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Common regions of the human frontal lobe recruited by diverse cognitive demands

John Duncan and Adrian M. Owen

Though many neuroscientific methods have been brought to bear in the search for functional specializations within prefrontal cortex, little consensus has emerged. To assess the contribution of functional neuroimaging, this article reviews patterns of frontal-lobe activation associated with a broad range of different cognitive demands, including aspects of perception, response selection, executive control, working memory, episodic memory and problem solving. The results show a striking regularity: for many demands, there is a similar recruitment of mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate cortex. Much of the remainder of frontal cortex, including most of the medial and orbital surfaces, is largely insensitive to these demands. Undoubtedly, these results provide strong evidence for regional specialization of function within prefrontal cortex. This specialization, however, takes an unexpected form: a specific frontal-lobe network that is consistently recruited for solution of diverse cognitive problems.

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WITHIN a brain structure as large and complex as the primate prefrontal cortex, it seems obvious that there must be some regional specialization of function. Despite over a century of research, however, there is still only modest evidence to indicate what specializations exist or, more broadly, how frontal functions can be divided into useful components.

A good number of studies, for example, have compared groups of patients or animals defined by lesions in different subregions of frontal cortex. In such a study, the strongest evidence for regional specialization comes from double dissociation, that is, a finding that one group is significantly more impaired in task A, while the other is significantly more impaired in task B. In the human literature, such dissociations are extremely rare, being all but restricted to a few suggestions of differential deficit following left and right hemisphere lesions[1]. In the monkey literature, double dissociations should be easier to find, as lesions can be more precisely targeted. Again, however, we know of only a few such demonstrations, largely restricted to comparisons between extensive lesions of the orbital and lateral surfaces (see Refs 2,3; for somewhat similar human data see Ref. 4). Though finer comparisons – for example, between dorsolateral and ventrolateral lesions – might sometimes give suggestive results[5], the common finding is that even restricted lesions produce some degree of deficit in a broad array of different tasks[5,6].

Electrophysiological studies provide a similarly ambiguous picture. On the one hand, there are elegant studies detailing the highly specific properties of single neurones in particular frontal regions during particular tasks. In the region of the principal sulcus, for example, there are neurones with selective coding of specific remembered locations in tests of spatial working memory[7]. On the other hand, there are also results suggesting that neurones broadly distributed through lateral frontal cortex might to some extent adapt their properties dependent on current behavioural demands. Recording from an extensive region of lateral frontal cortex, for example, Rao *et al.*[8] found that individual frontal neurones carried object information during parts of a task in which this information was needed in working memory, but switched to location information when it no longer mattered what object

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had been seen, only where it had occurred. Such neurones were widely distributed across both dorsal and ventral regions of the lateral surface.

Even anatomical data tell a somewhat mixed story. On the one hand, it is obviously true that subregions of frontal cortex are differentiated in terms of their local architecture and connectivity, implying some kind of difference in function[9]. On the other hand, the pattern of connectivity within frontal cortex again indicates caution. Any small region of frontal cortex is connected not only to the immediately surrounding region, but also to a network of small, structured patches of cortex that are widely spread throughout much of the frontal lobe[10]. Though such connectivity might suggest functional modules, each module would consist of many small, widely distributed parts. At the coarse level of resolution usually considered in brain–behaviour studies, no clear regional specialization might be expected.

Evidently data of this sort are insufficient to show how prefrontal functions can be divided into useful, well-specified components. Correspondingly, even the most attractive current conceptions of such functions are at best rather general and ill defined: executive control[11,12], monitoring in working memory[13], temporal structuring of behaviour[14], control of behaviour by context[15] and so on. Though such views are sometimes contrasted, the truth is that they are all so general as to generate few strong, testable predictions.

This article considers the contribution of recent functional imaging data to this state of affairs. Indeed, although these data show strong evidence for regional differentiation within prefrontal cortex, they also help to explain the difficulty of defining component frontal functions at the cognitive level. For many different cognitive demands, there is joint recruitment of three frontal regions: mid-dorsolateral; mid-ventrolateral, extending along the frontal operculum to the anterior insula; and the dorsal part of the anterior cingulate. To this extent, cognitive activation studies give results that are very regionally specific within prefrontal cortex. This recruitment, however, is extremely similar from one cognitive demand to another, suggesting a specific network of prefrontal regions recruited to solve diverse cognitive problems. While components of this network have previously been considered in the context of specific cognitive demands – working memory[16], response competition[17] and so on – and while they might indeed have somewhat separate functions, these functions must be sufficiently abstract to explain recruitment in many different task settings.

