Appendix 3

The prefrontal cortex and cingulate cortex

In arriving at our conclusions below, we will be greatly aided by recent advances in anatomy which allow the prefrontal cortex to be viewed in terms of a fairly general, consistent plan. The anatomy has the advantage of being easily compared across species, permitting very fine differentiation of subareas and, given some lesion data, suggesting detailed functional organization. However, our overall conclusions must be treated with some caution since at present they are heavily dependent on the anatomy and are supported, at the functional level, by single-cell recording from only a few areas (often with insufficiently precise identification of position) and by lesions which, because of the folding of the cortical mantle, cut across not just the boundaries of specific areas but even the major functional divisions implied by the anatomy.

A3.1 Anatomy of the prefrontal cortex

Barbas and Pandya (1991) present a neatly ordered view of the intrinsic organization and cortical connections of the prefrontal region from which we will borrow wholesale. The foundation of their analysis is the progressive increase in number of cell layers, architectonic differentiation, and myelination as one progresses from the most caudal basomedial areas, first rostrally to the frontal pole (over the basal and medial surfaces for the lateral and dorsal trends respectively) and then dorsally (from the basal edge) or ventrolaterally (from the medial edge) in the direction of area 8 which has the highest degree of organization. Areas 8 and 46 have separate dorsal trend and ventral trend components, separated by the principal sulcus. Once we reach area 8, there is no clear architectonic basis for dividing prefrontal cortex categorically from area 6 and then area 4 (each of which has likewise a dorsal and ventral component). Although this goes against the conventional distinction between prefrontal and motor cortices, we will find it useful to treat the progressively less differentiated prefrontal areas as representing a functional progression which is lowest in area 4 and becomes progressively higher through areas 6, then 8, then 9/46, then 46, etc.

The architectonic progression in frontal cortex is most easily understood by imagining the convolutions of the frontal cortical mantle unfolded into a flat sheet (which is attached only at the most rostral point of the subcortex and which is only resting, like a sheet on a bed, on more caudal subcortex). Then imagine the most caudal edge of this sheet pulled off the subcortex (as you would pull the top sheet off a bed, leaving it attached at the foot) so that it is effectively rotated 180° rostrally about its point of rostral subcortical attachment. The whole of the sheet would now flow forward from the most rostral subcortical areas. The least differentiated areas of prefrontal cortex would now be seen to be closest to the subcortex with progressively more rostral strips becoming progressively more differentiated. Thus much of the apparent topographic complexity of prefrontal cortex is the result of the folding of part of the cortical sheet over the remainder of the brain, the tucking in (like the edge of the sheet on a bed) of the medial surface, and the general wrinkling of the sheet.

The progressive delineation of layers in prefrontal areas is reflected in their intrinsic connections. . . . A given area projects to and receives input from cortices in two directions . . . more architectonically differentiated areas, on the one hand, and regions with lesser laminar definition, on the other. . . . The intrinsic connections have several other consistent features. For example, . . . a low degree of laminar organization is associated with widespread [intrinsic] connections, whereas a high degree of laminar organization is associated with restricted connections [to closely adjacent areas]. The widespread connections . . . are not randomly distributed. They seem rather to respect the observed architectonic progression, projecting to several architectonic stages, but avoiding areas exhibiting a high degree of laminar organization. (Barbas and Pandya 1991, p. 42.)

This general pattern is, of course, subject to local detailed variations (e.g. Carmichael and Price 1996) and the projections of small parts of a field may show discontinuous rather than diffuse innervation patterns (Pucak *et al.* 1996) but can be taken as reasonably accurate for the level of analysis we will undertake.

Unimodal sensory cortical areas are also connected to the prefrontal cortex in an ‘architectonotopic’ manner. ‘For example, the limbic orbitofrontal and medial prefrontal cortices receive the majority of their auditory projections from the rostral [auditory cortex] which has the least architectonically differentiated laminar pattern within the cortical auditory system’ (Barbas and Pandya 1991, p. 46). Progressively more posterior auditory cortex projects to progressively more postero-dorsal prefrontal cortex. This pattern is also true ‘for the premotor to prefrontal, and for the somatosensory to prefrontal projections’ (Barbas and Pandya 1991, p. 46).

A final important architectonic organizing principle of cortical connections is that the relatively undifferentiated areas receive polymodal input both from the convergence of unimodal inputs and from input from polymodal areas, while highly differentiated areas are largely unimodal.

Cutting across this basic cytoarchitectonic and connectional organization is a division into two aspects of cortex which are distinguished by an ‘olfactory’ and ‘hippocampal’ origin, respectively. Thus one can see an evolutionary, cytoarchitectural, connectional, and functional ‘dorsal trend’ (see Pandya and Barnes 1987; Barbas and Pandya 1991; also referred to as ‘medial’, Goldberg 1987) originating in hippocampal allocortex and progressing frontally through pyramidal regions until it reaches area 8 (see below). This dorsal trend is mirrored by an equivalent ‘ventral trend’ (Pandya and Barnes 1987; ‘lateral’ according to Goldberg 1987) originating in olfactory allocortex and progressing frontally through granular regions until it too reaches area 8 (see Fig. 1.9 in the printed text).

The basoventral and mediodorsal aspects of the prefrontal cortex each conform, separately, to the architectonic description we have given so far. However, 'the origin of projections directed to basoventral and mediodorsal cortices differs. Thus, for the most part, basoventral prefrontal regions are connected with other prefrontal, premotor, somatosensory, and visual areas situated on the ventrolateral surface [of the cerebral hemisphere], whereas mediodorsal prefrontal cortices are connected with premotor, somatosensory and visual cortices situated on the dorsolateral and dorsomedial aspects' (Barbas and Pandya 1991, p. 50). Thus there are dorsal and ventral prefrontal trends which are innervated primarily by the dorsal and ventral trends within each primary sensory system. (For example, the ventral visual trend can be viewed as running lateral geniculate nucleus–V1–V2–V4–inferotemporal, whereas the dorsal visual trend can be viewed as running superior colliculus–V1–V2–V3–posterior parietal.)

The impression we are left with, then, is of two essentially parallel systems which mirror each other's subdivisions, intrinsic connections and organizing principles, including topographic mapping (Fig. 1.9, printed text). These parallel structures receive slightly different qualities of each type of, for example, sensory information. Thus the dorsal trend (in posterior as well as frontal cortex) can be thought of as dealing with 'where' some stimulus feature is, whereas the ventral trend can be thought of as dealing with 'what' it is. It should be noted that conventional 'mesial', 'dorsolateral', and 'orbitofrontal' lesions cut across both the mediodorsal–basoventral boundary and the boundaries of architectonic differentiation and hence should produce quite mixed effects with respect to the distinctions we have just made. It should also be emphasized that in neither frontal nor posterior cortex are the trends completely independent. There are extensive interconnections between the trends, usually at the same level. Thus, in frontal cortex for example, mesial area 9 and orbital area 12 are interconnected (9m and 12o in Fig. 1.9). This type of interconnection (orthogonal to the nominal flow of information away from the periphery) occurs at virtually every level of both sensory and frontal cortex. Finally, it should be noted that there can be direct convergence of dorsal and ventral trend afferents and efferents, as shown by the case of the frontal eye fields (Schall *et al*. 1995; Stanton *et al.* 1995).

The topography of the interconnections of the frontal cortex with the thalamus also appears to be determined by the divisions we have just discussed (see Goldman-Rakic and Friedman 1991). For both the anterior thalamus and the mediodorsal thalamus, two lines of nuclei can be discerned—one with connections to the dorsal trend and one to the ventral trend of the frontal cortex. Within each line, successive nuclei are connected to progressively more differentiated frontal cortex (Fig. 1.9; see Goldman-Rakic and Porrino 1985).

A3.2 The prefrontal cortex and motor control

If we trace our way retrogradely in the motor system, starting at the periphery, we can follow pathways that take us to the primary motor cortex. The central sulcus between the primary motor cortex and the primary somatosensory cortex divides the posterior, perception part of the cortical mantle from the anterior, action part. As we move away from the central sulcus, first rostrally and then gradually ventrally over adjacent areas, we find that the primary motor cortex (which can be loosely thought of as moving specific parts of the body) is connected to the premotor area (which can be thought of as organizing actions) and this is in turn connected to the dorsolateral prefrontal cortex.

Given this connectivity (and the anatomical considerations we dealt with above), we will treat the prefrontal cortex proper as involving a steady progressive elaboration of the functions present in area 4 and area 6. Area 4 (the primary motor cortex) contains cells which are involved in the control of specific limb movements with the cells being organized in a somatopic map (the motor homunculus pictured in innumerable textbooks). Area 6 (supplementary motor area and premotor cortex), which can be viewed as a parallel strip providing input to area 4, also contains a somatotopic map. This is of a slightly more complex kind and can be viewed as more sensory than motor.

