Emotion and Motivation **NST 1B Psychology 2003**

Lecture 2 (Saturday 8 March)

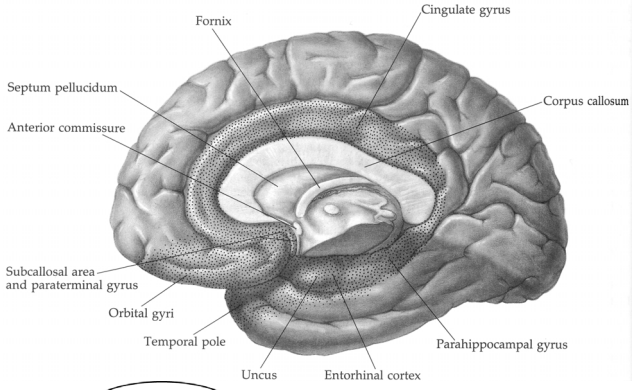
Rudolf N. Cardinal Neurobiology of emotion

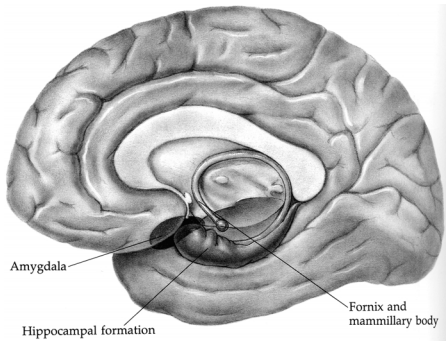
Overview

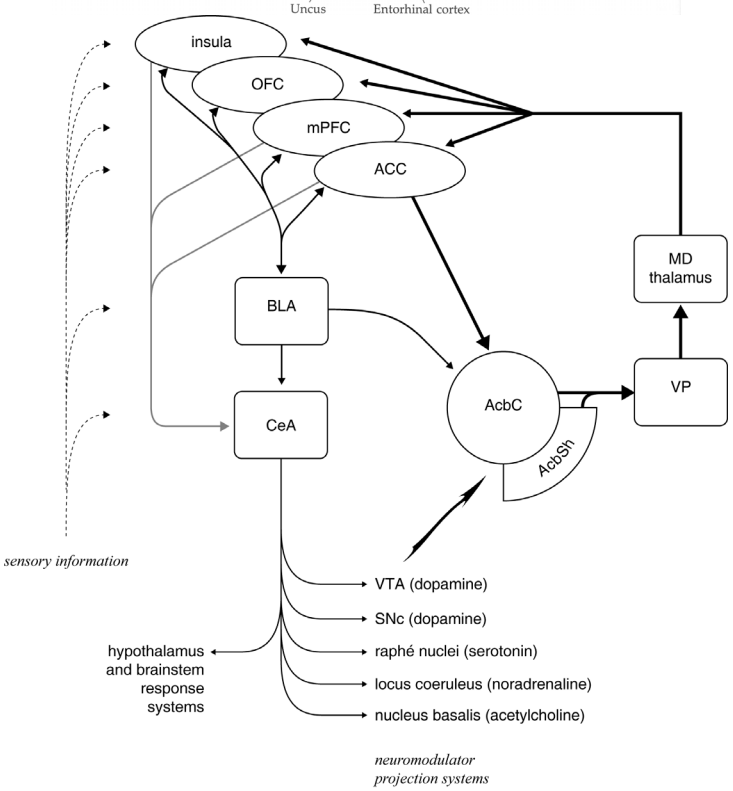
The study of the psychology of emotion goes hand in hand with the study of its neural basis. We will examine the development of neurobiological theories of emotion and look at modern-day views of the role of 'limbic' structures such as the amygdala in emotional processing.

