THE ANATOMICAL BASIS OF FUNCTIONAL LOCALIZATION IN THE CORTEX

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The functions of a cortical area are determined by its extrinsic connections and intrinsic properties. Using the database CoCoMac, we show that each cortical area has a unique pattern of cortico-cortical connections — a 'connectional fingerprint'. We present examples of such fingerprints and use statistical analysis to show that no two areas share identical patterns. We suggest that the connectional fingerprint underlies the observed cell-firing differences between areas during different tasks. We refer to this pattern as a 'functional fingerprint' and present examples of such fingerprints. In addition to electrophysiological analysis, functional fingerprints can be determined by functional brain imaging. We argue that imaging provides a useful way to define such fingerprints because it is possible to compare activations across many cortical areas and across a wide range of tasks.

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doi:10.1038/nrn893

Historically, there has been a long controversy concerning functional localization in the cortex. Franz and Lashley[1] were the first to devise an experimental method for tackling the question, making lesions in the cortex and testing their effects on the performance of behavioural tasks. Although experimental lesions had been made before, it was the use of psychological tasks that was crucial in these studies. Experiments of this sort led Lashley[2] to challenge the degree to which functions were localized in the cerebral cortex.

Lashley worked with rats, which have a lissencephalic brain, and he was not able to make lesions reliably in specific cytoarchitectural areas. It was not until the 1950s that lesions were placed in specific cytoarchitectonic areas in non-human primates[3,4]. These and subsequent studies supported a greater degree of localization than Lashley had been prepared to accept. It could be shown, for example, that lesions in inferotemporal cortex area 21 impaired visual-discrimination learning[5], lesions in the premotor cortex (area 6) impaired visuomotor associative learning[6,7], and lesions in the dorsal prefrontal cortex (area 46) impaired the learning of spatial delayed-response tasks[4,8]. Now that it is possible to locate lesions in the human brain using computerized tomography (CT) and magnetic resonance imaging (MRI), it is also possible to show similar dissociations between areas for human subjects[9,10].

It is a limitation of these studies that they attempt to derive the normal function of an area from the effects of damage to that area[11]. More recently, it has become possible to use functional brain imaging to compare activation patterns in different cortical areas when healthy human subjects perform specific tasks. The hope is that, by comparing tasks that differ in just one respect, it will be possible to identify the contributions made by particular cytoarchitectonic areas. For example, in an early study, Petersen *et al.*[12] compared verb generation with noun repetition, and showed a difference in activation of the ventral prefrontal area 47. By introducing the subtraction method, this study opened up the use of imaging for cognitive neuroscience[13]. Given the subsequent proliferation of functional studies that make use of neuroimaging, we think that it is time to re-assess what is meant by functional localization, and to try to provide a conceptual basis for the enterprise.

Connectional fingerprints

The operation that can be performed by an area is determined by its extrinsic and intrinsic connectivity, by the distribution of receptor types, and by the information-

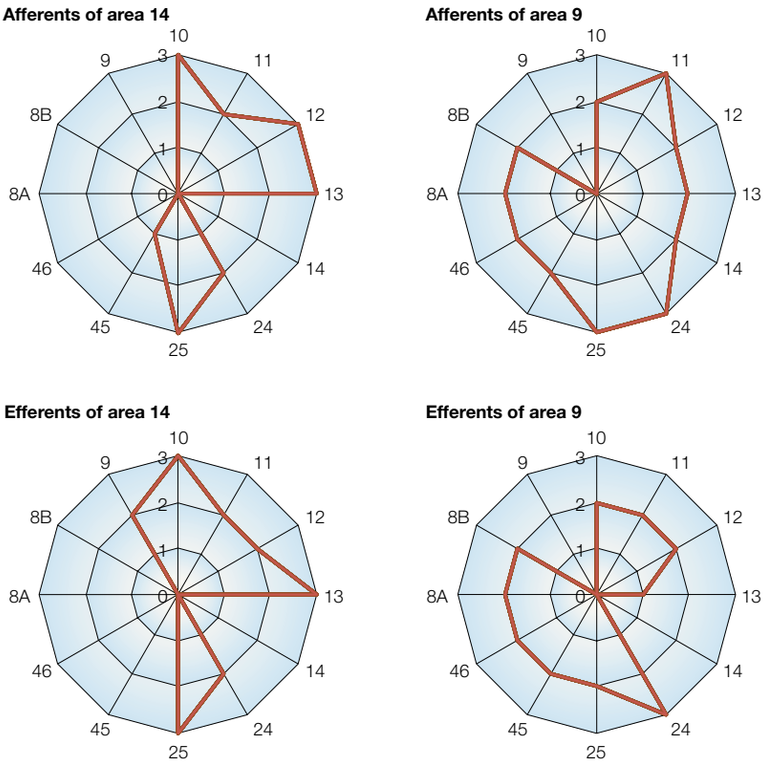

Figure 1 | **Diagram of anatomical fingerprints for two prefrontal areas — Walker's areas 9 and 14.** Afferent (upper row) and efferent (lower row) connections of Walker's areas 9 and 14, with other prefrontal areas that are identified by their cytoarchitectonic numbers, as designated by Walker[21]. The strength of any connection (rated as weak = 1, medium/ambiguous/unknown strength = 2, strong = 3) is shown by the radial distance. When visually comparing the figures for the two areas, it is necessary to ignore the direct connections between them. Based on data from REF. 20.

processing properties of the intrinsic neurons. The unique cytoarchitecture of an area might be an indirect reflection of these properties. For example, the division of layer IV in the striate cortex (area 17) into IVa, IVb, IVcα and IVcβ reflects the extent of the afferents from the lateral geniculate, and the separation of the magnocellular and parvocellular pathways. The existence of large pyramidal neurons — BETZ CELLS — in layer V of motor cortex reflects the extent of the efferent projections through the pyramidal tract and the importance of speed of conduction through this pathway. The number and definition of the cortical layers in the different prefrontal regions can be related to the laminar pattern of the connections[14].