Clustering of frontal activations

A general impression of clustering in the frontal activations associated with widely different cognitive demands is easy to obtain from the imaging literature. Figure 1 provides an initial illustration. To produce this figure, reported peak activation foci were taken from six studies that concerned, respectively, auditory discrimination[18], visual divided attention[19], self-paced response production[20], task switching[21], spatial problem solving[22] and semantic processing of words[23]. Studies were chosen to reflect frontal-lobe activations associated with widely different cognitive domains. Because studies adopted different analysis methods and significance criteria, all foci were accepted when reported as significant by the criteria of the individual studies. In one case[23], where two reported foci from the same contrast were separated by less than 1 cm, the single more-significant focus was taken. The Talairach and Tournoux[24] atlas was then used as a standard criterion for identifying foci within the frontal lobe, excluding those lying in Brodmann areas 4 or 6 (primary motor or premotor cortex). Though use of this atlas is doubtless imperfect, for example, at the junction of frontal operculum and anterior insula, it allows consistent treatment of all data sets. Finally, all identified prefrontal foci have been rendered together onto lateral and medial views of a canonical brain image.

Though task requirements in these studies are so diverse, the results certainly suggest some clustering of the frontal activations obtained. On the medial surface, activations are entirely restricted to a region immediately dorsal to the corpus callosum, largely within the dorsal part of the anterior cingulate. On the lateral surface, activations are more scattered, but again, most points lie within two rather confined regions. First, there are points within and immediately surrounding the middle and posterior parts of the inferior frontal sulcus. In this article, we group these together under the heading 'mid-dorsolateral'. This distinguishes them from a cluster of more ventral foci, immediately dorsal and anterior to the Sylvian fissure. Though plotted here on the lateral surface, these ventral foci in fact spread along the frontal operculum to become continuous with reported activations in the anterior insula. These we term 'mid-ventrolateral'. Not a single activation peak is reported in any of these studies on the orbital frontal surface (not shown). In this last connection, it should be remembered that functional magnetic resonance imaging (fMRI) can suffer severe signal loss in the orbitofrontal region; in fact, however, four of these six studies employed positron emission tomography (PET), which does not suffer the same restriction.

From a data set of this sort little more can be said. One problem concerns statistical power. As power is limited in any one study, inevitably only a part of the truly active brain region will achieve significance by a conventional criterion. It follows that, through noise alone, any two studies will reveal somewhat different regions of significant activation, and if these studies manipulate different cognitive demands, it is tempting to conclude that their different regions of activation are associated with those different demands. Evidently, however, this conclusion must be drawn with caution. Even if the two demands in fact recruited exactly the same frontal regions, limited power makes it inevitable that results would not be identical in the two experiments. A case in point in Fig. 1 is auditory discrimination (green), whose foci are clustered relatively ventrally in the left hemisphere. Is the failure to obtain more dorsal activation a chance result in this particular study, or a reliable characteristic of this cognitive domain? (It is worth noting that, on the medial surface, activation spreading into the dorsal anterior cingulate was in fact reported in this experiment. It is not plotted in Fig. 1 because the peak activation lay higher, in area 6.)

A second problem is possible bias introduced by selection of the six studies to include. Is clustering of activations within mid-dorsolateral, mid-ventrolateral

and dorsal anterior cingulate regions a property of these particular studies, or a general result in a wide range of experiments?

Systematic comparison of five cognitive demands

To address these problems requires some more systematic comparison of activation patterns associated with different cognitive demands. For this purpose it is especially useful to find studies in which a well-specified demand has been manipulated in the context of an otherwise identical task. In recent years, a number of reviews of imaging data have appeared in an attempt to compare regional recruitment for different cognitive demands. Often, however, results have been disappointing: combining data from multiple studies has produced a diffuse activation pattern, with no clear difference between patterns associated with different cognitive domains[25,26]. In part, this might reflect a combination of results over too broad a set of experiments. Combining data from multiple experiments all concerned with 'memory' or 'language', for example, might produce a diffuse result because very many different cognitive processes contribute to different 'memory' or 'language' tasks. A second problem is comparison of 'experimental' conditions, which involve some function of interest, with much simpler 'control' tasks such as pressing a fixed key in response to each stimulus onset. When experimental and control tasks involve very different decisions and processes, they are likely to show a broad variety of differences in brain activity, only some of which are related to the particular factor the experiment is intended to investigate. Such problems can be minimized by focusing on studies with the purest possible manipulations of tightly defined demands.

In Table 1, five demands are listed for which we were able to identify several appropriate studies in the literature. For this exercise, studies were selected only on the criterion of having manipulated a specified demand in the context of an otherwise identical task. Also listed in Table 1 are reported peak prefrontal activations from each study, using the same inclusion criteria as before. In more detail, the five demands included are as follows.

