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Limbic systems for emotion and for memory, but no single limbic system

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ABSTRACT

The concept of a (single) limbic system is shown to be outmoded. Instead, anatomical, neurophysiological, functional neuroimaging, and neuropsychological evidence is described that anterior limbic and related structures including the orbitofrontal cortex and amygdala are involved in emotion, reward valuation, and reward-related decision-making (but not memory), with the value representations transmitted to the anterior cingulate cortex for action–outcome learning. In this 'emotion limbic system' a computational principle is that feedforward pattern association networks learn associations from visual, olfactory and auditory stimuli, to primary reinforcers such as taste, touch, and pain. In primates including humans this learning can be very rapid and rule-based, with the orbitofrontal cortex overshadowing the amygdala in this learning important for social and emotional behaviour. Complementary evidence is described showing that the hippocampus and limbic structures to which it is connected including the posterior cingulate cortex and the fornix-mammillary body-anterior thalamus-posterior cingulate circuit are involved in episodic or event memory, but not emotion. This 'hippocampal system' receives information from neocortical areas about spatial location, and objects, and can rapidly associate this information together by the different computational principle of autoassociation in the CA3 region of the hippocampus involving feedback. The system can later recall the whole of this information in the CA3 region from any component, a feedback process, and can recall the information back to neocortical areas, again a feedback (to neocortex) recall process. Emotion can enter this memory system from the orbitofrontal cortex etc., and be recalled back to the orbitofrontal cortex etc. during memory recall, but the emotional and hippocampal networks or 'limbic systems' operate by different computational principles, and operate independently of each other except insofar as an emotional state or reward value attribute may be part of an episodic memory.

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1. Introduction

The concept of the limbic system has a long history, and is a concept that has endured to the present day (Catani, Dell'acqua, & Thiebaut de Schotten, 2013; Mesulam, 2000).

In this paper I describe evidence that there are separate systems in the brain for emotion and for memory, each involving limbic structures, but that there is no single limbic system. We might term the system for emotion the 'emotional limbic system', and the system for memory the 'memory limbic system', but there are non-limbic components to both systems. The important concept I advance here is that the systems for emotion and for episodic memory involve largely different brain structures and connections, and different computational principles of operation, which are described. I argue here that of course some links from the emotional system into the memory system are present, for often an emotional state is part of an episodic memory, and when that episodic memory is recalled, the emotional state must be included in what is recalled. These concepts are important not only within neuroscience, but also for neurology (Catani et al., 2013; Mesulam, 2000), neuropsychology (Aggleton, 2012), and psychiatry.

2. Historical background to the concept of a limbic system

The use of the term 'limbic' has changed over time, but the concept of a limbic system is still in use (Catani et al., 2013). The term 'limbic' was introduced by Thomas Willis (1664) to designate a cortical border encircling the brainstem (limbus, Latin for 'border'). Paul Broca (1878) held the view that 'le grand lobe limbique' was mainly an olfactory structure common to all mammalian brains, although he argued that its functions were not limited to olfaction. Limbic structures are frequently taken to include cortical structures such as the hippocampus and cingulate cortex, and structures to which they are connected such as the mammillary bodies, septal area, and amygdala (Isaacson, 1982). After Broca's publication, the accumulation of experimental evidence from ablation studies in animals broadened the role of limbic structures to include other aspects of behaviour such as controlling social interactions and behaviour (Brown & Schäfer, 1888), consolidating memories (Bechterew, 1900), and forming emotions (Cannon, 1927). Anatomical and physiological advances led James Papez (1937) to describe a neural circuit for linking action and perception to emotion. The Papez circuit consists of the hippocampus connecting via the fornix to the mammillary body, which connects via the mammillo-thalamic tract to the anterior nuclei of the thalamus and thus back to the cingulate cortex. According to Papez, emotion arises either from cognition entering the circuit from the cortex through the hippocampus, or from visceral and somatic perceptions entering the circuit through the hypothalamus. Some of Papez' evidence on his circuit and emotion was that in rabies where the disease appears to have a predilection for the hippocampus and cerebellum, the patient is subject to anxiety, apprehensiveness, and paroxysms of rage or terror. Papez held that 'the cortex of the cingular gyrus may be looked on as the receptive region for the experiencing of emotion as the result of impulses coming from the hypothalamic region or the hippocampal formation' (Papez, 1937). A decade later, Paul Yakovlev (1948) proposed that the orbitofrontal cortex, insula, amygdala, and anterior temporal lobe form a network underlying emotion and motivation. Paul MacLean crystallised previous works by incorporating both Papez' and Yakovlev's views into a model of the limbic system (MacLean, 1949, 1952). MacLean concluded that the limbic cortex, together with the limbic subcortical structures, is a functionally integrated system involved especially in emotion. Robert Isaacson assembled evidence on the functions of this system in emotion and memory in a book entitled *The limbic system* (Isaacson, 1982).

In the remainder of this paper I describe evidence that there are separate systems in the brain for emotion and for episodic memory, each involving limbic structures; introduce a hypothesis about the nature of the links between these systems; show that the computations in the two systems are very different; and argue that there is no (single) limbic system.

3. Brain systems involved in emotion: the orbitofrontal cortex, amygdala, and anterior cingulate cortex (ACC)

3.1. *Emotions defined*

A very useful working definition of emotions is that they are states elicited by rewards and punishers, that is, by instrumental reinforcers (Gray, 1975; Rolls, 2005, 2014; Weiskrantz, 1968). Instrumental reinforcers are rewards and punishers that are obtained as a result of an action instrumental in gaining the reward or avoiding the punisher. This approach is supported by many considerations (Rolls, 2014), including the following three. First, the definition is conceptually acceptable, in that it is difficult to think of exceptions to the rule that rewards and punishers are associated with emotional states, and to the rule that emotional states are produced by rewards and punishers (Rolls, 2014). Second, the definition is powerful in an evolutionary and explanatory sense, in that the functions of emotion can be conceived of as related to processes involved in obtaining goals, and in states that are produced when goals are received. Indeed, my evolutionary Darwinian account states that the adaptive value of rewards and punishers is that they are gene-specified goals for action, and that it is much more effective for genes to specify rewards and punishers, the goals for action, than to attempt to specify actions (Rolls, 2014). Examples of such primary (i.e., unlearned or gene-specified) reinforcers include the taste of food, pain, stimuli that promote reproductive success, and face expression. Other stimuli become secondary reinforcers by learned associations with primary reinforcers in parts of the brain involved in emotion such as the orbitofrontal cortex and amygdala. An example is the sight of food, which by learned association with a primary reinforcer, taste, becomes a secondary reinforcer. Third, this approach provides a principled way to analyse the brain mechanisms of emotion, by

examination of where in the brain stimuli are represented by their reward value (Rolls, 2014).

3.2. *An anatomical and functional framework for understanding the neural basis of emotion*

I now provide a framework for understanding some of the brain structures involved in emotion, and at the same time contrast them with the structures that in terms of connectivity and function precede them and succeed them in the anatomical and functional hierarchy moving from left to right in Fig. 1 (Rolls, 2014).

In Tier 1 (Fig. 1), information is processed to a level at which the neurons represent 'what' the stimulus is, independently of the reward or punishment value of the stimulus. Thus neurons in the primary taste cortex represent what the taste is, and its intensity, but not its reward value (Rolls, 2014). In the inferior temporal visual cortex, the representation is of objects, invariantly with respect to the exact position on the retina, size, and even view. Forming invariant representations involves a great deal of cortical computation in the hierarchy of visual cortical areas from the primary visual cortex V1 to the inferior temporal visual cortex (Rolls, 2008c, 2012a). The fundamental advantage of this separation of 'what' processing in Tier 1 from reward value processing in Tier 2 is that any learning in Tier 2 of the value of an object or face seen in one location on the retina, size, and view will generalize to other views etc. In rodents there is no such clear separation of 'what' from 'value' representations. For example in the taste system, satiety influences taste processing at the first central synapse in the taste system (Rolls & Scott, 2003), and this property makes the processing in rodents not only different from that in primates including humans, but also much more difficult to analyse (Rolls, 2014).

There are brain mechanisms in Tier 2 in the orbitofrontal cortex that are involved in computing the reward value of primary (unlearned) reinforcers, as shown by devaluation experiments in which for example a food is fed to satiety (Critchley & Rolls, 1996a; Kringelbach, O'Doherty, Rolls, & Andrews, 2003; Rolls & Grabenhorst, 2008; Rolls, Sienkiewicz,

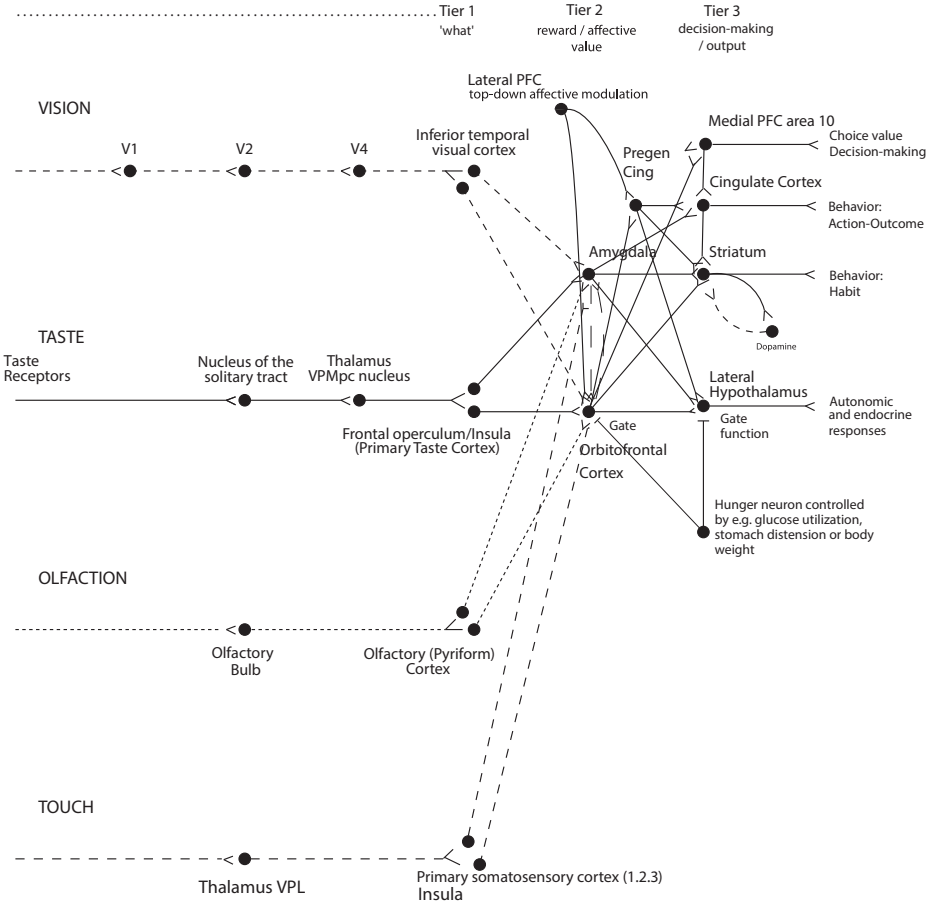

Fig. 1 – Schematic diagram showing some of the connections of the taste, olfactory, somatosensory, and visual pathways in the brain. V1, primary visual (striate) cortex; V2 and V4, further cortical visual areas. PFC, prefrontal cortex. VPL, ventro-postero-lateral nucleus of the thalamus, which conveys somatosensory information to the primary somatosensory cortex (areas 1, 2 and 3). VPMpc, ventro-postero-medial nucleus pars parvocellularis of the thalamus, which conveys taste information to the primary taste cortex. Pregen Cing, pregenual cingulate cortex. For purposes of description, the stages can be described as Tier 1, representing what object is present independently of reward value; Tier 2 in which reward value is represented; and Tier 3 in which decisions between stimuli of different value are taken, and in which value is interfaced to behavioural output systems.