Much less is known about the intrinsic connectivity of the different cytoarchitectonic areas than about their extrinsic connectivity. It has been reported that different cytoarchitectonic areas of the neocortex, with the exception of the striate cortex, have the same complement of neurons when counts are taken through a vertical slab[15]. Although the claim has been challenged, few data have been presented to refute it[16]. But we also know that different areas differ in the thickness of the laminae, and therefore in the number of pyramidal, stellate and other cell types. Moreover, the different cell types have different dendritic trees[17]. So, the different cytoarchitecture of different areas has consequences for processing within those areas.

However, here we propose that each cytoarchitectonic area also has a unique set of extrinsic inputs and outputs, and this is crucial in determining the functions that the area can perform. We call this unique set a 'connectional fingerprint'. The term fingerprint was first introduced by Hudspeth *et al.*[18] to describe the distribution of cell density across cortical layers in the human primary visual cortex. Subsequently, Zilles and colleagues[19] used it to describe the particular pattern of receptor architecture for each cortical region, as shown by the degree of binding for the different receptor types.

FIGURE 1 presents an example of two anatomical fingerprints. These are based on a meta-analysis of data for prefrontal regions in the macaque connectivity database CoCoMac[20]. The areas are designated according to the numbers given by Walker[21]. In these fingerprints, the strength of any connection (rated as weak = 1, medium = 2, strong = 3) is shown by the radial distance. For simplicity of presentation, the fingerprints include only the local connections between prefrontal areas; more detailed fingerprints could be produced by including the afferents from and efferents to other regions of the brain. It can be seen that area 9 and 14 share some connections. For example, both receive afferents from area 25 and send efferents to area 24. However, even when they have common afferents or efferents these might differ in strength. For example, the strength of the efferents to area 13 differs for these two areas. Last, there also connections that are unique to one area or the other. This is true of the afferents to area 9 from areas 8A and 8B, or of the efferents from area 9 to area 46. It is the overall pattern that distinguishes the two areas.

The hypothesis of unique connectional fingerprints has been supported by statistical analyses of cortical connectivity in primate[22] and feline cortex[23]. For example, Young[22] compared the connectivity of visual, auditory and somatomotor regions in the macaque cortex. A strong test of the hypothesis is provided by analyses that restrict their focus to areas from a single cortical region. For example, the recent analyses by Stephan *et al.*[20] and Kötter *et al.*[24] used data from CoCoMac to examine the connectional organization of subregions within the prefrontal cortex. Fortunately, the connectivity of different prefrontal regions has been well studied[25,26], and an extensive account of these data is available in CoCoMac. We have used these data to examine the hypothesis of unique connectional fingerprints, adapting the statistical analyses of Kötter and colleagues[24]. Methodological details have been reported elsewhere[20,24,27–29].

In our formal analysis, we used two independent multivariate techniques — MULTIDIMENSIONAL SCALING (MDS) and HIERARCHICAL CLUSTER ANALYSIS (HCA). These methods reveal similarities and dissimilarities between elements in a multidimensional feature space. Applied to the SPEARMAN CORRELATION MATRIX of the connectivity data, MDS and HCA provide intuitive visual representations of the relationships between cortical areas on

BETZ CELLS
Giant pyramidal neurons that are located in layer V of the primary motor cortex. Their axons project to the spinal cord, terminating directly on motor neurons.

MULTIDIMENSIONAL SCALING
A multivariate statistical method that provides a visual representation of the pattern of similarities between data sets. For example, given a matrix of similarities between various phenotypes, multidimensional scaling plots them on a map such that phenotypes that are perceived to be similar are placed near to each other, and those that are perceived to be different are placed far apart.

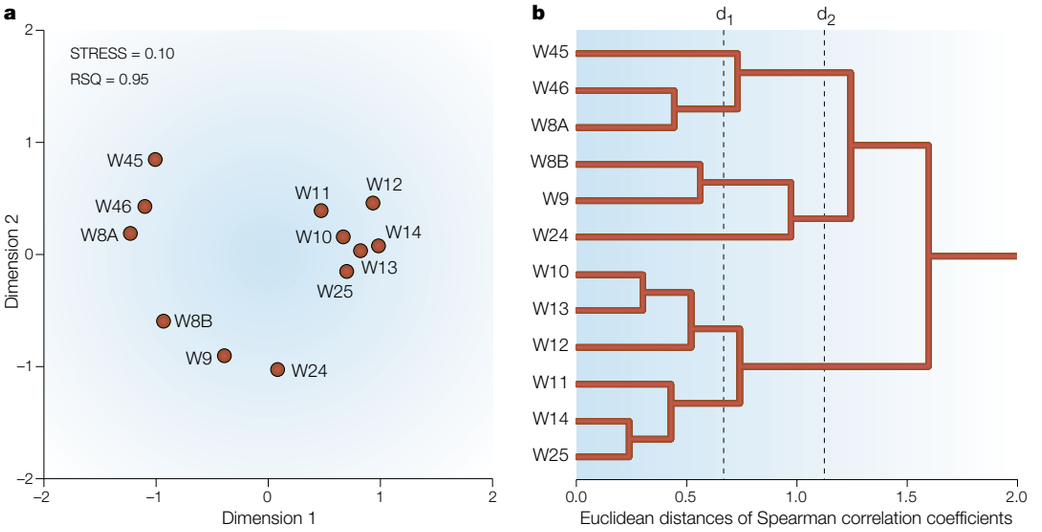

Figure 2 | **Analysis of prefrontal connectivity. a** | Multidimensional scaling creates a high-dimensional metric representation in which distances between elements optimally reflect the overall similarity between their properties; in this case, the connectional patterns of the cortical areas (identified by their cytoarchitectonic numbers, as designated by Walker[21]). Spearman correlation coefficients between the connectivity vectors of the individual areas were computed, and MDS was then applied to these correlation coefficients, with Kruskal's STRESS values to determine the goodness-of-fit. Values approaching zero denote a better fit. RSQ gives the proportion of variance of the scaled data that is explained by the distances computed by MDS. **b** | Hierarchical cluster analysis was applied to the same correlation coefficients between area-connectivity vectors using a Euclidean distance metric. Distances between areas are an inverse measure of the correlation between their connectional patterns. The fact that no two areas are merged at a distance of zero means that each of the prefrontal areas has a unique connectional fingerprint. The figure also shows that the definition of families of areas depends on the somewhat arbitrary choice of the threshold for similarity (see main text for details). Both parts of the figure are based on data from REF. 20.

the basis of the similarities of their connectional fingerprints.

