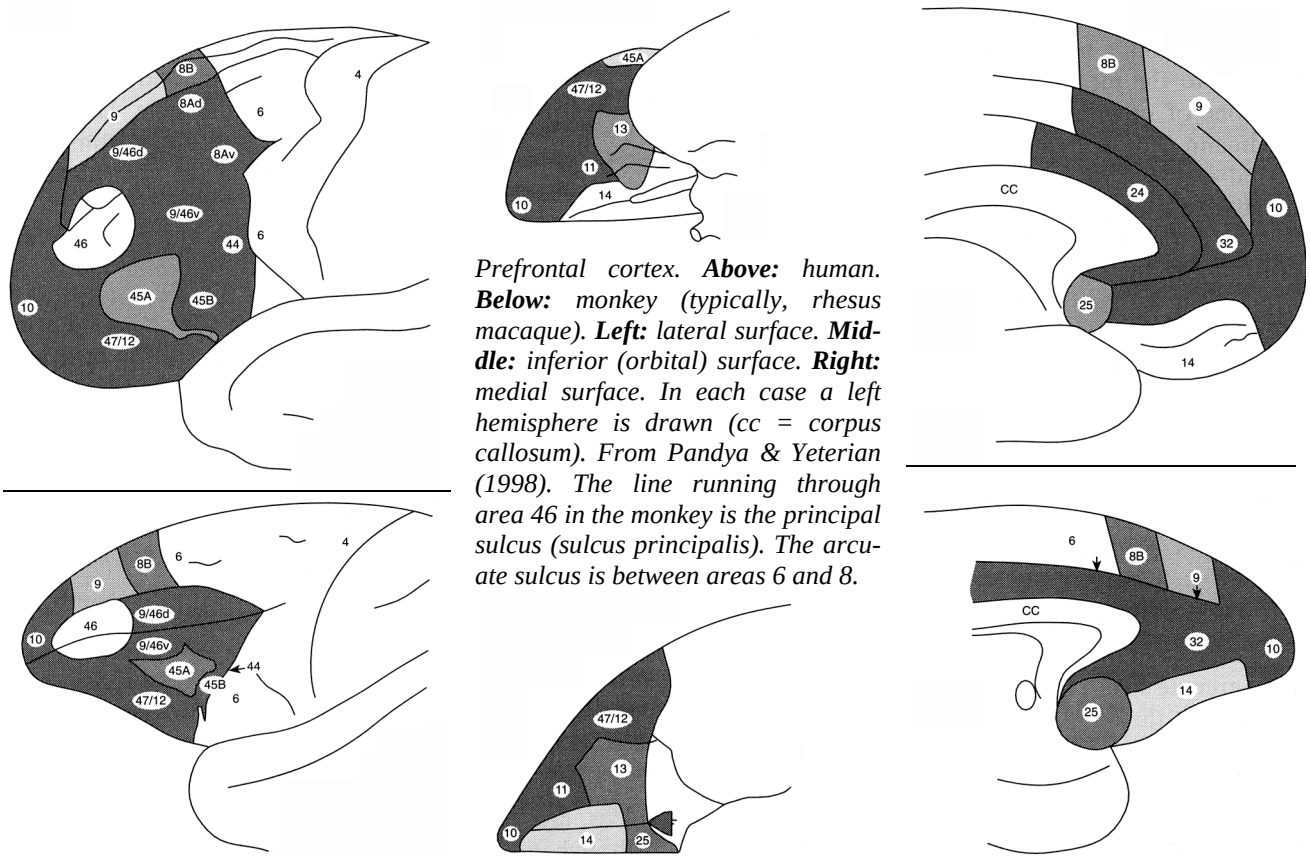
This is the last lecture in this series — so please fill in a feedback form. Thank you. I hope you've enjoyed them.

Overview

We will consider the anatomy of the prefrontal cortex (PFC), and syndromes that follow PFC damage in humans, illustrating their heterogeneity. Studies that aim to model human PFC dysfunction in animals will be considered; these also illustrate the modularity of processing in subregions of the PFC. This is an enormous literature, so we will be selective. Neuropsychiatric implications will be highlighted.

Anatomy of the prefrontal cortex (PFC)

The PFC is that region of the frontal lobes anterior to primary motor cortex (Brodmann's area 4) and premotor cortex (area 6). The PFC can be defined by cytoarchitectonic features (e.g. a distinct granular layer 4 in primates), by corticocortical connections, by thalamocortical projections (e.g. the cortex that receives input from the mediodorsal nucleus of the thalamus), and by neuromodulatory inputs (e.g. a dopaminergic projection from the midbrain). The size of the PFC varies enormously across species; for example, defined cytoarchitectonically, the PFC is 3.5% of total cortex in the cat and 29% in the human (see Fuster, 1997). There has been debate on cytoarchitectonic grounds as to whether the rat has a PFC at all, but it does (as defined by input from the MD thalamus, dopaminergic afferents, and homologies in lesion-induced behavioural deficits).



*Prefrontal cortex. **Above:** human. **Below:** monkey (typically, rhesus macaque). **Left:** lateral surface. **Middle:** inferior (orbital) surface. **Right:** medial surface. In each case a left hemisphere is drawn (cc = corpus callosum). From Pandya & Yeterian (1998). The line running through area 46 in the monkey is the principal sulcus (sulcus principalis). The arcuate sulcus is between areas 6 and 8.*

In the monkey, the cortical regions surrounding the principal and arcuate sulci comprise the *dorsolateral* prefrontal cortex. Behind the arcuate sulcus lie the *frontal eye fields* (FEF; area 8, at least in monkeys). Medially, there is *ventromedial* and *orbitofrontal* cortex. The rim of midline cortex running around the corpus callosum is the *anterior cingulate* cortex; some would not consider this part of the PFC, while others would (Fuster, 1997, p. 41) — it does receive inputs from the mediodorsal (MD) thalamus (and therefore is part of the rat PFC; Zilles & Wree, 1995). The posterior part of the left inferior frontal gyrus in humans (Brodmann's areas 44 and

45) corresponds to Broca's speech area (see Fuster, 1997, p. 17), and we won't be talking about that.