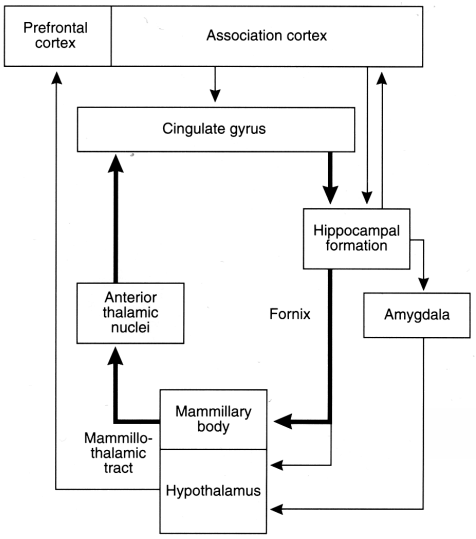
The limbic system

The term 'limbic' was coined by Broca (1878) for the cortical structures encircling the upper brain stem (*limbus*, Latin for edge or border). These cortical regions are considered phylogenetically 'primitive' cortex, based on their microscopic appearance. The 'limbic lobe' was suggested to have a role in emotional experience and expression by Papez (1937) (his name rhymes with 'apes'). This concept was later elaborated by MacLean (1949), who introduced the expression 'limbic system' to refer to the limbic lobe and its connections with the brainstem, and added further







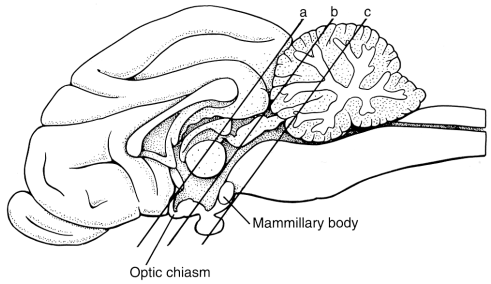


Different views of the limbic system. ***Top left:*** *Medial views of the brain, with 'limbic' cortex stippled.* ***Top right:*** *The same view but showing the location of the amygdala and hippocampus deep within the medial temporal lobe. From Martin (1989).* ***Bottom left:*** *A schematic of the limbic corticostriatal circuit, from Cardinal et al. (2002). This diagram omits the hippocampus and related structures. (OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; AcbC, nucleus accumbens core; AcbSh, nucleus accumbens shell; VP, ventral pallidum; MD, mediodorsal.)* ***Bottom right:*** *Papez's original circuit (thick lines), together with other functionally important connections now known to exist. From Kupferman (1991).*

structures to the system. The limbic system is not precisely defined: as the limbic lobe was considered the neural substrate for emotions, structures whose functions have to do with motivation and emotion have since been added to the anatomical definition. A modern definition of the limbic system in primates would certainly include cingulate and orbitofrontal cortex (both part of the frontal lobe); the amygdala, hippocampal formation, and parahippocampal gyrus (part of the medial temporal lobe); the septal nuclei (or septum, within the basal forebrain); the mammillary bodies, the rest of the hypothalamus, and the anterior and medial thalamic nuclei (in the diencephalon); and the nucleus accumbens and ventral pallidum (part of the basal ganglia).

Attribution of emotional processing to the limbic system

In the 1920s a series of experiments looked at the expression of *sham rage* in cats. *Decorticated* cats (whose neocortex has been removed, leaving the basal ganglia and diencephalon intact) exhibited tail-lashing, back-arching, clawing, biting, and autonomic responses including piloerection, sweating, urination, defaecation, and hypertension, accompanied by an endocrine stress response (adrenaline and corticosteroid secretion). Although such a cat appears enraged, these 'rage' responses can be brief and triggered by very nonspecific stimuli, and the rage is also poorly directed (they sometimes even bit themselves); hence, it was termed 'sham rage' (Cannon & Britton, 1925). *Decerebrate* cats, where only the hindbrain and spinal cord are connected to the body, did not exhibit sham rage. Bard (1928) found that the posterior hypothalamus was critical for the coordinated rage response (see figure). Hess (1932) found that stimulation of hypothalamic subregions could produce sham rage, or indeed more directed attacks. It was later established that large portions of the cerebral cortex could be removed *without* producing sham rage, but these rage phenomena appeared when the lesions included limbic cortex, such as the cingulate cortex (Bard & Mountcastle, 1948).



Bard's (1928) transections of the cat brain. Transection of the forebrain (a) produces sham rage. Transection through the mid-hypothalamus (b) also produces sham rage. Transection that disconnects the posterior hypothalamus (c) abolishes this coordinated rage response; only isolated (not coordinated) responses could be elicited, and required much stronger stimuli to do so than when the posterior hypothalamus was intact.

It was data such as these that prompted Papez (1937) to propose that a circuit connecting the structures of the 'limbic lobe' was critical for emotion. His circuit (see figure) projected from the cingulate cortex to the hippocampal formation, then on via the fornix (a major tract of fibres — axons — emerging from the hippocampus) to the mammillary bodies (part of the posterior hypothalamus), from there via the mammillothalamic tract to the anterior thalamic nuclei, and then back to the cingulate cortex — suggested to be a 'higher centre' for the conscious perception of emotion and the interaction between emotion and cognition, in contrast to the unconscious basic mechanisms orchestrated by the hypothalamus.