Response conflict

One major theme in discussions of frontal executive function is suppression of prepotent but inappropriate responses. The first set of studies in Table 1 manipulated strength of response conflict, including three studies of the Stroop effect[27,28] (in addition Experiment 1 of Ref. 29), one of reversing previously learned stimulus–response associations[30], and two of incompatible stimulus–response mappings[31,32]. Further details of the tasks of each study are given in Table 1, together with peak activations for a subtraction of high-conflict minus low-conflict tasks. Several further Stroop studies were initially considered for inclusion in this set. They were excluded because of unwanted differences between high- and low-conflict conditions; either low-conflict stimuli were not words[47–49] (in addition Experiment 2 of Ref. 29), or the low-conflict condition did not strictly require colour naming[17].

Task novelty

The second set of studies compared the initial learning of an unfamiliar cognitive task with later, well-practised performance[33–37]. Again, it is frequently suggested that frontal executive functions are especially important in the early, more intentional phase of learning, as compared with the later, more automatic phase. Table 1 describes the range of tasks employed; here, peak activations concern a subtraction of early minus late in learning. Two free recall studies were also considered for inclusion in this set. They were excluded because of very different rates of response output in novel and well-learned cases[50,51].

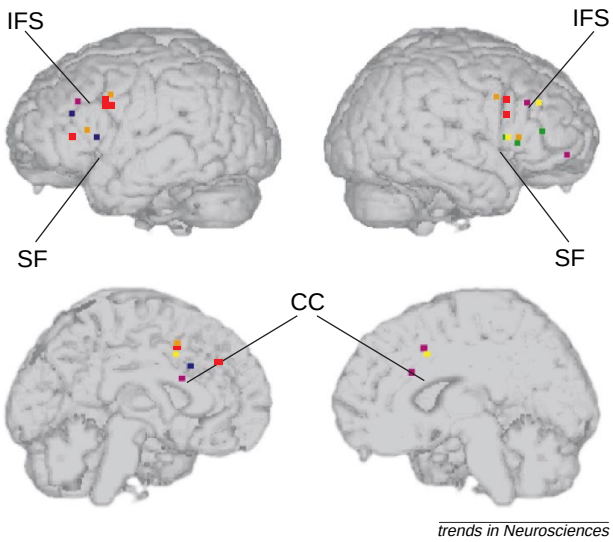

Fig. 1. ***Clustering of frontal activations produced by widely different cognitive demands.*** *Prefrontal activations from six experiments – concerned, respectively, with auditory discrimination[18] (green), visual divided attention[19] (blue), self-paced response production[20] (yellow), task switching[21] (orange), spatial problem solving[22] (pink) and semantic processing of words[23] (red) – have been plotted together onto a 3D rendered canonical brain image (SPM96, Wellcome Department of Cognitive Neurology, London). Shown are lateral (upper) and medial (lower) views of each hemisphere. Despite the diversity of cognitive demands in these experiments, frontal activations show apparent clustering, with most points within mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions (see definitions in text). Abbreviations: CC, corpus callosum; IFS, inferior frontal sulcus; SF, Sylvian fissure.*

Working memory: number of elements

Working memory is a further major theme in current accounts of frontal-lobe function. As one reflection of the demands of simple working-memory storage, the third variable considered is the number of elements to be retained, represented by two studies of short-term recall[38] or recognition[39]. Peak activations in Table 1 are for a subtraction of higher memory load minus lower memory load. Further studies considered for inclusion in this set used the *N*-back task, in which each element in a series must be compared against the element *N* steps preceding it[52–54]. They were excluded because this task requires complex reorganization and manipulation functions in addition to simple working-memory storage.

Working memory: delay

In a further assessment of working-memory storage, the fourth set of studies manipulated delay in tasks requiring simply that 1–4 stimuli be remembered across a few seconds for subsequent test[40,41] (in addition Experiment 2 of Ref. 42). Peak activations in Table 1 are for a subtraction of long delay minus short delay. Several further studies were considered for inclusion in this set. They were excluded because working memory (for example, successive matching, delayed saccades) was compared with some kind of non-memory control (for example, simultaneous comparisons

