



The Functional Architecture of the Brain

Author(s): Richard S. J. Frackowiak

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The Functional Architecture of the Brain

INTRODUCTION

WE LIVE IN AN AGE in which people are increasingly accepting the proposition that our emotional, intellectual, and indeed biological lives are determined uniquely by our brains. Nevertheless, as though we were yet in a time when the seat of the soul was thought to be the heart or the pineal gland, we continue to discuss our emotions, intentions, and acts of will in terms that deliberately eschew any reference to the biology of the brain. A popular intellectual pursuit of our time is that loosely termed “neurophilosophy,” which attempts to formulate ideas about our humanity by reconciling biological facts about the brain with abstract and historical concepts about behavior. There are a number of reasons why this program has proceeded slowly. A major limitation, imposed by a lack of knowledge, has been the formulation of attributes of human behavior in biological and especially evolutionary terms. A second, related limitation has been our relative ignorance of the physiology and biochemistry of the brain, even of its functional anatomy. This technical impotence has been reversed with the introduction of powerful noninvasive brain monitoring methods. We now have the ability to collect data about how our brains produce all the complex facets of human behavior. It is my belief that, as a result, we will develop a novel, organic view of conscious life—banishing to oblivion endless and essentially

Richard S. J. Frackowiak is Professor of Neurology at the Institute of Neurology, University College London.

specious discussions about whether the brain is capable of investigating itself.

That this enterprise is of paramount importance in modern society is beyond debate. As our populations age and our awareness increases about degenerative diseases that lead to progressive destruction of the personality and humanity of individuals, we confront the fact that we must understand the brain better to have any hope of counteracting the individual and social impact of these diseases. There are those who are frightened of this perspective. The possibility that one day we might be manipulated by malevolent forces through an improved knowledge of brain mechanisms worries scientists and nonscientists alike. But the manipulation of social conscience and individual aspirations is already a fact of life. The impact of images through film and television, sound through recordings and radio, propaganda through the popular press, and indeed ideas through literature are all examples of the modification of human thought and feelings that have their impact on individuals through common brain mechanisms. Why a better knowledge of how our brains are functionally organized would result in an increase of malevolent influences on behavior is not obvious. Indeed, to many the opposite might seem more likely. Such issues, however, need to be addressed when knowledge is ours—and not in a climate of ignorance.

Why do we know so little about the functional architecture of the human brain in comparison with other organs of the body, such as the kidney, liver, and heart? The answer to this legitimate and somewhat puzzling question is almost mundane: The brain—like these other organs apparently homogeneous in composition, at least to the naked eye—is much less readily accessible in life. The average brain weighs approximately 1.4 kilograms and is contained within a bony and relatively impenetrable box, the skull. More problematically, the removal of pieces of tissue during life for examination by microscopy and other anatomical and vital techniques can cause impairments of behavior that make such biopsies ethically unacceptable. The science of brain function has therefore largely depended upon inferences made from observations of abnormal behavior in patients and subsequent correlations with the site and size of

damage determined from the brain in postmortem examinations. Though remarkably fruitful over the last 120 years in generating hypotheses about how the brain is functionally organized, there is a weak assumption in this approach. Conclusions depend upon the idea that the human brain is composed of functionally discrete, separable modules, which if removed will leave behind the remaining parts of the brain with their functions relatively unchanged. This assumption is now known to be false in certain circumstances. The damaged brain, just like the normal learning brain, can adapt and reorganize functionally. For example, clinical experience shows that patients with paralysis resulting from brain strokes may show spontaneous recovery of function for many months following an initial lesion. Likewise, regions of the brain that receive sensory signals from one body part may accommodate signals from other body parts under appropriate circumstances.

The new noninvasive techniques for monitoring brain function are providing vast collections of new data about human brain organization—so vast that a significant chapter in the history of our self-understanding is being opened. This chapter began in 1972 with the invention of computerized tomography, or the CT scanner, which offered researchers the ability to reconstruct images of a body in transverse sections. These scanners used x-radiation to generate images of the anatomical structure of the brain with remarkable clarity and without necessitating the physical penetration of the skull. The basic principles of scanning, pioneered by Hounsfield and McCormack (who shared the Nobel prize for their work), were rapidly applied in the mid-1970s to the detection of minute quantities of chemicals rendered visible to scanners by tagging with radioisotopes. Such chemicals could be used to follow vital pathways in the brain using a technique known as positron emission tomography (PET), so called because positron-emitting radioisotopes are used for the tagging. For physical reasons associated with the way such isotopes disintegrate and how the emitted radiation is detected, high reliability can be accorded to PET scan images. The images of brain function generated in this way can be matched with anatomical scans, thus providing a means to examine brain function in life.

There have been enormous technical advances in the performance of scanning machines over the last ten years, and new technologies have joined the arsenal. This essay will review the types of information about brain function that are being obtained. To anticipate somewhat, it can be claimed at present that changes in brain activity associated with pure thought, emotion, and cognitive processes are readily and reproducibly measurable. We are being provided with much new data about how our organ of cognition is functionally organized. In short, our brains are now able to reflect upon themselves using rigorous scientific methods and instrumental forms of measurement.