Much of Papez's circuit is *not* considered to be involved in emotional behaviour today. In particular, there is not good evidence that damage to hippocampal structures affects emotional processing; however, other structures added to the 'limbic system' by MacLean certainly are.

The amygdala

In 1937, Klüver and Bucy described a syndrome that developed in rhesus monkeys following bilateral removal of the temporal lobes (Klüver & Bucy, 1937; Klüver & Bucy, 1939). This syndrome included striking *tameness* (noted many years previously by Brown & Schaefer, 1888), *emotional unresponsiveness*, 'psychic blindness' (an *inability to recognize familiar objects*), *hypersexuality* and *hyperorality* (they try to put all sorts of objects in their mouth and/or have sex with them), 'hypermeta-

morphosis' (this meant a strong tendency to react to every visual stimulus), and difficulties with memory. Klüver–Bucy syndrome was later found in humans following similar lesions (Terzian & Dalle Ore, 1955); the patient had undergone temporal lobectomy to remove epileptic foci, and displayed all elements of the syndrome postoperatively except placing objects in his mouth. Complete K–B syndrome has since been described in humans (Marlowe *et al.*, 1975). Allegedly, one patient was arrested whilst attempting to have sex with the pavement. (Hypersexuality and hyperorality might be a consequence of a failure to identify visual objects correctly, or failure to attribute the correct significance to the stimuli.)

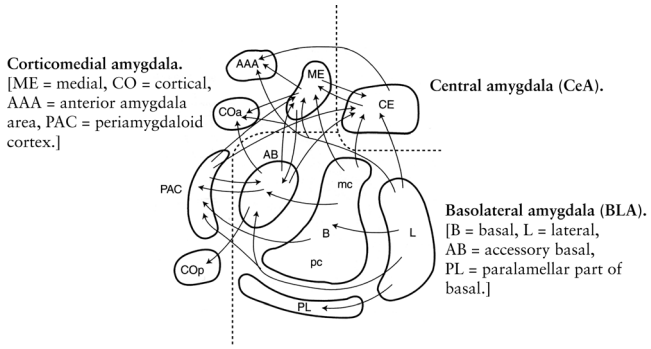
This raises a question: damage to which structure was responsible for the emotional changes in K–B syndrome? While the problems in visual processing and memory have since been attributed to damage to structures including inferior temporal cortex, rhinal cortex, and the hippocampus, the emotional changes ('fearlessness') have been localized to the *amygdala.* Named for its supposed resemblance to an almond, the amygdala is probably the structure most implicated in emotional processing.

Abnormalities in emotional processing following amygdala damage in humans

Damage to the amygdala in humans may lead to an increase in threshold of emotional perception and expression (see Aggleton & Saunders, 2000); amygdala lesions certainly cause impairments in emotional learning (Bechara *et al.*, 1995; 1999), deficits in the perception of emotions in facial expressions (Adolphs *et al.*, 1994), and impaired memory for emotional events (see Cahill, 2000).

Subdivisions of the amygdala

The amygdala comprises three major groups of nuclei, termed the *corticomedial, basolateral,* and *central* divisions (see figure). We will consider primarily the basolateral amygdala (BLA) and central nucleus of the amygdala (CeA).

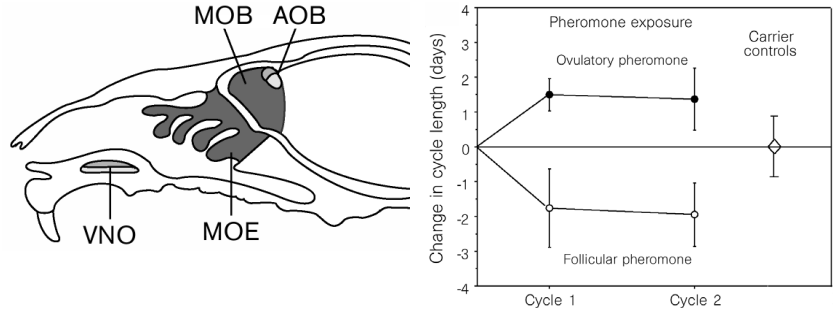


Subdivisions of the amygdala (and intra-amygdaloid connections) in the rhesus macaque monkey. Modified from Aggleton & Saunders (2000).