MDS (FIG. 2a) arranges the prefrontal cortical areas in a sequence of lateral (45, 46, 8A), dorsal (8B, 9), dorsomedial (24) and orbitomedial (10, 11, 12, 13, 14, 25) areas. So, we find clusters of regions with varying degrees of resemblance. However, no two areas share the identical location, even after scaling similarities down to only two dimensions. This means that no two areas have exactly the same pattern of connections. This result is not trivial; although any sparse parcellation divides the cerebral cortex into areas with distinct characteristics, Walker's map[21] is based on cytoarchitectural rather than connectional distinctions.

The same message is conveyed independently by HCA. This procedure amalgamates the individual areas to groups on the basis of the similarities of their connectional fingerprints (FIG. 2b). Clearly, no two areas share the same pattern of connections. If any pair of areas did so, the distance at which the two areas merge would be zero. Compared with the MDS results, there are minor differences in the detailed arrangements (for example, areas 14 and 25 are the first to merge, but not the closest in MDS), but the groups of areas that emerge from HCA correspond exactly to the MDS arrangement.

To show that the validity of our conclusions is not restricted to the prefrontal cortex, a similar analysis has been carried out for the premotor cortex[27]. Whereas Brodmann[30] divided the prefrontal cortex into several different cytoarchitectonic regions, he defined the premotor areas as a single area — that is, area 6. However, on the basis of staining with cytochrome oxidase, it is possible to distinguish several subregions[31,32]. FIGURE 3 shows the anatomical fingerprints for areas F3 and F5 (REF. 27). These correspond to the supplementary motor area (SMA) proper and the ventral premotor area, respectively. As in FIG. 1, for simplicity, these fingerprints include only the local connections between the motor areas.

FIGURE 4a presents the results of MDS. Again, no two areas share the same space. The analysis distinguishes between motor cortex (F1), the medial premotor cortex (SMA and pre-SMA, F3 and F6), the dorsolateral premotor cortex (F2 and F7) and the ventrolateral premotor cortex (F4 and F5). FIGURE 4b shows the results of HCA. The same subdivisions result, but with the added information that there is a relationship between the dorsolateral and medial sectors, and between the ventrolateral sector and the motor cortex.

In the analysis of prefrontal and premotor areas, the pattern of connections has been studied using boundaries defined by either cytoarchitecture (prefrontal) or cytochrome oxidase staining (premotor). Kötter *et al.*[27] have used a formal method for comparing the classification of areas by their connectivity with the classification of areas on the basis of other criteria, such as receptor architecture. The same method could now be used to compare formally the classification of prefrontal areas by connectivity (FIG. 2a,b) with the classification obtained for these areas on the basis of cytoarchitecture[33].

HIERARCHICAL CLUSTER ANALYSIS
A multivariate method for solving classification problems. The object is to sort items into groups such that the degree of association is strong between members of the same cluster and weak between members of different clusters. In addition, this technique visualizes the hierarchical structure of similarity between all identified clusters.

SPEARMAN CORRELATION MATRIX
A matrix of so-called Spearman correlation coefficients, each of which represents a measure of association between two sets of rank-ordered measurements.

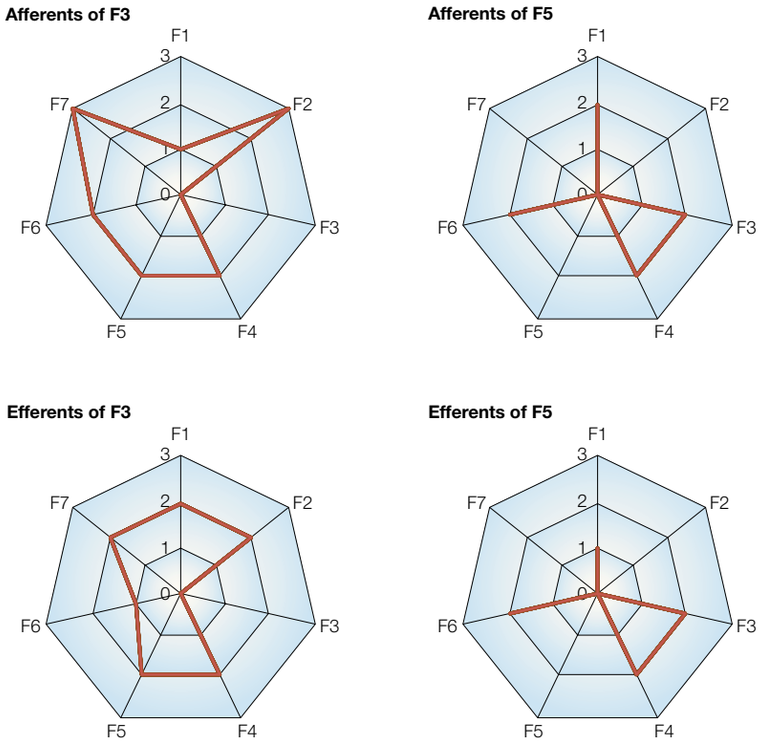

Figure 3 | **Diagram of anatomical fingerprints for two premotor areas — F3 and F5.** The upper row shows the afferent and the lower row the efferent connections of the supplementary motor area (F3), the ventral premotor area (F5) and other motor areas that are defined on the basis of staining with cytochrome oxidase[31,32]. The strength of any connection (rated as absent = 0, weak = 1, medium/ambiguous = 2, strong = 3) is shown by the radial distance. Based on data from REF. 27.

Connectional families

In functional systems, different areas share some of their inputs and outputs. For example, Selemon and Goldman-Rakic[34] have pointed out that there are similarities in the pattern of outputs of the parietal lobe area 7a and the lateral intraparietal area (LIP), and the prefrontal area 46 with which they are interconnected. They form part of the same distributed system. It is presumably the common connectivity patterns that lead to the functional co-activation of areas within this distributed system. For example, studies using 2-deoxyglucose[35], single-unit recording[36], positron emission tomography (PET)[37] and functional MRI (fMRI)[38] show co-activation of the dorsal prefrontal cortex and intraparietal cortex during a spatial working memory task.