& Yaxley, 1989), and by neuroeconomics experiments which show that the amount and quality of each commodity is encoded by orbitofrontal cortex neurons (Grabenhorst & Rolls, 2011; Padoa-Schioppa, 2011; Padoa-Schioppa & Assad, 2008). The primary reinforcers include taste, touch (both pleasant touch and pain), and to some extent smell, and perhaps certain visual stimuli such as face expression. There is evidence that there is a representation of the (reward/punishment) value of many primary reinforcers in the orbitofrontal cortex, including taste, positive touch and pain, face expression, face beauty, and auditory consonance/dissonance. In neuroeconomics, these are termed 'outcome value' representations (Rolls, 2014). Further evidence for value representations is that orbitofrontal cortex activations in humans to these stimuli are linearly related to the subjectively reported pleasantness of stimuli (medially), or to their unpleasantness (laterally) (Rolls, 2014).

Brain regions in Tier 2 are also concerned with learning associations between previously neutral stimuli, such as the sight of objects or of individuals' faces, with primary reinforcers. These brain regions include the amygdala and orbitofrontal cortex, with the orbitofrontal cortex being especially important in the rapid, one-trial, learning and reversal of stimulus-reinforcer associations. In neuroeconomics, these are termed 'expected value' representations. Once the Tier 2 brain regions have determined whether the input is reinforcing, whether primary or secondary, the signal is passed directly to output regions of the brain, with no need to produce and then feed back peripheral body or autonomic responses to the brain.

In the orbitofrontal cortex in Tier 2, the representation is of the value of stimuli, and actions are not represented. The values of very many different types of stimuli, events or goals are represented separately at the neuronal level, providing the basis for choice between stimuli, and the selection at later stages of processing of an appropriate action to obtain the chosen goal.

Whereas the orbitofrontal cortex in Tier 2 represents the value of stimuli (potential goals for action) on a continuous scale, an area anterior to this, medial prefrontal cortex area 10 (in Tier 3), is implicated in decision-making between stimuli, in which a selection or choice must be made, moving beyond a representation of value on a continuous scale towards a decision between goods based on their value (Grabenhorst, Rolls, & Margot, 2011; Rolls, 2014; Rolls, Grabenhorst, & Parris, 2008).

The brain regions in which the reinforcing, and hence emotional, value of stimuli are represented interface to three main types of output system:

The first is the autonomic and endocrine system, for producing such changes as increased heart rate and release of adrenaline, which prepare the body for action. Structures receiving from the orbitofrontal cortex, amygdala, and ACC that provide a route for these autonomic effects include the hypothalamus and parts of the anterior insula close to the insular taste cortex (Critchley & Harrison, 2013; Rolls, 2014).

The second type of output is to brain systems concerned with performing actions unconsciously or implicitly, in order to obtain rewards or avoid punishers. These brain systems include the basal ganglia for habit ('stimulus–response') behaviour, and the ACC for action–outcome learning (The 'outcome' is the reward or punisher that is or is not obtained when the action is performed.). The ACC contains representations of reward and punisher value, and thus of outcome, which are essential for learning associations between actions and the outcomes that follow actions. The midcingulate area contains representations of actions.

The third type of output is to a system capable of planning many steps ahead, and for example deferring short-term rewards in order to execute a long-term plan. This system may use syntactic processing to perform the planning, and is therefore part of a linguistic system which performs explicit (conscious) processing, as described more fully elsewhere (Rolls, 2014).

It is notable that the orbitofrontal cortex and amygdala do not receive inputs from the dorsal visual 'where' processing areas such as the parietal cortex including the retrosplenial cortex (which is part of the *posterior* cingulate cortex) that provide inputs via parahippocampal areas TF/TH to the hippocampus for its spatial ('where') functions in memory, which are described in Section 4. In a complementary way, the hippocampus and parahippocampal areas do not contain value representations of stimuli, except insofar as value may be part of a memory such as reward-place memory (Rolls, 2010b; Rolls & Xiang, 2005, 2006). This is part of the evidence that the emotional and episodic memory systems have different connections and functions, as described in Section 4 and elsewhere (Rolls, 2008c, 2010b; Rolls & Xiang, 2005, 2006), and thus that there is no single and unified limbic system.

Because of the intended relevance to understanding human emotion and its disorders, the focus of the research described here is on humans and macaques. This is important, for many of the brain systems that are involved in emotion have undergone considerable development in primates (e.g., monkeys and humans) (Rolls, 2014), as summarized next.

First, the temporal lobe has undergone great development in primates, and several systems in the temporal lobe are either involved in emotion (e.g., the amygdala), or provide some of the main sensory inputs to brain systems involved in emotion and motivation. For example, the amygdala and the orbitofrontal cortex, key brain structures in emotion, both receive inputs from the highly developed primate temporal lobe cortical areas, including those involved in invariant visual object recognition, and face identity and expression processing (Rolls, 2000a, 2008c, 2011a, 2012a).

Second, there are many topological, cytoarchitectural, and probably connectional similarities between macaques and humans with respect to the orbitofrontal cortex (see Fig. 1 and Carmichael & Price, 1994; Kringelbach & Rolls, 2004; Öngür & Price, 2000; Petrides & Pandya, 1995; Price, 2006, 2007).

Third, the prefrontal cortex has also undergone great development in primates, and one part of it, the orbitofrontal cortex, is very little developed in rodents, yet is one of the major brain areas involved in emotion and motivation in primates including humans. Indeed, it has been argued that the granular prefrontal cortex is a primate innovation, and the implication of the argument is that any areas that might be

termed orbitofrontal cortex in rats (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009) are homologous only to the agranular parts of the primate orbitofrontal cortex (shaded mid grey in Fig. 2), that is to areas 13a, 14c, and the agranular insular areas labelled Ia in Fig. 2 (Passingham & Wise, 2012; Wise, 2008). It follows from that argument that for most areas of the orbitofrontal and medial prefrontal cortex in humans and macaques (those shaded light grey in Fig. 2), special consideration must be given to research in macaques and humans. As shown in Fig. 2, there may be no cortical area in rodents that is homologous to most of the primate including human orbitofrontal cortex (Passingham & Wise, 2012; Preuss, 1995; Wise, 2008).

Fourth, even the taste system (which might have been supposed to be phylogenetically old and preserved) of primates and rodents may be different, with obligatory processing from the nucleus of the solitary tract via the thalamus to the cortex in primates, but a subcortical pathway in rodents via a pontine taste area to the amygdala, and differences in where satiety influences taste-responsive neurons in

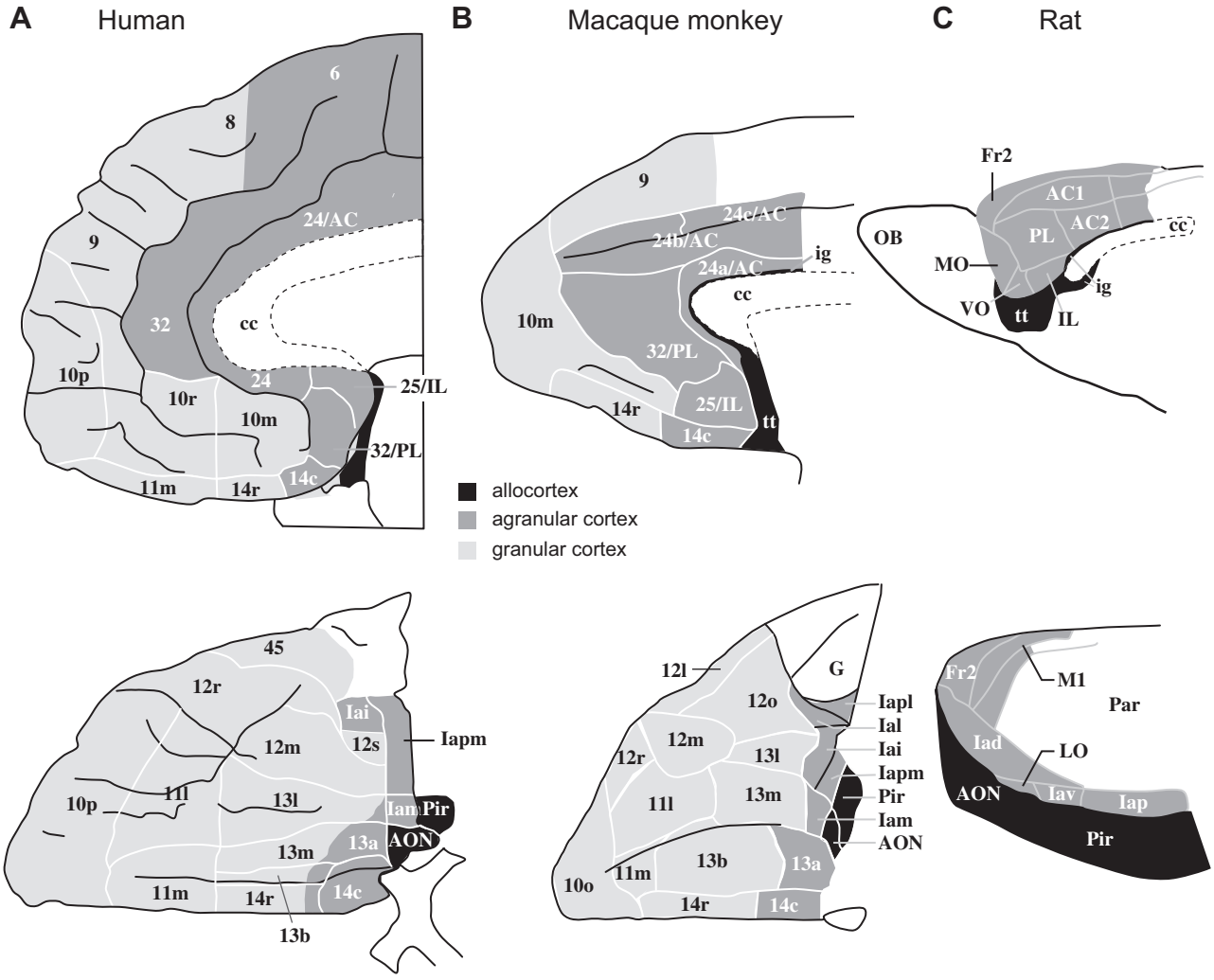

Fig. 2 – Comparison of the orbitofrontal (below) and medial prefrontal (above) cortical areas in humans, macaque monkeys, and rats. (A) Medial (top) and orbital (bottom) areas of the human frontal codex (Öngür et al., 2003). (B) Medial (top) and orbital (bottom) areas of the macaque frontal cortex (Carmichael & Price, 1994). (C) Medial (top) and lateral (bottom) areas of rat frontal cortex (Palomero-Gallagher & Zilles, 2004). Rostral is to the left in all drawings. Top row: dorsal is up in all drawings. Bottom row: in (A) and (B), lateral is up; in (C), dorsal is up. Not to scale. Abbreviations: AON, anterior olfactory 'nucleus'; cc, corpus callosum; Fr2, second frontal area; Ia, agranular insular cortex; ig, indusium griseum; IL, infralimbic cortex; LO, lateral orbital cortex; MO, medial orbital cortex: OB, olfactory bulb; Pr, piriform (olfactory) cortex; PL, prelimbic cortex; tt, tenia tecta; VO, ventral orbital cortex; Subdivisions of areas are labelled caudal (c); inferior (i), lateral (l), medial (m); orbital (o), posterior or polar (p), rostral (r), or by arbitrary designation (a, b). (After Passingham & Wise, 2012). (a) Adapted from Dost Ongur, Amon T. Ferry, & Joseph L. Price. Architectonic subdivision of the human orbital and medial prefrontal cortex. *Journal of Comparative Neurology*, 460(3), 425–49 Copyright 2003 Wiley-Liss, Inc. (b) Adapted from Carmichael, S. T., & Price, J. L. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *Journal of Comparative Neurology*, 346(3), 366–402 Copyright 1994 Wiley-Liss, Inc. (c) Adapted from Palomero-Gallagher, N. & Zilles, K., Isocortex, In G. Paxinos (Ed.) *The rat nervous system* (3rd ed., pp. 729–57) copyright 2004, Elsevier Academic Press.

primates and rodents (Norgren, 1984; Rolls, 2014; Rolls & Scott, 2003; Small & Scott, 2009).