The corticomedial amygdala: an aside on pheromones

We won't say much about the corticomedial amygdala, except to note that it is highly connected to the olfactory system, and is an important route through which olfactory information (particularly *pheromones*) influence such things as maternal behaviour (e.g. in the rat, vomeronasal organ → accessory olfactory bulb → corticomedial amygdala → medial hypothalamus) (Numan & Sheehan, 1997). Pheromones are airborne chemical signals released by an individual into the environment that affect the physiology or behaviour of other members of the same species, without consciously being detected. The vomeronasal organ (VNO) is an 'accessory' olfactory system that detects pheromones in many species including the rat, though the main olfactory system also detects some pheromones. The VNO is small in humans, it was thought to be vestigial and the existence of human pheromones was disputed. However, it has long been known that women living together can develop synchronized menstrual cycles (McClintock, 1971), and Stern & McClintock (1998) recently showed that odourless compounds taken from women's axillae could alter the menstrual cycles of other women, confirming the existence of pheromones in humans. Whether the human VNO is functional is debated (Berliner *et al.*, 1996; Døving & Trotier, 1998; Keverne, 1999), though pheromones appear to have be-

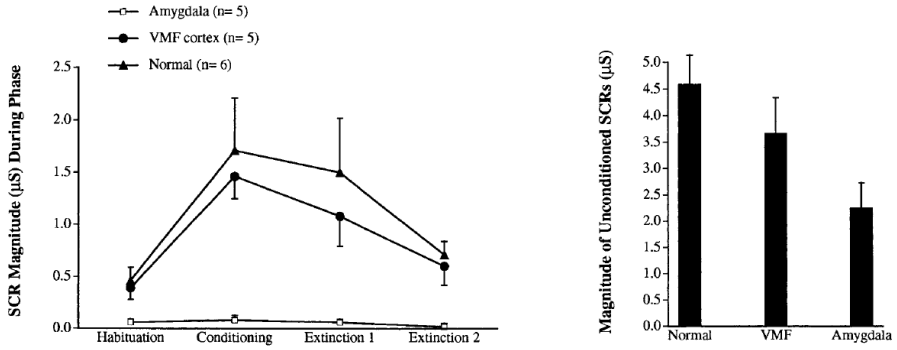
haviour as well as physiological effects (Grosser *et al.*, 2000). However, whether the corticomedial amygdala is involved in humans is unknown.



Far left: *the VNO in rats (MOE = main olfactory epithelium; MOB = main olfactory bulb; AOB = accessory olfactory bulb).* ***Left:*** *pheromone effects on ovarian cycle in humans (Stern & McClintock, 1998). Odours from the axillae of women in the ovulatory or follicular (pre-ovulatory) phase of their menstrual cycle prolong or shorten, respectively, the cycle of the women smelling them.*

Aversive (fear) conditioning and the amygdala

We mentioned last time that a Pavlovian conditioning paradigm can be used to study learned fear. If we give a human or a rat pairings of a CS with an aversive stimulus (electric shock, or loud noises), they will develop conditioned responses to that CS. Recently, Bechara *et al.* (1995; 1999) have shown that humans with amygdala lesions (some of them with the rare Urbach–Weithe disease, in which the amygdalae calcify bilaterally) are impaired at this sort of learning (see figure).



Damage to the amygdala impairs conditioned skin conductance responses (SCRs) in humans (Bechara et al., 1999). The CS was a blue slide; the US was a foghorn. (VMF: another group of patients with ventromedial prefrontal lesions, not relevant to our present discussion.)

This work builds upon a much older and more extensive literature in rats. The prototypical task involves CS→shock pairings; rats will subsequently *freeze* to the CS. This depends on the amygdala (see LeDoux, 2000).