Connections of the PFC

Different regions of the PFC have different connections. Let's generalize: in primates, the orbitofrontal cortex (OFC) is primarily connected to the medial thalamus, hypothalamus, septum, ventromedial caudate, nucleus accumbens, and amygdala; the dorsolateral PFC (DLPFC) is primarily connected to the lateral thalamus, dorsal caudate, hippocampus, and other regions of neocortex (see Fuster, 1997). For example, the arcuate gyrus is one site of multimodal sensory convergence (and lesions of it impair tactile/visual cross-modal matching; Petrides & Iversen, 1976). However, this does not paint the full picture; for example, the OFC receives major visual, auditory, somatosensory, and gustatory cortical inputs (see Rolls, 1998). (The striatal projections, DLPFC→dorsal head of caudate and OFC→ventrolateral caudate and nucleus accumbens, are the start of parallel segregated 'loops' that run from cortex → striatum → globus pallidus → thalamus → cortex. You may have come across another such loop before, the 'motor' loop, whose striatal component is the putamen and which projects back to premotor cortex.) The projections from MD thalamus, which are reciprocated by the PFC, are also separable: the pars magnocellularis (which receives information from the amygdala) projects to OFC (Brodmann's areas 11, 12, 47), the pars parvocellularis to DLPFC (including areas 9, 10, and 44–46), and the pars paralamellaris to the FEF (area 8).

The PFC has extensive, reciprocated projections from all major 'association' cortical regions. The *arcuate fasciculus* connects the posterior parietal cortex (areas 5 and 7) with the PFC, particularly the DLPFC (Pandya & Yeterian, 1998). The *uncinate fasciculus* connects the anterior temporal lobe with the OFC (Martin, 1989). The *cingulum* connects the OFC and regions of cingulate cortex with the parahippocampal gyrus. The left and right PFC also communicate with each other via the corpus callosum. The PFC provides major outputs to premotor areas. It also projects to the brain stem; the PFC is the only neocortical region to project directly back to monoaminergic (NA, DA, 5-HT) and cholinergic cell groups, presumably to regulate their activity. The FEFs receive visual input from areas MT and MST, and project to subcortical oculomotor nuclei via the superior colliculus.

Effects of frontal lobe lesions in humans

Clinical investigation of frontal lobe function will be covered in much more detail by R.A. McCarthy's lectures. Often, patients with frontal damage have normal IQ (as assessed by the Wechsler Adult Intelligence Scale), but this leads us into a debate about what IQ tests measure. However, they may perseverate, be distractible, show poor planning and initiative, and be disinhibited (in a variety of domains, including emotional and social disinhibition, but also in the sense that 'primitive' reflexes such as the oral rooting reflex may be released). Certain aspects of memory (such as self-ordered memory searching) may be impaired.

A number of tasks are thought of as 'classic' tests of frontal lobe function. In the Wisconsin Card Sorting Task (Grant & Berg, 1948), patients must sort cards according to an unspoken rule (sort by colour, number, shape…) on the basis of feedback (correct / wrong) from the experimenter. Every so often, the experimenter changes the rule, without announcing the fact. Patients with DLPFC lesions are impaired on this task (Milner, 1963), typically *perseverating* with an outdated sorting strategy. Frontal-lesioned patients are also impaired on the Tower of Hanoi (Shallice, 1982), a test of *planning*.

Encoding, retrieval, and the prefrontal cortex

The PFC may contribute to memory encoding and / or recall, probably via its extensive back-projections to posterior neocortical regions. For example, humans with PFC lesions are profoundly impaired on *verbal fluency* tests (Milner, 1964) — e.g. 'please say as many words beginning with S as you can in the next minute'.

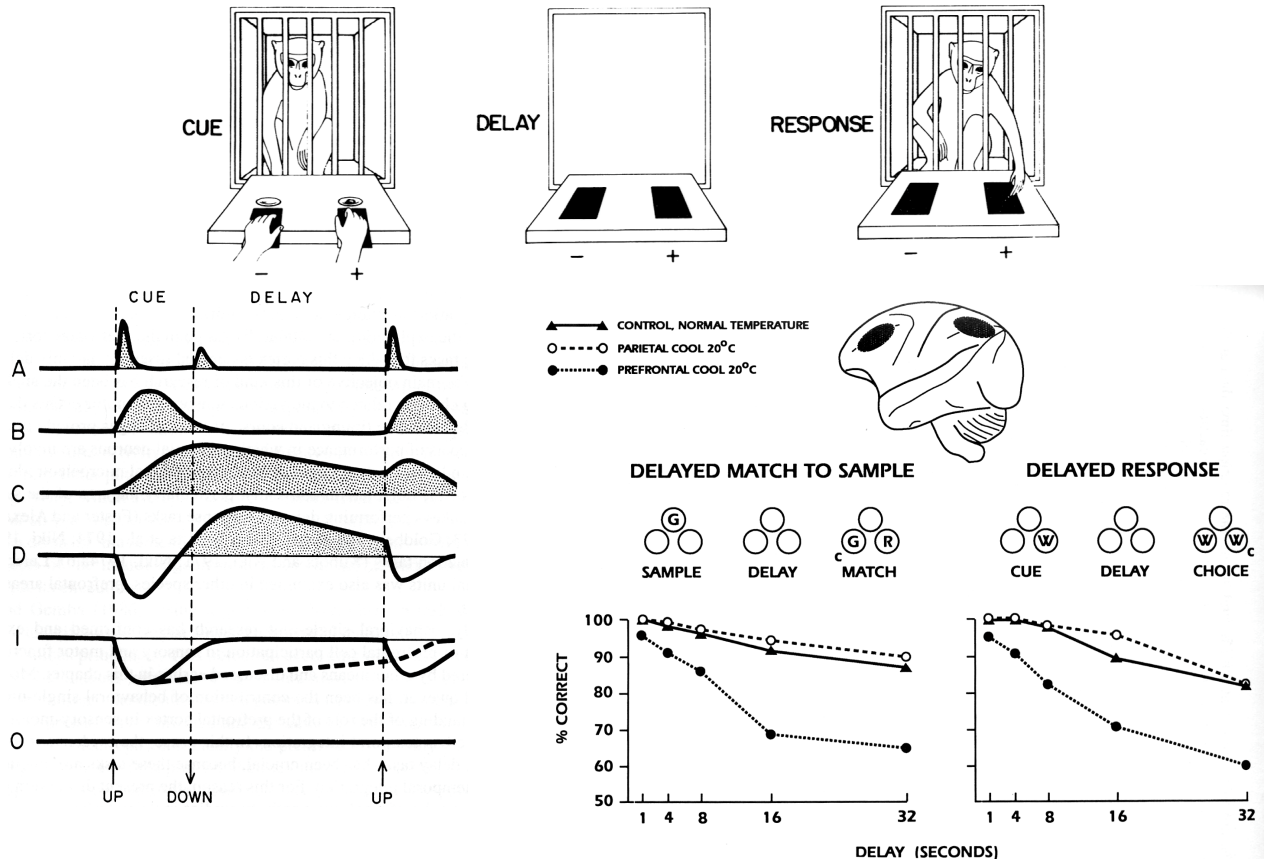
Many of the data regarding this function of the PFC come from neuroimaging studies (see e.g. Buckner *et al.*, 1999; Buckner & Wheeler, 2001). Tulving *et al* (1994) proposed a *hemispheric encoding/retrieval asymmetry (HERA)* model on the basis of PET studies of memory tasks; they suggested that the left PFC is more involved than the right in encoding episodic memory (and retrieving semantic memory), whereas the right PFC is differentially more involved in episodic memory retrieval. As an example, left PFC activity at the time of processing verbal material ('is this word abstract or concrete?') predicts how well people subsequently remember that material ('did you see this word earlier?') (Wagner *et al.*, 1998). It has been suggested that the nature of the material also determines the degree of left versus right activation (Kelley *et al.*, 1998).