Cells in area 6 have both somatosensory and visual receptive fields. The visual fields are of particular interest in that they move when the body part containing the somatosensory field is moved. Thus, if the somatosensory field is on the arm and the arm is moved to the left, then the visual receptive field also moves to the left. Cells with this type of receptive field are also found in the parietal cortex (area 7b), which projects to area 6, in area 6 itself, and in the putamen which receives input from area 6 (Graziano and Gross 1993, 1994*a*,*b*). 'These cells appear to measure the location of the stimulus with respect to the arm. This type of arm-centred coordinate system would be useful for hand–eye coordination, such as guiding the arm toward or away from visual targets . . . Ventral premotor cortex . . . the putamen . . .[and] area 7b . . . appear to form a system for the coding of near extrapersonal space and for guidance of movement in that space' (Graziano *et al.* 1994, p. 1056). While cells in this system can be categorized as having bimodal somatosensory–visual perceptual fields, functionally they must be seen as providing the basis for specific planned movements (thus blurring the distinction between perception and action, or at least requiring that motor programmes be phrased in terms of goals rather than responses). Compared to the primary motor area, at least one critical aspect of the functions of the supplementary motor area is a greater involvement in motor output in memory-guided tasks (see Tanji 1994 for review) including saccadic eye movements (Anderson *et al*. 1994). Similarly, the supplementary eye fields show more mnemonic activity than do the frontal eye fields (Chen and Wise 1995) although even the latter show clear learned target selectivity (Bichot *et al.* 1996).

Next we come to area 8 which is strongly associated with the frontal eye fields. Again, area 8 can be viewed to some extent as a strip parallel to area 6 and projecting to it. Stimulation of this area can produce eye movement and it appears to be involved in the conscious as opposed to reflexive control of eye movements. It should be noted here that control of eye movements implies the control of the centre of gaze and hence control of what aspects of the visual world can be attended to. Thus, in the same way that area 6 can be viewed as encoding the aspects of current visual space which are necessary for the planning of specific movements (which themselves can be encoded in area 4), area 8 can be viewed as encoding the direction of gaze which will be necessary in advance of any somatosensory–visual analysis by area 6.

It is now thought that:

first, the eye field as described using unit recording and electrical stimulation in behaving monkeys trained to fixate visual targets is much larger than the 4 mm^2 area originally described. Second, the eye field and forelimb field share a similar neural space within the dorsomedial frontal cortex (DMFC); thus the electrophysiological studies that have been conducted on visually guided and sensory-triggered forelimb movements must be re-evaluated, since none of these studies controlled eye movement and eye position independently. Third, a topographic map representing eye position in orbit has been discovered in the DMFC; it is proposed that this topographic map records the order of positions of the eyes and forelimbs during the acquisition of visually guided movement processes (review by Tehovnik 1995, p. 147; see also Lee and Tehovnik 1995).

Recently, it has been shown that cells in the frontal eye fields respond to the requirement to attend to a visual stimulus even when eye movement is not in fact required (Kodaka *et al.* 1997). Similarly, stimulation of area 8b can produce ear as well as eye movements, implying that the 'frontal eye fields' have a much more general, attentional function (Bon and Lucchetti 1994).

Thus, as we focus on ever higher levels of frontal cortex, we see first motor control in area 4, then pre-motor control (the preplanning of a movement) in area 6, then pre-pre-motor control in the shape of the directing of attention (i.e. target detection rather than orienting or vigilance; Jackson *et al.* 1994) in area 8. Our next step takes us into the prefrontal cortex proper in the case of area 46, but this can be viewed as a strip parallel to area 8 and projecting to it (as well as to area 6). By inference from the transitions between areas 4–6–8, we would expect area 46 to be involved in pre-pre-pre-motor control or pre-attention, and in a sense it is. Indeed, there are many ways in which frontal cortex as a whole can be viewed as being an attentional control system (see Knight *et al.* 1995 for review, and Ishiai *et al*. 1994 for evidence that frontal neglect is attentional rather than hypokinetic). But, in the same way that it was simplest to label 'pre-pre-motor control' as 'attention', it is better to label 'pre-pre-attention' and the like with different cognitive function labels. Considerable recent work has implicated prefrontal cortex in general (e.g. Pascual-Leone and Hallett 1994), and area 46 in particular, in the control of working memory. (See Grafman 1995 for a slightly different but similarly hierarchical view.)

A3.3 The prefrontal cortex and working memory

A particularly accessible review of the role of the prefrontal cortex in working memory (Baddeley 1986)[1] is presented by Goldman-Rakic (1992; see also Goldman-Rakic 1995*b*; Petrides 1989, 1994). Her conclusions can be summarized as follows.

In the view of Goldman-Rakic, at least some part of the prefrontal cortex is the neural substrate of working memory. Working memory 'complements associative memory by providing for the short-term activation and storage of symbolic information, as well as by permitting the manipulation of that information. . . . Working memory in humans is considered fundamental to language comprehension, to learning and to reason' (Goldman-Rakic 1992, p. 73). Working memory is presumed to be most extensive in human beings, but to be present also in other species. It is to subserve this function that the prefrontal cortex receives the direct projections from many primary and secondary perceptual areas which we have already described but it is in these latter areas that perception and long-term memory reside. Goldman-Rakic also suggests that 'the prefrontal cortex is divided into multiple memory domains, each specialized for encoding a different kind of information, such as the location of objects, the features of objects (color, size, shape) and, additionally, in humans, semantic and mathematical knowledge' (Goldman-Rakic 1992, p. 77; see also Goldman-Rakic 1995*b*, pp. 482–3). Note that, while the anatomy (and some other data; Schoenbaum and Eichenbaum 1995; Sawaguchi 1996) suggests that there are discrete patches for different types of sensory information within the working memory part of prefrontal cortex, these will be relatively close together, and even complex semantic information appears to be dealt with in much the same general areas (45, 46, 47, 10) as other types of information (Kapur *et al*. 1994). Major divisions between frontal cortical areas may then reflect, not the sensory modality or even complexity of information, but rather its attributes (e.g. Dias *et al*. 1996; Kesner *et al*. 1996; see McCarthy *et al*. 1996 for some suggestive evidence from human beings).

'Working memory' might seem to be just another type of memory—by implication a very perceptual or cognitive function. However, the fact that working memory is required, by definition, during the performance of tasks means that the main effect of activity in the working memory portion of the prefrontal cortex is to alter the operation of the motor system. Goldman-Rakic emphasizes, here, projections to 'areas beyond the cortex, including the caudate nucleus and putamen (which regulates a variety of motor activities) and the superior colliculus (which specifically processes visual motor functions)' (Goldman-Rakic 1992, p. 78). In this context it should be noted that, while 'prefrontostriatal and prefrontothalamic connections in rhesus monkeys have been shown to be organized in a

topographic manner . . . [and] arise from similar topographic regions, their laminar origins are distinctive . . . [and] originate from separate neuronal populations. The differential laminar distribution of neurons projecting to the head of the caudate nucleus and the mediodorsal nucleus suggest that these structures may receive independent types of information from the prefrontal cortex' (Yeterian and Pandya 1994). Note that the output from area 46 to the basal ganglia matches that from area 6, while that to the superior colliculus matches that from the frontal eye fields.

As an example of prefrontal operation involving the superior colliculus, consider the following experiment described by Goldman-Rakic (1992). A monkey is trained to perform the following delayed response task. First, a target appears at a particular position on a computer screen while the monkey fixates the centre of the screen. Next, the target disappears and still the monkey must fixate the centre of the screen. Finally, at the end of the delay, the monkey must move its eye to fixate the point on the screen at which the target originally appeared. As shown in Fig. 6.10 of the printed text, during the delay there are pyramidal neurons in layer V of the prefrontal cortex which fire throughout the delay and further increase their rate when the eye movement must be made. These changes in rate produce, or at least contribute to, the various increases and decreases in rate in the pathway from the prefrontal cortex through the striatum and then the substantia nigra to the superior colliculus which finally elicits the eye movement. Feedback from the nigra, via the mediodorsal thalamus to the prefrontal cortex, indicates 'completion of the motor response and signal(s) the prefrontal neuron to return to a baseline level of activity' (Goldman-Rakic 1992, p. 78).

Goldman-Rakic (1992, p. 78) notes that 'the prefrontal cortex probably cannot independently trigger motor responses. Nevertheless, it may regulate motor behaviour by initiating, programming, facilitating and cancelling commands to brain structures that are more immediately involved in direct muscular movement.' It is worth taking a moment or two to reconsider the connections of Fig. 6.10 and see just how this might be so.

We have previously (McNaughton 1989, Chapter 2) emphasized the strong relation between the ethological idea of innate releasing mechanisms and the idea that inhibition of inhibition (disinhibition) is a fundamental motor control mechanism (see Roberts 1984*a*,*b*). This leads naturally to the idea of a 'state-dependent reflex' (Goddard, personal communication). That is a conventional reflex, or higher order motor programme, which is normally checked by inhibition and which is released by disinhibition when a particular state occurs, usually provided also that an adequate stimulus is present. An important feature of such organization is the high degree of conditionality which is possible, since disinhibition permits a programme to control behaviour but does not compel it to do so. Hence, disinhibition will not result in motor output if the disinhibited node is neither intrinsically nor extrinsically activated. Similarly, two separate inputs may inhibit the same node. Here the node will not be fully disinhibited until both of two quite separate conditions are concurrently met.

The motor circuit described in Fig. 6.10 has just such a disinhibitory organization (see also Carpenter 1994). It seems likely, therefore, that the firing of the prefrontal neuron disinhibits a specific small pool of nigral neurons, coding for the correct position of the target. However, during the delay there is no observable effect on the nigra as it is being inhibited from elsewhere. Finally, the cue for the end of the interval disinhibits (or excites) the nigral cells also, with the resultant motor cascade producing the appropriate eye movement. Note that, on this view, the cue for the end of the interval could affect the entire nigra but only the appropriate cells would fire because all other cells would be, effectively, inhibited by the lack of output to them from prefrontal cortex.