Fifth, with the great development of the orbitofrontal cortex in primates, the amygdala may become relatively less important in humans in emotion than in other vertebrates (Rolls, 2014) (see Section 3.4).

To understand the functions of the orbitofrontal cortex and connected areas in humans, the majority of the studies described here were therefore performed with macaques or with humans.

3.3. *The orbitofrontal cortex*

The first structure considered is the orbitofrontal cortex, and although not a limbic structure such as the amygdala, has similar connections to the amygdala, is connected to the amygdala, and has considerably eclipsed in primates including humans the functions of the amygdala (Rolls, 2014). The amygdala has evolutionarily old origins and can be identified, as can the hippocampus, in amphibia (Isaacson, 1982; Medina, Bupesh, & Abellan, 2011), whereas most of the orbitofrontal cortex, the granular parts, is new to primates (Passingham & Wise, 2012; Wise, 2008) (Fig. 2).

3.3.1. *Anatomical and functional connectivity*

Maps of the architectonic areas in the orbitofrontal cortex and medial prefrontal cortex are shown in Fig. 2 for humans (left) and monkeys (middle) (Carmichael & Price, 1994; Öngür, Ferry, & Price, 2003). The connections of the orbitofrontal cortex (Barbas, 1995; Carmichael & Price, 1994, 1995b; Öngür & Price, 2000; Pandya & Yeterian, 1996; Petrides & Pandya, 1995; Price, 2006, 2007) are summarized in Fig. 3. Conceptually, the orbitofrontal cortex can be thought of as receiving from the ends of each modality-specific 'what' cortical pathway as shown in Fig. 1, and this functional connectivity is emphasized in the following.

Rolls, Yaxley, and Sienkiewicz (1990) discovered a taste area with taste-responsive neurons in the lateral part of the

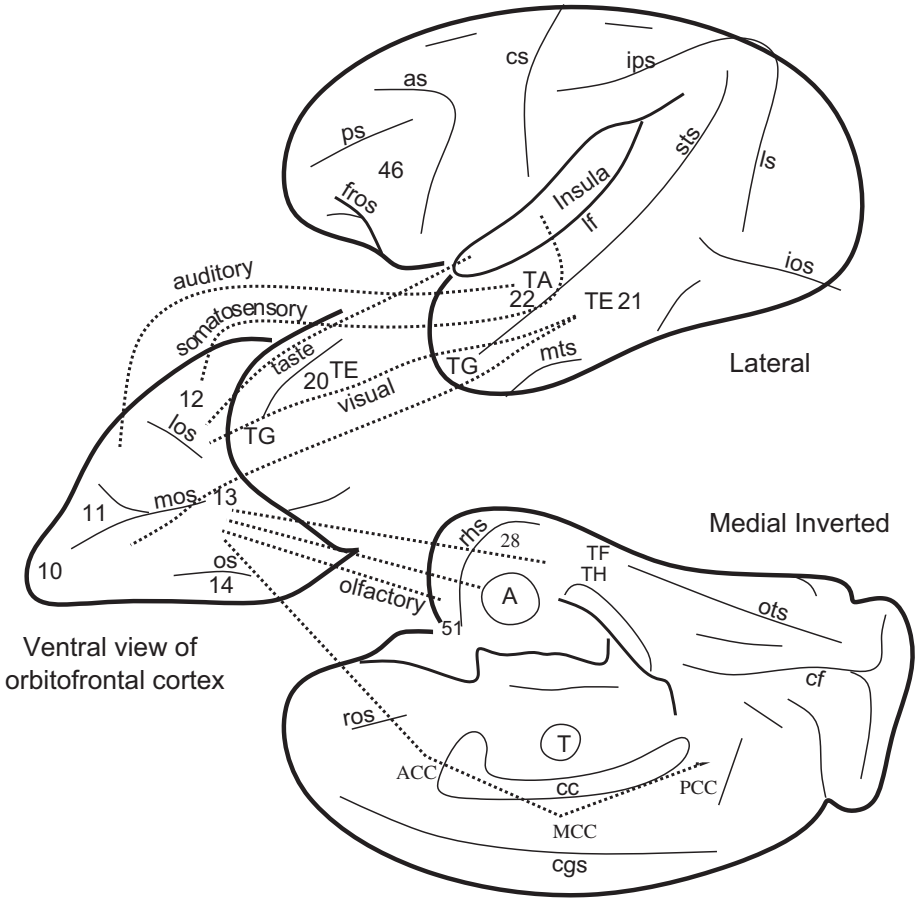

Fig. 3 – Schematic diagram showing some of the gustatory, olfactory, and visual pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex. The secondary taste cortex and the secondary olfactory cortex are within the orbitofrontal cortex. V1, primary visual cortex. V4, visual cortical area V4. Abbreviations: as, arcuate sulcus; cc, corpus callosum; cf, calcarine fissure; cgs, cingulate sulcus; cs, central sulcus; ls, lunate sulcus; ios, inferior occipital sulcus; mos, medial orbital sulcus; os, orbital sulcus; ots, occipito-temporal sulcus; ps, principal sulcus; rhs, rhinal sulcus; sts, superior temporal sulcus; lf, lateral (or Sylvian) fissure (which has been opened to reveal the insula); A, amygdala; INS, insula; MCC, midcingulate cortex; PCC, posterior cingulate cortex; T, thalamus; TE (21), inferior temporal visual cortex; TA (22), superior temporal auditory association cortex; TF and TH, parahippocampal cortex; TG, temporal pole cortex; 12, 13, 11, orbitofrontal cortex; 28, entorhinal cortex; 51, olfactory (prepyriform and periamygdaloid) cortex.

macaque orbitofrontal cortex, and showed anatomically with horseradish peroxidase pathway tracing that this was the secondary taste cortex in that it receives a major projection from the neurophysiologically identified primary taste cortex (Baylis, Rolls, & Baylis, 1995). This region projects on to more anterior areas of the orbitofrontal cortex (Baylis et al., 1995). Taste neurons are also found more medially (Critchley & Rolls, 1996c; Pritchard et al., 2005; Rolls, 2008b; Rolls & Baylis, 1994; Rolls, Critchley, Wakeman, & Mason, 1996).

In the mid-orbitofrontal cortex, there is an area with olfactory neurons (Rolls & Baylis, 1994), and anatomically there are direct connections from the primary olfactory cortex, pyriform cortex, to area 13a of the posterior orbitofrontal cortex, which in turn has onward projections to a middle part of the orbitofrontal cortex (area 13) (Barbas, 1993; Carmichael, Clugnet, & Price, 1994; Morecraft, Geula, & Mesulam, 1992; Price, 2007; Price et al., 1991) (see Fig. 1).

Thorpe, Rolls, and Maddison (1983) found neurons with visual responses in the orbitofrontal cortex, and anatomically, visual inputs reach the orbitofrontal cortex directly from the inferior temporal cortex [where object and face identity are represented (Rolls, 2007b, 2008c)], the cortex in the superior temporal sulcus [where face expression and gesture are represented (Hasselmo, Rolls, & Baylis, 1989)], and the temporal pole cortex (see Barbas, 1988, 1993, 1995; Barbas & Pandya, 1989; Carmichael & Price, 1995b; Morecraft et al., 1992; Seltzer & Pandya, 1989). There are corresponding auditory inputs (Barbas, 1988, 1993; Rolls, Critchley, Browning, & Inoue, 2006; Romanski & Goldman-Rakic, 2001; Romanski et al., 1999).

Some neurons in the orbitofrontal cortex respond to oral somatosensory stimuli such as the texture of food (Rolls, Critchley, Browning, Hernadi, & Lenard, 1999; Rolls, Verhagen, & Kadohisa, 2003), and anatomically there are inputs to the orbitofrontal cortex from somatosensory cortical areas 1, 2 and SII in the frontal and pericentral operculum, and from the insula (Barbas, 1988; Carmichael & Price, 1995b). The caudal orbitofrontal cortex receives inputs from the amygdala (Price et al., 1991). The orbitofrontal cortex also receives inputs via the mediodorsal nucleus of the thalamus, pars magnocellularis, which itself receives afferents from temporal lobe structures such as the prepyriform (olfactory) cortex, amygdala, and inferior temporal cortex (see Öngür & Price, 2000). These connections provide some routes via which the responses of orbitofrontal cortex neurons can be produced. Within the orbitofrontal cortex, there are many intrinsic connections (Öngür & Price, 2000), and these may be part of what enables many orbitofrontal cortex neurons to have multimodal responses, as described below and elsewhere (Rolls, 2005, 2008b, 2008c, 2014; Rolls & Grabenhorst, 2008).

The orbitofrontal cortex projects back to temporal lobe areas such as the amygdala via the uncinate fasciculus (Barbas, 2007). The orbitofrontal cortex also has projections to the ACC (Carmichael & Price, 1996; Price, 2006), the ventral striatum (Ferry, Ongur, An, & Price, 2000) and head of the caudate nucleus (Haber, Kim, Mailly, & Calzavara, 2006; Kemp & Powell, 1970), medial prefrontal cortex area 10 (Price, 2007), preoptic region and lateral hypothalamus [where neurons respond to the sight and taste of food, and show sensory-specific satiety (Burton, Rolls, & Mora, 1976; Rolls, Burton, & Mora, 1976)], and the ventral tegmental area (Johnson, Rosvold, & Mishkin, 1968; Nauta, 1964; Price, 2006), and these connections provide some routes via which the orbitofrontal cortex can influence behaviour (Rolls, 2014). The orbitofrontal cortex also has connections to the entorhinal and perirhinal cortex (Barbas, 2007; Insausti, Amaral, & Cowan, 1987; Price, 2006) providing a route for reward information to reach the hippocampus where it can become linked into memories about for example where reward is located, though not about which objects are associated with reward (Rolls, 2010b; Rolls & Xiang, 2005), which is an orbitofrontal/amygdala function important in emotion. In turn, connections back to the orbitofrontal cortex from the entorhinal cortex, and even from CA1 and the subiculum (Price, 2006), provide a route for the reward value and emotional state to be recalled to the orbitofrontal cortex as part of the recall of an episodic memory.

