon brain processes more generally concerned with reward, perhaps linking to the autonomic functions of AI/FO and ACC. While one component of a complex task executes, others must be kept latent for later use; interface between active and latent task components has been proposed as a core function of RPF [68].

More work is needed to develop such ideas. At present, fMRI data are clear in defining the MD pattern, but much less clear in defining the separate functions of its components. Meanwhile, I suggest, the needs of sequential mental programming provide a critical perspective on the control functions of the frontoparietal cortex. The essential function of the MD system might lie in separating, organizing, storing and controlling the parts of complex, intelligent mental activity.

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