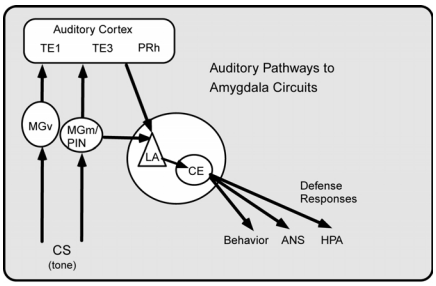
- Sensory inputs carrying information about CSs (such as auditory tones) arrive at the lateral amygdala, part of the BLA complex, from sensory thalamus and cortex.
- Rats will also freeze to the *context* in which they experienced the shock; information about the context appears to arrive at a slightly different part of the BLA, this time from the hippocampus.
- Information about electric shocks arrives at the BLA (spinothalamic tract → thalamus → lateral amygdala).
- Lesions of the BLA impair conditioned freezing to discrete CSs (tones) and contexts.
- The BLA exhibits long-term potentiation (LTP) of its glutamatergic synaptic inputs.
- Neuronal plasticity (LTP) is seen the BLA during fear conditioning — the response to the CS increases.
- Blockade of glutamate NMDA receptors (which prevents NMDA-receptor-dependent LTP) in the BLA during conditioning prevents the acquisition (learning) of conditioned freezing.
- The BLA projects to the CeA.
- Lesions of the CeA impair conditioned freezing.
- The CeA projects to a host of brainstem targets, which have different functions — the periaqueductal grey is critical for freezing behaviour.

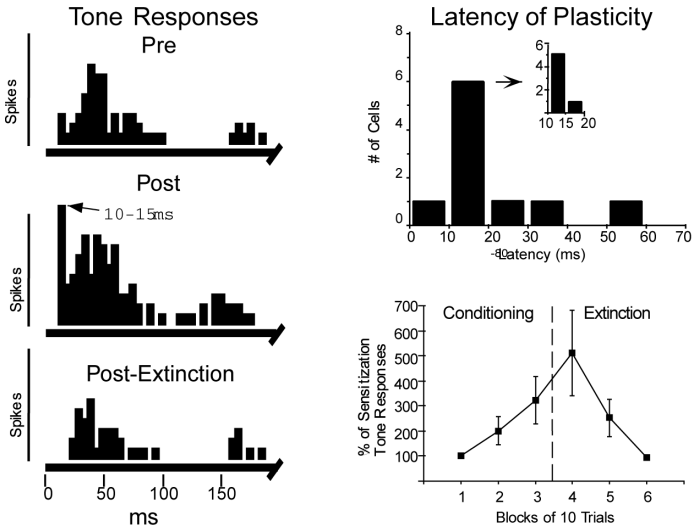
There are several caveats (see LeDoux, 2000) that we won't go into in detail, but this summary paints a clear picture (see figure). It suggests that the BLA is respon-

sible for emotional Pavlovian learning; it receives sensory information, acts as a site of CS–US association and uses this learned information to control the activity of the CeA. In turn, the CeA acts as a 'controller of the brainstem', using its widespread projections to the hypothalamus, midbrain reticular formation and brainstem to orchestrate behavioural, autonomic, and neuroendocrine responses.

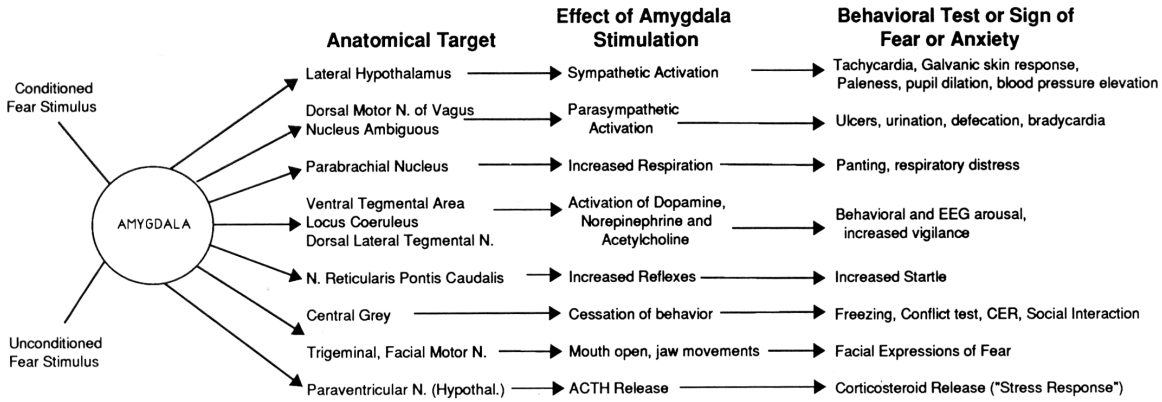
Double dissociations between the BLA and CeA