3.3.2. *Effects of damage to the orbitofrontal cortex on emotion and emotion-related learning*

Part of the evidence on the functions of the orbitofrontal cortex in emotion comes from the effects of lesions of the orbitofrontal cortex. Macaques with lesions of the orbitofrontal cortex are impaired at tasks that involve learning about which stimuli are rewarding and which are not, and are especially impaired at altering behaviour when reinforcement contingencies change. The monkeys may respond when responses are inappropriate, e.g., no longer rewarded, or may respond to a non-rewarded stimulus. For example, monkeys with orbitofrontal cortex damage are impaired on Go/NoGo task performance in that they Go on the NoGo trials (Iversen & Mishkin, 1970); in an object reversal task in that they respond to the object that was formerly rewarded with food; and in extinction in that they continue to respond to an object which is no longer rewarded (Butter, 1969; Izquierdo & Murray, 2004; Izquierdo, Suda, & Murray, 2004; Jones & Mishkin, 1972; Murray & Izquierdo, 2007; Rudebeck & Murray, 2011). Rapid associations between visual stimuli and reinforcers such as taste, and the rapid reversal of these associations, is an important function of the orbitofrontal cortex as shown by neurons with one-trial object-reward reversal learning (Rolls, 2014; Rolls, Critchley, Mason, & Wakeman, 1996; Thorpe et al., 1983). Consistent with this, in humans rapid reversal is impaired by orbitofrontal cortex damage (Fellows & Farah, 2003; Hornak et al., 2004; Rolls, Hornak, Wade, & McGrath, 1994).

Orbitofrontal cortex damage affects reward value as also shown by devaluation investigations. Sensory-specific satiety (a method of reward devaluation in which a food is fed to satiety), which is implemented neuronally in the orbitofrontal cortex (Rolls, Sienkiewicz, et al., 1989), is impaired by orbitofrontal cortex lesions (but perhaps less by amygdala lesions) (Murray & Izquierdo, 2007; Rudebeck & Murray, 2011). In relation to neuroeconomics, the estimation of expected reward value as influenced by reward size, and delay to reward, or both, is impaired by orbitofrontal cortex lesions in macaques (Simmons, Minamimoto, Murray, & Richmond, 2010).

It is suggested that difficulty in processing reinforcers, and especially in rapid visual discrimination reversal learning, underlies some of the impairments in emotion produced by

damage to the orbitofrontal cortex (Rolls, 2014). In humans, euphoria, irresponsibility, lack of affect, and impulsiveness can follow frontal lobe damage (Damasio, 1994; Kolb & Whishaw, 2003; Rolls, 1999a; Zald & Rauch, 2006), particularly orbitofrontal cortex damage (Berlin, Rolls, & Iversen, 2005; Berlin, Rolls, & Kischka, 2004; Hornak et al., 2003; Hornak, Rolls, & Wade, 1996; Rolls, 1999a, 2014; Rolls et al., 1994). These emotional changes may be related at least in part to a failure to rapidly update the reinforcement associations of stimuli when the contingencies are changed as in a visual discrimination reversal task (Berlin et al., 2004; Fellows, 2007, 2011; Fellows & Farah, 2003; Hornak et al., 2004; Rolls, 1999b, 2014; Rolls et al., 1994). Similar mechanisms may contribute at least in part to the poor performance of humans with ventromedial prefrontal cortex damage on the Iowa Gambling Task (Bechara, Damasio, & Damasio, 2000; Maia & McClelland, 2004). It is of interest that the patients with bilateral orbitofrontal cortex damage who were impaired at the visual discrimination reversal task had high scores on parts of a Social Behaviour Questionnaire in which the patients were rated on behaviours such as emotion recognition in others (e.g., their sad, angry, or disgusted mood); in interpersonal relationships (such as not caring what others think, and not being close to the family); emotional empathy (e.g., when others are happy, is not happy for them); interpersonal relationships (e.g., does not care what others think, and is not close to his family); public behaviour (is uncooperative); antisocial behaviour (is critical of and impatient with others); impulsivity (does things without thinking); and sociability (is not sociable, and has difficulty making or maintaining close relationships) (Hornak et al., 2003, 2004), all of which could reflect less behavioural sensitivity to different types of punishment and reward. Further, in a Subjective Emotional Change Questionnaire in which the patients reported on any changes in the intensity and/or frequency of their own experience of emotions, the bilateral orbitofrontal cortex lesion patients with deficits in the visual discrimination reversal task reported a number of changes, including changes in sadness, anger, fear and happiness (Hornak et al., 2003).

3.3.3. *Reward outcome value for taste, olfaction, flavour, oral texture, and oral temperature in the orbitofrontal cortex*

3.3.3.1. Taste and oral texture. One of the discoveries that have helped us to understand the functions of the orbitofrontal cortex in behaviour is that it contains a major cortical representation of taste (see Kadohisa, Rolls, & Verhagen, 2005a; Rolls, 1995a, 1997, 2014; Rolls & Scott, 2003; Rolls et al., 1990) (cf. Fig. 1). Given that taste can act as a primary reinforcer, that is without learning as a reward or punisher, we now have the start for a fundamental understanding of the function of the orbitofrontal cortex in stimulus-reinforcer association learning (Rolls, 1999a, 2004, 2008c, 2014). We know how one class of primary reinforcers reaches and is represented in the orbitofrontal cortex. A representation of primary reinforcers is essential for a system that is involved in learning associations between previously neutral stimuli and primary reinforcers, e.g., between the sight of an object and its taste.

The representation in the orbitofrontal cortex (shown by analysing the responses of single neurons in macaques) is for the majority of neurons the reward value of taste (Baylis & Rolls, 1991; Kadohisa et al., 2005a; Rolls, 1995a, 1997, 2000c; Rolls, Critchley, Browning, & Hernadi, 1998; Rolls, Critchley, Wakeman, et al., 1996; Rolls & Scott, 2003; Rolls et al., 1990) and oral texture including viscosity (Rolls, Verhagen, et al., 2003), fat texture (Rolls et al., 1999; Verhagen, Rolls, & Kadohisa, 2003), and astringency as exemplified by tannic acid (Critchley & Rolls, 1996c). The evidence for this is that the responses of orbitofrontal cortex taste neurons are modulated by hunger (as is the reward value or palatability of a taste). In particular, it has been shown that orbitofrontal cortex taste neurons gradually stop responding to the taste of a food as the monkey is fed to satiety, but not to the taste of other foods, revealing a mechanism for sensory-specific satiety and reward devaluation (Rolls, Critchley, Wakeman, et al., 1996; Rolls, Sienkiewicz, et al., 1989). In contrast, the representation of taste in the primary taste cortex (Scott, Yaxley, Sienkiewicz, & Rolls, 1986; Yaxley, Rolls, & Sienkiewicz, 1990) is not modulated by hunger (Rolls, Scott, Sienkiewicz, & Yaxley, 1988; Yaxley, Rolls, & Sienkiewicz, 1988). Thus in the primate including human primary taste cortex, the reward value of taste is not represented, and instead the identity and intensity of the taste are represented (Grabenhorst & Rolls, 2008; Grabenhorst, Rolls, & Bilderbeck, 2008; Rolls, 2008c, 2014).

Additional evidence that the reward value of food is represented in the orbitofrontal cortex is that monkeys work for electrical stimulation of this brain region if they are hungry, but not if they are satiated (Mora, Avrith, Phillips, & Rolls, 1979; Rolls, 2005). Further, neurons in the orbitofrontal cortex are activated from many brain-stimulation reward sites (Mora, Avrith, & Rolls, 1980; Rolls, Burton, & Mora, 1980). Thus there is clear evidence that it is the reward value of taste that is represented in the orbitofrontal cortex (see further Rolls, 1999a, 2000d, 2014), and this is further supported by the finding that feeding to satiety decreases the activation of the human orbitofrontal cortex to the food eaten to satiety in a sensory-specific way (Kringelbach et al., 2003). Some orbitofrontal cortex neurons respond to the 'taste' of water in the mouth (Rolls et al., 1990), and their responses occur only when thirsty and not when satiated (Rolls, Sienkiewicz, et al., 1989); and correspondingly in humans the subjective pleasantness or affective value of the taste of water in the mouth is represented in the orbitofrontal cortex (de Araujo, Kringelbach, Rolls, & McGlone, 2003). This is part of the evidence for the separation of a 'what' tier of processing, which in this case is the primary taste cortex, from a reward and affect-related representation in the orbitofrontal cortex tier of processing, as shown in Fig. 1.

Functional neuroimaging studies in humans have shown that the most medial part of the human orbitofrontal cortex is activated by taste, oral texture, and olfactory stimuli (de Araujo, Kringelbach, Rolls, & Hobden, 2003; de Araujo & Rolls, 2004; de Araujo, Rolls, Kringelbach, McGlone, & Phillips, 2003; de Araujo, Rolls, Velazco, Margot, & Cayeux, 2005; Francis et al., 1999; Gottfried, Small, & Zald, 2006; McCabe & Rolls, 2007; O'Doherty et al., 2000; Rolls, Kringelbach, & de Araujo, 2003; Rolls & McCabe, 2007; Small, Gerber, Mak, & Hummel, 2005; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001), and that the activations correlate with ratings of subjective pleasantness and so are in

the domain of affective representations (Kringelbach & Rolls, 2004; Rolls, 2014). This most medial part of the human orbitofrontal cortex may have moved medially when compared with the representation in macaques, probably because of the extensive development of the dorsolateral prefrontal cortex in humans (Rolls, 2008b; Rolls & Grabenhorst, 2008). Affectively pleasant stimuli are often represented medially, and unpleasant or aversive stimuli laterally, in the human orbitofrontal cortex. Evidence consistent with this has been found for taste (de Araujo, Kringelbach, Rolls, & Hobden, 2003; O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001), pleasant touch (Francis et al., 1999; Rolls, O'Doherty, et al., 2003), and pleasant versus aversive olfactory stimuli (Francis et al., 1999; O'Doherty et al., 2000; Rolls, 2000d; Rolls, Kringelbach, et al., 2003) (see further Grabenhorst & Rolls, 2011; Kringelbach & Rolls, 2004). An important point for those seeking to understand the hedonic topology of the human orbitofrontal cortex is that it should not be assumed to be the same as that in macaques.

3.3.3.2. An olfactory reward representation in the orbitofrontal cortex. For 35% of orbitofrontal cortex olfactory neurons, the odours to which a neuron responded were influenced by the taste value (glucose or saline) with which the odour was associated (Critchley & Rolls, 1996b). Thus the odour representation for 35% of orbitofrontal neurons appeared to be built by olfactory-to-taste association learning. This possibility was confirmed by reversing the taste with which an odour was associated in the reversal of an olfactory discrimination task. It was found that 68% of the sample of neurons analysed altered the way in which they responded to odour when the taste reinforcement association of the odour was reversed (Rolls, Critchley, Mason, et al., 1996). The olfactory-to-taste reversal was quite slow, both neurophysiologically and behaviourally, often requiring 20–80 trials, consistent with the need for some stability of flavour representations formed by a combination of odour and taste inputs.