Here the neural facts sit ill with any wish we may have to distinguish between working memory and motor command. Certainly, the prefrontal neurons firing during the delay code for position. In that sense they perform the 'cognitive' function of working memory. However, the neurons which code for the end of the interval are, in this same sense, purely sensory. The ultimate precise motor command, then, resides in the conjoint activity of these two types of neurons and, of the two, the prefrontal delay neurons have probably a much better claim to be the ones defining and controlling the appropriate action than the neurons which initiate the action. The prefrontal cortex, on this view, sets the goal while other inputs determine the actual timing of the goal-directed action. In this sense the function of area 46 can be seen as being essentially similar to that of area 8 and area 6—but with each of areas 6, 8 and 46 respectively removed further from area 4 both in logical space and in time before the planned action. It also appears that the prefrontal region is required particularly with large stimulus sets (Petrides 1995).

On this view a specific pattern of activity in area 46 of the prefrontal cortex provides at one and the same time both working memory *and* motor command—and should not be thought of as unconditionally *triggering* motor responses. Equally, sufficient excitation of motor centres by some other input could clearly generate identical motor output while bypassing the prefrontal cortex entirely.

Thus, while fully accepting the importance of the prefrontal cortex (particularly in the region of the principal sulcus) for working memory, we prefer to see this nominally memorial function as part and parcel of the control of specific motor performances. This is entirely consistent with the 'alternative' view of frontal cortical function with which we initially contrasted working memory—that of motor control. It is also consistent with the fact that 'pure' short-term memory in the perceptual sense appears to be more a function of the posterior than the prefrontal cortex (see General Discussion in *Philosophical Transactions of the Royal Society of London, Series B*, 1996, *351*, 1481–2).

It should also be noted, here, that 'the ventrolateral frontal cortical areas, including the sulcus principalis of the dorsolateral frontal cortex, are the initial recipients of information from posterior association areas and are the locus of the initial interaction of executive processing with short-term memory for modality-specific and multimodal information. [But] the dorsolateral frontal cortex that lies above the principal sulcus, on the other hand, constitutes a

second-level interaction with short-term memory when planning and organization – that is, monitoring within working memory – are required' (Petrides 1994, p. 208; see also Petrides 1996; Goldman-Rakic 1995a, 1996 on the neural basis of the central executive; Baddeley 1986; Robbins 1996). Thus, dorsolateral prefrontal cortex also appears to be involved in implicit procedural learning (Pascual-Leone *et al.* 1996).

A second point, which we discuss also when we consider the role of the septo-hippocampal system in memory, is that the memory component of 'working memory' may be equally distributed. That is, the firing of cells in the principal sulcus region may well act to maintain information in working memory, but it is likely, given the multiple reciprocal connections between prefrontal and sensory cortices, that the specific memory, so maintained, is supplied by the specific pattern of activity in the relevant sensory cortex. In this sense, working memory, as a psychological function, would simply be a form of directed attention. In the same way, then, that area 8 (in particular the frontal eye fields) can maintain actual or 'attentional' (Kodaka *et al.* 1997) gaze on a specific object in the visual field—holding it in the real eye—area 46 can maintain gaze on a specific object in the visual memory field—holding it in the 'mind's eye'. The mechanism for this would be a recursive refreshing (akin to verbal rehearsal) of the activity in sensory areas by input from the prefrontal cortex. Consistent with this 'recent studies have provided evidence that the delay-period activity recorded in inferotemporal cells during memory tasks may reflect afferent input from the prefrontal areas' (Goldman-Rakic 1995*b*, p478; see also Friedman and Goldman-Rakic 1994).

Circuits which could be involved in such control of working memory are shown in Fig. 6.9 of the printed text. Note that while it is often easiest to think of working memory tasks in visual terms, we can assume that virtually all sensory systems are represented in the same way; for example, there is evidence of impairment in haptic delayed matching-to-sample with prefrontal dysfunction (Shindy *et al.* 1994).

A3.4 The prefrontal cortex and cognition

From this point of view, even (or perhaps particularly) in relation to its working memory functions, the prefrontal cortex can be viewed as the highest level of the motor system. As we move from area 46 to, for example, area 10, then 14, then 25, it seems likely, therefore, that we are moving to ever more anticipatory levels of a goal-oriented system. Thus in the same way as, in the previous section, we viewed 'working memory' as a form of 'pre-attention' to a goal which must not yet be responded to, we can view the various activities of the deeper levels of the prefrontal cortex as pre-working memory, pre-pre-working memory, and so on. Here the psychological vocabulary becomes insufficient to the task—but it is not unreasonable to lump all of the different processes into the broad term 'anticipation' (and to dignify the result with the term 'plan'; Miller *et al.* 1960).

We should remind ourselves here that, as we move away from the primary motor areas, not only are we moving to progressively higher levels of the motor system but we are moving to areas which receive their input from progressively higher levels of the unimodal sensory cortices. Thus area 8 receives its input largely from primary sensory association cortex, while area 14 receives its input primarily from tertiary sensory association cortex (Fig. 1.9 of the printed text). Furthermore, in the higher levels of the system the convergence of unimodal inputs to produce multimodal fields is much greater.

This suggests a general hierarchical organization for the entire system. Direct primary sensory to primary motor links produce immediate, relatively simple responses. Next there is the area surrounding the principal sulcus which in one sense we have categorized as dealing with 'working memory'. In essence, this detects the requirements of a simple delay task and substitutes a more conditional, delayed response for the more immediate (in this case incorrect) response which would otherwise have occurred. The deeper levels of the system code for yet more complex, conditional or delayed, goals (superseding the coding of a simple delayed goal), and this function is based on their input from the higher levels of the sensory systems. In all of this, we should view the neural coding in the frontal cortex as representing, simultaneously, both predictions about forthcoming events *and* the generation of the programmes ('plans') which will result in appropriate responding to those events.

To produce these predictions/plans/goals the dorsal and ventral trends provide, respectively, the 'where' and the 'what' information required to cope with events. The heavy reciprocal interconnections of one level of one trend with the equivalent level of the next trend (e.g. dorsal area 8 with ventral area 8, or orbital area 12 with mesial area 9) are necessary because, especially in terms of formulating a motor programme, 'what' and 'where' are closely related. Thus the dorsal and ventral systems should not be viewed as operating independently, and over half the cells in some prefrontal areas may code both (Rao *et al.* 1997).

For example, when this type of dorsal/ventral scheme was applied to the, inherently simpler, visual system by Ungerleider and Mishkin it was sometimes:

simplified to the point of caricature by others and therefore several caveats should be kept in mind, most of which were explicit or implicit in their original or subsequent formulations. First both the dorsal and ventral systems are interconnected along their entire course and must continually interact (i.e. be 'bound' to each other just as objects are to their locations). Second, each is undoubtedly subdivided. For example, there is evidence for two streams within the dorsal system, one specialized for space and proceeding to posterior parietal cortex and one specialized for analysis of stimulus movement and proceeding to area STP . . . Third, even within a stream or substream, the processing is probably parallel as well as serial. (Gross 1994, p. 463.)

Thus, both the complexity and the order within the frontal cortex may well be a simple reflection of the organization of each of the sensory systems which project to it, coupled with the requirement for both separation and overlap of the input from the different sensory modalities to frontal areas.

On this view the function of the prefrontal cortex is to maintain what could loosely be called attention (e.g. gaze directed at a point in visual space by area 8, working memory directed at a point in, for example, visual cortex by area 46); and this, at the higher levels of abstraction, is a matter of maintaining information about current goals and plans. However, it should be emphasized that this area operates in parallel with other brain systems (such as the visual cortex–amygdala system) which can control behaviour when the contingencies are simple. Thus, as emphasized by Petrides (1991, pp. 269–70), 'patients with frontal cortical excisions exhibit severe impairments in the performance of *conditional* associative tasks. These patients can learn and perform without any difficulty the various responses [used in these tasks] and can readily discriminate between the different stimuli that are used as cues for the production of these responses. They are, however, severely impaired when they have to retrieve from the set of alternative responses those that must be performed in the presence of the various cues' (our emphasis). This is a highly specific form of the distinction between frontal anticipatory/avoidance tendencies and parietal responsive/approach tendencies made by Goldberg (1987) and described in the next section.

As noted by Petrides (1989, p. 86) 'the specialized contributions of different regions of the lateral frontal cortex to learning and memory must not be viewed in isolation from its more general role in the organization of complex behaviour. The capacity to monitor the performance of a series of events is probably an essential component of a neural system which contributes significantly to the development of plans of action and to the execution of such plans.' Indeed, we can suggest that the various types of working memory are not primarily information-holding devices but rather highly anticipatory response programming devices—albeit ones that are coding responses in terms of 'goals' rather than patterns of muscular movement. It should be noted that coding of goal sequencing may be fairly simple, akin to the computer device of a push-down stack.