THE AIMS OF NONINVASIVE HUMAN BRAIN MAPPING

Imaging neuroscience attempts a description of how the brain works at the level of brain systems, that is, functionally segregated populations of nerve cells. The brain looks similar over its entire surface (the cortex), but there are variations in the disposition of nerve cells and of layers of cells in the cortex. These differences have been associated with functional specializations in the cortex, but it has been difficult to identify relevant variations because of a paucity of methods for defining them in detail. Brain areas are activated differently during different behaviors. The functional organization of the brain can therefore be described in terms of the relationships between populations of nerve cells, which themselves may be organized into interacting networks and integrated functional systems. This method of description at the systems level addresses how brain functions arise from the physical structure of the brain. It allows us to ask meaningfully a far broader range of questions than was ever before imaginable: How are primary sensations, such as touch and vision, processed by the human brain? Where are the resultant nervous signals mapped? How are percepts generated, recognized, named, and used to guide subsequent behavior? How do patterns of neural activity in certain brain areas that represent evoked sensations interact with brain areas where patterns of neural activity cause muscles to contract and generate movement? What is the cerebral basis for cognitive functions such as memory, language, and emotion? Are they the result of activity

in restricted and highly specialized brain areas, or do they depend on interactions between a number of brain areas with more basic or modular functions?

Early sensory input to the human brain (except for the sense of smell) and late motor output areas are organized as sets of separate maps in the cerebral cortex. That much has been known for many years from neurology and animal studies. The limitations of patient studies have been discussed already. Despite the progress they have made possible, it is unclear how far deductions based on experimentation with nonhuman primate brains can be assumed to be true for the brains of humans. Can rules governing functional brain organization determined in one species be transferred to another? There are obvious changes in the size of the brain between species. Certain functions—for example, spoken language and silent speech—are apparently unique attributes of the human brain; certain areas (such as the frontal lobes) are greatly developed in comparison with even our closest evolutionary relatives in the animal kingdom. This observation implies an addition of cortical areas and of specializations with evolution. A wider understanding of the implementation of a function such as language in the human brain may, through comparative paleontological study, provide a clue as to how this complex means of communication evolved and what its biological antecedents were.

Nerve cells (neurons) are grouped together in the brain and communicate with each other by conveying signals in time-dependent patterns (or codes) with an enormous amount of divergence and convergence of signals between them. This organization can be described at various levels or magnifications, both in space and time. Neurons, neuronal groups, and large-scale functionally homogeneous neuronal populations represent different spatial levels of brain organization. Brain electrical activity can last from milliseconds to seconds. For example, an action potential, the basic unit of electrical signal transmission in the brain, or transmission across the connection between nerve cells (the synapse) last a few milliseconds; the evoked potential, an expression of integrated electrical activity from the cerebral cortex, is measured in hundreds of milliseconds; the readiness potential and the delta wave are evoked and spontane-

ous brain signals that are recorded with electroencephalography (EEG) and last seconds. These different temporal levels of organization have been brought within the range of measurement by new noninvasive techniques, so that a systematic analysis of both the spatial and temporal functional architecture of the human brain is now possible.

DESCRIBING THE BRAIN'S ANATOMY AND FUNCTION

Using CT scanning, it is possible to image the anatomical arrangement of living human brain tissues by capitalizing on the differential ability of such tissues to attenuate X rays directed through them. CT scanning generates structural images, but the contrast between gray and white matter (containing, respectively, the neurons and the connections between them) is limited by their similar capacity to attenuate X rays. Magnetic resonance imaging (MRI) can generate a broad variety of different structural images of the brain. These images are generated by altering scanning characteristics to sensitize the pictures to differences between gray and white matter. The precision of anatomical information that can be obtained, combined with a lack of dependence on ionizing radiation, makes MRI the present method of choice for anatomical studies. Images can be shown as slices through the brain in any desired orientation. Alternatively, images can be rendered by a computer to provide surface pictures of the cortex of the brain, with its valleys (sulci) and folds (gyri). The resolution normally achievable with comfortable scanning times is 1mm^3 , which is comparable to the normal 3 to 4 mm thickness of the cerebral cortex.

How then can we obtain detailed information about the function of the human brain in life? Regional human-brain function can be investigated with a variety of techniques, each of which provides unique information. Each technique has limitations and strengths, and many are still under development. The principle of positron emission tomography has already been described: radiolabeled tracers are introduced into the brain via the blood stream, and the resulting regional distribution of radioactivity in the brain is recorded by scanning. This distribution and subsequent detection of the tracer provides information about the

biological function in which the tracer participates. In functional mapping (activation) studies the usual variable of interest is the distribution of local blood flow, because blood flow supplies energy to the brain and is a reliable index of local firing in nerve cells; the activity of nerve cells is an energy-dependent process.