These studies are vulnerable to a number of criticisms. One relates to whether the memory processes being observed in the scanner are episodic, semantic, both, etc. A more serious criticism is that this imaging-based model is purely *correlative*; what process the PFC is playing in these tasks is hard to fathom.

Dorsolateral prefrontal cortex and working memory

Jacobsen (1936) was the first to demonstrate an impairment in monkeys with frontal lobe lesions on a *delayed response* task. In this, a monkey is shown a peanut in one of two locations; a screen then comes down for a delay period, and the monkey then has to respond to the previous location of the peanut. (A related task is *delayed alternation*, when the monkey has to remember from trial to trial which response is correct on the basis of its previous response.) The suggestion is that the frontal lobes contribute to *working memory* — holding the relevant stimulus 'on line' during the delay.

This deficit has since been localized to the sulcus principalis (i.e. DLPFC) in monkeys. Neurons here respond during the delay (Fuster & Alexander, 1971); cooling



Top: *Delayed response task.* ***Bottom left:*** *types of neuronal response in DLPFC during delayed-response tasks.* ***Bottom right:*** *Cooling DLPFC (but not parietal cortex) produces delay-dependent deficits on DMTS and delayed response tasks (figure from Fuster, 1997, p. 93). Note that cooling may affect fairly large areas of cortex; irreversible lesion studies have shown that the DMTS deficit depends upon lesions of the inferior convexity, while the DR deficit depends upon principal sulcus lesions (Passingham, 1975; Mishkin & Manning, 1978).*

(Fuster & Alexander, 1970) or lesions (Goldman & Rosvold, 1970) of the DLPFC impair delayed-response performance (see figure). Lesions of the other regions of the PFC tend to have less of an effect (though they are not always without effect; see Fuster, 1997, chapter 4); for example, lesions of DLPFC sparing the principal sulcus do not impair performance (Goldman *et al.*, 1971).

The delayed response task has a spatial component, a working memory component, and potentially other 'executive' components. Goldman-Rakic and colleagues found that neither similar spatial non-delayed tasks, nor non-spatial delayed tasks, require the principal sulcus (Goldman & Rosvold, 1970; Goldman *et al.*, 1971). So she argued that the principal sulcus is critical for *spatial working memory*. Using an oculomotor delayed response task, her group showed that focal lesions in and around the principal sulcus can produce memory deficits in specific areas of space (Funahashi *et al.*, 1993). She suggested that the regions that appear to subserve performance in the delayed response and DMTS tasks reflect different *domains* of working memory in different subregions of the DLPFC (e.g. spatial WM = principal sulcus, object WM = inferior convexity and / or ventrolateral PFC) (Levy & Goldman-Rakic, 2000).

Petrides (1996; 2000) emphasizes a different, *process*-specific view of this and adjacent parts of the DLPFC. He points out that patients with DLPFC damage can perform quite well on standard short-term memory tests. However, they are impaired on *self-ordered working memory (self-ordered monitoring)* tasks (Petrides & Milner, 1982); a typical task might be to point to one stimulus out of six on a card, then turn to another, identical card and point to another stimulus, until all six stimuli have been selected. This task cannot be solved by any form of recognition or recency memory (all the stimuli have been seen equally often); the idea is that the subject has to monitor or manipulate information in working memory. Mid-dorsolateral PFC lesions (these include part of the principal sulcus but additional cortex in area 9, above it) impair even nonspatial self-ordered tasks, but do not impair recognition memory (Petrides, 1991; 1995). PFC lesions also impair self-ordered sequencing tasks in marmosets (Collins *et al.*, 1998). Petrides contrasts this region with mid-ventrolateral PFC, which he has suggested serves to encode and retrieve information actively. Functional imaging studies have not entirely supported Goldman-Rakic's 'domain-specific' hypothesis (Owen, 2000), but have provided some support for the idea that different regions of DLPFC implement different cognitive operations (D'Esposito *et al.*, 2000).