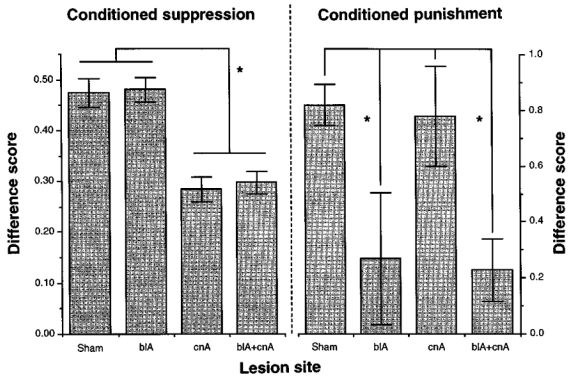
However, the BLA does more than control the CeA: it projects to structures includ-





Amygdala circuits involved in conditioned freezing (Davis, 2000; LeDoux, 2000). ***Top left:*** *pathways by which information about auditory CSs can reach the amygdala.* ***Top right:*** *contextual information takes a different route to the amygdala.* ***Left:*** *plasticity in the BLA during tone→shock conditioning.* ***Below:*** *the amygdala (more specifically, the CeA) controls a range of simple behaviours and autonomic responses via hypothalamic and brainstem targets. ('Central grey' = periaqueductal grey.)*





Data from Killcross et al. (1997). See text for a description of the task. Conditioned suppression (responding less during the CS+) is abolished by CeA, but not BLA lesions; conditioned punishment (avoiding the lever that produces the CS+) is abolished by BLA but not CeA lesions. Combined lesions of the BLA and CeA impair both.

ing the ventral striatum and prefrontal cortex, enabling it to influence complex behaviour. Also, the CeA itself receives direct sensory input and can operate capable independently of the BLA.

Here's perhaps the most famous example. Killcross *et al.* (1997) demonstrated a *double dissociation* of the effects of BLA and CeA lesions. They used a task in which rats responded on two levers (in part, an instrumental conditioning task). Both levers occasionally produced food. In addition, one lever occasionally produced a 10-second auditory CS+ that ended with mild footshock. The other produced a similar CS– but no shock. Normal rats exhibit two phenomena: (1) they respond less on the lever that produces the CS+ and shock, because they're not stupid (an effect that can be termed *conditioned punishment*); (2) on those occasions when they do trigger the CS+, their responding is generally suppressed (*conditioned suppression*). The footshock is too mild for the rats to exhibit full-blown conditioned freezing and immobility, so they do carry on responding during the CS+, but much less than at other times. Rats with BLA lesions showed normal conditioned suppression, but failed to bias their responding (their voluntary choice?) away from the lever producing the CS+. Rats with CeA lesions showed normal choice behaviour but no conditioned suppression. These results indicate (1) that the BLA and CeA receive information about the CS independently of each other; (2) they control different response systems.

Anxiety and the amygdala

Fear is an emotional response to stimuli that predict aversive consequences. Anxiety is related; while some people say that fear is more specifically directed at a stimulus than anxiety, both have similar symptoms. Lesions of parts of the amygdala block an number of *unlearned* 'emotional' responses, such as the corticosteroid response to being forcibly restrained (see Davis, 2000).

Benzodiazepines (BZs) such as diazepam (Valium®) increase the effects of the inhibitory neurotransmitter GABA. Clinically, they are highly effective as anxiolytic drugs. In a commonly-used rat model of anxiety, the *elevated plus maze*, rats normally spend less time in the open (exposed, dangerous?) arms than in the closed arms; anxiolytics increase the amount of time they spend in the open arms (they're less nervous?). In tasks like this, BZs have anxiolytic effects in tasks when infused into the amygdala, and local infusion of the BZ antagonist flumazenil into the amygdala attenuates the effects of BZs given systemically. However, some anxiolytic effects of BZs survive amygdala lesions (see Davis, 2000).

Memory modulation and the amygdala

The BLA also has a prominent role in the emotional modulation of memory storage. It is part of the mechanism by which emotionally-arousing situations improve memory (see Cahill, 2000; McGaugh, 2000; McGaugh *et al.*, 2000). Humans remember emotionally-charged events better than others — in a previous generation most people would recall where they were when J.F. Kennedy was shot; today, most people would be able to report where they were on 11 September 2001. The memory-enhancing effects of emotion can be blocked by the β-adrenoceptor blocker propranolol in humans (Cahill *et al.*, 1994); this difference in memory for emotional versus neutral memories is not apparent in humans with amygdala lesions (Cahill *et al.*, 1995); intra-amygdala injections of β agonists enhance some kinds of memories even if given shortly after training, while intra-amygdala β antagonists prevent this (Liang *et al.*, 1986). It appears that the BLA is the critical site for the memory-enhancing effects of systemic adrenaline and glucocorticoids, and for the amnesic effects of benzodiazepines (see McGaugh *et al.*, 2000).