TABLE 1. Studies and activation foci for comparison of five cognitive demands

Task	Foci[a]			Ref.
Response conflict				
Manual response to number of words on screen, either low conflict (non-number words) or Stroop (number words)	43,27,34	−46,18,25	12,9,34	27
Name colour in which word is printed, either low conflict (non-colour word) or Stroop (colour word)	−8,22,28	12,44,20		28
Name colour in which word is printed, either low conflict (non-colour word) or Stroop (colour word)	26,53,27 44,44,2 3,35,18	33,41,16 −48,26,14	42,26,−2 19,30,11	29
Respond to simple stimulus following previously trained or opposing stimulus–response mapping	38,30,13 −47,13,30 −3,32,20 −4,30,17	−43,25,24 −39,58,6 7,27,29 7,34,22	−36,18,−3 −42,22,20 −1,22,49 3,18,44	30
Saccade towards or away from visual target	−40,26,32	26,36,28		31
Respond to letter with its own or different letter name	−39,17,2	37,17,−2	−10,14,43	32
Novelty				
Eight-movement finger sequence, early or late in learning	36,20,4 36,32,28 6,30,28	28,50,−4 −30,46,−4	40,38,16 −40,20,28	33
Eight-movement finger sequence, early or late in learning	−28,42,20 −2,14,44	38,24,28	2,20,28	34
Choose picture paired with sound, early or late in learning	39,10,39	−1,26,44		35
Reproduce set of 15 abstract designs, early or late in learning	22,40,−12 −34,52,20 −28,24,16 −14,28,20	−18,44,−12 −44,22,28 −32,6,32	24,38,0 −18,28,−20 −8,20,36	36
Generate verb appropriate for noun, novel or practised noun list	−43,28,13	−4,28,36		37
Working memory: number of elements				
Spoken list of one or three words followed by immediate recall	−40,34,4			38
Array of one or six letters followed by recognition probe; array offset to probe onset 5 s	−27,53,1 29,31,32 35,28,24 −52,5,20 24,22,1	−37,29,20 −48,43,8 −49,26,1 41,5,32 0,24,45	28,35,12 25,53,1 −39,35,12 −38,22,12 1,20,32	39
Working memory: delay				
Categorize letter pair; first letter retention interval 1 or 8 s	−30,47,26	32,41,32	−54,9,17	40
Array of four spatial positions followed by recognition probe; array offset to probe onset 0 or 7 s	−46,8,24 −20,40,−12	30,34,12	36,34,20	41
Array of two spatial positions followed by recognition probe; array offset to probe onset 0.25 or 3 s	32,18,−1	40,36,22	1,14,43	42
Perceptual difficulty				
Categorize normal or degraded letter	48,19,23	50,19,2	4,25,43	43
Categorize normal or degraded face	26,42,32			44
Categorize normal or degraded letter	39,15,36 0,30,45 9,45,−9	48,12,21 9,33,21	−51,15,42 −3,30,18	45
Identify object from conventional or unconventional view	35,15,28	−22,40,−8		46

[a]*x,y,z* coordinates according to Talairach and Tournoux[24], negative left/posterior/inferior. For each study foci are listed in arbitrary order.

within a display, immediate saccades to a visual target)[31,55–58] (in addition Experiment 1 of Ref. 42).

Perceptual difficulty

The final set of studies manipulated perceptual difficulty, including three studies of stimulus degradation (Refs 43,44,45 and pers. commun.) and one of object recognition from conventional versus unconventional viewpoint[46]. Perceptual demand has not been conventionally associated with either executive or working-memory function. For this reason it is particularly interesting to compare the frontal-lobe activations of these studies with those of more standard frontal tasks. Peak activations in Table 1 are for a subtraction of more demanding minus less demanding conditions (or in one case[44], a corresponding linear contrast across several levels of demand).