The temporal and spatial resolution of functional images obtained with PET are, however, limited. Recording signals for tens of seconds is necessary to generate images that, theoretically, have an optimal spatial resolution of approximately 3 mm³. In practice, the resolution is often worse—typically a sphere with a diameter of 6 to 10 mm. Even in ideal circumstances, events with short, millisecond-range time constants cannot be demonstrated with PET. A technique that helps to overcome some of these shortcomings is functional MRI (in contrast with the use of MRI to obtain structural information), which records changes in successive images that are related to tissue function. The most useful fMRI method is dependent on local brain oxygen levels (BOLD) and is totally noninvasive. Equivalent brain activity tends to produce smaller changes in image intensities with BOLD fMRI than with PET, but there is greater spatial resolution (roughly 3 mm³). The relatively low sensitivity to changes in local brain activity of the BOLD fMRI method has led to the elaboration of analysis techniques capitalizing on the fact that images can be acquired very rapidly (50 msec per scan). Changes in a behavioral or physiological state induced during scanning can be conveniently yoked to changes of the image signal by repeated fast imaging. A problem with this strategy is that the BOLD signal has a long (and locally heterogeneous) half-life of several seconds. It is this unfortunate fact, rather than the rapidity with which scans can be recorded, that limits the temporal resolution of this method.

Even so, mapping and analyzing very short-timed brain events and transient correlations of activity in different brain regions is possible with techniques such as magnetoencephalography (MEG) and electroencephalography (EEG), both of which record spontaneous electrical brain activity. EEG-based measurements are made from electrodes physically attached to the scalp. The sampling of brain activity by these methods is limited by the size of the head to roughly 120 scalp locations, which results in the

poor localization of the number and origin of electrical signals from the brain. One way of increasing the detectability of the evoked electrical activity is provided by event-related potential (ERP) mapping. A cognitive or physiological task of interest is repeated, and recording the evoked electrophysiological activity is time-locked to the stimulus or response in some defined way. The records are averaged to maximize the relevant signal (relative to underlying measurement noise) and then mapped. Recently, improvements in the accuracy with which sources of electrical or magnetic activity are localized have been attempted by the integration of such results with PET or fMRI imaging data. The primary goal of electrical methods is to obtain information about the time course of brain activation, particularly in networks consisting of a number of cooperatively activated brain regions.

THE MAPPING OF SENSORY SIGNALS ONTO THE HUMAN CEREBRAL CORTEX

Our sensory world depends on stimuli that evoke neural activity, which then maps onto primary sensory areas of the brain. We have some knowledge of these maps, and of the early stages of sensory processing, from experimental results obtained in monkeys and by observations in brain-damaged humans. The visual system has been relatively well studied by some of the modern neuroimaging methods described above and will be used here to illustrate some general principles. A simple imaging experiment to imagine is the measurement of the distribution of brain activity during an eyes-open and an eyes-closed state. The comparison of brain activities in these two states shows the areas of the brain that are activated in association with vision. When early sensory processing is the object of study this comparative approach is relatively free of assumptions; but when more complex cognitive functions are studied, more sophisticated experiments and analyses must be used.

The visual world is mapped from retina to cortex; it is produced by patterns of light hitting the retinas of the eyes. The evoked retinal signals are transmitted to the visual cortex in a point-to-point manner. Signals coming from adjacent patches of

the retina (and hence parts of the visual field) are mapped onto adjacent patches of the cortex, a fact that was known from studies of patients with focal lesions of the visual cortex. This retinotopic organization of the primary visual cortex (also known as visual area V1) has been clearly confirmed with scanning in normal humans. Activity recorded in the brain with visual targets in the periphery of vision can be compared to that recorded with a central presentation of the same target. Each quadrant of the visual field is located in the opposite cerebral hemisphere and quadrant of the visual cortex. The point of visual fixation is represented at the pole of the occipital cortex at the back of the brain while peripheral vision is represented in front, at the forwardmost part of the fissure that contains the rest of the primary visual cortex (figures 2 and 3, plates 4 and 5). One can calculate from such data the magnification factor—that is, the length of the cortex that maps a given “length” of the visual field.

FUNCTIONAL SPECIALIZATION IN THE OCCIPITAL CORTEX

The extrastriate occipital cortex (that which lies outside the visual cortex proper) receives an output from visual area V1. This cortex is functionally heterogeneous: different parts are active in conjunction with different visual percepts (for example, form, color, and movement). Visual area V5 is one of these extrastriate areas; activity in it is associated with perceived visual motion. It has been mapped using a visual target in motion and then activity in the brain is compared with that produced when the same target is stationary. Area V5 is found in a circumscribed part of the occipital lobe in front and to the side of area V1 (figure 4, plate 6). When moving objects of different colors and shapes are viewed and attention is drawn to the movement, rather than to the color or shape, activity in area V5 is augmented. The attentional process is implemented by an increase of the response of V5 neurons to the same incoming visual stimulus. How this increased responsiveness is mediated, and whether it depends on the quality of visual signals coming to the brain or on influences altering V5 activity from other brain centers, is crucial to an understanding of attentiveness.