To analyse the nature of the olfactory representation in the orbitofrontal cortex, Critchley and Rolls (1996a) measured the responses of olfactory neurons that responded to food while they fed the monkey to satiety. They found that the majority of orbitofrontal olfactory neurons decreased their responses to the odour of the food with which the monkey was fed to satiety. Thus for these neurons, the reward value of the odour is what is represented in the orbitofrontal cortex (cf. Rolls & Rolls, 1997), and this parallels the changes in the relative pleasantness of different foods after a food is eaten to satiety (Rolls, 1997; Rolls, Rolls, Rowe, & Sweeney, 1981a, 1981b; see Rolls, 1999a, 2000d, 2014). The subjective pleasantness or reward or affective value of odour is represented in the orbitofrontal cortex, in that feeding humans to satiety decreases the activation found to the odour of that food, and this effect is relatively specific to the food eaten in the meal (O'Doherty et al., 2000; Francis et al., 1999; cf. Morris & Dolan, 2001). Further, the human medial orbitofrontal cortex has activation that is related to the subjective pleasantness of a set of odours, and a more lateral area has activation that is related to the degree of subjective unpleasantness of odours (Rolls, Kringelbach, et al., 2003). A functional magnetic resonance imaging (fMRI) investigation in humans showed that whereas in the orbitofrontal cortex the pleasantness versus unpleasantness of odours is represented, this was not the case in primary olfactory cortical areas, where instead the activations reflected the intensity of the odours (Rolls, Kringelbach, et al., 2003), providing a further example of the hierarchy of 'what' followed by reward processing shown in Fig. 1.

3.3.3.3. Convergence of taste and olfactory inputs in the orbitofrontal cortex: the representation of flavour. In the orbitofrontal cortex, not only unimodal taste neurons, but also unimodal olfactory neurons are found. In addition some single neurons respond to both gustatory and olfactory stimuli, often with correspondence between the two modalities (Rolls & Baylis, 1994). It is probably here in the orbitofrontal cortex of primates including humans that these two modalities converge to produce the representation of flavour (de Araujo, Rolls, et al., 2003; Rolls & Baylis, 1994), for neurons in the primary taste cortex in the insular/frontal opercular cortex do not respond to olfactory (or visual) stimuli (Verhagen, Kadohisa, & Rolls, 2004).

The importance of the combination of taste and smell for producing affectively pleasant and rewarding representations of sensory stimuli is exemplified by findings with umami, the delicious taste or flavour that is associated with combinations of components that include meat, fish, milk, tomatoes, and mushrooms, all of which are rich in umami-related substances such as glutamate or inosine 5′ monophosphate. Umami taste is produced by glutamate acting on a fifth taste system (Chaudhari, Landin, & Roper, 2000; Maruyama, Pereira, Margolskee, Chaudhari, & Roper, 2006; Zhao et al., 2003). However, glutamate presented alone as a taste stimulus is not highly pleasant, and does not act synergistically with other tastes (sweet, salt, bitter and sour). However, when glutamate is given in combination with a consonant, savoury, odour (vegetable), the resulting flavour can be much more pleasant (McCabe & Rolls, 2007). We showed using functional brain imaging with fMRI that this glutamate taste and savoury odour combination produced much greater activation of the medial orbitofrontal cortex and pregenual cingulate cortex than the sum of the activations by the taste and olfactory components presented separately (McCabe & Rolls, 2007). Supra-linear effects were much less (and significantly less) evident for sodium chloride and vegetable odour. Further, activations in these brain regions were correlated with the subjective pleasantness and fullness of the flavour, and with the consonance of the taste and olfactory components. Supra-linear effects of glutamate taste and savoury odour were not found in the insular primary taste cortex. We thus proposed that glutamate acts by the non-linear effects it can produce when combined with a consonant odour in multimodal cortical taste-olfactory convergence regions. We suggested that umami can be thought of as a rich and delicious flavour that is produced by a combination of glutamate taste and a consonant savoury odour (Rolls, 2009c). Glutamate is thus a flavour enhancer because of the way that it can combine supra-linearly with consonant odours in cortical areas where the taste and olfactory pathways converge far beyond the receptors (McCabe & Rolls, 2007).

3.3.3.4. Oral texture and temperature. A population of orbitofrontal cortex neurons responds when a fatty food such as

cream is in the mouth. These neurons can also be activated by pure fat such as glyceryl trioleate, and by non-fat substances with a fat-like texture such as paraffin oil (hydrocarbon) and silicone oil [$(Si(CH_3)_2O)_n$]. These neurons thus provide information by somatosensory pathways that a fatty food is in the mouth (Rolls et al., 1999). These inputs are perceived as pleasant when hungry, because of the utility of ingestion of foods that are likely to contain essential fatty acids and to have a high calorific value (Rolls, 2000d, 2014). Satiety produced by eating a fatty food, cream, can decrease the responses of orbitofrontal cortex neurons to the texture of fat in the mouth (Rolls et al., 1999).

We have shown that the orbitofrontal cortex receives inputs from a number of different oral texture channels, which together provide a rich sensory representation of what is in the mouth (Rolls, 2011b, 2012b). Using a set of stimuli in which viscosity was systematically altered (carboxymethylcellulose with viscosity in the range 10–10,000 cP), we have shown that some orbitofrontal cortex neurons encode fat texture independently of viscosity (by a physical parameter that varies with the slickness of fat) (Verhagen et al., 2003); that other orbitofrontal cortex neurons encode the viscosity of the texture in the mouth (with some neurons tuned to viscosity, and others showing increasing or decrease firing rates as viscosity increases) (Rolls, Verhagen, et al., 2003); and that other neurons have responses that indicate the presence of texture stimuli (such as grittiness and capsaicin) in the mouth independently of viscosity and slickness (Rolls, Verhagen, et al., 2003). Ensemble (i.e., population, distributed) encoding of all these variables is found (Rolls, Critchley, Verhagen, & Kadohisa, 2010; Rolls & Treves, 2011). In a complementary human functional neuroimaging study, it has been shown that activations of parts of the orbitofrontal cortex, primary taste cortex, and mid-insular somatosensory region posterior to the insular taste cortex have activations that are related to the viscosity of what is in the mouth, and that there is in addition a medial prefrontal/cingulate area where the mouth feel of fat is represented (de Araujo & Rolls, 2004). Moreover, the subjective pleasantness of fat is represented in the orbitofrontal cortex and a region to which it projects the pregenual cingulate cortex (Grabenhorst, Rolls, Parris, & D'Souza, 2010).

An overlapping population of orbitofrontal cortex neurons represents the temperature of what is in the mouth (Kadohisa, Rolls, & Verhagen, 2004), and this is supported by a human fMRI study (Guest et al., 2007).

3.3.4. *Outcome value and somatosensory and temperature inputs to the orbitofrontal cortex*

In addition to these oral somatosensory inputs to the orbitofrontal cortex, there are also somatosensory inputs from other parts of the body (Rolls, 2010a), and indeed an fMRI investigation we have performed in humans indicates that pleasant and painful touch stimuli to the hand produce greater activation of the orbitofrontal cortex relative to the somatosensory cortex than do affectively neutral stimuli (Francis et al., 1999; Rolls, O'Doherty, et al., 2003). In an fMRI investigation in humans, it was found that the mid-orbitofrontal and pregenual cingulate cortex and a region to which they project, the ventral striatum, have activations that are correlated with the subjective pleasantness ratings made to warm (41 °C) and cold (12 °C) stimuli, and combinations of warm and cold stimuli, applied to the hand (Rolls, Grabenhorst, & Parris, 2008). Activations in the lateral and some more anterior parts of the orbitofrontal cortex were correlated with the unpleasantness of the stimuli. In contrast, activations in the somatosensory cortex and ventral posterior insula were correlated with the intensity but not the pleasantness of the thermal stimuli. Further, cognitive modulators of affective value such as the description of cream being rubbed on the arm as 'rich and moisturizing' increase activations to the sight of rubbing of the arm in the orbitofrontal and pregenual cingulate cortex, and increased correlations there with the subjectively rated pleasantness of the touch (McCabe, Rolls, Bilderbeck, & McGlone, 2008).

A principle thus appears to be that processing related to the affective value and associated subjective emotional experience of thermal stimuli that are important for survival is performed in different brain areas to those where activations are related to sensory properties of the stimuli such as their intensity. This conclusion appears to be the case for processing in a number of sensory modalities, including taste (Grabenhorst & Rolls, 2008; Grabenhorst, Rolls, & Bilderbeck, 2008) and olfaction (Anderson et al., 2003; Grabenhorst, Rolls, Margot, da Silva, & Velazco, 2007; Rolls, Kringelbach, et al., 2003), and the finding with such prototypical stimuli as warm and cold (Rolls, Grabenhorst, & Parris, 2008) provides strong support for this principle (see Fig. 1).

Non-glabrous skin such as that on the forearm contains C fibre tactile afferents that respond to light moving touch (Olausson et al., 2002). The orbitofrontal cortex is implicated in some of the affectively pleasant aspects of touch that may be mediated through C fibre tactile afferents, in that it is activated more by light touch to the forearm than by light touch to the glabrous skin (palm) of the hand (McCabe et al., 2008).

3.3.5. *Expected value visual inputs to the orbitofrontal cortex, visual stimulus-reinforcement association learning and reversal, and negative reward prediction error neurons*

We have been able to show that there is a major visual input to many neurons in the orbitofrontal cortex, and that what is represented by these neurons is in many cases the reinforcement association of visual stimuli. The visual input is from the ventral, temporal lobe, visual stream concerned with 'what' object is being seen (see Rolls, 2000a, 2012a). Many neurons in these temporal cortex visual areas have responses to objects or faces that are invariant with respect to size, position on the retina, and even view (Rolls, 2000a, 2007b, 2008a, 2008c, 2009d, 2012a), making these neurons ideal as an input to a system that may learn about the reinforcement association properties of objects and faces, for after a single learning trial, the learning then generalizes correctly to other views etc. (see Rolls, 2000a, 2008c, 2012a, 2014). Using this object-related information, orbitofrontal cortex visual neurons frequently respond differentially to objects or images depending on their reward association (Rolls, Critchley, Mason, et al., 1996; Thorpe et al., 1983). The primary reinforcer that has been used is taste, and correlates of visual to taste association learning have been demonstrated in the human orbitofrontal cortex with fMRI (O'Doherty, Deichmann, Critchley, & Dolan, 2002). Many of these neurons show visual-taste reversal in

one or a very few trials [In a visual discrimination task, they will reverse the stimulus to which they respond, from e.g., a triangle to a square, in one trial when the taste delivered for a behavioural response to that stimulus is reversed (Thorpe et al., 1983).]. This reversal learning probably occurs in the orbitofrontal cortex, for it does not occur one synapse earlier in the visual inferior temporal cortex (Rolls, Judge, & Sanghera, 1977), and it is in the orbitofrontal cortex that there is convergence of visual and taste pathways onto the same single neurons (Rolls & Baylis, 1994; Rolls, Critchley, Mason et al., 1996; Thorpe et al., 1983).

The probable mechanism for this learning is an associative modification of synapses conveying visual input onto taste-responsive neurons, implementing a pattern association network (Rolls, 2008c, 2014; Rolls & Deco, 2002; Rolls & Treves, 1998) (see Fig. 8), with the reversal facilitated by a rule for which stimulus is currently rewarded held in short-term memory (Deco & Rolls, 2005c).