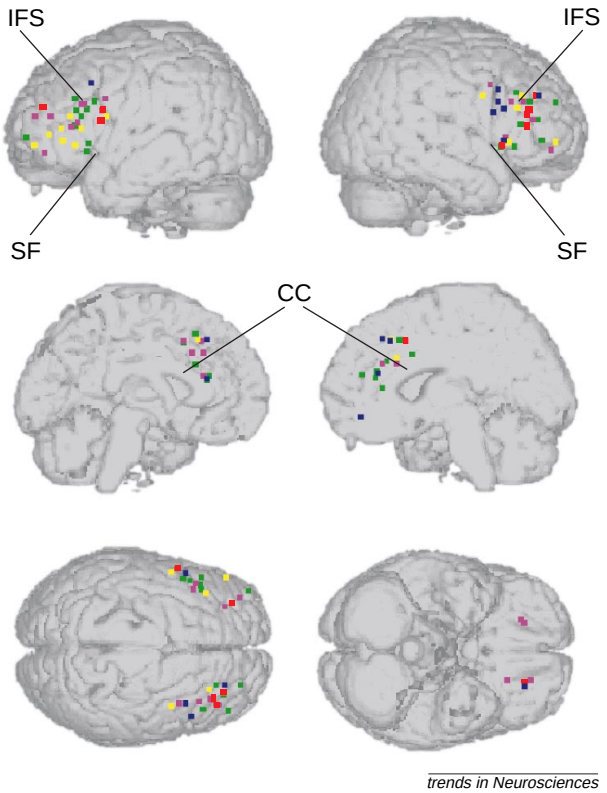

Fig. 2. ***Systematic comparison of frontal activations associated with five cognitive demands.*** *Activations are from studies of response conflict (green), task novelty (pink), number of elements in working memory (yellow), working memory delay (red) and perceptual difficulty (blue). Shown are lateral (top row) and medial (middle row) views of each hemisphere, along with whole brain views from above (bottom left) and below (bottom right). With this extended data set, clustering in mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions is compelling, and very similar for the five different forms of demand. Abbreviations: CC, corpus callosum; IFS, inferior frontal sulcus; SF, Sylvian fissure.*

Combined data from all studies are shown in Fig. 2. As before, all reported activation foci have been rendered together onto a canonical brain image. 'Deactivations' (decreases in activity with increased demand) have been ignored as they were inconsistently analysed or reported in the studies reviewed. Each focus is plotted according to our determination of whether it lay on the lateral (see also dorsal view), medial or orbital frontal surface. This determination was based simply on proximity to the corresponding surface, where appropriate taking sulcal patterns into account. In Fig. 2, different colours are used to distinguish foci associated with different cognitive demands.

The results of this more systematic analysis amply confirm the impression gained from Fig. 1. The most striking result is the tight definition of the region within which activation foci fall. On the medial surface (middle row) this definition is particularly sharp, with activations being almost entirely restricted to the dorsal part of the anterior cingulate (cf. Ref. 59). On the lateral surface (upper row), the activated region is somewhat broader. One prominent cluster appears in the mid-dorsolateral region of both hemispheres. A second, particularly evident in the right hemisphere, appears in the mid-ventrolateral region; again, this cluster spreads from the outer surface along the frontal operculum and becomes continuous with activation in the anterior insula. Further scattered points appear towards the frontal pole; as on the medial surface, however, much of the lateral surface is clearly excluded from the region of activation, as shown most clearly in the dorsal brain view (bottom left). The ventral view (bottom right) shows only occasional activations on the orbital surface, with complete exclusion of the orbitomedial region; in this connection it again should be noted that PET was the imaging modality in 15 of the 20 studies included.

The second important result is similarity of activation for different demands. For each of the five demand factors, foci are broadly distributed throughout the general region of activation. This is true in both hemispheres, and on both lateral and medial surfaces. All five demands, in particular, are associated with a similar pattern of activations in the dorsal anterior cingulate and in both mid-dorsolateral and mid-ventrolateral regions.

Three points might be made in support of these conclusions. For each demand, data have only been combined from experiments that deal with apparently similar cognitive manipulations. Is it possible, nevertheless, that the somewhat broad region of activity associated with each demand is an artefact of combining data from ostensibly similar but in fact rather different experiments? Related to this possibility is the noise undoubtedly introduced by different analysis methods (for example, methods of normalization), which increases the spread of activations associated with any given demand. The data shown in Fig. 3 rule out the possibility that conclusions are severely distorted by such concerns. This figure includes foci from just four selected studies: the Taylor *et al.*[29] study of Stroop conflict, the Jenkins *et al.*[33] study of motor performance early and late in learning, the Rypma *et al.*[39] study of memory set size, and the Smith *et al.*[42] study of working-memory delay. Each of these individual experiments makes a highly specific comparison between minimally different task conditions. For the reasons given before, chance considerations must

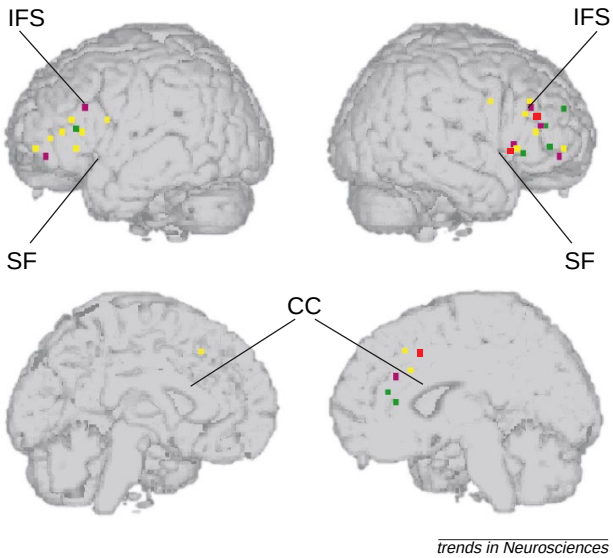

Fig 3. ***Frontal activations from four individual studies.*** *Demands represented are response conflict (Taylor* et al.[29]*, green) task novelty (Jenkins* et al.[33]*, pink), number of elements in working memory (Rypma* et al.[39]*, yellow) and working memory delay (Smith* et al.[42]*, red). Even though these data come from four individual studies, it is clear that each demand is associated with joint activity in mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions. Abbreviations: CC, corpus callosum; IFS, inferior frontal sulcus; SF, Sylvian fissure.*