The brains of individuals vary one from another quite markedly, not only in shape, but also in the disposition of the folds and fissures of the parts of the cortex. However, accurate co-alignment of functional and anatomical images is a trivial issue with the use of modern computers. It is possible to show precise relationships between structure and function despite considerable anatomical variability in the normal occipital cortex between individuals. Area V5 is always found in relation to two folds of the human occipital cortex. This anatomical site is also characterized by being relatively developed in infants; the nerve connections are well myelinated, or insulated. In summary, there is a remarkable correlation between developmental factors, functional specialization, and anatomical location, despite considerable variability in the absolute spatial location of the anatomical structure in different individuals. Attempts to demonstrate the heavy myelination characteristic of area V5 when examined under the microscope by high-resolution anatomical MRI in life have been partially successful, which is remarkable given that these features are only a millimeter in thickness. The stria of Gennari, a unique structural characteristic of the primary visual cortex (area V1), has also been demonstrated. An informative analysis of structure-function relationships in a normal living brain certainly requires this degree of spatial resolution.

Human color perception, in the sense of seeing a red rose as red whatever the ambient illumination, is associated with the activation of another distinct part of the occipital cortex. This area, known as human area V4, also lies in front of area V1 on the underside of the occipital lobe on both sides of the brain. It has proved possible to correlate the position of area V4 in normal subjects with the damage produced by strokes that lead to a selective inability to perceive color in people who previously had normal color vision. In conclusion, neuroimaging studies of this cardinal sensory system indicate that different visual areas are functionally segregated in the occipital cortex.

We come then to the question of whether the neuroimaging methods now in use and being developed are sensitive enough to detect maps in higher areas of the sensory pathways. The reconstitution of a unique visual percept from activity in functionally segregated, anatomically distinct areas of the brain is a central

problem for vision research—and, moreover, for a broader understanding of the biology of perception. The problem of integrating segregated signals and forming a unitary visual percept is more difficult to address at present. One approach has been to use stimuli that generate illusions—for example, form percepts from moving stimuli and motion percepts from nonmoving forms. These stimuli are interesting because among them there are some in which the brain elaborates visual attributes that are not physically present in the stimuli themselves and hence in the real world. They therefore speak to interactions between perceptually specialized areas. Activation of brain areas that include visual motion area V5 by a motion-from-form stimulus shows that unique patterns of visual input do sometimes activate area V5 in the absence of real motion, and that such V5 activation is associated with the perception of nonexistent visual motion. This raises the important idea that the brain *generates* percepts rather than “analyzes” or “interprets” them—and that at times these are elaborated “beyond the information given,” resulting in illusions.¹

Anatomy tells us that there are visual pathways (albeit small compared to the major optic radiation that joins the retina and the visual cortex) that reach functionally specialized visual areas directly, bypassing the primary visual area. Activity in area V5 that is dissociated from the normal preprocessing in area V1 has been shown in a patient whose area V1 was destroyed after a head injury. The patient was sufficiently aware of residual but degraded visual motion in an otherwise completely blind visual field to be able, when tested, to describe the presence and direction of stimuli verbally, without error. This observation leads to the rather interesting conclusion that, in humans, significant visual signals can reach the functionally specialized visual cortex directly. Presumably these signals may also be fed back to area V1 to modulate activity there in response to signals arriving by the classical route. This is an interesting example of a potential control mechanism that involves preparing area V1 for a volley of sensory signals it is about to receive by the major pathway coming to it. Secondly, the perception of visual motion (albeit a degraded form of perception) is, at least in part, a property of the activity in the functionally specialized area alone. Finally,

signals from the functionally specialized cortex acting alone can, in abnormal circumstances, be propagated to “inform” function in other areas of the brain—for example, those associated with the language needed to report the visual motion.

BEYOND THE EXTRASTRIATE CORTEX

The awareness of the position of an object and the knowledge of its physical qualities leading to recognition are two visual cognitive functions that depend, at least in part, on a recognition of the object’s shape, color, and direction of motion. Imaging studies suggest that the pathways activated in association with these two attributes of objects overlap substantially, but there is also some segregation relevant to each attribute in brain areas forward of the occipital cortex. Activation of posterior parts of the inferior temporal lobes (adjoining the lower occipital cortex) occurs when objects are recognized (for example, to be named). Identification of an object’s position in space preferentially activates posterior parts of the parietal lobe (which lies above the temporal lobe and in front of the upper part of the occipital lobe). A third pathway, in which activity is associated with visually guided reaching for objects, has been demonstrated in the parietal lobes between those areas activated by recognition and those by awareness of position. The recognition of further pathways is to be expected because, in general, integration of visual signals with behavior occurs at multiple anatomical levels in the human brain. Each specialized brain area that has connections to another specialized area receives signals back. Each area sends and receives signals to and from multiple other dispersed areas and draws on signals from these areas as the behavioral context demands. Yet signal traffic is not chaotic, a remarkable and often ignored result provided by functional neuroimaging.