When monkeys were trained on a delayed sequential reaching task, two main types of delay neurons were found. There were those which coded a goal position on all trials, and those which coded goal position only when that goal was the first in sequence (Funahashi *et al.* 1993). If we assume that the second type of cell has priority in accessing response releasing mechanisms, we can see that the response sequence is effectively held in memory by the fact that 'first goal' cells will control behaviour initially (since they have priority) and, once that goal is reached, they will become silent and thus allow the cells coding the second location to take over. Thus, for both the first and second goals, there is delay activity bridging the necessary intervals, and the specific order of goals is coded by the *lack* of delay activity in cells which would code (in a different version of the task) with high priority for what is in this case the second goal. (Note that this suggestion does not fit with the coding suggested in the computer model of Guigon *et al*. 1995, but it may be more neurally realistic.) Recording from several neurons concurrently also suggests that networks of neurons make 'transitions among distinct states that may reflect discrete steps in the monkey's mental processes' (Seidemann *et al*. 1996, p. 752) which are not obvious from simple post-stimulus time histograms of the activity of any individual cell.

A3.5 The prefrontal cortex, inhibition, and emotion

The orbitofrontal cortex, in contrast to the motor and premotor area, must be viewed as being generally inhibitory of action tendencies. After removal of the prefrontal cortex, monkeys can learn to make a response but suffer not only from the loss of conditional discrimination described by Petrides (1989) but also from a failure of behavioural inhibition similar to that seen in septo-hippocampal-lesioned animals. It is possible, however, that this is the result of the loss of 'somatic markers' which would secondarily result in inhibition rather than a loss of inhibition per se (Damasio 1996). (It has also been suggested that the difference between dorsolateral and orbital cortex is that the former is involved in inhibitory attentional control and the latter in inhibitory affective control; Dias *et al.* 1997.)

The similarity in the effect of orbitofrontal lesions in monkeys to septo-hippocampal lesions in rats extends to increased resistance to extinction (Butter 1969), impaired reversal learning (McEnaney and Butter 1969; Deuel and Mishkin 1977), and impaired single alternation (Iversen and Mishkin 1970; Butters *et al.* 1973), although these deficits do not all follow from the same lesions within the general orbitofrontal area (Rosenkilde 1979). Lesion of the rat homologue of prefrontal cortex has also been reported to reduce the response suppressant effects of punishment (Lipska *et al*. 1998). A final parallel which may be significant is that the hippocampal formation, like the orbital frontal cortex, projects to the dorsolateral frontal cortex. The orbital frontal cortex appears to be distinct from the hippocampus in not affecting conditioned inhibition of fear-potentiated startle or the extinction of freezing (Gewirtz *et al.* 1997).

Lhermitte recently 'made use of a less structured setting than is customarily used for neuropsychological assessment . . . to show that patients with inferior prefrontal lesions display a remarkable tendency to imitate the examiner's gestures and behaviours even when no instructions have been given to do so and even when this imitation entails considerable personal embarrassment. Furthermore, . . . the mere sight of an object may elicit the compulsion to use it, although the patient has not been asked to do so and the context is inappropriate . . . [likewise] a certain setting elicits stereotyped responses that fit the setting but ignore the incongruity of the context. . . . Lhermitte suggests that these behaviours . . . stem from an excessive control of behaviour by external stimuli at the expense of behavioural autonomy. . . . Perhaps this means that the prefrontal cortex underlies functions that are much less 'hard-wired' [than

other areas] and that it acts predominantly as an orchestrator for integrating other cortical areas and for calling up behaviour programs that are appropriate for context' (review by Mesulam 1986, pp. 322, 324).

In monkeys there appears to be an especially close involvement with emotional behaviour in the orbitofrontal cortex, that is the segments which Rosenkilde (1979) terms the inferior prefrontal convexity and the medial orbital cortex, particularly the latter. Stimulation of the medial orbital cortex produces a variety of changes in vegetative and autonomic responses, including slowing or arrest of respiration, changes in blood pressure, inhibition of peristalsis, pupillary dilation, salivation, changes in body temperature, increased plasma cortisol, and decreased levels of circulating eosinophils (Rosenkilde 1979). These changes are generally consistent with a stress reaction. In humans, ventromedial prefrontal damage does not affect autonomic responses to penalties and rewards but does block *anticipatory* autonomic responses during response selection (Bechara *et al*. 1996).

Both the therapeutic effects of prefrontal lesions on anxiety in human beings and the loss of behavioural inhibition in monkeys with orbitofrontal lesions are consistent with an involvement not only in stress but more particularly in anxiety. The specificity to anxiety is sharpened by the fact that prefrontal cortex lesions *increase* the response to fear when this is engendered by a doll, a model snake, a human stare (Butter *et al.* 1968, 1970; Butter and Snyder 1972), or even by another monkey (Deets *et al*. 1970). As can be deduced from their respective functional requirements (Chapter 2), anxiety and fear often involve opposite reactions. The results we have just considered link, therefore, the orbital prefrontal cortex firmly with anxiety, that is reactions to potential threat in the context of conflict, rather than fear or panic, that is simple avoidance and escape reactions to present threat, or defensive reactions in general.

The antagonism between potential and present threat which we have adduced here from the animal data appears to be reflected also in the human data. Thus, there are cases of intractable pain which appear to be helped by prefrontal lesions. Patients treated in this way report that the pain of which they formerly complained is still present, but no longer bothers them; at the same time, the threshold for detection of externally imposed pain is actually lowered (Chapman *et al*. 1948). The same may be true of cingulate lesions (see Vogt 1985, p. 131; see also below). In contrast to cingulate lesions (Tow and Whitty 1953; Powell 1979) and to hippocampal lesions, one of the major side-effects seen after prefrontal leucotomy is apathy and inertia. However, this may be particularly associated with the mesial and dorsolateral areas rather than the orbitofrontal. Given its close anatomical relation to the 'pure' motor areas, this suggests that the dorsal trend in the prefrontal cortex takes an active part in the initiation of motor programmes. In this context, note that the main cortical area which is activated during human orgasm is area 10, which is largely dorsolateral (Tiihonen *et al*. 1994), and the lateral prefrontal cortex appears to influence cardiovascular function by a direct input to the posterolateral hypothalamus, which in turn projects to the rostral ventrolateral medulla (Hardy 1994). The inputs from the homologous areas of the ventral trend, which we have already mentioned, could well have a net inhibitory effect on such initiation. Thus, hippocampal formation, posterior cingulate, and the ventral trend of the frontal cortex could all maintain inhibitory control of the dorsal trend of the frontal cortex.

As noted earlier, the location of frontal lesions is difficult to relate simply to the anatomical subdivisions of Fig. 1.9. However, taken together with the other data we have considered, the effects of these lesions are consistent with the view that progressively higher levels of the frontal cortex contain progressively more anticipatory motor systems which are of two basic types.

The ventral/lateral trend of the frontal cortex (following on from the 'what' analysis carried out by the ventral sensory trends to which it is connected):

controls action that is environmentally based (i.e. data driven). It is normally used when action must be generated in a 'responsive' mode rather than a predictive one. In this operational mode, action follows directly in response to external information *indicating*, or 'triggering,' the action. This control mode would normally be used when (1) there is no inherent temporal structure in the sensory information which would allow predictive control to be utilized, or (2) the situation in which action is occurring takes place in a novel context and/or there is no prior knowledge available that would permit predictive control. . . . This lateral system must be involved in the registration, recognition, and assignment of affective value to an external stimulus which then triggers a responsive, environmentally driven action. (Goldberg 1987, pp. 274, 288; see also Rolls 1996.)

The ventral trend also has major links with the cerebellum rather than the basal ganglia, has its evolutionary origin in the olfactory cortex rather than the hippocampus; and has insular rather than cingulate pro-isocortex.

The dorsal/medial trend (following on from the 'where' analysis of the dorsal sensory trends with which it is connected), is:

probably significantly more developed in human than in primate brain [and] is used to control action when temporal structure is present and memory (i.e. some form of internal model) can be used in conjunction with the selective perception of such temporally ordered information to allow *prospective control of behaviour*. . . . The organism is engaged in a continual process of actively extracting consistent temporal structure from its interactions with the environment. This information . . . is, in turn, used to synthesize a 'model of the future,' which, through the operation of the putative medial frontal premotor system, supports the capacity to prospectively control behaviour and successfully achieve desired outcomes' (Goldberg 1987, pp. 274–5.)

The dorsal trend is also memory driven, prospective, intentional, and anticipatory. As emphasized by Goldberg, these functions are linked to the hippocampal origins of this trend. This link reflects two facts: (1) the proisocortical component of the dorsal trend can be viewed as being essentially cingulate cortex (though, as seen below, we prefer

to treat area 25 as being prefrontal proisocortex and as distinct from cingulate cortex proper); and (2) its subcortical projections are to the basal ganglia (as emphasized above). The functions of the dorsal trend are not only anticipatory but, according to Goldberg, largely designed to produce withdrawal behaviour by the inhibition of approach tendencies organized by the parietal cortex. Thus, frontal and parietal cortical interactions may maintain a balance between approach and avoidance. However, the inhibition may be more complex than this. In rats, at least, lesions of the prelimbic cortex (which may have encroached on anterior cingulate areas) increase fear reactivity during conditioning of a fear response (in contrast to the loss of avoidance usually seen with cingulate lesions, see below). 'One possible scenario is that, while the amygdala determines the emotional significance of threatening stimuli, medial prefrontal cortex uses this information to monitor and give feedback about the internal state of the animal and to update appropriate response outputs dependent on this internal state. Without the internal feedback as to the level of threat posed by the stimulus at any given time, the animal might, for adaptive purposes, remain in the defensive response state longer than necessary' (Morgan and Le Doux 1995, p. 687).