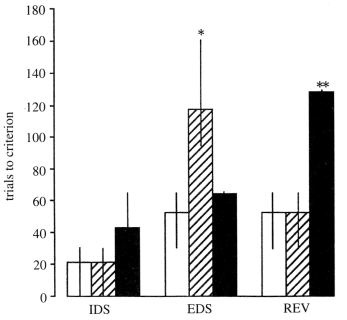
There are several lines of evidence that the PFC implements working memory via its *back projections* to posterior cortex. Fuster and colleagues have shown that cooling of either DLPFC or inferotemporal cortex impair visual delayed matching-to-sample. There is a robust projection between these two regions. Furthermore, cooling one region affects the responses of neurons in the other (Fuster *et al.*, 1985); for example, DLPFC cooling diminished the discrimination shown by IT neurons in the delay, perhaps suggesting that the PFC is *maintaining* the response of the posterior cortical region during the delay (see Cohen *et al.*, 1997; Fuster, 1997, chapter 5; Rushworth & Owen, 1998). Ruchkin *et al.* (in press 2002) argue along similar lines based on event-related EEG work in humans. There is a functional argument to be made here: it is implausible that the PFC 'contains' the memory being held online, for it would have to duplicate all the perceptual capabilities of (e.g.) visual cortex in order to 'hold' a visual memory. Rather, by maintaining activation in visual processing areas, working memory is achieved without duplicating perceptual systems.

Attentional set and set-shifting

What kind of animal model is there of performance on the Wisconsin Card Sorting Task? Frontal-lesioned patients fail the WCST because they perseverate in sorting cards according to an incorrect category. One possible model of this is the ability of animals to develop and subsequent switch *attentional set* (Mackintosh, 1974, pp. 597-598). For example, monkeys may be trained to respond to compound stimuli, each consisting of a shape and a line. Initially, shape A is correct, shape B is wrong, and they must ignore the lines (which vary unpredictably and may distract the subject). Typically, monkeys develop an *attentional set*, such that if you introduce a

new set of stimuli, they are faster to learn the shape discrimination than they were initially (this is called an *intradimensional shift* — the stimuli change, but the relevant dimension, shapes, remains the same). Consequently, they are much slower when faced with an *extradimensional shift* — when all the stimuli change, and this time they must attend to a new dimension, i.e. learn which line is correct, ignoring the now-irrelevant shapes. Lesions of the DLPFC do not impair monkeys' ability to form an attentional set, but they do impair the extradimensional shift stage (Dias *et al.*, 1996b; Dias *et al.*, 1996a; Robbins, 1998) (see figure). Posterior parietal lesions have the same effect in rats (Fox *et al.*, 2003) — does the DLPFC alter an attentional set maintained by the attentional circuits of the parietal cortex? Perhaps this is not quite right: Fox *et al.* found that posterior parietal cortex lesions didn't prevent the formation of an attentional set, but impaired extradimensional shifts; maybe the DLPFC uses the attentional networks of the posterior parietal cortex to shift attentional set somehow.

Top right: *example of a design of an attentional set experiment (Fox et al., 2003). SD simple discrimination; CD compound discrimination; IDS intradimensional shift; EDS extradimensional shift.* ***Bottom left:*** *Dias et al. (1996a) showed that DLPFC lesions in the marmoset selectively impaired extradimensional set shifts.* ***Bottom right:*** *Fox et al. (2003) have shown that the posterior parietal cortex is also critical for extradimensional set shifting, in rats.*

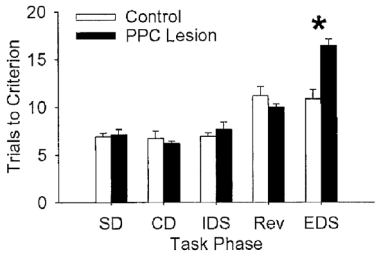


Open bars = sham-operated controls; hatched bars = DLPFC (area 9) lesions; filled bars = OFC lesions.

Table 1. Example of a possible combination of stimulus pairs for a rat shifting from digging medium to odor as the relevant dimension

	Dimensions		Exemplar combinations	
Discrimination	Relevant	Irrelevant	S+	S−
SD	Medium		**M1**	M2
CD	Medium	Odor	**M1**/01	M2/02
			M1/02	M2/01
IDS	Medium	Odor	**M3**/03	M4/04
			M3/04	M4/03
Reversal	Medium	Odor	**M4**/03	M3/04
			M4/04	M3/03
EDS	Odor	Medium	**05**/M5	06/M6
			05/M6	06/M5

Half of the rats switched from medium to odor, and half switched from odor to medium. The correct exemplar is shown in bold and can be paired with either exemplar from the irrelevant dimension. In the IDS and EDS, the stimuli were novel exemplars of each dimension.



Neuropsychiatric links: schizophrenia

Many diseases have been suggested to involve DLPFC dysfunction; schizophrenia is an interesting one. The effectiveness of antipsychotic ('neuroleptic') drugs at alleviating psychotic symptoms, such as hallucinations, correlates with their potency as dopamine (DA) D_2 receptor antagonists (see Feldman *et al.*, 1997, ch. 18). The DLPFC is directly regulated by DA, and may regulate DA function; it is also regulated indirectly by striatal DA (through its corticostriatal 'loop'). Schizophrenics perform badly on 'dorsolateral frontal' tests such as the WCST; their blood flow does not increase normally when they perform the task (but is this simply because they perform badly for another reason?), and so on (see Kotrla & Weinberger, 1995; Cowan *et al.*, 2000). Nobody understands schizophrenia. But consider this. Mental imagery uses the same (or nearly the same) set of brain regions as perception (Farah, 2000). Hallucinations may be due to the inability of schizophrenics to perceive internally-generated (auditory or visual) imagery as being self-generated (see Frith, 1998). Lesions of prelimbic cortex in rats (the likely homologue of DLPFC) prevent them from perceiving the consequences of their own acts (Balleine & Dickinson, 1998). Interesting, at the least.

Inhibitory control and the PFC

Over the years, many effects of PFC lesions have been chalked up to 'disinhibition' — a classic description of the effects of frontal lobe damage in humans. Perseveration (Mishkin, 1964; Iversen & Mishkin, 1970) can be considered disinhibition (failure to inhibit a previously correct response). Therefore, 'inhibitory control' can

be considered a feature of attentional set switching (failure to inhibit a previously useful attentional set), reversal learning (failure to inhibit responding to a previously rewarded stimulus), and other tasks (see Fuster, 1997, pp. 85-86; Roberts *et al.*, 1998a, pp. 223-226). It's not always clear that a true inhibitory process has been proven to exist in all the tasks for which it's been claimed!