Motor associated cortices are functionally specialized and organized into a nested hierarchy of areas comprising a widely distributed system. The brain’s representation of simple movements is also organized in maps, so that movements of different parts of the body lie in a reasonably ordered strip along the motor cortex (known as somatotopy). Illustrations of a deformed “homunculus,” in which the amount of cortex devoted to sensa-

tion or movement is reflected by the size of the body part, are well known. For example, the lips and fingertips are very sensitive and mobile, with correspondingly large cortical representations. Activated areas actually tend to overlap to some extent, but the centers of mass of such activations are clearly separated along each side of the major central fissure of the brain in which the sensory and motor cortices lie.

Somatotopy has also been described in other motor areas that can be found in the front of the brain. Such multiple motor representations have been demonstrated by a selection of appropriate motor tasks during scanning. Brain activations related to movement have been found in at least fourteen parts of the brain, including the primary motor area. A pertinent question is why so many representations of action in the brain can be detected. The most extensive activation of motor-related areas is found when actions are self-selected. Choosing a movement of one's own volition is clearly a complicated process involving cooperation between a multitude of separate, functionally specialized brain areas. Activations of gray-matter structures in the base of the brain (especially two nuclei called putamen and thalamus) are most evident when movements are self-paced or constant, as opposed to when repetitive movements are made. We will next discuss whether the imaging techniques described previously are as informative in studies of more complex functions of the brain as they are in the case of early sensory perception or execution of a motor action. Such complex functions at times appear mysterious because there is no easy way to access them scientifically in animals who lack the ability to communicate them in detail. In short, can the physiological basis of human thought and planning be brought under scientific scrutiny by imaging neuroscience?

Imagining a complex or skillful movement can help improve its performance, a fact well known by musicians and athletes. Brain activity associated with imagined actions can be compared with that at rest or during preparation of a motor act or with its actual execution. The brain areas involved in motor imagery surround those areas in which activity is associated solely with the execution of a motor act. Imagining a complex arm movement is associated with the activation of a number of brain

regions in front of and behind the primary motor areas (the premotor and parietal cortices identified in figure 2). Execution of the same complex motor task activates these areas, which are thought to program the movement, and the additional areas that form the executive core” of the motor system and are centered on the primary motor cortex. Such simple experiments illustrate dramatically that it is possible to image brain activity associated with “pure thought”; hence, the idea that thought and introspection can be physiologically studied is, at least in principle, realized.

What brain structures are involved in choosing movements? When brain activity during imagined movements is compared with that at rest, prominent additional activations to those described above are found. Some of these activated areas appear to be specialized for the initiation and selection of movements from a mental repertoire. They are almost exclusively located in the prefrontal cortex near the front of the brain (figure 2). Such areas play supramodal roles, performing functions that are pertinent to memory and other cognitive aspects of action. In particular, these areas are activated when self-generated and stimulus-driven actions are compared. This result is obtained by scanning identical tasks in terms of sensory stimulation and motor response, while giving subjects different instructions during different scans. They are told to do different things with the same stimuli—either responding in a predetermined way or in a self-selected, free manner. In other words, only the nature of the mental operation involved is different during different scans. In this instance it is difficult not to conclude that the activated brain areas, many of them again in the frontal lobes, are directly responsible for the engagement of purely cognitive functions. A description of the physical basis of pure mental activity with even this degree of precision is astonishing and poses challenging questions to philosophers interested in the nature of the “mind.”

Indeed, neuroimaging data can be used to investigate functional interactions between brain regions. When scans collected during self-generated and stimulus-driven action are compared, there are frontal activations as described above, whatever the precise detail or modality of the sensory stimulus or action involved. However, modality-specific changes in brain activity

are also found. They are usually deactivations when self-generated task scans are compared to stimulus-driven ones. This pattern of response is opposite to that found when stimulus-driven behavior is examined; in that case, modality-specific brain areas show enhanced activity. This constitutes evidence of correlated activity linking task-dependent, modality-specific areas usually found in the back half of the brain and amodal (hence higher) areas located in the frontal cortex. Correlated activity implies a functional interaction between neuronal populations, and the images provide data that can be used to test and inform population-level models of brain function based on the observed functional connectivity between brain regions. More generally, the frontal cortex, which differs hugely in volume between humans and even our closet primate relatives, is greatly implicated by neuroimaging in processes involving planning, choice, volition, memory, and similar cognitive functions.

In general, multiple scans recorded over time generate the image data needed to describe the spatial distribution of brain activity correlated in time. The volumes of data can be processed using advanced statistical mapping techniques to generate images that reflect functional or effective connections between brain areas. Further, it is possible to dissociate independent systems that interact at common sites in the brain. *Functional connectivity* is the correlation of activity in different brain regions evoked by a stimulus or behavior. Such correlations may be found because of direct or indirect interactions between brain areas or by virtue of common activation from lower (subcortical) structures. *Effective connectivity* is the influence one brain region exerts on another; it can be assessed quantitatively. The ability to measure effective connectivity presents opportunities to measure modifications in the strength of connections between brain areas by allowing us to observe how such interconnections are affected by behavioral manipulations or drugs.