partly determine which parts of the recruited frontal region or regions are shown as most significant in the different experiments. Each individual experiment, nevertheless, shows the full pattern of joint activity in dorsal anterior cingulate, mid-dorsolateral and mid-ventrolateral regions. Evidently this pattern is not artefactually created by combination of data across studies. Though no comparable single study could be found for the perceptual difficulty manipulation, it seems highly likely that the conclusion applying to the other four demands applies also to this one.

A second important question concerns possible dependence of the conclusions on the exact studies selected for analysis. Would different results have been obtained with different inclusion criteria for experiments in each demand category? To address this point, data were examined from all those studies (listed above) initially considered for inclusion in the main analysis, but rejected because of unwanted, additional differences between high- and low-demand tasks. Frontal activations were listed as before, and plotted together onto a standard brain. The results were closely similar to those shown in Fig. 1; though the overall pattern of activation was perhaps slightly more diffuse, again it was predominantly focused in dorsal anterior cingulate, mid-dorsolateral and mid-ventrolateral regions. Evidently this pattern of co-recruitment is robust across large changes in experimental design and procedure.

A third point concerns statistical testing for differences in activation pattern across different cognitive demands. The Kolmogorov–Smirnov is a well-known nonparametric test for difference between two distributions; though familiarly applied to one-dimensional distributions, it can be extended to those of higher dimensionality[60], making it suitable for present purposes. For each demand, the list of coordinates in Table 1 defines a 3D distribution of activation foci. Using the Kolmogorov–Smirnov, the distribution for each demand was compared in turn with each of the others. For none of the 10 resulting comparisons was the difference in distributions close to significant (minimum $P = 0.15$; median $P = 0.49$).

It seems safe to conclude that, to a very substantial extent, much the same specific regions of the frontal lobe are activated by different forms of cognitive demand. This common network of active regions includes mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions. Whatever the functions of these regions, they seem to be recruited by modest increases in demands as diverse as response selection, working memory maintenance and stimulus recognition.

Finer functional specializations

Of course, the finding of frequent co-recruitment of mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions does not rule out finer specializations within this network. Three variants of this possibility might be considered.

The first is specialization within each of these regions at a level of scale beyond the resolution of functional imaging. For example, if several, interdigitated subregions of dorsolateral prefrontal cortex were recruited to solve problems in any given cognitive domain, the distinction between domains might be invisible to functional imaging. This is especially likely in group studies that combine data from individuals whose detailed local anatomy will undoubtedly differ. Indeed, it seems inevitable that, as the scale of analysis approaches the single neurone, there must be increasing local specialization of function.

The second possibility is specialization in degree rather than kind. A plausible example is specialization for materials in working memory. It is clear that overlapping frontal regions are recruited in working memory for spatial, verbal and other materials[61–63]. Within this broad distribution of recruitment, however, there might be some relative specializations, for example, relatively stronger left hemisphere recruitment in verbal tasks[63,64]. The implication might be that broadly distributed frontal neurones have some relevance to any given activity, but that from one activity to another, these distributions have somewhat different peaks[65].

A final possibility concerns the coarse overall distinction between mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions. Plausibly, these three might have rather different functions, but functions sufficiently abstract as to contribute to the solution of a broad range of cognitive problems[66]. At present, the imaging literature contains only hints in this direction. In the domain of working memory, a contrast has been drawn between simple tasks such as forward digit span, which requires relatively straightforward encoding, storage and retrieval, and more complex reorganization tasks such as *N*-back or reverse span[67,68]. While both mid-ventrolateral and mid-dorsolateral regions can be recruited in simple tasks (see working memory tasks and results in Table 1), the addition of a major reorganization component has several times shown a selective additional recruitment of the mid-dorsolateral region[62,67,69]. Possible dissociations between mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions have also been suggested in the domain of episodic memory. In one experiment, a direct comparison of free and cued recall showed higher dorsolateral activity in free recall but higher ventrolateral activity in cued recall[70]. In another, adding a difficult concurrent task to memory encoding showed a tendency to decrease encoding-related activity in the lateral frontal cortex, but to increase this activity in the dorsal anterior cingulate[71]. Certainly, it is too early to attempt a detailed interpretation of these results; at the same time it would evidently be wrong to assume that, because mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions are so commonly recruited together, their functional contributions will not in future be separated.