Appetitive conditioning and the amygdala

The emphasis so far has been on aversive stimuli. However, the amygdala appears to be equally involved in assessing the value of appetitive stimuli. Let's start with a task directly analogous to that used by Killcross *et al.* (1997). Killcross *et al.* (1998, N.B. not yet fully published) described the effects of amygdala lesions on a two-

lever task. Both levers produced food occasionally; one also produced a CS+ that ended with extra food being delivered, while the other produced a CS– (and no extra food). Normal rats showed (1) a preference for the lever producing the CS+; (2) general elevation of their responding while the CS+ was being presented. The results were exactly analogous to the aversive task. Rats with BLA lesions showed the conditioned elevation, but not the preference for the CS+ lever; rats with CeA lesions showed normal preference, but no conditioned elevation.

BLA lesions affect a whole range of appetitive tasks. Second-order conditioning (CS1→US; CS2→CS1; test responding to CS2) often depends upon the *value* of CS1 (see Mackintosh, 1974; Gewirtz & Davis, 1998). BLA-lesioned rats cannot acquire second-order appetitive conditioning (Hatfield *et al.*, 1996). They are also impaired at another test of the acquired *value* of a CS: *conditioned reinforcement*. If you pair a CS with food, normal rats will subsequently work for that CS on its own. The CS is then termed a *conditioned* reinforcer (as opposed to the primary reinforcer, food). BLA-lesioned rats cannot use a CS as a conditioned reinforcer (Cador *et al.*, 1989; Burns *et al.*, 1993).

CeA lesions also affect a whole range of appetitive tasks — but different ones. For example, rats tend to *orient* to and *approach* a CS that's been paired with food; both these phenomena require the CeA, but not the BLA (Gallagher *et al.*, 1990; Parkinson *et al.*, 2000). CeA lesions also affect subtle tests of *attention* (Holland & Gallagher, 1993b; 1993a; Holland *et al.*, 2000).

Changing value and the BLA

If you pair a CS with food, BLA-lesioned rats can acquire *some* forms of conditioned responding. If you subsequently give normal or BLA-lesioned rats this food and poison them with lithium chloride — which makes them feel sick — they'll avoid the food in future. Normal rats will also stop responding to the CS, but BLA-lesioned rats (and monkeys) won't (Hatfield *et al.*, 1996; Málková *et al.*, 1997). This suggests that the way the lesioned rats respond to the CS is a simple 'stimulus–response' manner (see figure at end of last lecture) — unlike normal rats, their responding doesn't take account of the value of the US.

There is very recent evidence that the BLA is specifically involved in *changing* the value of stimuli. If you pair a CS with food and only *then* destroy the BLA, rats can use the acquired value of the CS to support new learning, but they can't *get rid of* (extinguish) that value normally (Setlow *et al.*, 2002; Lindgren *et al.*, 2003).

Drawing these results together

We haven't got time to summarize the whole literature on the amygdala — it's vast. But we could get pretty close to a good description by saying

1. The BLA is required to change the motivational value of a CS, and to use this value to control certain types of behaviour (including freezing, and instrumental choice behaviour).
2. The CeA, in addition to its role in controlling brainstem and hypothalamic structures on behalf of the BLA, is responsible for simple conditioned responses in its own right (but it can't, for example, affect choice behaviour).
3. The BLA also has a role in modulating 'emotional' memory storage.
4. The CeA also has a role in modulating attention.

Nobody knows whether amygdala lesions impair transreinforcer blocking, the test we talked about last time for detecting pure 'emotion' states in animals!

The orbitofrontal cortex

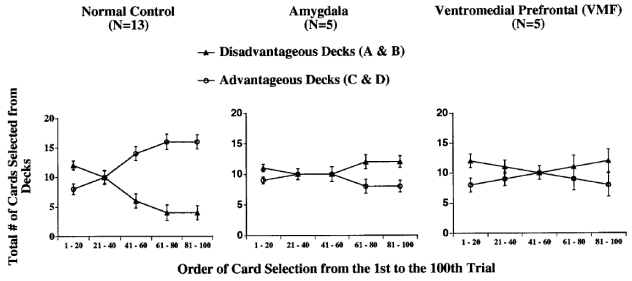
The amygdala seems to interact heavily with the *orbitofrontal cortex* (OFC), which is also strongly implicated in the way emotional stimuli control behaviour.