As a result, 'Prefrontal lesions could promote not only an excessive approach to the environment . . . but perhaps also an excessive distance from the intrapsychic processes necessary for insight, foresight and abstraction. In contrast, lesions of the parietal network could promote an avoidance of the extrapersonal world and perhaps an excessive reliance on intrapsychic data, even when those are in conflict with external reality' (Mesulam 1986, cited by Goldberg 1987, p. 287). It is our contention that, in the same way that the operation of working memory is an analogue in the memory domain to the operations of gaze control in the visual domain (or to 'attention' in any of the sensory domains), 'insight, foresight, and abstraction' are related analogues at higher levels of abstraction. Thus the changes observed would not simply be a shift in an approach–avoidance dimension but rather, as demonstrated in the fear-conditioning case, a general loss of anticipatory mechanisms which would give the appearance of an approach–avoidance shift only in some tasks (and probably depending on the precise site of lesion).

It might be thought that, having dealt with 'what' and 'where', we would have all the ingredients required to formulate a plan of action. However, we are still missing 'why'—the critical affective component which determines many of the plans of mice and men. While it is true that the thalamic inputs to the ventral trend in prefrontal cortex carry some information relayed from the hypothalamus, this is relatively modest and discretely organized. By contrast, the thalamic input to cingulate cortex is predominantly of hypothalamic origin and this hypothalamic information is distributed widely in the cingulate cortex. The cingulate, in turn, projects not only to the higher (i.e. less laminated and less myelinated) levels of the ventral trend (where it overlaps with hypothalamic input relayed by the thalamus) but also to all levels of the dorsal trend. We will argue below, therefore, that the cingulate cortex can be viewed as an approximately parallel system which supplies the missing 'why' to the 'where' and 'what' of the parallel dorsal and ventral trends in the prefrontal cortex.

A3.6 The cingulate cortex

The *gyrus cinguli*, together with the hypothalamus and hippocampus, was proposed by Papez 'as representing theoretically the anatomic basis of the emotions' (Papez 1937, in Arnold 1968, p. 302). It receives major input from the mammillary bodies of the hypothalamus via the anterior thalamic nuclei and so 'may be looked on as the receptive region for the experiencing of emotion as a result of impulses coming from the hypothalamic region, in the same way as the area striata is considered the receptive cortex for photic excitations coming from the retina' (Arnold 1968, pp. 305–6). Given the input from the anterior thalamus, the cingulate cortex should be viewed as being more similar to the frontal than the simple sensory receptive cortex, since major input from the anterior and mediodorsal thalamus is one of the features which conventionally distinguishes the frontal cortex from the posterior cortex. The cingulate cortex can, in particular, be related to the ventral trend of the prefrontal cortex to which the thalamus relays hypothalamic information.

A relation to the prefrontal cortex is particularly obvious with anterior aspects of the cingulate which are contiguous with motor, premotor, and frontal cortex proper. However, we will also argue that emotional perception has a much tighter relationship to action than perception of the external world. As a result of this, despite its links with the frontal and particularly the motor cortex, we can still view the cingulate as 'the receptive region for the experiencing of emotion'. This latter view is also consistent with the contiguity of posterior aspects of the cingulate cortex to the somatosensory cortex.

We will argue that the cingulate cortex should be viewed as consisting of two fundamentally distinct (but reciprocally connected) modules. The cingulate cortex posterior to the central sulcus is related to (but not part of) the posterior cortex (with its thalamic input playing something of the role of, for example, the geniculate and collicular input to the striate cortex). The cingulate cortex anterior to the central sulcus is related to (but not part of) the frontal (motor/premotor) cortex (with its thalamic input playing an equivalent part to the anterior and dorsomedial thalamic input to the frontal cortex). However, the thalamic nuclei which provide input to the posterior cingulate include ones which project to the frontal cortex; and, at least with input from the pain pathways, the anterior cingulate acts as the primary sensory cortex (Rainville *et al*. 1997). So, both anterior and posterior cingulate combine, in their different ways, features from both frontal 'action' systems and posterior 'perception' systems. In this sense the cingulate cortex is quite distinct from both the frontal and posterior cortex, and we will treat it (together with the septo-hippocampal system) as a third major, 'mesial', division of the cortical mantle. On this view, the posterior and

anterior cingulate cortex are differentiated, not by relations to the posterior and anterior cortex respectively, but, as with the frontal and posterior cortex, by the division of the mesial cortex into parallel 'dorsal' and 'ventral' trends. Thus, while the cingulate cortex as a whole receives input, relayed by the thalamus, from the mammillary bodies, and while the posterior cingulate receives direct input from the lateral hypothalamus and the ventral tegmental area, there are many reasons why we can treat the cingulate neither as a homogeneous area nor solely as primary receiving cortex for hypothalamic information (Vogt 1985). (In the following paragraphs, where no reference is given for a statement, the source is Vogt's review; see Vogt *et al*. 1995 for the equivalence between subdivisions of monkey and human cingulate.) We must divide the cingulate cortex into a number of quite discrete areas and, exactly as with the frontal cortex, will do so on the basis of parallel 'dorsal' and 'ventral' trends, each subdivided into architectonically progressive levels.

A3.7 Anatomy of the cingulate cortex

The least laminated, and the most posterior and ventral, of the divisions of the cingulate is the periallocortex of areas 29a and 29b which, following Vogt (1985), we will treat as a single region 29ab. (The fact that 29ab abuts the allocortex of the subiculum and receives unidirectional input from it will prove important shortly.) Next, and effectively transitional between the periallocortex and the proisocortex, are area 29c in the posterior cingulate and area 24a in the anterior cingulate. These can be viewed, cytoarchitectonically, as a continuous strip parallel to the corpus callosum, but because of their connections with other parts of the brain we will treat them as quite separate areas (posterior and frontal, respectively). Next we have the proisocortex of areas 29d (posterior) and 24b (frontal) and finally, in monkeys but probably not rats, we have the true isocortex of area 23 (posterior). In much of what follows we will be forced to conflate area 24a with area 24b since the literature refers simply to area 24, but if there is parallelism with the organization of the frontal cortex then area 24a would project more diffusely and to less laminated areas of the frontal cortex than would area 24b. Certainly, the information received by 24a and 24b differs at least in respect to their inputs from 29a–c and 29d, respectively—which in turn differ (see below) in that 29a–c receive input from the subiculum, whereas 29d does not. If there is a high degree of differentiation of area 24, this could account for the rather wide spread of its afferents to the prefrontal cortex. We can speculate that the individual architectonic subareas of area 24 each have distinct connections to the prefrontal cortex which follow the rules for frontal–frontal connections (Barbas and Pandya 1991, p. 42) better than does area 24 as a whole.

Since area 24 is reciprocally connected to all of the subdivisions of the posterior cingulate cortex, and since areas 23 and 24 have partially overlapping efferents to the defence system, we have chosen to represent the anterior and posterior cingulate as two parallel, interconnected, related modules. As noted above, we see this parallelism as matching that of the dorsal and ventral trends of the prefrontal cortex discussed above. However, unlike the frontal cortex, the two components of the cingulate are not distinguishable by connections to the dorsal and ventral trends of the unimodal sensory cortex, respectively. Rather, any dorsal/ventral distinction must be derived by analogy to the functional differentiation of external sensory information by the classic sensory cortices.

Vogt argues that area 25 should be classified as cingulate rather than prefrontal cortex (because of its extensive connections with the cingulate), but we will treat area 25 as prefrontal. Our argument is as follows. As we move to progressively less laminated cortex within the dorsal and ventral trends of the prefrontal cortex we come to areas of the proisocortex which abut the periallocortex (areas 13, 25, 32, and, potentially, 24). Area 32 does not abut the periallocortex directly but is continuous with area 25 which does. Area 24 extends some way into prefrontal territory but, particularly in terms of its thalamic connections, should clearly be classified as cingulate. This leaves area 13 (part of the ventral trend) and area 25. If area 25 were not classified as prefrontal cortex then the dorsal trend would be discontinuous with its supposed periallocortical primordium. Furthermore, area 25, like area 32 and area 13, receives input from the tertiary auditory association cortex whereas area 24 does not. For all these reasons (and for the symmetry it provides to Fig. 1.9) we prefer to classify area 25 as prefrontal cortex. What of its connections with the cingulate? Certainly, as we shall see, cingulate cortical areas are greatly interconnected and this is a property shared by area 25. However, the proisocortex and least laminated isocortex of the dorsal and ventral trends in the prefrontal cortex are extensively interconnected with each other and with, at least, area 24 of the cingulate cortex. In that sense, the relatively weak projection of area 25 to posterior cingulate can be viewed as following the same connectional principles as other frontal proisocortex but reaching somewhat more posteriorly because of its more posterior location. Finally, in addition to providing a symmetrical picture of the prefrontal cortex, exclusion of area 25 will allow us to provide a symmetrical picture of the cingulate cortex also.