The visual and olfactory neurons in primates that respond to the sight or smell of stimuli that are primary reinforcers such as taste clearly signal an expectation of reward that is based on previous stimulus-reinforcement associations (Rolls, Critchley, Mason, et al., 1996; Thorpe et al., 1983). So do the conditional reward neurons which reflect the reward value only for one of a pair of stimuli (Rolls, Critchley, Mason, et al., 1996; Rolls & Grabenhorst, 2008; Thorpe et al., 1983). With visual-taste association learning and reversal in primates, in which the orbitofrontal cortex neurons and the behaviour can change in one trial (Rolls, Critchley, Mason, et al., 1996; Thorpe et al., 1983), the changing responses of the orbitofrontal cortex neurons can contribute to the reversed behaviour, a view of course supported by the impaired reversal learning produced in primates including humans by orbitofrontal cortex damage (e.g., Berlin et al., 2004; Fellows & Farah, 2003; Hornak et al., 2004; Murray & Izquierdo, 2007; Rolls et al., 1994).

To analyse the nature of the visual representation of food-related stimuli in the orbitofrontal cortex, Critchley and Rolls (1996a) measured the responses of neurons that responded to the sight of food while they fed the monkey to satiety in a devaluation investigation. They found that the majority of orbitofrontal visual food-related neurons decreased their responses to the sight of the food with which the monkey was fed to satiety. Thus for these neurons, the expected reward value of the sight of food is what is represented in the orbitofrontal cortex.

In addition to these neurons that encode the reward association of visual stimuli, other, 'error', neurons in the orbitofrontal cortex detect non-reward, in that they respond for example when an expected reward is not obtained when a visual discrimination task is reversed (Thorpe et al., 1983), or when reward is no longer made available in a visual discrimination task. These may be called "negative reward prediction error neurons" (Rolls, 2014; Rolls & Grabenhorst, 2008). Evidence that there may be similar error neurons in the human orbitofrontal cortex is that in a model of social learning, orbitofrontal cortex activation occurred in a visual discrimination reversal task at the time when the face of one person no longer was associated with a smile, but became associated with an angry expression, indicating on such error trials that reversal of choice to the other individual's face should occur (Kringelbach & Rolls, 2003).

The orbitofrontal cortex negative reward prediction error neurons respond to a mismatch between the reward expected and the reward that is obtained. Both signals are represented in the orbitofrontal cortex, in the form of for example neurons that respond to the sight of a learned reinforcer such as the sight of a stimulus paired with taste, and neurons that respond to the primary reinforcer, the taste (or texture or temperature). The orbitofrontal cortex is the probable brain region for this computation, because both the signals required to compute negative reward prediction error are present in the orbitofrontal cortex, so are the negative reward prediction error neurons, and lesions of the orbitofrontal cortex impair tasks such as visual discrimination reversal in which this type of negative reward prediction error is needed [see above and Rolls (2014)].

3.3.6. *Orbitofrontal cortex neurons compared to dopamine neurons*

The dopamine neurons in the midbrain that respond to positive reward prediction error (a greater reward than expected) may not be able to provide a good representation of negative reward prediction error, because their spontaneous firing rates are so low (Schultz, 2004) that much further reduction would provide only a small signal. In any case, the dopamine neurons would not appear to be in a position to compute a negative reward prediction error, as they are not known to receive inputs that signal expected reward, and the actual reward (outcome) that is obtained, and indeed do not represent the reward obtained (or 'outcome'), in that they stop responding to a taste reward outcome if it is predictable. Although some dopamine neurons do appear to represent a positive reward prediction error signal (responding if a greater than expected reward is obtained) (Schultz, 2004, 2006, 2013), they do not appear to have the signals required to compute this, that is, the expected reward, and the reward outcome obtained, so even a positive reward prediction error must be computed elsewhere. The orbitofrontal cortex does contain representations of these two signals, the expected reward and the reward outcome, and has projections to the ventral striatum, which in turn projects to the region of the midbrain dopamine neurons, and so this is one possible pathway along which the firing of positive reward prediction error might be computed (see Fig. 1) (Rolls, 2014). Consistent with this, activations in parts of the human ventral striatum are related to positive reward prediction error (Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; Rolls, McCabe, & Redoute, 2008c). Thus the dopamine projections to the prefrontal cortex and other areas are not likely to convey information about reward to the prefrontal cortex, which instead is likely to be decoded by the neurons in the orbitofrontal cortex that represent primary reinforcers, and the orbitofrontal cortex neurons that learn associations of other stimuli to the primary reinforcers to represent expected value (Rolls, 2008c; Rolls, Critchley, Mason, et al., 1996; Rolls, McCabe, et al., 2008; Thorpe et al., 1983). Although it has been suggested that the firing of dopamine neurons may reflect the earliest signal in a task that indicates reward and could be used as a reward prediction error signal during learning (see Schultz, 2006; Schultz, Tremblay, & Hollerman, 2000), it is likely, partly on the basis of the above evidence, though an interesting topic for future

investigation, that any error information to which dopamine neurons fire originates from representations in the orbitofrontal cortex that encode expected value and reward outcome, and which connect to the ventral striatum (Rolls, 2008c, 2009b, 2014). A further problem is that some dopamine neurons respond to aversive or salient stimuli (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Matsumoto & Hikosaka, 2009), and overall the population may not code a reward prediction error (Rolls, 2014).

3.3.7. *Face-selective processing in the orbitofrontal cortex*

Another type of visual information represented in the orbitofrontal cortex is information about faces. There is a population of orbitofrontal cortex neurons that respond in many ways similarly to those in the temporal cortical visual areas (Rolls, 1984, 1992a, 1996a, 2000a, 2007b, 2008a, 2008c, 2011a, 2012a; Rolls & Deco, 2002). The orbitofrontal cortex face-responsive neurons, first observed by Thorpe et al. (1983), then by Rolls, Critchley, et al. (2006), tend to respond with longer latencies than temporal lobe neurons (140–200 msec typically, compared to 80–100 msec); also convey information about which face is being seen, by having different responses to different faces; and are typically rather harder to activate strongly than temporal cortical face-selective neurons, in that many of them respond much better to real faces than to two-dimensional images of faces on a video monitor (Rolls, 2011a; Rolls, Critchley, et al., 2006) (cf. Rolls & Baylis, 1986). Some of the orbitofrontal cortex face-selective neurons are responsive to face expression, gesture or movement (Rolls, Critchley, et al., 2006). The findings are consistent with the likelihood that these neurons are activated via the inputs from the temporal cortical visual areas in which face-selective neurons are found (see Fig. 1). The significance of the neurons is likely to be related to the fact that faces convey information that is important in social reinforcement in at least two ways that could be implemented by these neurons. The first is that some may encode face expression (Rolls, Critchley, et al., 2006) (cf. Hasselmo et al., 1989), which can indicate reinforcement. The second way is that they encode information about which individual is present (Rolls, Critchley, et al., 2006), which by stimulus-reinforcement association learning is important in evaluating and utilising learned reinforcing inputs in social situations, e.g., about the current reinforcement value as decoded by stimulus-reinforcement association, to a particular individual. Between them, these neurons represent whose face has a particular expression, and this is important in social situations.

This system has also been shown to be present in humans. For example, Kringelbach and Rolls (2003) showed that activation of a part of the human orbitofrontal cortex occurs during a face discrimination reversal task. In the task, the faces of two different individuals are shown, and when the correct face is selected, the expression turns into a smile (The expression turns to angry if the wrong face is selected.). After a period of correct performance, the contingencies reverse, and the other face must be selected to obtain a smile expression as a reinforcer. It was found that activation of a part of the orbitofrontal cortex occurred specifically in relation to the reversal, that is when a formerly correct face was chosen, but an angry face expression was obtained. In a control task, it was shown that the activations were not related just to showing an angry face expression. Thus in humans, there is a part of the orbitofrontal cortex that responds selectively in relation to face expression specifically when it indicates that behaviour should change, and this activation is error-related (Kringelbach & Rolls, 2003) and occurs when the error neurons in the orbitofrontal cortex become active (Thorpe et al., 1983).

Also prompted by the neuronal recording evidence of face and auditory neurons in the orbitofrontal cortex (Rolls, Critchley, et al., 2006), it has further been shown that there are impairments in the identification of facial and vocal emotional expression in a group of patients with ventral frontal lobe damage who had socially inappropriate behaviour (Hornak et al., 1996). The expression identification impairments could occur independently of perceptual impairments in facial recognition, voice discrimination, or environmental sound recognition. Poor performance on both expression tests was correlated with the degree of alteration of emotional experience reported by the patients. There was also a strong positive correlation between the degree of altered emotional experience and the severity of the behavioural problems (e.g., disinhibition) found in these patients (Hornak et al., 1996). A comparison group of patients with brain damage outside the ventral frontal lobe region, without these behavioural problems, was unimpaired on the face expression identification test, was significantly less impaired at vocal expression identification, and reported little subjective emotional change (Hornak et al., 1996). It has further been shown that patients with discrete surgical lesions of restricted parts of the orbitofrontal cortex may have face and/or voice expression identification impairments, and these are likely to contribute to their difficulties in social situations (Hornak et al., 2003).

3.3.8. *Top–down effects of cognition and attention on taste, olfactory, flavour, somatosensory, and visual processing: cognitive enhancement of the value of affective stimuli*

How does cognition influence affective value? How does cognition influence the way that we feel emotionally? Do cognition and emotion interact in regions that are high in the brain's hierarchy of processing, for example in areas where language processing occurs, or do cognitive influences descend down anatomically to influence the first regions that represent the affective value of stimuli?

An fMRI study to address these fundamental issues in brain design has shown that cognitive effects can reach down into the human orbitofrontal cortex and influence activations produced by odours (de Araujo et al., 2005). In this study, a standard test odour, isovaleric acid with a small amount of cheese flavour, was delivered through an olfactometer (The odour alone, like the odour of brie, might have been interpreted as pleasant, or perhaps as unpleasant.). On some trials the test odour was accompanied with the visually presented word label "cheddar cheese", and on other trials with the word label "body odour". It was found that the activation in the medial orbitofrontal cortex to the standard test odour was much greater when the word label was cheddar cheese than when it was body odour (Controls with clean air were run to show that the effect could not be accounted for by the word label alone.). Moreover, the word labels influenced the

subjective pleasantness ratings to the test odour, and the changing pleasantness ratings were correlated with the activations in the human medial orbitofrontal cortex. Part of the interest and importance of this finding is that it shows that cognitive influences, originating here purely at the word level, can reach down and modulate activations in the first stage of cortical processing that represents the affective value of sensory stimuli (de Araujo et al., 2005; Rolls, 2014).

Also important is how cognition influences the affective brain representations of the taste and flavour of a food. This is important not only for understanding top–down influences in the brain, but also in relation to the topical issues of appetite control and obesity (Rolls, 2007c, 2007d, 2010c, 2011c, 2012b). In an fMRI study it was shown that activations related to the affective value of umami taste and flavour (as shown by correlations with pleasantness ratings) in the orbitofrontal cortex were modulated by word-level descriptors (e.g., "rich and delicious flavour") (Grabenhorst, Rolls, & Bilderbeck, 2008). Affect-related activations to taste were modulated in a region that receives from the orbitofrontal cortex, the pregenual cingulate cortex, and to taste and flavour in another region that receives from the orbitofrontal cortex, the ventral striatum. Affect-related cognitive modulations were not found in the insular taste cortex, where the intensity but not the pleasantness of the taste was represented. Thus the top–-down language-level cognitive effects reach far down into the earliest cortical areas that represent the appetitive value of taste and flavour. This is an important way anatomically in which cognition influences the neural mechanisms that control appetite and emotion.