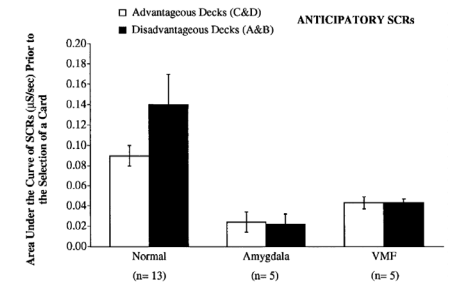
Human OFC damage

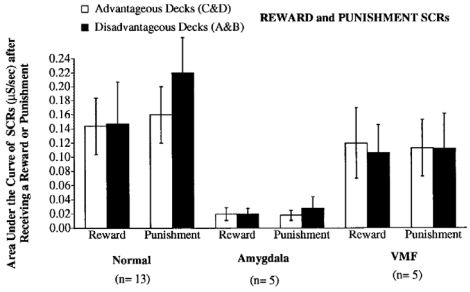
The OFC shot to fame in 1848 when Phineas Gage, a railroad construction worker in Vermont, was distracted while setting explosives in a rock and banged on the explosive with a tamping iron. The powder exploded, blowing the 6kg rod into his cheek and out of the top of his head, landing about 25 metres away. He regained consciousness rapidly and survived the subsequent infection. However, his personality was completely altered (Harlow, 1848; Harlow, 1868). He became profane, capricious, and irresponsible; his emotionality appeared altered. The tamping iron had destroyed both left and right orbitofrontal cortex (Damasio, 1994; Damasio *et al.*, 1994). Modern-day patients with OFC damage exhibit similar problems.

These patients are normal on many tests of 'intelligence', but are impaired on one task — 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. These are (1) they learn to choose decks C and D, and avoid the risky decks; (2) they generate skin conductance responses (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).







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).*

The somatic marker hypothesis

Damasio has proposed what he terms a *somatic marker hypothesis* of OFC function (Damasio, 1994). He suggests that there is an underlying defect in emotional processing in OFC-lesioned patients. We may choose a number of actions; each may have effects that have a certain value to us (good or bad). Damasio has argued that 'somatic markers' ('gut feelings') provide a way of speeding up decision making. Somatic markers are signals relating to body states that we learn to associate with potential actions, probably unconsciously, as we experience the outcomes to which they lead. When we next have to make a decision involving this action, these markers influence our choice (consciously or unconsciously), so we can avoid actions that lead to particularly bad outcomes. OFC-lesioned patients are suggested not to be able to do this.

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 gener-

ates the SCR, or is the SCR itself the marker? This is reminiscent of the James–Lange versus Cannon–Bard debate.) 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

Humans with amygdala lesions perform badly on the gambling task, like 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).

The anterior cingulate cortex (ACC) and emotional processing

The primate ACC seems to have many functions, including a range of motivationally-oriented unlearned behaviours. 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).

Emotional significance of stimuli

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

Depression and the anterior cingulate cortex

The anterior, ventral ('affective') ACC 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). The ACC is innervated by noradrenaline- and serotonin-producing neurons (as are many areas of cortex) and drugs that increase the function of these transmitters are the mainstay of treatment for depression (e.g. selective serotonin/noradrenaline reuptake inhibitors; SSRIs/SNRIs). Metabolic activity in anterior ACC is 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 the ACC is a primary factor in sadness and depression. This may explain the efficacy of surgical destruction of part the ACC as a therapy for refractory depression.

Summary

We have looked at the development of the concept of the 'limbic system', and examined modern theories of the roles of the amygdala (especially the BLA and CeA) appetitive and aversive tasks. We have briefly discussed two other major limbic areas involved in emotional processing, the OFC and ACC. Next time, we will look at motivation. *(Note that phobias, anxiety disorders and depression will be covered in depth in S. Baron-Cohen's lectures next term.)*

All references cited in the handout

I'm not suggesting that you read these! They are here as pointers to the original literature; so if you are for some reason keen to read more, or if you disagree with something I've claimed, you can check for yourself.

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