We suggest the term 'family' for a cluster of areas that share a similar pattern of connections. We take the term from Zilles *et al.*[39], who noted that related areas within the motor system, such as the SMA and the pre-SMA, can be grouped into neurochemically similar families on the basis of receptor mapping. A formal proof of the existence of connectional families was provided by Young[22,40] for the macaque brain and by Scannell *et al.*[23,41] for the feline brain. Young[22] used MDS to distinguish between visual areas in the dorsal and ventral visual stream, and between the auditory system, somatosensory motor system and 'frontolimbic complex'. More recently, Hilgetag *et al.*[42] introduced optimal set analysis (OSA), a cluster analysis that is based on an evolutionary algorithm, to determine clusters of cortical areas on the basis of their anatomical connections. Similar clusters have been shown using data from STRYCHNINE NEURONOGRAPHY[43]. Applying several independent statistical approaches to these data on functional interactions, Stephan *et al.*[43] showed that these interactions are not equally distributed. Instead, they are clustered into three main groups of areas — sensorimotor, visual and orbito-temporo-insular clusters.

We have shown that, in the prefrontal cortex (FIG. 2b) and premotor cortex (FIG. 4b), it is possible to detect clusters of areas with a similar, although not identical, pattern of connections. However, it is important to note that there is no objective criterion for defining the size of a family. As shown in FIG. 2b, the threshold for defining 'families' of areas is arbitrary. For example, if one chooses d_2 (dashed line in FIG. 2b) as a similarity threshold, one finds exactly the same three groups of areas that were identified by MDS (FIG. 2a). On the other hand, if a stricter threshold is chosen (d_1 in FIG. 3), each of these three groups is broken up into two smaller clusters. We make the assumption that, for the purpose of functional localization, the more dissimilar their pattern of connections, the easier it will be to distinguish between the functions of areas.

Until now, the standard for functional localization has been the double dissociation[44]. A lesion in area X should have an effect on task A but not on task B, whereas a lesion in area Y should have an effect on task B but not on task A. So, removal of superior temporal area 22 impairs the performance of auditory but not visual discriminations, and removal of inferior temporal area 21 impairs the performance of visual but not auditory discriminations[5,45]. Similarly, removal of parieto-occipital cortex impairs the ability to choose spatial locations on the basis of a landmark, but has much less effect on the performance of visual discriminations[46,47]; and removal of the inferotemporal cortex impairs the performance of visual discriminations, but has much less effect on the performance of the landmark task[47]. Removal of dorsal prefrontal area 46 leads to a very severe impairment on spatial delayed-response tasks, but does not impair the performance of visual discriminations[4,8,48]. Correspondingly, lesions in inferotemporal area 21 impair the performance of visual discriminations, but do not impair performance on delayed-response tasks[5,49].

These dissociations occur between areas with a very different pattern of connections — that is, between areas belonging to different large families in parallel systems. For the above examples, these are the visual and auditory streams, the dorsal and ventral visual stream, and the ventral visual stream and the extension of the dorsal stream into the prefrontal cortex[50]. It has been more difficult to find double dissociations within streams, although they can be found. For example, Buckley *et al.*[51] were able to show that lesions in inferotemporal area 21 impair the performance of colour discriminations but

STRYCHNINE NEURONOGRAPHY
A method in which (potentially polysynaptic) anatomical connections are identified by applying strychnine to one area and then recording spikes in other areas.

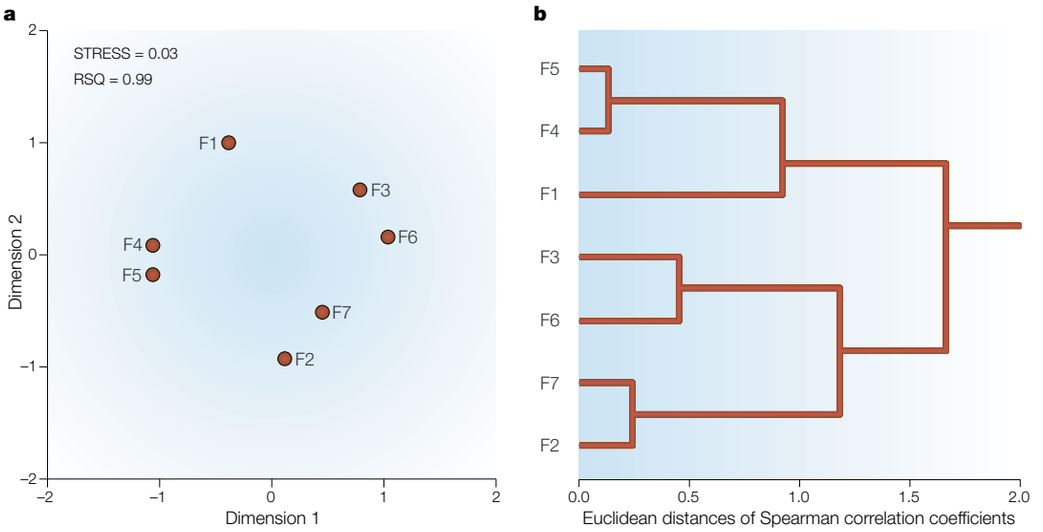

Figure 4 | **Analysis of premotor connectivity.** Areas are defined on the basis of staining with cytochrome oxidase[31,32]. **a** | Analysis using multidimensional scaling (see legend to FIG. 2a). **b** | Analysis using hierarchical cluster analysis (see legend to FIG. 2b). The fact that no two areas are merged at a distance of zero means that each of the motor areas has a unique connectional fingerprint. Both analyses are based on data from REF. 27.

not the recognition of objects, whereas lesions in the perirhinal cortex had the opposite effect. In general, the more connections two areas share, the more difficult it is to find double dissociations between them. Young *et al.*[11] have discussed at length the problems associated with making functional interpretations on the basis of double dissociations, but have shown formally how knowledge about connectivity can help in interpreting the effects of lesions.