Other prefrontal regions

What then of the large frontal regions outside the active zones revealed by our analysis – including the majority of the medial and orbital surfaces, and much of the superior frontal gyrus from the anterior limit of premotor cortex to the frontal pole? Again there are interesting hints in the imaging literature. Many authors, for example, have noted the affective and motivational changes that can follow frontal-lobe injury. In imaging studies, correspondingly, both dorsomedial and orbitomedial activations have been associated with emotional[72], social[73] and motivational[74] manipulations.

Another noteworthy case is retrieval from episodic memory. Generally speaking, retrieval has not been studied with a design that is directly comparable with

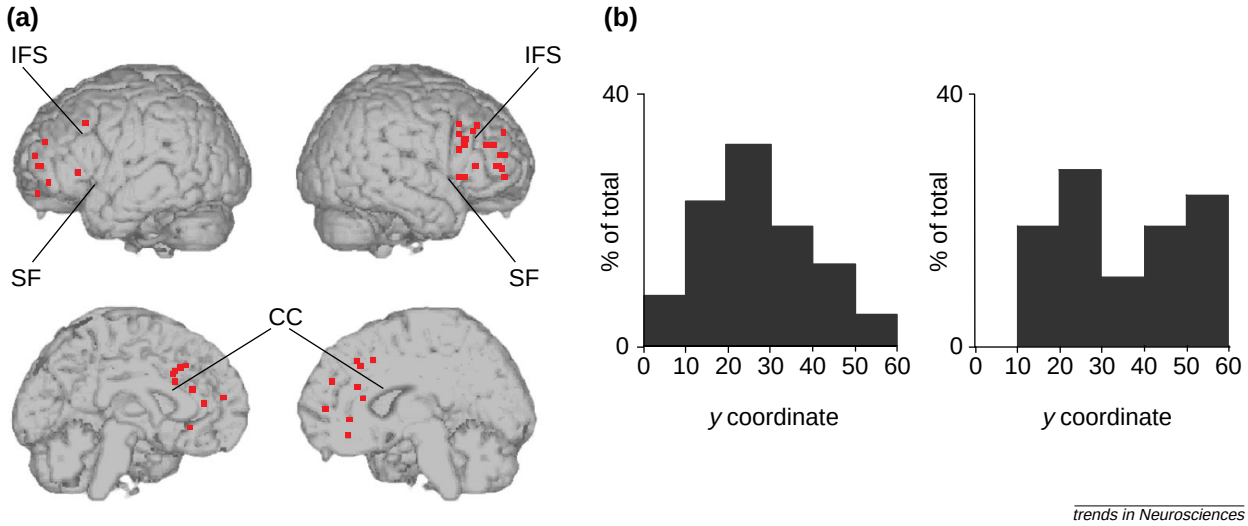

Fig. 4. ***Retrieval from verbal episodic memory.*** **(a)** *Combined frontal activation foci from 14 verbal retrieval studies. Again, activations are evident in mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions, especially (for the two lateral regions) in the right hemisphere. This time, however, there is additional clustering towards the frontal pole.* **(b)** *To make this anterior clustering clear, y coordinate distributions are compared for combined cognitive demands from Table 1 (left) and retrieval (right).*

those of the studies reviewed above. Instead, retrieval conditions have been compared with a wide variety of non-retrieval 'controls', including some that are undoubtedly much simpler (for example, word reading), and some that are arguably more complex (for example, completion of novel word fragments). In Fig. 4a, results (peak increases of activity in retrieval as compared to control conditions) have been combined from 13 such studies. These are a substantial subset of verbal episodic retrieval studies published up to the beginning of 1999, selected independent of where activations were reported within prefrontal cortex[70,75–86]. For comparability with Fig. 2, data have not been included from multiple contrasts with a common control condition in a single experiment; in such cases, only data from the most demanding retrieval condition have been taken.