A3.8 The anterior cingulate (area 24)

Papez's 'sensory' view of the cingulate cortex has this to recommend it—the relationship of the cingulate cortex to the hypothalamus and the thalamus is appropriate if it were the primary emotional receiving cortex and the hypothalamus were the source of emotional information.

The anterior cingulate receives relatively less topographically organized thalamic input than the posterior cingulate, with input from the anteromedial nucleus (which it shares with the posterior cingulate) and from the mediodorsal nucleus (which it shares with the prefrontal cortex but not the posterior cingulate). Of most importance for the picture we shall present of cingulate function, the anterior cingulate also receives direct input from the 'affective' (medial, diffuse, non-localized) pain system and sends direct output to the periaqueductal grey and the amygdala. As

a result, stimulation of the anterior cingulate generates a wide variety of autonomic and somatic responses (affecting blood pressure, heart rate, respiration, pupils, piloerection, vocalization). Likewise, 'behavioural deficits which result from [anterior] cingulate cortex ablation may be interpreted in the light of the role of cingulate cortex in producing affective responses to noxious stimuli. Numerous studies have shown that ablations of cingulate cortex produced deficiencies in active, shock avoidance learning . . . [without] sensory (visual or auditory) or motor deficits [and] neurons in area 24 . . . develop differential responsiveness to positive and negative conditioned stimuli before neurons in posterior cingulate cortex' (Vogt 1985, p. 132; but see also Morgan and Le Doux 1995). Likewise, anterior and posterior cingulate cortex can be doubly dissociated, with disruption of the anterior cingulate impairing serial reversal learning and classically conditioned bradycardia but not spatial learning in the water maze, conditional visual discrimination or passive avoidance, and disruption of the posterior cingulate impairing spatial learning in the water maze and the later stages of conditional visual discrimination but not any of the tasks affected by anterior cingulate lesions (see Riekkinen *et al.* 1995; Bussey *et al*. 1996).

Thus anterior cingulate appears to be the major cortical motor component of the active defence system for which the amygdala is the major subcortical component. In this, anterior cingulate–amygdala links can be seen as equivalent to frontal–basal ganglia links, but dealing with a range of relatively phylogenetically fixed, primary affective effector programmes (including skeletal, autonomic, and hormonal systems; Mason 1975; see McNaughton 1989, p. 55) as opposed to the more flexible motor programmes controlled by the frontal–basal ganglia system.

From this point of view, the cingulate cortex as a whole appears much more like an emotional motor programming area than simply 'the receptive region for the experiencing of emotion' of Papez's view. First, a large number of the output areas are cortical or subcortical motor control areas. Second, the pattern of connection with the prefrontal cortex does not match that of the true sensory cortices: in these, the most laminar sensory cortex projects to the most laminar areas of the prefrontal cortex, and the least laminar sensory cortex projects to the least laminar areas of the prefrontal cortex (see below). Cingulate projections appear to show no such laminar relation and to be much more widespread (stretching all the way from area 32 through to area 6) even than those of other frontal areas. Third, the anterior cingulate cortex is continuous with areas 4 and 6 and is closely connected to them. Indeed, area 24c (which contains somatotopic motor maps, see below) might by some be considered to be cingulate cortex—although we would see 24ab as the likely limit in the context of our present analysis.

However, given their different cytoarchitectonics, the anterior cingulate cannot represent an internal 'visceral' extension of the external 'motor homunculus' any more than the posterior cingulate could represent the internal visceral extension of the 'somatosensory homunculus'. Rather, as with the increasing depth of processing associated with the less laminar areas of the dorsal (where) and ventral (what) trends in the frontal cortex, it seems likely that the progressive lamination of the cingulate provides increased depth of processing in relation to 'why'.

Here we should note that some types of basic emotional information may not require the same degree of sophisticated analysis as visual, auditory, and somatosensory data. Pain, hunger, thirst, and lust are all fairly elemental and probably need no complicated machinery either to assess their quality or deduce their presence from varied scraps of environmental evidence. The anterior cingulate cortex may best be viewed then as *both* primary emotional receiving cortex *and* primary emotional motor cortex—with no logical distinction possible between these nominally different functions. Certainly, with emotional events we have the clearest case for MacKay's (1987) equation of perception with action. To perceive pain in the *affective* as opposed to simple sensory meaning of the word *is* to generate a motor command to escape it, and we should note here that 'cingulumotomy can alleviate a patient's affective responses to painful stimuli, without interrupting his or her ability to localize a noxious stimulus . . . However, frontal cortex shares many of the pharmacological and connectional characteristics noted for cingulate cortex, so it is unlikely that the cingulate region is the only cortex involved in 'pain-related' functions' (Vogt 1985, p. 131).

In this context, the cortical connections of area 24 are particularly interesting. As we will see, this region connects reciprocally, and apparently topographically, with all the subareas of the posterior cingulate, each of which has their own distinctive thalamic input. It also has extensive, and probably reciprocal, connections with most of the dorsal trend (and much of the ventral trend) of the prefrontal cortex. Finally, its distinctive thalamic input is from the anteromedial nucleus (which innervates all of the subdivisions of the posterior cingulate except area 23) and from the mediodorsal nucleus (which innervates all of the subdivisions of the prefrontal cortex, but none of the posterior cingulate). Since (see above) the input from the mediodorsal nucleus to the prefrontal cortex is topographically organized with respect to architectonic subdivisions, it seems likely that there is similar, if not identical, topographic organization of its input to area 24 (but to our knowledge this has not yet been demonstrated).

On this view, the same information would be sent to the prefrontal cortex from the mediodorsal thalamus, in a topographic manner, both directly and via matching topographic subfields of area 24. Area 24 would also receive information from each of the subdivisions of the posterior cingulate (areas 29a–d, 23) each with its distinct thalamic, sensory cortical, and temporal influences and also (matching the parallel topographic input from the mediodorsal nucleus to both the prefrontal cortex and area 24) would receive topographically mapped input from the anteromedial nucleus both directly and via the different subdivisions of the posterior cingulate.

By analogy with the frontal cortex, then, we can see the anterior cingulate as paralleling the ventral trend of the prefrontal cortex in being 'responsive' rather than 'anticipatory', in being connected to many levels of the dorsal trend of the prefrontal cortex, and in dealing with the 'what' (e.g. a non-localized pain signal) rather than the

'where' of things. It may be no accident that it is relatively smaller than the posterior cingulate in the same way as the ventral trend in the frontal cortex is relatively smaller than the dorsal. The extensive reciprocal connections of the cingulate with the prefrontal cortex and the connections of the cingulate with the motor cortex are, then, accounted for by the necessity to coordinate the control of behaviour by two separate areas which control motor programmes: a cingulate area (more affectively dominated and concerned with more innate motor plans) and a frontal area (more cognitively dominated and concerned with less innate and more flexible motor plans).
Area 24 also has major (apparently reciprocated) input from the entorhinal cortex, perirhinal cortex, parahippocampal cortex, and prosubiculum (Arikuni *et al.* 1994).
It is interesting to preview here the parallelism between the anterior and posterior cingulate which we will discuss below. Both receive fairly similar thalamic input and both send fairly similar direct output to the defence system. They differ in that the anterior cingulate is the primary target of the 'affective' pain system, while the posterior cingulate is the primary target of posterior cortical input (much of it very highly processed). Despite their reciprocal interconnections, stimulation of the posterior cingulate produces none of the autonomic reactions of the anterior cingulate and must, therefore, be presumed to be largely inhibitory.
This raises a possibility: can we identify the posterior cingulate as a functional equivalent of the dorsal trend in the prefrontal cortex in the same way as we have just identified the anterior cingulate as a functional equivalent of the ventral trend?

A3.9 The posterior cingulate (areas 29, 30, 23)