Can cognitive processes be added and subtracted as independent unitary processes? A direct comparison of brain scans in different states is not always appropriate for the study of cognition; such a strategy rests on the assumption that interactions between brain areas and activity in them can be regarded as additive (or subtractable) one with the other. Simple sensory

stimulation is associated with correlated activity in primary sensory areas of the brain. Correlations between the activity and the strength of the stimulation are often simple and linear. However, when sensory signals are distributed among brain areas for the purposes of guiding or modifying behavior, the evoked activations are rarely simply correlated with the amount of sensory input. There are two principal reasons for this. Sensory signals may drive activity of a region (bottom-up activation). On the other hand, the response to a volley of sensory signals in a brain region may be altered by top-down influences from yet other areas. These areas may be mediating activations that set a behavioral context, mediate the degree of attention, reflect how well a behavior has been learned, and so on. Such context-modifying signals will interact with the sensory volley in a nonlinear manner and will, in this way, result in interactions between experimental factors that themselves determine the distribution of activity. Techniques are available that take into account such complex, higher-order interactions within and between activated brain regions. They search for nonlinear responses and the context-sensitive modulation of activity in brain regions.

Certain brain processes are activated by tasks despite the absence of explicit instructions designed to engage them. When subjects are asked to recognize particular orthographic features of words rather than to read them, a network of brain areas comprising a large number of anterior and posterior brain regions is activated. Many of these regions are known, from other studies, to activate with a variety of language-related functions, including the appreciation of meaning. There is thus obligatory activation, in the absence of explicit instruction or conscious effort, by word-like visual stimuli of areas in which activity is associated with the appreciation of meaning. It may not always be possible therefore to make assumptions about the constituent cognitive processes engaged by a task.

THE PROBLEM OF SELF-REPORTING

Many functional neuroimaging results depend on the cooperation or the self-reporting by subjects during or after scanning.

This fact is sometimes used to suggest that the data obtained are “soft.” Introspection and the reporting of observations or actions is an intimate part of everyday existence, even in the sphere of science. A statement that an object is a meter long is an example of self-reporting by the measurer. We do not doubt the report, because it is consistent, can be repeated by others, and is demonstrably true in practice (for example, reliable working machinery can be made based on the correctness of the measurement). Introspection has been used to investigate human brain function by neurologists and neuropsychologists with the clinico-pathological lesion method for at least a century. The repeated demonstration of consistent patterns of local brain activation during defined mental activity now provides objective measurements that are difficult to refute. Such measurements bring the investigation of thought, consciousness, emotion, and similar brain functions into the realm of “hard” scientific inquiry.

Cognitive tasks dependent on self-reporting are associated with responses that can be recorded or physiological changes that can be measured. Scanning that depends on recording task performance and correlating such results with scan data can be used to identify brain regions in which activation is coupled in some way to a task. The difficulty of the tasks involved may be varied. Such correlated observations remove the need for control scans and potentially circumvent the assumption of pure subtraction. For example, in the visual system, activity in the visual cortex increases with the increasing frequency of a flickering light, reaches an apex, and then falls at fast frequencies when it becomes difficult or impossible to discriminate individual flashes perceptually. Scanning while listening to pure tones of different frequencies results in brain signals that line up along the primary auditory cortex in a “tonotopic” map. One tone played at different volumes can be used to identify its representation in a tonotopic map by correlating brain activity with volume.

Patterns of brain activity are transformed as the signals they process are transmitted to new regions of the brain. The primary auditory cortex is the brain area to which nerves coming from the ear that are associated with hearing project. In the primary auditory cortex, activity increases in proportion to the number of words spoken per unit of time. The posterior temporal cortex,

to which the auditory cortex projects and which lies just behind it, shows a different response with the same stimulation; activation is apparent as soon as words are heard, but no further detectable change in local brain activity occurs across a range of word frequencies. The conversion of a rate-dependent response in the primary auditory cortex to one in which activity is not rate-dependent suggests a mechanism for integrating frequency-determined neural activity into a form that signals words having a phonological and semantic identity (sound and meaning).

Similar findings have been observed in the motor system. The activity in the primary motor cortex and associated regions of the “executive” motor system increases exponentially with the rate of repetitive movement or the amount of constant force exerted. There are no such exponential changes in other motor-related areas associated with the initiation or sequencing of movements.

THE LOCALIZATION OF MEMORY

Thus far we have discussed functional neuroimaging in brain systems related to input (sensory) and output (motor) systems. Our discussion has progressed beyond these into the cognitive domain with examples of increasing complexity and an analysis of task-dependent issues relevant to informative experimental design. The final part of this essay will deal with the functional neuroanatomy of human memory, a topic characterized by a large and increasing variety of identified memory processes and the complex interactions between them. This fact makes particular demands on an appropriate choice of both imaging methods and task definition for the attribution of function to structure.