Proportions of functional cell types

A crucial question is the extent to which differences in the patterns of activity of cell firing in different areas are determined by differences in extrinsic connectivity of these areas. Unfortunately, we do not have adequate information on intrinsic connectivity, which also differs between areas. However, the extrinsic connections must set a limit for the processing that can occur within the area. This idea has been previously expressed by Young[22], who stated that "the place of an area in the cortical macro-circuitry might determine in large part the area's functional properties".

The analysis is clearly easier the nearer we are to the sensory inputs. For example, reviewing physiological studies of visual areas V4 and V5, DeYoe and Van Essen[52] found that 85% of cells in V5 showed direction selectivity, whereas only 5% of cells in V4 did so. By contrast, 50% of the cells in V4 showed neuronal activity that was selective to wavelength, whereas no cells had been found in V5 that did so. In both areas, there was orientation-selective activity, accounting for 75% of the cells in V5 and 50% of the cells in V4. The difference in the pattern of activity can be directly related to the visual inputs to these areas from the magnocellular and parvocellular pathways[53]. However, even in the case of early visual processing, there is considerable complexity in trying to account for the processing of form or motion in terms of the detailed anatomy of the pathways[53,54].

Clearly, the problem of relating the physiology to the extrinsic connections becomes much more intractable the further one is from peripheral sensory inputs. If one compares any two areas, both will have a very large number of inputs, and the two areas might be connected through one or two synaptic relays[22]. Consider, for example, the premotor cortex, the SMA and the motor cortex. These structures lie within the somatomotor system that was defined by Young[22] on the basis of multivariate statistics. They share many inputs and outputs, and are interconnected[55–57].

It is therefore not surprising that cells can be found in these three areas that fire in association with the same task events. For example, one can find similar cell types in the SMA and the motor cortex[58–61], in the premotor cortex and the motor cortex[62,63], in the pre-SMA and the SMA[64,65], and in the premotor cortex and the SMA[66,67]. However, the proportions of cells with activity that is related to particular tasks or task components differ between these areas. For example, Shen and Alexander[62,63] compared the activity of cells in the premotor and motor cortices. They distinguished between cells that fired in relation to the target location and cells that fired in relation to the direction of the movement. There were more 'target' cells in the premotor than in the motor cortex, and more 'direction' cells in the motor cortex.

The crucial question is whether it can be shown that differences in the proportions of functional cell types between areas relate to their different inputs or outputs. FIGURE 5 presents a worked example from Mushiake *et al.*[66]. The comparison was made between the ventral premotor cortex (F5), the SMA (F3) and the motor cortex (F1). The monkeys were trained on two tasks. In the first, they performed a sequence of three movements

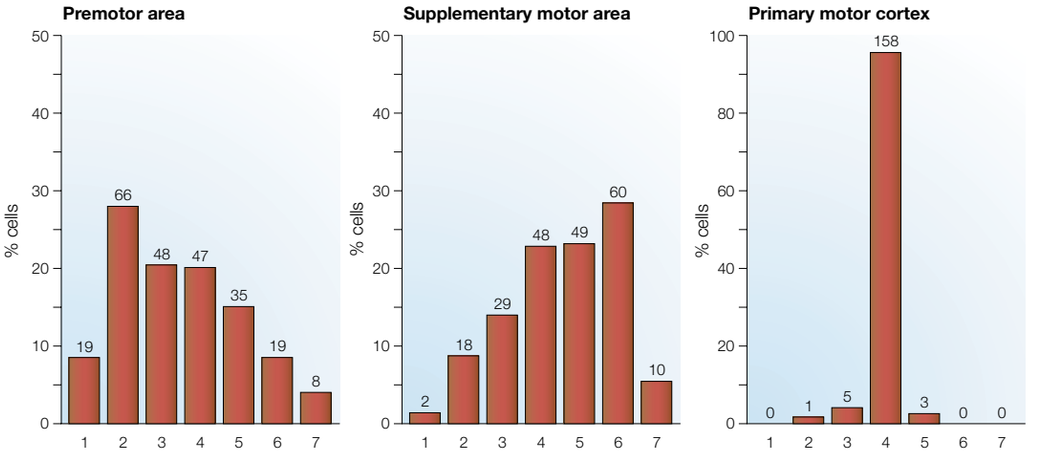

Figure 5 | **Cell firing associated with a pair of visually and memory-guided tasks.** Distribution of cells in ventral premotor area F5, supplementary motor area F3 and motor cortex (F1), classified according to the degree to which they were active in association with the visually guided sequence (VS) or the same sequence performed from memory (MS). 1 = exclusively related to VS, 2 = much more related to VS, 3 = more related to VS, 4 = equally related to VS and MS, 5 = more related to MS, 6 = much more related to MS, 7 = exclusively related to MS. Reproduced, with permission, from REF. 66 © 1991 The American Physiological Society.

as instructed by visual cues. In the second, they performed the same sequence from memory. The figure shows the percentage of cells that fall into one of seven categories, with the actual number of cells above each histogram; the analysis is for the movement period, but similar results were found for the pre-movement period. Category 4 was given to cells that fired equally on the two tasks, category 1 to cells that fired exclusively on the visually guided task, and category 7 to cells that fired exclusively on the memory guided task. The other categories are for activity that was associated more with one task than the other.

As shown previously, MDS of connectivity data places the motor cortex (F1) on its own among the motor areas (FIG. 5). In the motor cortex, almost all the cells fired equally on the two tasks (category 4). In other studies, it has also been shown that, when monkeys perform sequences of movement, cells in the motor cortex tend to fire in association with the execution of individual movements[61,67]. FIGURE 5 also shows that, even in the premotor cortex and the SMA, many cells also fire equally (category 4) irrespective of whether the sequence is guided by visual cues or performed from memory.

However, the overall pattern differs between the areas. MDS (FIG. 4a) and HCA of connectivity data (FIG. 4b) distinguish between the ventrolateral premotor cortex (F5) and the SMA (F3). In area F5, the greater proportion of cells fired in association with sequences guided by visual cues (categories 1–3), whereas in area F3 the greater proportion of cells fired in association with sequences performed from memory (categories 5–7). There was a statistically significant difference between the overall pattern for the motor cortex and those for other areas, and between the patterns seen for F5 and F3 (REF. 66). Other studies have also shown that many cells in F3 fire when monkeys perform sequences from memory, with many cells firing differently according to the specific sequence that is performed[61,67].