The posterior cingulate, like the anterior, receives major input from the thalamus. The anteromedial nucleus projects to all of the subdivisions of the cingulate (anterior and posterior) except area 23. However, the other nuclei are somewhat more localized in their terminations and (as with their projections to prefrontal cortex) can be used to differentiate the subdivisions of the posterior cingulate. The anterodorsal nucleus projects predominantly to area 29ab and the anteroventral nucleus to area 29c, while area 29d receives input from the lateroposterior and laterodorsal nuclei (which some suggest should therefore be classified as 'anterior thalamus'). The projections from the anterodorsal and anteroventral nuclei are topographically organized, with caudal aspects of the nuclei projecting to rostral aspects of the posterior cingulate and rostral aspects projecting to the caudal cingulate (Van Groen and Wyss 1995). We have not seen any report which demonstrates whether or not area 23 receives thalamic input. On the other hand, in apparent distinction to the other parts of the posterior cingulate, it receives input from a variety of tertiary sensory association cortices, from auditory association cortex (Yukie 1995), and from the polymodal parahippocampal cortex. (Areas 29ab and 29d receive input from the primary visual cortex.)
Of particular interest is the input from hippocampal regions. The parahippocampal isocortex (areas TH and TF) projects to the isocortical area 23, while the relatively undifferentiated, allocortical, subiculum projects to the relatively undifferentiated periallocortical and transitional 29a–c. This matching of cytoarchitectonics between sending and receiving areas is something we have already seen in the connections between sensory cortex and frontal cortex and in the interconnections of the dorsal and ventral trends. The subicular input is of especial interest because it is one of the few major inputs to the cingulate and prefrontal cortex which is not reciprocated. Here, we have a further reason to see the posterior cingulate (which receives the subicular input) as distinct from the anterior cingulate, and a functional linking of the posterior cingulate with the hippocampal formation is reinforced by its involvement, unlike the anterior cingulate, in water maze learning (e.g. Riekkinen *et al.* 1995)—a paradigmatic test of hippocampal dysfunction.
This organization suggests a hierarchical parallel system, with a general flow of information from the parahippocampal area to area 23 proceeding at a number of levels of processing. If we consider the fate of information originating in the parahippocampal cortex, we see that this information is sent directly to the most laminated part of the cingulate cortex (area 23), and it is also relayed, after passage through the entire hippocampal formation, to the least laminated part of the cingulate cortex (area 29a–c). This would fit with a general flow of information within the posterior cingulate from relatively undifferentiated and less myelinated cortex to more differentiated and more myelinated, with the slower, more complex processing (parahippocampal–hippocampal–29–23) ultimately exerting control over the faster, simpler processing (parahippocampal–23). Note that, as with the connections of the prefrontal cortex, which we dealt with above, 'lower' levels, informationally speaking, have the most differentiated cortex and most myelinated, fastest operating neurons. In this context, it would be particularly interesting to know the precise connectivity and main direction of flow of information between the different levels of the posterior cingulate.
The posterior cingulate cortex also has return projections to the presubiculum, subiculum, entorhinal, perirhinal, and parahippocampal cortex, which show some signs of a mapping on the basis of the degree of differentiation of the areas concerned (Shibata 1994; see Wyss and Van Groen 1992 for review).
These data all suggest that the cingulate cortex stands in the same relation to the hippocampal and parahippocampal areas as the frontal cortex stands to the unimodal sensory cortices. Since the hippocampal formation itself has a largely unidirectional flow of information within it (unlike most connections within either the frontal or posterior cortex), and since the subiculum (as the main output station of the hippocampal formation) has a largely unidirectional connection with the posterior cingulate, it appears that the hippocampal formation and the posterior cingulate are very closely related. Certainly, the subiculum receives essentially the same thalamic inputs as does

area 29. If we see the posterior cingulate as analogous to the frontal cortex, then this would argue that the hippocampal formation is analogous to the unimodal association cortex. Thus, if the parahippocampal and perirhinal cortex can be viewed as the 'dorsal' and 'ventral' components, respectively, of the 'primary' polysensory cortex (and hence, like the primary unimodal cortex, as the most laminated part of the system), then the subicular allocortex could be viewed as the tertiary polymodal association cortex.

While, as we have noted, the subiculum projects directly (and unidirectionally) mainly to area 29c, it can also influence area 29c via the anteroventral thalamus (AVT; through both a direct reciprocal projection to the AVT and a relay to the AVT in the medial mammillary bodies). It also projects directly to 29ab (which it can in addition influence via the AMT and a relay to the AMT from the mammillary bodies). It can influence the remainder of the cingulate (and some areas of the prefrontal cortex) indirectly via the anteromedial thalamic nucleus (to which it projects both directly and via the medial mammillary bodies).

As already noted, the dorsolateral prefrontal cortex and the orbital frontal cortex project to both area 24 and, to a lesser extent, area 23. The dorsolateral prefrontal cortex is also reciprocally connected to the parahippocampal area (see Goldman-Rakic and Friedman 1991) and so can influence information travelling from the parahippocampal area to area 23, not only directly at its origin and its termination, but also indirectly via its influence on area 24, which projects to area 23. It should be noted that, like its projection to the cingulate cortex, the subicular projection to the dorsolateral prefrontal cortex is unidirectional (Goldman-Rakic *et al.* 1984).

Finally, we should consider the specific role of area 24 which provides one 'major source of cortical afferents to posterior cingulate cortex' (Vogt 1985, p. 118) and appears to occupy a nodal position with respect to the posterior cingulate (Fig. 1.9). Area 24 as a whole is connected with each of 29ab, 29c, 29d, and 23. However, there is some indication that these connections may be topographically and architectonically mapped. Thus area 24a connects to area 29c, while area 24b connects to area 29d. All of these connections appear to be reciprocal, as would be expected from the reciprocal connections between similar architectonic levels of the dorsal and ventral trends in the prefrontal cortex. Area 24 (the anterior cingulate), like areas 29a–d, receives input from the anteromedial nucleus of the thalamus. It is distinguished from them by receiving input also from the mediodorsal nucleus.

All of these anatomical data are consistent with the view of the posterior cingulate as coding the 'where' of affectively significant information to match the 'what' of the anterior cingulate. However, they leave very much open the precise significance of 'where' in this context—and for this, and a full view of the functions of the posterior cingulate, we will need to consider both its outputs and some recent detailed theoretical views.

A3.10 Outputs of the cingulate cortices

So far, we have discussed the cingulate cortex as though the flow of information is solely in one direction: from the thalamus, the temporal cortex, or the frontal cortex to the cingulate cortex. However, there are reciprocal connections in virtually all these cases. (The exceptions are the subiculum and anterodorsal thalamus, which send input to the cingulate, and the postsubiculum, which receives output from the cingulate.) We have ignored these reciprocal connections so far because they appear to carry feedback, while the connections we have been discussing have the general properties of feedforward links (they terminate in layer I of the cingulate, are generally heavier, and are more discretely organized). Thus, there appears to be considerable recursive processing capacity in this system, but the general flow of information appears to be in the direction we described at the outset.

It remains to describe the non-feedback outputs of the cingulate cortex. 'The rostral portion of the cingulate gyrus (Area 24) projects to the premotor cortex (Areas 8 and 6), the supplementary motor region (MII), and the orbitofrontal cortex (Area 12). The posterior part of the cingulate gyrus (Area 23) projects to the lateral prefrontal (Area 46) and orbitofrontal (Area 11) regions. . . . Most of these connections . . . are reciprocal' (Pandya and Barnes 1987; see also Arikuni *et al.* 1994). In addition, both areas 23 and 24 (like the dorsolateral frontal cortex) project to the inferotemporal cortex (area 7). The anterior cingulate is connected subcortically to the basolateral amygdala, the periaqueductal and pontine grey. The posterior cingulate is connected to the periaqueductal grey, the superior colliculus, and, crucially for recent theoretical views, to the caudate nucleus. These subcortical connections of the cingulate cortex show 'a very precise topography of brainstem connections which may underlie the visceral and somatic motor functions of the cingulate cortex, as well as the ability of the cingulate cortex to modulate sensory information and emotional behaviour' (Wyss and Sripanidkulchai 1984).

In terms of the theory of this book, it is also particularly important, as pointed out by Swanson (1978), that access to the cingulate cortex allows the septo-hippocampal system to influence, albeit at one remove, activity in the striato-thalamo-motor cortical system, the prefrontal cortex (see below) and the cerebellum as well as, more directly, the cingulate–basal ganglia–thalamus–cingulate loop. Also, in relation to our ascent of the hierarchical 'threat' system, it is important to note that the anterior cingulate cortex is directly connected to both the periaqueductal grey and the amygdala. Thus, the hippocampus receives a major input from the amygdala, and can reciprocally affect the amygdala and lower levels of the threat system via the posterior and thence the anterior cingulate. But note that it is the anterior cingulate rather than the hippocampus that receives direct pain input. Thus, the hippocampal system must be seen as being in a position to modulate action which would otherwise be taken by the anterior cingulate.

In drawing parallels between the frontal and the cingulate cortex, we have suggested that the anterior cingulate represents the equivalent of the ventral trend in the frontal cortex—being largely responsive and dealing with immediate emotional expression. For this purpose, it receives direct input from the pain system and has, as one of its

major outputs, the amygdala. Thus the anterior cingulate and the amygdala are both involved in the control of active avoidance behaviour and the anterior cingulate can be viewed as an alternative motor programming area to the ventral trend of the prefrontal cortex—the cingulate being in control when output needs to go via areas such as the amygdala, and the ventral trend of the prefrontal cortex being in control when output needs to go through areas such as the basal ganglia.

On this view, the posterior cingulate should represent the equivalent of the dorsal trend in the prefrontal cortex and should, therefore, be largely memory driven and prospective, with an emphasis on the anticipation of events rather than reaction to them. For this purpose, it receives highly processed information which has originated not only in the polymodal cortex but also in the amygdala and which has then been further processed by the various layers of the hippocampal formation (in its guise of polymodal association cortex). The posterior cingulate has as major outputs the superior colliculus and the basal ganglia, which would give it similar 'attentional' and 'motor' control to the prefrontal cortex. If we see the distinction between the anterior cingulate and the prefrontal cortex as lying in a major involvement of the former in responsive, motor programmes (or plans) which are affective, then we would predict that the posterior cingulate should be involved in affective, *anticipatory*, motor programmes (or plans).

A3.11 Firing of single cells in the cingulate cortex

A role for the cingulate cortex in the control of specific movements is suggested by the fact that within the immediately adjacent (and interconnected) area 23c (or in a transitional zone between 23c and 24c) there are cells which 'exhibited strong activity modulations during grasping, lifting and holding an object with the contralateral thumb and index finger . . . the dense concentration of hand-related neurons . . . suggests that this territory can be considered a distinct hand area, which can be dissociated from a region representing the more proximal arm. These data support the notion of a clear somatotopic organization within the ventral cingulate area' (Cadoret and Smith 1995). Microstimulation of recording sites in this area elicited brief movements of fingers, wrist, or thumb. This and two adjacent related areas (a second area within the cingulate sulcus and the supplementary motor area) all have similar, topographically organized, corticospinal projections (He, Du, and Strick, 1995; see also Luppino *et al*. 1994). These two maps within the cingulate sulcus are within a transitional area between the supplementary motor area and what we have considered above as the cingulate proper (which would start at 24a,b and 23a,b), but their close relation to the cingulate proper implies a role for this in some fairly immediate aspect of motor control.