How do we keep snippets of information in mind for short periods (working memory)? Many cognitive processes are composed of a number of subprocesses, some of which can be inferred from the fact that one can find patients who have deficits in one and not another component, and others who have the reverse pattern—an observation known in clinical neuropsychology as “double dissociation.” Psychological data based on reaction times in specially designed series of interrelated tasks in normal subjects provide additional information. An influential

model of verbal working memory developed by Alan Baddeley and his coworkers incorporates at least two subprocesses—a rehearsal system and a phonological store. The former refreshes the contents of the latter, which acts as a limited buffer (of three to four words) with a half-life of approximately two seconds. A common experience that illustrates what is meant by working memory is remembering a new telephone number before finding pencil and paper to write it down. If interrupted in the process of repeating the number to oneself, the information is lost.

The validity of this conceptual framework has been investigated with neuroimaging. The subprocesses of working memory were identified separately, and activity due to confounding memory processes was accounted for. This was done by controlling for potential confounds by the use of experimental designs in which independent factors are separately varied in different scans. For example, the ability to retain a series of letters in verbal working memory can be controlled by a task in which shapes are remembered that have no phonological connotations during identical conditions of visual presentation. The difference between these scans represents the dimension of verbal memory load. According to the model, an ability to make rhyming judgments is a function that primarily engages rehearsal. A scan during rhyming can be controlled by scanning during judgments of shape identity where (again) no phonological processing—an absolute requirement for making rhyming judgments—is involved. The difference between these scans represents the dimension of phonological load. The interaction between mnemonic and phonological dimensions eliminates contributions to the activation pattern from known and unknown interfering processes, while identifying brain areas associated with the two subprocesses and their interactions alone. Such studies have shown a critical role for the inferior frontal lobe at the front of the brain on the left in the rehearsal function, and for the inferior parietal lobe (again on the left) in the functions of the phonological store.

How then do we remember events in our personal lives? Longer-term autobiographical memories available to consciousness (episodic memories) present a particularly interesting object of study. The process of remembering lists of words, for example, can be contaminated by mechanisms that permit recall

with above-average success in the absence of explicit learning. Use has been made of the known interference caused by difficult distractor tasks with the acquisition of explicit memories. Scanning can be carried out during the performance of a paired associated-word learning task or a controlled, repetitive passive-listening task with and without concurrent distraction. The passive-listening task controls for auditory and other known and unknown components of the memory task. The effect of distraction on learning eliminates efficient episodic encoding (learning), thus providing a control activation map representing areas associated with priming and other irrelevant processes. (Priming is the well-recognized facilitation of recognition caused by prior exposure to a stimulus that a subject is not deliberately trying to remember.) The difference between this map and that comparing episodic learning with control in the nondistracting state indicates areas specifically associated with the episodic learning process. From such a task design it is possible to show that episodic learning is selectively associated with the activation of a localized posterior midline region of the cortex (retrosplenial) and a region of the left-sided (dorsolateral) frontal cortex that has already been implicated in other cognitive tasks discussed above (figure 5, plates 7 and 8). It is important to remember that, though these areas have a particularly critical importance to normal episodic memory acquisition, memory function remains a property of the whole network.

Anatomical correlates of the recall of previously learned episodic memories have also been discovered. Scanning is performed while subjects view the first of a previously presented pair of words (a category such as countries) and attempt to recall the second of the pair (a specific example, say, "England"). In this task a strategy involving semantic knowledge about the category might contaminate episodic recall, especially if subjects resort to guessing the example if it does not immediately come to mind from the learning period. Scanning can be carried out during a similar task in which a novel (rather than previously learned) series of category words are presented. This task depends entirely on previous knowledge and can be used as a control in experimental episodic recall tasks. A repetition task is used to control out common aspects of listening to words and

other less-identifiable subprocesses. A comparison of scans performed during a repetition-control task with scans performed during experimental episodic tasks gives a map of areas involved in both episodic recall and recall from an individual's knowledge base (semantic memory). On the other hand, a comparison of repetition scans with semantic recall scans gives a map of areas specifically associated with semantic memory. The difference between the two results will isolate areas associated with episodic recall alone. The result indicates a prominent role for the right frontal cortex and another, separate posterior cortical area (the precuneus) in the recall of episodic memories (figure 5). This right/left frontal distinction between cerebral activations evoked by remembering and laying down episodic memories is a clear functional specialization in a very high-order cognitive system, and it has been confirmed in many studies using a wide variety of different materials for remembering.

Extending these analytic tools in other ways shows us that learning new skills involves large-scale, time-dependent changes in patterns of neuronal activation. Behaviorally, repetitive task performance results in habituation and adaptation effects. Learning to play a new piece on the piano or to play tennis initially demands great effort—but progressively becomes more automatic, or skillful. The physiological correlates of such general mechanisms have been shown with neuroimaging. For example, in a verbal task requiring responses to novel categories by giving a specific example, there is activation in a distributed network that includes the frontal cortex and a number of language-related areas in the temporal lobe. If such a task is repeated until the responses are overlearned, the pattern of activation is attenuated and resembles that obtained with the simple repetition of words. This result indicates that response selection has become automatic, that is, subjects no longer have to think about what they are doing. Introducing a new category target brings about a return to the original pattern of activation.