However, there are some data bearing directly on this issue. First, the PFC has been implicated in *extinction* of Pavlovian conditioning in rodents (Morgan *et al.*, 1993; Morgan & LeDoux, 1995; Garcia *et al.*, 1999; Morgan & LeDoux, 1999; Quirk *et al.*, 2000; Milad & Quirk, 2002). Extinction does not represent 'unlearning' but may involve the learning of new, inhibitory ('CS → no US') associations (see Mackintosh, 1974, pp. 481-483). Second, direct measures of response inhibition reveal a role for the PFC. PFC-lesioned animals have long been known to perform poorly on *'go/no-go'* tasks in which they have to respond on some trials and withhold responses on other trials; they respond too much (see Fuster, 1997, p. 68). In a *stop signal task*, subjects regularly respond (e.g. reporting whether an arrow on a screen is pointing left or right). On a small proportion of trials ('stop' trials), a stop signal (e.g. beep) is played after the trial has begun, and they must inhibit their response. If the task is designed cleverly, one can calculate the *stop signal reaction time* (SSRT), measuring the time it takes internally to suppress a response. Such tasks activate the right inferior frontal gyrus in normal humans, and patients with lesions of the right inferior frontal gyrus exhibit impaired inhibitory control, i.e. have a longer SSRT (Aron *et al.*, 2003).

Anterior cingulate cortex (ACC)

First, we need to bear in mind that many primate studies of the ACC (and, historically, of the frontal lobe in general) have used non-excitotoxic lesion techniques. This is a particular problem for ACC studies: any lesion that destroys the cingulum bundle will disconnect large portions of cortex (including all afferents and efferents of the cingulate cortex and connections between the OFC and the medial temporal lobe) (Vogt, 1993). The primate ACC seems to have many functions, including a range of motivationally-oriented unlearned behaviours (Devinsky *et al.*, 1995). In humans, ACC lesions have produced a wide variety of symptoms, including apathy, inattention, autonomic dysregulation, emotional instability, and akinetic mutism (Devinsky *et al.*, 1995; Bush *et al.*, 2000).

Emotional significance of stimuli

Imaging studies have shown that the human ACC responds to emotionally significant stimuli such as sexual imagery, and, in cocaine addicts, by cocaine-associated cues; such activation may be associated with cocaine craving (e.g. Volkow *et al.*, 1997; Maas *et al.*, 1998; Childress *et al.*, 1999; Garavan *et al.*, 2000).

Attention and action

In humans, PET studies have provided evidence that the ACC is involved in 'executive' attention. In attentional target detection tasks, blood flow increases with the number of targets to be detected, while flow to the anterior cingulate gyrus is reduced below baseline during the maintenance of vigilance (reviewed by Posner, 1995, pp. 620-621). These PET studies have also suggested a role for the ACC in 'willed' tasks, perhaps with a motivational role (Paus, 2001); along with dorsolateral PFC, blood flow to ACC is significantly increased in tasks requiring a voluntary choice of action, compared to routine, well-rehearsed actions (Frith *et al.*, 1991).

Detecting errors or response conflict

While studying choice reaction times (RTs) in humans, it was observed that a negative EEG potential was evoked when subjects made an error (Falkenstein *et al.*, 1990; Gehring *et al.*, 1990; Gehring *et al.*, 1993). This potential was named the error-related negativity (ERN) (for reviews, see Brown, 1999; Falkenstein *et al.*, 2000; Scheffers & Coles, 2000). The ERN is hypothesized to reflect part of a process in the brain that monitors ongoing actions, compares them with intended actions, de-

tects any mismatch, flags the presence of an error if mismatch exists, and takes action to correct ongoing or future performance (e.g. Gehring *et al.*, 1993; Bernstein *et al.*, 1995; Miltner *et al.*, 1997). The ACC is the likely source of the ERN (Gehring *et al.*, 1993; Dehaene *et al.*, 1994; Coles *et al.*, 1998; Bush *et al.*, 2000) — indeed, the ERN may have first been noticed by researchers recording directly from the ACC in macaque monkeys (Niki & Watanabe, 1979; Gemba *et al.*, 1986). The ACC has been likened to a supervisory attentional system (Norman & Shallice, 1986) (see Grossman *et al.*, 1992).

Comparable results have been obtained using functional imaging studies. Several such studies have used the Stroop task (Stroop, 1935): in a typical version of this task, the subject must report the colour of a series of words, while ignoring the word itself. In the critical, 'incongruent' condition each word is the name of a colour that differs from the colour in which the word is printed; performance is poorest in this condition. The Stroop task elicits an ERN from the ACC (Liotti *et al.*, 2000) and strongly increases metabolic activity within the ACC (Pardo *et al.*, 1990); indeed, versions of the task using neutral stimuli activate a different subregion of the ACC to versions that use emotionally-charged stimuli (Bush *et al.*, 1998; Whalen *et al.*, 1998; Bush *et al.*, 2000; MacLeod & MacDonald, 2000). However, the emphasis of functional imaging studies to date has been on the process of action selection (Paus *et al.*, 1993; Awh & Gehring, 1999; Turken & Swick, 1999), or the detection of response competition or conflict rather than overt errors (see Carter *et al.*, 1998; Carter *et al.*, 1999; Rogers *et al.*, 1999b; MacLeod & MacDonald, 2000).

Neuropsychiatric links: depression, OCD

The anterior, ventral ACC (Brodmann's areas 24a / b and 25), part of the 'affective' (emotional) subdivision of the ACC (Devinsky *et al.*, 1995), is now strongly implicated in the pathology of depression in humans (Bench *et al.*, 1992), as well as in the control of normal mood. Depressives show increased blood flow per unit volume in the ACC (Mayberg, 1997; Drevets, 2000). Metabolic activity in rostral (anterior) ACC is also unique in differentiating those depressed patients who eventually respond to antidepressant drug therapy from those that do not (Mayberg *et al.*, 1997; 2000). If normal subjects think sad thoughts, metabolic activity increases here (Mayberg *et al.*, 1999). Mayberg has suggested that hyperactivity of subgenual area 24 / area 25 is a primary factor in sadness and depression. This may explain the efficacy of surgical destruction of the subgenual cingulate as a therapy for refractory depression. There is also evidence for ACC (± OFC) dysfunction in obsessive–compulsive disorder (OCD; does an error-correcting system start correcting non-existent errors?) (Gehring *et al.*, 2000; Hajcak & Simons, 2002), and cingulotomy can also be used to treat refractory OCD (Spangler *et al.*, 1996).