There is also evidence from human depth-evoked potentials that the posterior and anterior cingulate respond to: rare or novel stimuli, regardless of whether they are task relevant or directly attended, and in both the visual and the auditory modalities. These task correlates imply involuntary orientation of attention and are similar to those which have been described for the orienting response. . . . [the form of evoked potentials observed] is most prominent in the supramarginal gyrus and posterior cingulate gyrus and frontally in the anterior cingulate gyrus and area 46 of the dorsolateral prefrontal cortex. These areas are strongly interconnected with each other and, in addition, have similar afferent and efferent connections with other cortical and subcortical areas. Together, these areas have been hypothesized to constitute the cerebral network for the orientation of attention. . . . Recording studies in monkeys suggest that [posterior cingulate cortex like parietal cortex] is concerned with spatial localization. [The evoked potential] thus appears to represent activity that is evoked by stimuli that demand processing because of their potential biological significance. This activity prominently engages areas that can localize in space the evoking stimuli, as well as those that can help prepare the organism to make a rapid response. (Halgren *et al*. 1995.)

In the anterior cingulate, in particular, 'biological relevance' appears to involve the perception of pain (Pagni and Canavero 1993)—the most imperative of all stimuli. Consistent with Halgren's 'attentional' view of the cingulate, patients who have received bilateral anterior cingulotomy for intractable pain show decreased habituation of orienting responses as measured by the galvanic skin response (Cohen *et al*. 1994). There is also evidence for activation of the cingulate cortex by visual stimuli during a difficult discrimination task, suggesting that there could be a 'cingulate visual area' (Vanduffel *et al*. 1995), but other interpretations are possible, as we will see when we discuss Gabriel's experiments, below. Niki and Watanabe (1976) recorded unit responses during the delay period while monkeys performed a delayed behavioural response task. Cingulate units fired in relation to the cue (no longer physically present, i.e. delay neurons) or the direction of the impending response.

Gabriel and co-workers have carried out an extensive analysis of the role of the cingulate cortex in avoidance conditioning (see Gabriel 1990 for review). In their basic paradigm, they recorded multi-unit[2] responses in rabbits during a discriminated avoidance response in a running wheel. The rabbit's task was to run in response to S+ but not to S– (tones of different frequencies). In some cases, after acquisition, the significance of S+ and S– was interchanged. In both the anterior and posterior cingulate cortex and the mediodorsal and anteroventral thalamus, unit responses differentiated between S+ and S– during acquisition, by firing at a greater rate to S+.

During reversal learning, neuronal firing in the anterior cingulate also demonstrates reversal. By contrast, at the start of reversal learning, neurons in the posterior cingulate showed an even *stronger* discrimination between the stimuli, and this continued to be appropriate to the *old* learning. Behavioural reversal was accomplished with no change in the pattern of unit responses in the posterior cingulate cortex, and only incomplete reversal of the pattern of firing of some thalamic neurons (Gabriel *et al.* 1977).

Other differences between the anterior and posterior cingulate are:

more rapid development and decline of training-induced activity in the anterior than in the posterior . . . anterior cingulate cortical neurons can alter their discharge magnitudes in accordance with day-to-day changes in CS duration . . . posterior cingulate records exhibited sensitivity to . . . unexpected durations [which] implicates this region in mismatch functions . . . CS rareness per se enhances anterior cingulate discharges [whereas] the discharge of neurons in the posterior cingulate in response to the CS+ appears to be governed primarily by CS novelty/familiarity. (Gabriel 1990, pp. 475, 476, 478, 480.)

Lesions of the anterior cingulate cortex block acquisition of this avoidance task (but not unconditioned responses to the stimuli used), as do lesions of the thalamus. The latter block training-induced cingulate activity, but cingulate lesions do not block thalamic training-induced activity. Interestingly (and importantly for our theory), lesions of the subiculum *decrease* cingulate activity, increase thalamic activity, and do not impair learning of the task. The subicular lesions increased avoidance responses at times when training contingencies were altered. Lesions restricted to either the posterior or the anterior cingulate produced only weak effects on avoidance. Anterior lesions delayed acquisition without impairing final performance, while posterior lesions produced a decrement in performance late in training.

In Gabriel's view:

diencephalic processes centered in the [anteroventral] and [anterodorsal] thalamic nuclei are critical to the operation of the GO system, which mediates acquisition and performance of the discriminative avoidance CR. Neurons in the anterior and cingulate cortices are also involved in GO system functions, but principally as conduits for discharges of diencephalic origin en route to the motor system. . . . [They] are not essential for CR acquisition or performance [but] govern the CR in an inhibitory fashion. That is, the telencephalic system acts as a STOP system to block CR output continuously, until and unless the criteria for the presence of the occasion-setting stimuli have been met. . . . The anterior and the posterior system share the GO and STOP functions . . . [but] the two systems differ in the manner in which they exhibit the GO and STOP functions. The anterior system exhibits properties suggesting that it functions as a recency or working memory system, whereas the properties of the posterior system implicate it in primacy, or intermediate/long-term memory functions. It should be noted that information provided by the primacy and recency systems is exactly the input needed by the hypothetical comparator, if it is to evaluate the compatibility of past and present environmental circumstances. That is, the recency code conveyed by anterior cingulate neurons may provide the comparator with the representation of the current status of the training environment, whereas the primacy code conveyed by posterior cingulate neurons may provide the comparator with mnemonic data representing environmental features expected on the basis of the animal's accumulation of task-related experience. (Gabriel 1990, p. 481.)

While developed from the study of avoidance learning, Gabriel's theory should be viewed as more general since 'rats' performance in delayed alternation and spatial mapping tasks, based on appetitive motivation, is disrupted by cingulate cortical and limbic thalamic damage. . . . Yet, it is possible that the principles of operation and specific information flows in these circuits differ depending on whether aversive or appetitive motivation is operating' (Gabriel 1990, p. 483). A role for the posterior (but not the anterior) cingulate in memory is suggested by its atrophy in Alzheimer's disease (Minoshima *et al.* 1994). Cingulate lesions which spare retrosplenial cortex do not appear to impair delayed non-matching to position (Murray *et al*. 1989).

However, it should be noted that cytotoxic lesions restricted to either the anterior or the posterior cingulate cortex have no effects on delayed non-matching to position, spatial reversal learning, or forced alternation (Neave *et al*. 1994). It may be that large cytotoxic lesions of both structures are required (cf. Gabriel's results), but another possibility (Aggleton *et al*. 1995; Warburton *et al.* 1998)) is that previously reported effects of cingulate damage on spatial tasks (e.g. Sutherland *et al*. 1988) are due to interruption of the cingulum bundle, or the angular bundle, both of which provide input to the hippocampus. This could account for the notable parallels in both lesion effects and sparing between fornix lesions and cingulate lesions (e.g. Markowska *et al*. 1989). Against this can be set the fact that posterior cingulate cells encode eye movement and position in a way 'which may reflect the participation of this area in assigning spatial coordinates to retinal images' (Olson *et al.* 1996, p. 3285).

A3.12 Conclusion

An overview of the data on the prefrontal cortex, cingulate cortex, and the relationship between them is provided in Chapter 6 of the printed text (Section 6.12, p. 131), along with our view of the possible role played by these two areas in anxiety (Section 6.13, p. 135). Following many others (Chapters 1 and 6 and Fig. 1.9), we see both areas as hierarchically organized, with 'higher' anatomical layers dealing with higher levels of anticipation of action. We also view the frontal and cingulate cortex, as a whole, as being organized into three parallel 'trends': dorsal, ventral, and mesial. These correspond to the processing of the 'where', 'what', and 'why' aspects of action respectively. Importantly, we see prefrontal and cingulate cortex as resolving (i.e. ordering) conflicts between *successive subgoals* in a task, thus differing from the hippocampus in that the latter resolves *concurrent goal–goal* conflicts. This distinction is additional to the one we make between this hippocampal role and the role of the defence system and other motor systems in resolving *motor programme conflicts* without goal conflict. Where there is concurrent goal conflict within a task which *also* involves conflict between successive goals, then both the septo-hippocampal system and the prefrontal cortex will be involved.

Analysing the fine grain details of septo-hippocampal functions is the business of the following appendices.

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Notes

1. We will follow Goldman-Rakic in this section in talking about ‘working memory’. This has some implication that the information being encoded is required for some ongoing motor programme. However, we should bear in mind that the same mechanisms could well be engaged outside the context of current motor acts and ‘working memory’ is likely to be just one form of ‘active memory’ (Fuster 1995; see also Section 9.3 in the printed text)—and that its ‘working’ aspect may be an accident of the fact that it is easily demonstrated for technical reasons only when an animal is required to execute some specific action.
2. The fact that multi-unit records combine activity from different types of neurons means that the results of these experiments must be treated with some caution.