When we see a person being touched, we may empathize the feelings being produced by the touch. Interestingly, cognitive modulation of this effect can be produced. When subjects were informed by word labels that a cream seen being rubbed onto the forearm was a "Rich moisturising cream" versus "Basic cream", these cognitive labels influenced activations in the orbitofrontal/pregenual cingulate cortex and ventral striatum to the sight of touch and their correlations with the pleasantness ratings (McCabe et al., 2008). Some evidence for top–down cognitive modulation of the somatosensory effects produced by the subject being rubbed with the cream was found in brain regions such as the orbitofrontal and pregenual cingulate cortex and ventral striatum, but some effects were found in other brain regions, perhaps reflecting backprojections from the orbitofrontal cortex (McCabe et al., 2008; Rolls, 2010a).

What may be a fundamental principle of how top–down *attention* can influence affective versus non-affective processing has recently been discovered. For an identical taste stimulus, paying attention to pleasantness activated some brain systems (including emotion-related limbic structures), and paying attention to intensity, which reflected the physical and not the affective properties of the stimulus, activated other brain systems (Grabenhorst & Rolls, 2008). In an fMRI investigation, when subjects were instructed to remember and rate the pleasantness of a taste stimulus, .1 M monosodium glutamate, activations were greater in the medial orbitofrontal and pregenual cingulate cortex than when subjects were instructed to remember and rate the intensity of the taste. When the subjects were instructed to remember and rate the intensity, activations were greater in the insular taste cortex. Thus, depending on the context in which tastes are presented and whether affect is relevant, the brain responds to a taste differently. These findings show that when attention is paid to affective value, the brain systems engaged to represent the sensory stimulus of taste are different from those engaged when attention is directed to the physical properties of a stimulus such as its intensity. This differential biasing of brain regions engaged in processing a sensory stimulus depending on whether the attentional demand is for affect-related versus more sensory-related processing may be an important aspect of cognition and attention. This has many implications for understanding attentional effects to affective value not only on taste, but also on other sensory stimuli (Ge, Feng, Grabenhorst, & Rolls, 2012; Luo, Ge, Grabenhorst, Feng, & Rolls, 2013; Rolls, 2013a, 2014).

Indeed, the concept has been validated in the olfactory system too. In an fMRI investigation, when subjects were instructed to remember and rate the pleasantness of a jasmin odour, activations were greater in the medial orbitofrontal and pregenual cingulate cortex than when subjects were instructed to remember and rate the intensity of the odour (Rolls, Grabenhorst, Margot, da Silva, & Velazco, 2008). When the subjects were instructed to remember and rate the intensity, activations were greater in the inferior frontal gyrus. These top–down effects occurred not only during odour delivery, but started in a preparation period after the instruction before odour delivery, and continued after termination of the odour in a short-term memory period. Thus, depending on the context in which odours are presented and whether affect is relevant, the brain prepares itself, responds to, and remembers an odour differently. These findings show that when attention is paid to affective value, the brain systems engaged to prepare for, represent, and remember a sensory stimulus are different from those engaged when attention is directed to the physical properties of a stimulus such as its intensity. This differential biasing of brain regions engaged in processing a sensory stimulus depending on whether the cognitive/attentional demand is for affect-related versus more sensory-related processing may be important for understanding how the context can influence how we process stimuli that may have affective properties, how different people may respond differently to stimuli if they process the stimuli in different ways, and more generally, how attentional set can influence the processing of affective stimuli by influencing processing in for example the orbitofrontal cortex and related areas (Rolls, 2013a, 2014).

The principle thus appears to be that top–down attentional and cognitive effects on affective value influence representations selectively in cortical areas that process the affective value and associated subjective emotional experience of taste (Grabenhorst & Rolls, 2008; Grabenhorst, Rolls, & Bilderbeck, 2008) and olfactory (Anderson et al., 2003; Grabenhorst et al., 2007; Rolls, Kringelbach, et al., 2003) stimuli in brain regions such as the orbitofrontal cortex; whereas top–down attentional and cognitive effects on intensity influence representations in brain areas that process the intensity and identity of the stimulus such as the primary taste and olfactory cortical areas (Anderson et al., 2003; Grabenhorst & Rolls, 2008; Grabenhorst, Rolls, & Bilderbeck, 2008; Grabenhorst et al., 2007; Rolls, Kringelbach, et al., 2003). This is computationally

appropriate in top–down models of attention (Deco & Rolls, 2005a; Rolls, 2008c, 2013a; Rolls & Deco, 2002).

To investigate the anatomical source of the top–down modulatory effects on attentional processing, we utilised fMRI psychophysiological interaction connectivity analyses (Friston et al., 1997) with taste stimuli when attention was being paid to the pleasantness or to the intensity (Grabenhorst & Rolls, 2010). We showed that in the anterior lateral prefrontal cortex at Y = 53 mm the correlation with activity in orbitofrontal cortex and pregenual cingulate cortex seed regions was greater when attention was to pleasantness compared to when attention was to intensity. Conversely, we showed that in a more posterior region of lateral prefrontal cortex at Y = 34 the correlation with activity in the anterior insula seed region was greater when attention was to intensity compared to when attention was to pleasantness (Ge et al., 2012; Grabenhorst & Rolls, 2010; Luo et al., 2013). We proposed a biased activation theory of selective attention to account for the findings (Grabenhorst & Rolls, 2010; Rolls, 2013a), and contrasted this with a biased competition (Deco & Rolls, 2005b; Desimone & Duncan, 1995; Rolls, 2008c, 2008d; Rolls & Deco, 2002) theory of selective attention.

Individual differences in these reward and top–down attentional effects, and their relation to some psychiatric symptoms, are described elsewhere (Rolls, 2014; Rolls & Grabenhorst, 2008).

3.3.9. *Representations of specific reward value on a common scale but with no common currency, and emotion*

In my book *Emotion and decision-making explained* (Rolls, 2014) I developed a unified approach to emotion, neuroeconomics, and decision-making. This showed how emotion could be considered as states elicited by rewards and punishers, which are the gene-specified goals for action in an evolutionary approach to how genes specify rewards and punishers in their (the genes' own) interests. The genes specify effectively the value of many different stimuli, together with mechanisms for devaluing the stimuli such as decreasing the reward value of a food as it is eaten to satiety, and for ensuring that the value of different specific rewards is on a common scale that ensures that each specific reward is chosen as frequently as it is advantageous to the collection of genes in an individual to enable that individual's genes to operate with high fitness, that is to be passed into the next generation by sexual reproduction. The value defined in neuroeconomics operates according to heuristics that help to meet these requirements, for example valuing an immediate reward more than a deferred reward, down-valuing risky choices (those with probabilistic outcomes), and trading of the quality of a commodity with the quantity (Rolls, 2014). Moreover these factors are all reflected in the responses of orbitofrontal cortex neurons, in which different neurons represent the value of different rewards on a continuous scale. After this, there must then be a system for making choices between these goods, which requires now a highly non-linear choice process, which we have suggested is implemented anterior to the orbitofrontal cortex, in or close to medial prefrontal cortex area 10 with attractor decision-making neuronal networks (Grabenhorst & Rolls, 2011; Rolls, 2014; Rolls & Grabenhorst, 2008; Rolls, Grabenhorst, & Deco, 2010b, 2010c; Rolls, Grabenhorst, & Parris, 2010).

For this system to operate, different neurons must represent by their firing different rewards on a continuous scale, and much evidence for this by orbitofrontal cortex neurons (Grabenhorst & Rolls, 2011; Rolls, 2005, 2014; Rolls & Grabenhorst, 2008) and from activations in fMRI studies (Grabenhorst, Rolls, & Parris, 2008; Rolls, et al., 2010b, 2010c; Rolls, Grabenhorst, & Parris, 2010) has been presented. The implication is that choices can be made between different neuronal populations each specifying the value of a particular good, so that there is no conversion to a common currency (Rolls, 2014).

However, a classical view of economic decision theory (Bernoulli, 1738/1954) implies that decision-makers convert the value of different goods into a common scale of utility. Ecological (McFarland & Sibly, 1975), psychological (Cabanac, 1992), and neuroeconomic approaches (Glimcher, 2011; Glimcher & Fehr, 2013; Montague & Berns, 2002) similarly suggest that the values of different kinds of rewards are converted into a common currency. Rolls and Grabenhorst (Grabenhorst & Rolls, 2011; Rolls, 2005, 2008c, 2014; Rolls & Grabenhorst, 2008) have argued that different specific rewards must be represented on the same scale, but not converted into a common currency, as the specific goal selected must be the output of the decision process so that the appropriate action for that particular goal can then be chosen (Rolls, 2014; Rolls & Grabenhorst, 2008). The key difference between the two concepts of common currency and common scaling lies in the specificity with which rewards are represented at the level of single neurons. While a common currency view implies convergence of different types of rewards onto the same neurons (a process in which information about reward identity is lost), a common scaling view implies that different rewards are represented by different neurons (thereby retaining reward identity in information processing), with the activity of the different neurons scaled to be in the same value range (Rolls, 2014).

An fMRI study demonstrated the existence of a region in the human orbitofrontal cortex where activations are scaled to the same range as a function of pleasantness for even fundamentally different primary rewards, taste in the mouth and warmth on the hand (Grabenhorst, D'Souza, Parris, Rolls, & Passingham, 2010). A different study found that the decision value for different categories of goods (food, non-food consumables, and monetary gambles) during purchasing decisions correlated with activity in the adjacent ventromedial prefrontal cortex (Chib, Rangel, Shimojo, & O'Doherty, 2009). Importantly, because of the limited spatial resolution of fMRI, these studies do not answer whether it is the same or different neurons in these areas that encode the value of different rewards. However, as shown most clearly by single neuron recording studies, the representations in the orbitofrontal cortex provide evidence about the exact nature of each reward (Rolls, 2009b, 2014; Rolls & Grabenhorst, 2008). Moreover, in economic decision-making, neurons in the macaque orbitofrontal cortex encode the economic value of the specific choice options on offer, for example different juice rewards (Padoa-Schioppa & Assad, 2006). For many of these "offer value" neurons, the relationship between neuronal firing rate and value was invariant with respect to the different types of juice that were available (Padoa-Schioppa & Assad, 2008),

suggesting that different types of juice are evaluated on a common value scale.

With our current computational understanding of how decisions are made in attractor neural networks (Deco & Rolls, 2006; Deco, Rolls, Albantakis, & Romo, 2013; Rolls, 2008c, 2014; Rolls & Deco, 2010; Wang, 2002, 2008) it is important that different rewards are expressed on a similar scale for decision-making networks to operate correctly but retain information about the identity of the specific reward. The computational reason is that one type of reward (e.g., food reward) should not dominate all other types of reward and always win in the competition, as this would be maladaptive. Making different rewards approximately equally rewarding makes it likely that a range of different rewards will be selected over time (and depending on factors such as motivational state), which is adaptive and essential for survival (Rolls, 2014). The exact scaling into a decision-making attractor network will be set by the number of inputs from each source, their firing rates, and the strengths of the synapses that introduce the different inputs into the decision-making network (Deco & Rolls, 2006; Deco, Rolls, & Romo, 2009; Rolls, 2008c; Rolls & Deco, 2010). Importantly, common scaling need not imply conversion into a new representation that is of a common currency of general reward (Grabenhorst & Rolls, 2011; Rolls, 2014; Rolls & Grabenhorst, 2008). In the decision process itself it is important to know which reward has won, and the mechanism is likely to involve competition between different rewards represented close together in the cerebral cortex, with one of the types of reward winning the competition, rather than convergence of different rewards onto the same neuron (Deco & Rolls, 2006; Deco et al., 2009; Rolls, 2008c, 2014; Rolls & Deco, 2010).