Orbitofrontal cortex (OFC)

Human OFC damage

The orbitofrontal cortex (OFC) has been widely suggested to guide behaviour based on the anticipated value of different actions (Nauta, 1971; Damasio, 1994). Let's begin with the famous case of Phineas Gage (Harlow, 1848; Harlow, 1868), a temperate and shrewd 25-year-old railroad construction worker in Vermont. He was distracted while setting explosives in a rock and banged on the explosive with a tamping iron. The powder exploded, blowing the 6 kg rod into his cheek and out of the top of his head, to land about 25 metres away. He regained consciousness rapidly, and, as amazing as anything else, survived the inevitable subsequent infection in a pre-antibiotic era. He lost all sight in his left eye but the vision in his right was normal; he suffered no paralysis and his speech was normal. However, his personality was completely altered. He became profane, capricious, and irresponsible; his employers would not take him back, he moved through a succession of labourer's jobs and exhibited himself for a while in a circus, with his tamping iron, before his death in 1861. The tamping iron had destroyed both left and right orbitofrontal cortex (Damasio, 1994; Damasio *et al.*, 1994).

Modern-day patients with OFC (ventromedial PFC) damage exhibit similar problems. E.V.R. had a frontal meningioma resected, destroying OFC tissue; like Gage, his personality changed dramatically and his life was wrecked. He could not manage his time; he perseverated or was inappropriately distracted; his emotional reactions to situations seemed inappropriate; he was fired; he entered into ill-advised business ventures, became bankrupt, divorced, and briefly remarried someone of whom his family and friends disapproved. His 'social cognition' seemed profoundly impaired. Yet he performed normally on classic 'frontal lobe' neuropsychological tests such as the WCST; his delayed recall performance was also normal (and as one might expect, his short-term verbal, visual and auditory memory was normal, as was his linguistic function).

The Iowa gambling task

Damasio *et al.* found one task that was sensitive to OFC damage — gambling. In the Iowa Gambling Task (Bechara *et al.*, 1994), patients choose cards from four decks. Decks A and B have constant moderate gains but occasional substantial losses; the losses outweigh the gains, so these are 'risky' decks. Decks C and D give constant small gains, but their losses are also smaller; they give a net gain and are 'safe' decks.

Normal humans exhibit a number of interesting phenomena on this task, especially if you measure their skin conductance response (SCR, a.k.a. galvanic skin response or GSR — i.e. sweating, a measure of sympathetic nervous system activity). These are (1) they learn to choose decks C and D, and avoid the risky decks; (2) they generate SCRs when they are rewarded and punished; (3) they generate *anticipatory* SCRs before they choose a card; (4) they generate a larger anticipatory SCR before they pick a risky deck than before they pick a safe deck; (5) as they're learning, the SCR difference between the risky and safe decks develops, and subjects start to choose the safe decks, *before* they can tell you that (or how) the decks differ. In contrast, patients with OFC damage choose poorly and do not develop anticipatory SCRs that discriminate between the decks (see figure).

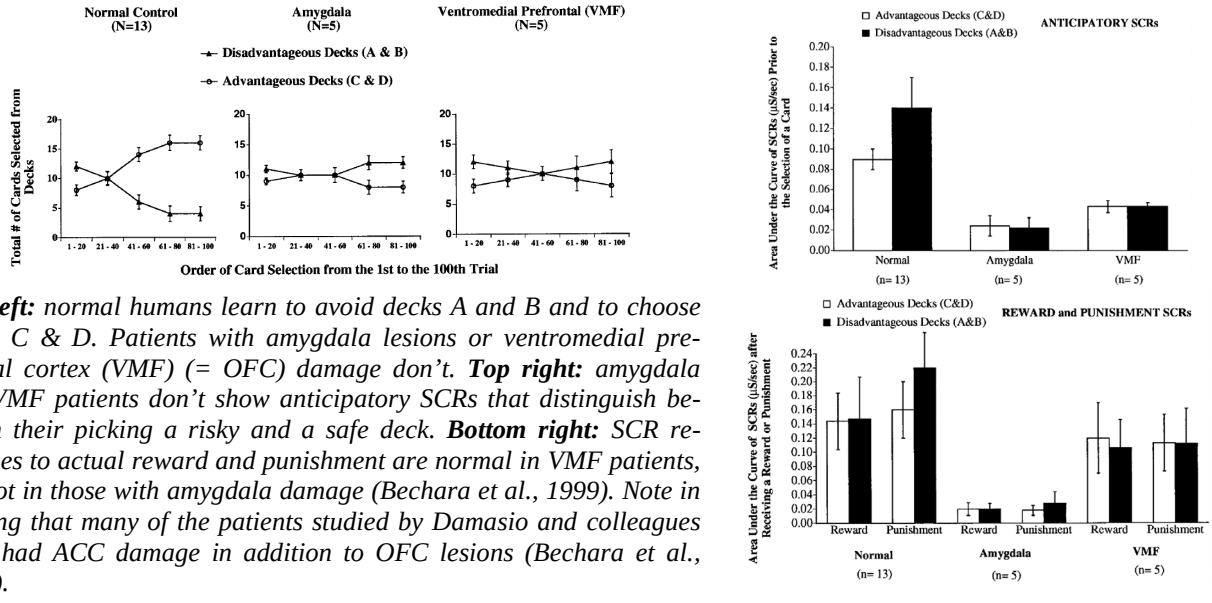
The somatic marker hypothesis

Damasio has proposed what he terms a *somatic marker hypothesis* of OFC function (Damasio, 1994; 1998). He suggests that there is an underlying defect in emotional processing in OFC-lesioned patients, and that this underpins their decision-making deficits. We may choose a number of actions; each may have effects that have a certain value to us (good or bad). For the brain to calculate the expected value of each possible action could take a long time. It is often better to make an imperfect decision quickly than eventually to make what would have been the perfect decision. Damasio has argued that 'somatic markers' provide a way of speeding up decision making. Somatic markers are signals relating to body states (in other words, representations of the body itself) that we learn to associate with potential actions, probably unconsciously, as we experience the outcomes to which they lead. They're 'gut feelings'. When we next have to make a decision involving this action, these markers influence our choice. They may act consciously, and/or covertly, to 'pre-bias' cognitive systems, preventing them from considering particularly bad courses of action. Somatic markers, therefore, constitute a rapidly-retrieved signal that improves performance by removing options from the consideration of a computationally intensive cognitive process. Patients without them are slow to choose, and consider inappropriate actions that normal humans would never think about.