The question is whether the differences in the overall pattern relate to differences in the pattern of inputs. The anterior intraparietal area (AIP) projects to F5, but not to F3 or F1 (for a review, see REF. 68). Many cells in AIP are visual in the sense that they fire when monkeys observe objects that they are going to grasp[69–72]. F5 also receives a heavy input from thalamic nucleus X (REFS 73–75), which in turn receives input from the dentate nucleus of the cerebellum[75]. Van Donkelaar *et al.*[76] recorded in nucleus X when monkeys were performing visually guided or internally generated movements, and found that most of the cells fired exclusively or preferentially in association with the visually guided task.

In the study by Mushiake *et al.*[66], there was also a tendency for cells in the dorsal premotor cortex (F7) to fire in association with the visually guided task. Furthermore, in progressing anteriorly from area 4 through dorsal area 6, there was a progressive increase in the proportion of cells that fired in association with the presentation of visual cues[77]. There are projections to the anterior part of dorsal area 6 (F7) from the middle intraparietal area (MIP) in the dorsal bank of the intraparietal sulcus[78], and there are visual responses in MIP[79]. There is also a decrease in the proportion of cells that fire at the time of movement as one progresses anteriorly from area 4 through area 6 (REF. 77). Motor cortex and the posterior part of the dorsal premotor cortex (area F2) receive the somatic input from parietal area 5 (REF. 68). These findings indicate a possible relationship between anatomical inputs and the electrophysiological data.

Functional fingerprints

The above examples provide informal support for the proposed relationship between connectional fingerprints and the functional properties of areas. To provide more formal support, we have analysed the data of Humphrey and Tanji[80]. These data give the response properties of cells in the motor cortex, the SMA, the

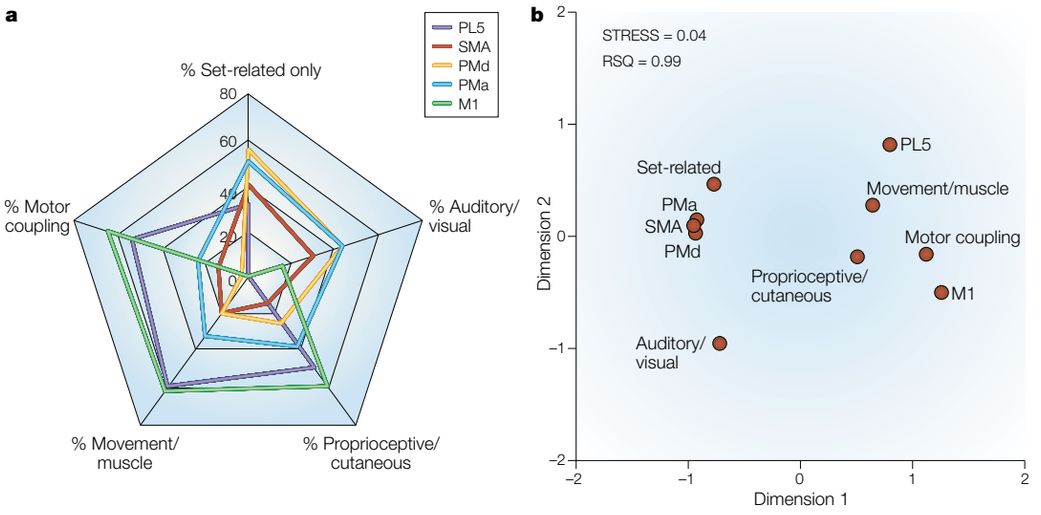

Figure 6 | **Functional fingerprints for five motor areas. a** | For each area, the radial plots give the proportions of cells that show set-related discharge only, that are responsive to auditory/visual stimulation, that are responsive to proprioceptive/cutaneous stimulation, that show specificity in their movement/muscle field, or that are coupled to motor variables. M1, motor cortex area 4; PL5, superior parietal area 5; PMa, post-arcuate premotor cortex (part of the ventral premotor area); PMd, dorsal premotor cortex; SMA, supplementary motor cortex. **b** | Multidimensional scaling (MDS) of these data. The unfolding model was used, which treats proximities between cortical areas and neuronal response properties as a submatrix of the regular MDS matrix[128]. M1 cells are the most strongly related to motor coupling, whereas premotor areas preferentially show set-related activity. Activity in parietal area 5 is mainly movement or muscle related. RSQ gives the proportion of variance of the scaled data that is explained by the distances computed by MDS. Both parts of the figure are based on data from REF. 80.

dorsal premotor cortex and the arcuate premotor area, which forms part of the ventral premotor cortex. The analysis includes the superior parietal cortex (area 5), which makes direct connections with the motor cortex[68]. Humphrey and Tanji[80] analysed published studies to rate cells in these five areas in terms of their discharge properties. There are five scales: first, the proportion of cells that show SET-RELATED ACTIVITY only; second, the proportion that are responsive to auditory/visual stimulation; third, the proportion that are responsive to proprioceptive/cutaneous stimulation; fourth, the proportion that show specificity in their movement/muscle field; and fifth, the relative coupling to motor variables.

FIGURE 6a shows the data for each area in the form of 'functional fingerprints'. We use this term to describe a polar plot in which the data are the proportions of active neurons with given response properties. These response properties can be assessed over a series of different tasks (such as memory-guided or visually guided sequences) or in terms of other properties of cellular discharge (such as set-related or muscle/movement fields). The same format is used for these plots as for the anatomical fingerprints, the difference being that the rating is for the proportion of cells with specific properties, rather than the strength of the connections. Parietal area 5 and the motor cortex are similar in their fingerprints, and they differ in their fingerprints from the three premotor areas. Because the ratings of Humphrey and Tanji[80] resulted from a meta-analysis of the literature, and not from a single study in which all five measures were obtained, we should be cautious in drawing any other firm conclusions from the fingerprints.