Certainly, there is some overlap of active regions in Figs 2 and 4a. Mid-dorsolateral and mid-ventrolateral regions are again represented in the memory data, especially in the right hemisphere, and again there is bilateral activation of the anterior cingulate. When compared with Fig. 2, however, Fig. 4a shows a higher proportion of points close to the frontal pole. Though this is especially evident in the left hemisphere, a careful comparison of Figs 2 and 4a reveals a similar trend on the right. The difference is illustrated in Fig. 4b, in which distributions only of *y*-coordinates are shown on the left for all foci from Table 1, and on the right for retrieval foci. To test for the specificity of memory activations, the Kolmogorov–Smirnov test was again used to compare the distribution of all retrieval points in Fig. 4a with the distribution of all 'demand' points combined from Table 1. According to this test, the difference in distributions was significant ($D_{93,54} = 0.29$, $P<0.05$), as was a unidimensional Kolmogorov–Smirnov test on the distributions of *y*-coordinates alone ($D_{93,54} = 0.32$, $P<0.01$). While undoubtedly retrieval shows frontal activations associated with general cognitive demand, there is also a strong suggestion of some additional processing requirement associated with more anterior recruitment.

Concluding remarks

Certainly functional imaging contributes something new to our understanding of regional specialization within prefrontal cortex. On the one hand, there is strong evidence for such specialization: very specific prefrontal regions are repeatedly recruited by simple cognitive demands. On the other hand, specialization takes an unexpected form: very much the same regions are recruited by different demands, suggesting a specific prefrontal network recruited in solution of diverse cognitive problems.

How mid-dorsolateral, mid-ventrolateral and dorsal anterior cingulate regions work together to meet such diverse challenges remains a challenging question. Indeed, the very generality of activity in these regions helps explain why most conceptions of prefrontal functions are themselves so general and ill defined; it is simply very hard to be precise about the function of a region when that region is important in such a diversity of behaviour. To this extent, the data confirm that understanding of prefrontal functions is a difficult problem. It is a problem, nevertheless, to which functional imaging has made an interesting and unexpected contribution.

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Live or let die – retinal ganglion cell death and survival during development and in the lesioned adult CNS

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Programmed cell death or apoptosis is a common and widespread phenomenon that is important for proper development of the nervous system. In the adult CNS, however, apoptosis contributes to secondary cell loss after various types of lesions. The retino-tectal system has been successfully used as a convenient model system to study the molecular mechanisms of neuronal apoptosis and survival during development and in the lesioned adult CNS. This review describes the current knowledge about the interactions of cell death and survival pathways in general and for retinal ganglion cells specifically.

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PROGRAMMED cell death (PCD) is a phylogenetically conserved mechanism, which controls cell numbers in multicellular organisms and is particularly important for the correct development of the PNS and CNS. In the retina, two cell-death periods can be distinguished: an early phase, which coincides with the onset of neuronal birth and migration[1], and a later phase, which occurs during target innervation[2,3]. Although some intracellular pathways of the apoptosis programmes might be similar during development and in the lesioned adult CNS, the induction mechanisms do not seem to be. During development, PCD is a widespread phenomenon that is necessary to control the final cell numbers of neurones and glia in the CNS and PNS. Nearly all classes of neurones are produced in greater numbers during development, these are then significantly reduced during the cell-death periods. The cell death that normally occurs during these periods is mainly apoptotic. It is still a matter of debate why so many neurones are generated and eliminated shortly thereafter. Some knockout animals, with defective cell-death genes or overexpression of genes for apoptosis inhibitors, have significantly increased cell numbers in their CNS. Nevertheless, some of these animals have a normal life span with neuronal systems that appear to be normal[4–6]. Thus, the general hypothesis that CNS neurones compete for a limited amount of target-derived trophic factors and that those neurones with incorrect projections receive insufficient neurotrophic support and are then eliminated by apoptosis, cannot be true for the CNS in general. Rather, matching the numbers of afferent neurones with their target-space seems to be an exception and not the only fundamental role of neurotrophic factors in the CNS (Ref. 7).

After the physiological cell-death periods, neurones need to be maintained for the entire life span of an individual. Aging, neurodegenerative disorders or lesions of the CNS involve neuronal cell loss, which can occur as apoptosis or necrosis. In the latter case, energy depletion, toxic insults, hypoxia and other factors lead to cell swelling and disintegration of the cell membrane (exogenous cell death). The main elements of the apoptotic programme (i.e. controllers such as BCL2 or BAX and executors such as caspases and possibly other protease classes) are constitutively generated. This accounts for the onset of apoptosis during different forms of injury, even in cases where protein synthesis is blocked. However, in several types of lesions, apoptosis involves new transcription and translation of death-signalling proteins or death-related genes. During recent years it has become evident that there is a continuum, rather than a clear-cut difference, between both modes of cell death. Some features that were initially regarded to be specific for one form of cell death have been recognized to be common in both. Furthermore, cells can switch from one mode of cell death to another in response to varying intensities of the same insult and depending on the availability of energy substrates[8].

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