In the gambling example, the somatic marker is suggested to be the SCR generated by the sympathetic nervous system. (Is the marker the internal state that also generates the SCR, or is the SCR itself the marker? This is reminiscent of the James–Lange versus Cannon debate about emotions.) Subjects associate decks A and B with 'bad' and consequently develop an anticipatory SCR when they're considering picking it; this helps them to avoid these decks. OFC-lesioned patients don't.

Amygdala–OFC interactions

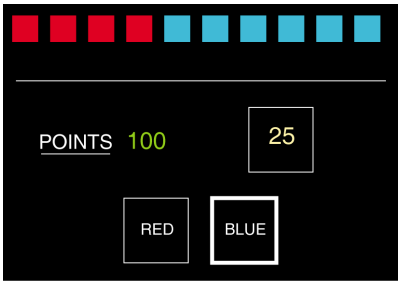
The OFC is extensively and reciprocally connected to the amygdala (reviewed by Öngür & Price, 2000), known to be involved in assessing the emotional significance of stimuli. Damasio's group have consequently examined the performance of patients with amygdala damage on the gambling task. Causes of such damage are rare, but include Urbach–Wiethe disease (bilateral calcification of the amygdalae) and encephalitis. The performance of these patients is comparable in most respects to that of OFC-lesioned patients (see figure) — the only difference being that while OFC-lesioned patients still show SCRs to actual reward and punishment, amygdala-lesioned patients don't. This *tends* to suggest that the more basic assessment of reward and punishment is performed by the amygdala, and the OFC response is secondary (but necessary to influence decision-making), but this is not clear-cut yet.



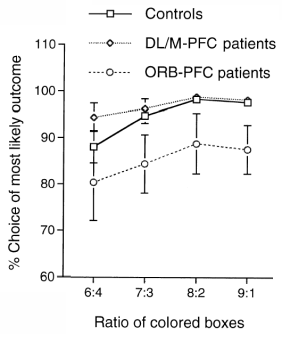
Top left: *normal humans learn to avoid decks A and B and to choose decks C & D. Patients with amygdala lesions or ventromedial prefrontal cortex (VMF) (= OFC) damage don't.* ***Top right:*** *amygdala and VMF patients don't show anticipatory SCRs that distinguish between their picking a risky and a safe deck.* ***Bottom right:*** *SCR responses to actual reward and punishment are normal in VMF patients, but not in those with amygdala damage (Bechara et al., 1999). Note in passing that many of the patients studied by Damasio and colleagues have had ACC damage in addition to OFC lesions (Bechara et al., 2000).*

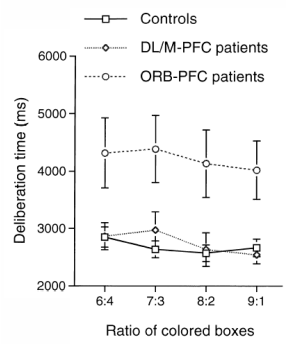
A closer look at gambling

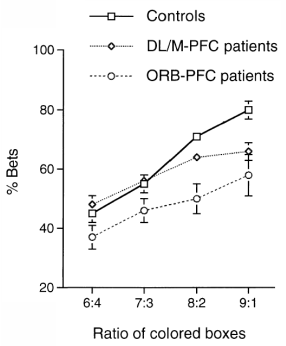
The reason for OFC patients' failure on the Iowa gambling task is difficult to establish, for in this task different punishment probabilities, and different magnitudes of reward and punishment are all intermixed. A number of groups are trying to understand the OFC deficit. Using a task quite similar to the Iowa version, Rogers *et al.* (1999b) found that choosing between large, unlikely rewards and small, likely rewards activated a set of prefrontal regions in normal subjects, including the OFC. Rogers *et al.* (1999a) recently modified their gambling task to separate out (to some

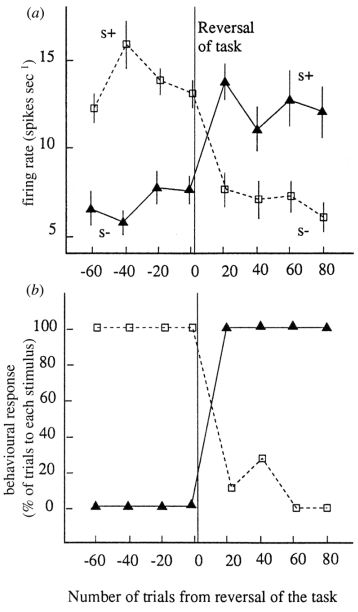


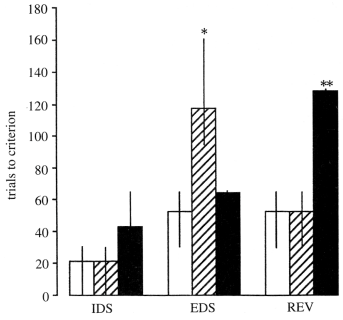
Top left: *Screenshot of the Rogers et al. (1999a) gambling task. Subjects choose whether a yellow token is hidden behind a red or a blue box; they must then interrupt the computer's ascending or descending sequence of bets in order to choose how much to bet.* ***Bottom left:*** *quality of decision making (how likely they are to choose red when there are more red boxes, etc.) is impaired in OFC-lesioned patients.* ***Bottom middle:*** *they're also slower to choose.* ***Bottom right:*** *but they bet less, rather than more (less 'risk-taking' in that sense).* ***Note also*** *that normal subjects bet less when there's a 6:4 ratio of boxes than when there's a 9:1 ratio; as your points total can go negative with no adverse consequences, this is not optimal (optimal behaviour would be to bet the maximum each time) and implies risk aversion in normal subjects as well as patients.*











Open bars = sham-operated controls; hatched bars = DLPFC (area 9) lesions; filled bars = OFC lesions.