To allow a comparison with the connectional fingerprints for the motor areas, we have analysed the data presented by Humphrey and Tanji[80] using the unfolding model of MDS. FIGURE 6b presents the results, which can be compared with those shown in FIG. 4 — the statistical analyses of anatomical connectivity. The SMA in FIG. 6 corresponds roughly to F3 in FIG. 4, arcuate premotor area in FIG. 6 to F5 in FIG. 4, and dorsal premotor cortex in FIG. 6 to F2/F7 in FIG. 4. In both figures, motor cortex area 4 (M1) is separate from all premotor areas. In FIG. 6, area 5 is closest to motor cortex M1, and there are direct connections from area 5 to M1 (REF. 68). The figure distinguishes between areas that are strongly related to movement and areas that are responsive to visual and auditory stimuli and show preparatory activity. The statistical analyses would have distinguished further between different premotor areas had data been included for other functional comparisons, such as those made by Muskiake *et al.*[66] (FIG. 5).

Brain imaging

There are practical problems in acquiring data to construct functional fingerprints: it is difficult to record electrophysiologically from more than one area at once, and it takes time to train the animals on the different tasks. It is therefore not practical to collect electrophysiological data on a wide range of areas over a wide range of tasks. Comparisons are made on the basis of either a few tasks in one experiment (as in FIG. 5) or an analysis across experiments in the literature (as in FIG. 6a). The chances of distinguishing between areas in their pattern of activity should increase in proportion to the number of sampled tasks. Connectional fingerprints are based

SET-RELATED ACTIVITY
Neuronal activity that reflects the behavioural 'set' of the animal, which can include information about a planned movement or about the state of readiness of the animal.

on a very large database, whereas functional data for the macaque are based on a slim one.

This is of consequence. Consider the comparison of two interconnected regions — dorsal prefrontal cortex and the ventral bank of the intraparietal sulcus. If we test monkeys on an oculomotor delayed-response task, the proportion of cells that fire in association with the cue, the delay period and the response are similar for these two areas[36]. But we know that lesions in these two areas have different effects: lesions in the dorsal prefrontal cortex severely impair performance on spatial delayed-response tasks[4,8], whereas parietal lesions do not[81]. A proper comparison of the cell populations in these two areas requires that the monkeys be tested over a wide range of tasks, not just on working memory tasks.

In contrast to single-cell recording, functional brain imaging is a whole-brain method, and this makes the comparison of many areas more feasible. As it can be used in humans, it takes little time to convey the task instructions, and it is therefore possible to sample many tasks. For imaging data, a functional fingerprint would consist of profiles of activations over a wide range of specific task comparisons.

In fMRI, the amplitude of the blood oxygen level dependent (BOLD) signal is proposed to be a function of the proportion of cells in an area that are active when subjects perform the particular task, and the firing rate of the cells[82–84]. By simultaneously recording electrophysiological signals and the BOLD signal in macaques, Logothetis *et al.*[85] have shown that the relation between neural activity and BOLD signal might be more complicated. The local field potential, which might reflect synaptic input to neuronal dendrites and somata, was a better predictor of the BOLD signal than multiunit activity, which largely represents action potentials. So, Logothetis *et al.*[85] concluded that "the BOLD signal reflects the input and intracortical processing of a given area rather than its spiking output". Other authors have questioned this conclusion, arguing that the neural mechanisms that underlie the production of local field potentials and multiunit activity are not entirely different but have considerable overlap[86]. Whatever the exact causal relationship between neural activity and the BOLD signal, it is clear that the relationship is tight.

It is, of course, possible that information be carried by the synchrony of firing of different cells. However, on the basis of computational modelling, Chawla *et al.*[87,88] have shown that mean firing rates and the synchronization of activity between different cells are tightly coupled. This relationship held true in almost the entire domain of the model's parameter space, both under 'steady state' conditions and for stimulus-evoked transients, and for different types of anatomical architecture and functional dynamics. These authors therefore suggested that the BOLD signal in fMRI not only reflects mean firing rates, but is also sensitive to changes in synchronous coupling.

There is, however, an important difference between single-unit recording and imaging. If one records from single cells, it is possible to derive population vectors. In the motor system, these vectors represent the net directional signal of the population of cells, in which the cells have votes[89,90]. Furthermore, one can show a shift in the vector of the population response as learning proceeds[91,92]. The difference is that the BOLD signal, reflecting the population response, has amplitude but no direction. This means that it is not possible, for example, to use fMRI to do the experiment of Shen and Alexander[62,63] in which they distinguished cell activity that was related to the targets of movement or to the direction of movement for the whole population. The BOLD signal would be the same for all directions.

Imaging makes it possible to carry out meta-analyses across studies. Whereas the absolute amplitude of the activations is difficult to compare across studies, it is easier to test whether tasks of type X lead to significantly greater activation in area A than do tasks of type Y. For example, both Paus and colleagues[93,94] and Duncan and Owen[95] collected studies that manipulated experimentally high versus low processing demands. They were able to show that the anterior cingulate cortex[93,94] and dorsal prefrontal cortex[95] are more active the greater the task difficulty and the processing demands. Analyses of this sort will be furthered by the development of databases of functional data from brain imaging studies[96].

Relating functional to anatomical fingerprints

One of the goals in neuroscience is to establish comprehensive and quantitative structure–function relationships across all levels of brain organization. A large number of variables would be required for a complete model of brain architecture and dynamics, and measuring these variables simultaneously and in real time is impossible. It is therefore essential that relatively simple metrics for brain architecture and dynamics be found to allow a sufficiently accurate description of the brain as a dynamic system[97].

We believe that connectional and functional fingerprints, as defined here, provide useful measures for this purpose. Anatomical connectivity fundamentally constrains effective connectivity — that is, how distinct brain structures causally influence each other at both the synaptic and population levels[98]. Effective connectivity is fundamental for the principles of brain dynamics, including population rates and synchrony[97], and is the most likely direct determinant of functional fingerprints, as defined here. So, connectional fingerprints are linked with functional fingerprints through effective connectivity.