Motor-skill learning can be measured during the repetitive performance of a manual dexterity task. Following a rapidly rotating target with a hand-held stylus is initially difficult; accuracy at different speeds and with practice can be recorded. Improved performance becomes observed as accuracy and time-on-

target increase. Such improvement correlates with increased activity in primary and other motor cortices. Activation of the brain during the performance of such tasks can be modified for two reasons. First, improved performance will result in greater motor activity during a scan that will be due simply to improved performance. Second, modifications of activity may occur due to the acquisition of a new motor skill (or the memory of a motor action). A proper interpretation of the imaging result therefore depends on a realization that improved performance and increased skill are separate, but confoundable, attributes of a motor act. When a motor task is performed repeatedly to the same performance criterion, thus eliminating any performance confound, then progressive attenuation of activity occurs in both the premotor cortex and the cerebellum. (The cerebellum lies underneath the occipital lobe; it is in the skull but is separate from the cerebral cortex above.)

Scanning during the learning of a novel sequence of key presses (such as in learning a piano piece) with error feedback via an auditory signal results in the greater activation of parts of the right frontal cortex when a performance is naive than when the sequence has been overlearned. Conversely, activity in other midline parts of the frontal lobe is greater in the automated state than in the naive state. Visual and language-associated cortices show considerably less activity during the naive state than when a key-press sequence is overlearned. When a task is novel and requires considerable attentional resources, there appear to be mechanisms for large-scale deactivations of whole systems that are not required for the task. When a task becomes overlearned, attentional needs decline and activity in extraneous areas normalizes relative to activity in the remainder of the brain.

Paying attention to stimuli is a general psychological mechanism that generates different patterns of activity depending on which attentional process is engaged. Selective attention, as noted already, results in the augmentation of activity in modality-specific areas specialized for the elaboration of a function or percept to which attention is directed. An example from studies in the visual system has already been given. Recent advances allow the measurement of the influence that activity in one brain region has on other regions. We have shown that in a visual categorization

task using objects presented at various rates, areas can be identified in which activity is dependent on the amount of attention required. Difficult (as compared to easy) categorization tasks activate frontal regions. Selective attention to object attributes at different levels of difficulty results in two types of modulation of activation in the inferior temporal cortex. The relationship between difficulty and activity changes so that there is a greater activation for equivalent rates when attention is engaged. The source for this modification of the stimulus-response relationship appears to be in the frontal cortex. In addition, there is a change in the unstimulated activity of the same inferior temporal cortex when the task provides an expectation of increased attentional requirements. These two mechanisms can be considered analogous to a change in the gain characteristic of the object recognition system (analogous to a change in the volume control in a radio set) and a change in its offset with expectation (in this instance, analogous to a change in the wavelength band or channel). This example serves to show that functional neuroimaging provides information about brain mechanisms as well as brain localization.

SYNTHESIS AND CONCLUSIONS

The field of functional neuroimaging is in a state of rapid technical development. The data derived from different scanning methods are often complementary, and there is much evidence to suggest that this state of affairs will continue, thereby providing a wide range of improved tools for the exploration of the functional architecture of the human brain. Neuroscientific progress will be made by judicious use of one or more methods to answer appropriate questions. We can conclude, on the basis of results to date, that it is now possible to embark on research into the functional architecture of the living human brain that goes beyond descriptive "neophrenology" (the attribution of functions to sites in the brain). Nevertheless, it remains a fact that our description of the anatomical arrangement of the functioning human brain is incomplete, and therefore even "neophrenology" remains an important area of continuing study. Uniquely human functions must be assigned to networks of brain areas; cognitive processes require definition in physiological and anatomical terms.

New techniques, such as the measurement of functional connections between brain areas, may have practical significance for the treatment and modification of mental diseases and cognitive function. For example, the symptoms of schizophrenia are modified by drugs working on the dopamine system. Patients show a number of cognitive abnormalities that can be related to disorganized function in well-defined brain systems. The restitution of normal functional relationships in such a system by a dopamine active agent has been demonstrated, and the locus of interaction between dopamine and cognition-related brain activity has been identified. Such basic neurobiological information will generate ideas relevant to drug design and assessment.

Above all, these new methods are leading to better human self-understanding through an appreciation of the unique nature of how our mental activity is implemented in the organic matter that we carry around in our skulls, that enormously complex organ that defines our personalities, hopes, wishes, actions, and ambitions.

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ENDNOTE

- ¹Semir Zeki, J. D. G. Watson, and Richard S. J. Frackowiak, "Going Beyond the Information Given: The Relation of Illusory Visual Motion to Brain Activity," *Proceedings of the Royal Society of London, Series B*, 252 (1993): 215–222.

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