Left: *Electrophysiological correlate of reversal learning.* ***(a)*** *Response of a single neuron in rhesus macaque OFC to two stimuli (a triangle and a square). On the left of the graph, responding to the square was rewarded (S+) and responding to the triangle wasn't (S–). At the vertical line, the contingency was reversed; the OFC neuron rapidly reverses its discriminated firing response, firing now to the newly-rewarded stimulus (the triangle).* ***(b)*** *Behavioural performance of the same monkey. Data from Rolls et al. (1996).* ***Right:*** *OFC lesions impair reversal learning in the marmoset (Dias et al., 1996a), but not extradimensional shifts, completing a double dissociation with the effects of DLPFC lesions (see earlier figure).*

extent) 'risk-taking' from speed of responding and sensitivity to the probability of reinforcement. The task and their results are shown in the figure.

Monkey studies of OFC: reversal learning

Electrophysiological studies of the OFC in monkeys have emphasized their *reward-related* responding. Like the amygdala, the OFC is well placed to process information about stimulus *value*; it receives projections from polymodal sensory cortex (Öngür & Price, 2000) in addition to motivational state information from the hypothalamus. OFC neurons respond rapidly to changes in the reward value of specific foods. For example, neurons in primate OFC respond to reward but discriminate between different rewards in doing so (Schultz *et al.*, 1998; 2000). When a monkey is fed to satiety with a particular food, the OFC responses to its flavour or odour decline, while the responses to other foods are unaffected (see Rolls, 2000), paralleling the behavioural change induced by sensory-specific satiety.

This ability of OFC neurons to change their response to particular stimuli has been studied in *reversal learning* tasks (see e.g. Rolls, 1998). A typical such task would involve rewarding choices of stimulus A, but not stimulus B (A+B–) and then reversing these contingencies (A–B+). The stimuli (A, B) might be visual; the reward (+) might be food or juice. Primate OFC neurons show rapid reversals that parallel the behavioural reversal (see figure). Moving from correlative to causal studies, Butter (1969) and then Jones & Mishkin (1972) were perhaps the first to observe that OFC lesions caused monkeys to *perseverate* on the previously correct stimulus after a reversal. Dias *et al.* (1996a; 1997) have shown that OFC lesions impair reversal learning in marmosets (see figure). Therefore, the OFC may be important for altering the *value* of stimuli, or in altering behaviour in response to changes in the value of stimuli (see also Gallagher *et al.*, 1999).

Finally, we saw earlier how the effects of OFC lesions closely resembled that of amygdala lesions in gambling humans; Baxter *et al.* (2000) recently showed that disconnecting the amygdala from the OFC in rhesus monkeys (unilateral amygdala lesion + contralateral unilateral OFC lesion + forebrain commissurotomy) prevented monkeys altering their behaviour in response to devaluation of a reinforcer. However, the precise relationship between the amygdala and OFC is still unclear (see e.g. Cardinal *et al.*, 2002).

Neuropsychiatric links: impulsivity, psychopathy

There is considerable interest in OFC pathology as a potential contributory cause for a number of disorders, including impulsivity (e.g. Rahman *et al.*, 2001; Mobini *et al.*, 2002), with all that can cause, but also antisocial personality disorder, sociopathic behaviour, and criminal psychopathy (Kiehl *et al.*, 2001; Mitchell *et al.*, 2002). OFC function may also be affected by long-term drug abuse (see Rogers *et al.*, 1999a).

Summary

We have examined the anatomy and connections of the PFC, considered the effects of PFC lesions in humans, and examined specific functions that the PFC may subserve, including memory encoding / retrieval, supporting working memory via its links to posterior cortical regions, and the 'top-down' control of attention. These appear to be predominantly DLPFC functions; the idea that the PFC provides 'inhibitory control' may be more general (but this idea is sometimes applied vaguely). We have examined dissociations between DLPFC and OFC function (sometimes referred to in the context of 'cold', or emotionless, versus 'hot', or emotional cognition) and considered the role of the OFC in stimulus–reinforcer association and decision-making. We have looked briefly at the ACC, and examined potential neuropsychiatric consequences of PFC malfunction.

Sample essay questions

- What is the role of the prefrontal cortex in working memory? (Alternative essay: just '… in memory'?)
- How well are the deficits of patients with frontal lobe lesions illuminated by neurobiological investigations in experimental animals?
- To what extent can functions be localized within the prefrontal cortex? What is the significance of this localization for unitary theories of frontal lobe function based on a 'central executive'?
- Discuss the organization and functioning of the prefrontal cortex with particular reference to the comparison between orbitofrontal and dorsolateral regions.

Suggested reading

- Aston-Jones (1999), pp. 1397–1402 (executive control) and Eichenbaum *et al.* (1999), pp. 1475–1480 (working memory and PFC) — basic chapters in *Fundamental Neuroscience*
- Roberts *et al.* (1998b) — multiple authors' perspectives on the PFC; also Fuster (1997) — monograph (long)
- Rushworth & Owen (1998) — on electrophysiology of delay tasks
- Petrides (2000) or Petrides (1996) — 'mid-DLPFC and mid-VLPFC serve two different executive functions'. The 2000 article is from *Experimental Brain Research* volume 133 (issue 1), a special issue on executive control and the frontal lobe. This also includes Levy & Goldman-Rakic (2000), presenting their 'domain-specific working memory' hypothesis.
- Damasio (1994) — very readable popular science book on the OFC and the somatic marker hypothesis
- Krawczyk (2002) — review of the PFC's contribution to decision-making.
- Wood & Grafman (2003) — review of different *classes* of PFC theory: should we think of the PFC in terms of processes that it performs or the representations that it stores?
- Robbins (2000) — chemical neuromodulation of the PFC (DA, NA, ACh, 5-HT), something we haven't covered

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