We do not claim to have provided a formal proof of the relationship between anatomical and functional fingerprints. This would require the investigation of large sets of connectional and functional data for various cortical areas. A pioneering step in this direction has been made by Scannell and co-workers[99]. They predicted the likely responses of cells in the anterior ectosylvian visual area of the cat to moving gratings and plaid stimuli. Their prediction was made on the basis of a multivariate analysis of a large database that comprised the entire network of feline cortico-cortical connections[23].

Subsequently, they confirmed their predictions by single-unit recordings. Their approach has recently been continued by Burns and Young[100], who also used a large database, and mathematically analysed on this basis the connectivity of hippocampus-related structures in the rat. They found good agreement between the connectional organization and known physiological properties of neurons in the various areas.

What we now need are formal analyses of connectional and functional fingerprints for the same cortical areas and in the same species. One methodological problem is that these two sets of data can be on different scales: connectivity data are on an ordinal scale, whereas electrophysiological data are on a ratio scale. Recently, a mixture of correlation analyses and multivariate techniques has been suggested to deal with this type of problem[27]. Briefly, the principle of this approach is to compute similarity profiles in each data modality by applying scale-dependent cross-correlation techniques to the feature vectors of all areas. The structure of the resulting correlation matrices can then be compared qualitatively by multivariate classification techniques such as MDS or HCA. In addition, MULTIPLE CORRESPONDENCE ANALYSIS (MCA) can be used to determine the overall classification of areas on the basis of the combined data sets. In addition, this method can show the correspondence between variables from different data modalities. Further advances towards a quantitative assessment of the direct relationship between data sets can be derived from the GENERAL LINEAR MODEL — that is, multivariate analysis of covariance or canonical correlation analysis[101]. Alternatively, INFORMATION THEORY could be used to quantify directly the degree of mutual information between different data sets[102].

So, it should be feasible to test the hypothesis that we have put forward in this paper. We suggest that it would be most practicable to attempt the task for the visual areas, and to collect the functional data by brain imaging. This would be done best in the macaque, in which both detailed information on anatomical connections and sophisticated fMRI technology are available[85,103]. The functional data could also be collected for the human brain, although this would introduce the added problem that assumptions have to be made about the correspondence of connections in the human and macaque brain. We have very little direct information, other than from studies of anterograde degeneration[104], about the connections of the human brain[105]. It is not yet clear to what extent DIFFUSION-WEIGHTED IMAGING[106–108] will be able to discriminate the fine details of anatomical connections that can be observed using tracing methods. For the time being, despite the uncertainty as to how well identical cytoarchitecture predicts functional equivalence, the inputs and outputs of areas that are activated in imaging experiments on human subjects must be inferred from the connections of areas with similar cytoarchitecture in the macaque brain[109].

This means that one must be able to identify the cytoarchitectonic area in which there is activation in the human brain. The problem can be solved by producing a probability atlas that incorporates data on the cytoarchitecture of a group of brains, and therefore provides the probability that an activation is localized in any particular area[110,111]. Information of this sort is available for only some regions, such as the primary somatosensory cortex[112] and Broca's area[113], and it will be a while before data are available for the entire brain.

These problems are perhaps of less concern for studies of the early visual areas. Much progress has been made in establishing homologies between visual areas in the human and macaque brain[114–117], and it is unlikely that there are significant differences between the connectivity of these areas in these species. However, the most reliable method would be to compare in macaque monkeys functional data from MRI[103,118] with connectional data. The connections of visual areas have been much researched and are well described[40,119].

It is feasible to present a wide variety of visual stimuli in the same fMRI experiment. Stimuli could be presented that make demands not only on the low-level processing of aspects such as colour, orientation and motion, but also on higher-level processing, as in the perception of objects[120,121], faces[122], aftereffects[123] and illusions[124]. The practicality of presenting a wide range of visual stimuli during a single fMRI session has already been shown. The results of such studies can be seen in Orban *et al.*[125], Sunaert *et al.*[126] and Moore and Engel[127]. So, by using the statistical methods described above, it should be possible to determine functional fingerprints of the various visual areas, and to relate them to connectional fingerprints, such as those as documented in the CoCoMac database[20].

Conclusions

Here, we have spelled out what many neuroscientists probably believe already. However, we hope that we have clarified the necessary stages of the argument, made it clear where we have relevant evidence, and indicated what evidence should be collected to establish the last stage of the argument.

The paper has made five claims. First, that each cytoarchitectonic area has a unique connectional fingerprint; we have provided worked examples for prefrontal and premotor areas using the CoCoMac database. Second, that there are families of areas that share a resemblance in their connections; again, we have provided examples for prefrontal and premotor areas using CoCoMac. Third, that the proportion of cells that fire in association with different tasks or task events differs between areas; areas have their own functional fingerprints. We have provided examples for the premotor areas. Fourth, that the differences between these functional fingerprints are determined by the extrinsic and intrinsic connections of these areas. Last, that imaging will be a useful tool for detecting functional fingerprints. Carrying out fMRI studies on the many areas of the visual system could allow a formal test of the relationship between functional and anatomical fingerprints.

MULTIPLE CORRESPONDENCE ANALYSIS
A method that aims to explain the relationships between multiple variables that are identified on identical or different measurement scales, and may include categorical data.

GENERAL LINEAR MODEL
A general mathematical framework from which many commonly used statistical procedures (for example, analysis of variance) are derived.

INFORMATION THEORY
A scientific discipline that is concerned with mathematical laws underlying systems that transmit, store and process information. It also deals with the quantitative measurement of various types of information.

DIFFUSION-WEIGHTED IMAGING
A magnetic resonance imaging method that makes use of the variability in the random movement of water molecules in nervous tissue, which is restricted by cell bodies, blood vessels, axon bundles and other structures. Two opposite magnetic field gradients are applied. The magnetic spins will be de-phased by the first gradient and, because of water diffusion, the second gradient will not completely re-phase them. As the directionality of diffusion is highly ordered in white matter, the spatial orientation of the bundles can be reconstructed.

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Acknowledgements
This work was supported by the Wellcome Trust (R.E.P.), the Brain Research Trust (K.E.S.) and the Deutsche Forschungs-gemeinschaft (R.K.). We are grateful to C. Hilgetag and K. Friston for their comments on the manuscript before submission, and to A. Duggins and W. Penny for helpful statistical discussions.

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