3.3.10. *Absolute value and relative value are both represented in the orbitofrontal cortex*

For economic decision-making both absolute and relative valuation signals have to be neurally represented. A representation of the absolute value of rewards is important for stable long-term preferences and consistent economic choices (Glimcher, Camerer, Fehr, & Poldrack, 2009; Padoa-Schioppa & Assad, 2008). Such a representation should not be influenced by the value of other available rewards. In contrast, to select the option with the highest subjective value in a specific choice situation, the relative value of each option could be represented. There is evidence for absolute value coding in orbitofrontal cortex, in that neuronal responses that encoded the value of a specific stimulus did not depend on what other stimuli were available at the same time (Padoa-Schioppa & Assad, 2008). It was suggested that transitivity, a fundamental trait of economic choice, is reflected by the neuronal activity in the orbitofrontal cortex (Padoa-Schioppa & Assad, 2008). This type of encoding contrasts with value-related signals found in the parietal cortex, where neurons encode the subjective value associated with specific eye movements in a way that is relative to the value of the other options that are available (Kable & Glimcher, 2009). The apparent difference in value coding between orbitofrontal cortex and parietal cortex has led to the suggestion that absolute value signals encoded in orbitofrontal cortex are subsequently rescaled in the parietal cortex to encode relative value in order to maximize the difference between the choice options for action selection (Kable & Glimcher, 2009). However, there is also evidence for relative encoding of value in the orbitofrontal cortex, in that neuronal responses to a food reward can depend on the value of the other reward that is available in a block of trials (Tremblay & Schultz, 1999). Two studies demonstrated that neurons in the orbitofrontal cortex adapt the sensitivity with which reward value is encoded to the range of values that are available at a given time (Kobayashi, Pinto de Carvalho, & Schultz, 2010; Padoa-Schioppa, 2009). This reflects an adaptive scaling of reward value, evident also in positive and negative contrast effects, that makes the system optimally sensitive to the local reward gradient, by dynamically altering the sensitivity of the reward system so that small changes can be detected (Rolls, 2014). The same underlying mechanism may contribute to the adjustment of different types of reward to the same scale described in the preceding section.

Given that representations of both absolute value and relative value are needed for economic decision-making, Grabenhorst and Rolls (2009) tested explicitly whether both types of representation are present simultaneously in the human orbitofrontal cortex. In a task in which two odours were successively delivered on each trial, they found that blood oxygenation-level dependent signal (BOLD) activations to the second odour in the antero-lateral orbitofrontal cortex tracked the relative subjective pleasantness, whereas in the medial and mid-orbitofrontal cortex activations tracked the absolute pleasantness of the odour. Thus, both relative and absolute subjective value signals, both of which provide important inputs to decision-making processes, are separately and simultaneously represented in the human orbitofrontal cortex (Grabenhorst & Rolls, 2009).

3.3.11. *Abstract monetary reward value, social value, and attractiveness are represented in the orbitofrontal cortex*

Many different types of reward are represented in the orbitofrontal cortex. They include quite abstract representations, such as monetary value. For example, the monetary outcome reward value is represented in the medial orbitofrontal cortex, and the monetary outcome loss in the lateral orbitofrontal cortex (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). All these signals are reflected in activations found for expected value and for reward outcome in the human medial orbitofrontal cortex. Moreover, the expected value of monetary reward as well as the outcome value of monetary reward is represented in the medial orbitofrontal cortex (Rolls, McCabe, et al., 2008). The beauty in a face is represented in the orbitofrontal cortex (O'Doherty et al., 2003). Many further types of value are represented in the orbitofrontal cortex (Grabenhorst & Rolls, 2011; Rolls, 2014).

3.3.12. *A representation of novel visual stimuli in the orbitofrontal cortex*

A population of neurons has been discovered in the primate orbitofrontal cortex that responds to novel but not familiar visual stimuli, and takes typically a few trials to habituate (Rolls, Browning, Inoue, & Hernadi, 2005). The memories implemented by these neurons last for at least 24 h. Exactly what role these neurons have is not yet known, though this

input might be part of a process whereby novel stimuli can be rewarding (Rolls, 2014), but there are connections from the area in which these neurons are recorded to the temporal lobe, and activations in a corresponding orbitofrontal cortex area in humans are found when new visual stimuli must be encoded in memory (Frey & Petrides, 2002, 2003; Petrides, 2007).

3.4. *The amygdala*

The amygdala is a limbic structure that appears early in evolution, before the orbitofrontal cortex, and although important in emotion in rodents, may be less important in primates including humans, in which it is in many ways overshadowed by the orbitofrontal cortex. Part of the anatomical basis for this may be that the orbitofrontal cortex, as a cortical structure, naturally finds its place in the cortical hierarchy, and can perform a number of computational functions better, including holding items in short-term memory, and reward reversal learning, because of its highly developed neocortical recurrent collateral design (Rolls, 2008c, 2014).

3.4.1. *Connections*

The connections of the amygdala are summarized in Figs. 1 and 4, are similar in many respects to those of the orbitofrontal cortex, and are described in more detail elsewhere (Amaral, Price, Pitkanen, & Carmichael, 1992; Freese & Amaral, 2009; Ghashghaei & Barbas, 2002; Rolls, 2014). The amygdala receives massive projections in the primate from the overlying temporal lobe cortex. These come in the monkey to overlapping but partly separate regions of the lateral and basal amygdala from the inferior temporal visual cortex, the superior temporal auditory cortex, the cortex of the temporal pole, and the cortex in the superior temporal sulcus. These inputs thus come from the higher stages of sensory processing in the visual and auditory modalities, and not from early cortical processing areas. Via these inputs, the amygdala receives inputs about objects that could become secondary reinforcers, as a result of pattern association in the amygdala with primary reinforcers. The amygdala also receives inputs that are potentially about primary reinforcers, e.g., taste inputs (from the insula, and from the secondary taste cortex in

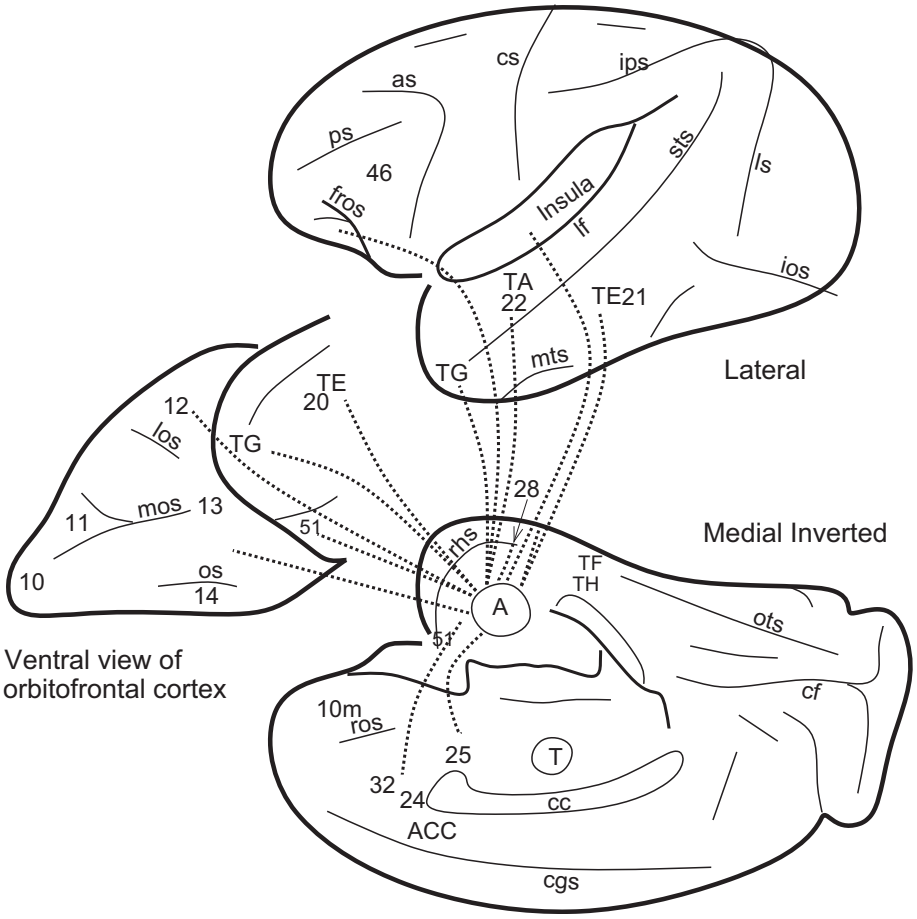

Fig. 4 – Connections of the amygdala shown on lateral, ventral, and medial inverted views of the monkey brain. Abbreviations: as, arcuate sulcus; cc, corpus callosum; cf, calcarine fissure; cgs, cingulate sulcus; cs, central sulcus; ls, lunate sulcus; ios, inferior occipital sulcus; mos, medial orbital sulcus; os, orbital sulcus; ots, occipito-temporal sulcus; ps, principal sulcus; rhs, rhinal sulcus; sts, superior temporal sulcus; lf, lateral (or Sylvian) fissure (which has been opened to reveal the insula); A, amygdala; INS, insula; T, thalamus; TE (21), inferior temporal visual cortex; TA (22), superior temporal auditory association cortex; TF and TH, parahippocampal cortex; TG, temporal pole cortex; 10m, medial prefrontal cortex area 10; 12, 13, 11, orbitofrontal cortex; 24, part of the cingulate cortex; 28, entorhinal cortex; 51, olfactory (prepyriform and periamygdaloid) cortex. The cortical connections shown provide afferents to the amygdala, but are reciprocated.

the orbitofrontal cortex), and somatosensory inputs, potentially about the rewarding or painful aspects of touch (from the somatosensory cortex via the insula). The amygdala receives strong projections from the posterior orbitofrontal cortex where there are value representations, and from the ACC (Carmichael & Price, 1995a; Freese & Amaral, 2009; Ghashghaei & Barbas, 2002). It is notable that the amygdala is connected with only anterior areas of the cingulate cortex (pregenual cingulate cortex areas 24 and 32, and subgenual cortex area 25) (Van Hoesen, 1981; Vogt & Pandya, 1987; Yukie & Shibata, 2009). This helps to make it clear that the emotional and memory/spatial limbic 'systems' are separate. The emotional parts of the limbic system such as the amygdala have connections with the ACC; whereas the cingulate connections to the hippocampus (via parahippocampal areas TF and TH, entorhinal cortex etc.) include strong connections from the posterior cingulate cortex (Yukie & Shibata, 2009), which is strongly connected to visual parietal cortex areas involved in spatial functions (Section 4).

3.4.2. *Effects of amygdala lesions*

Bilateral removal of the amygdala in monkeys produces striking behavioural changes which include tameness, a lack of emotional responsiveness, excessive examination of objects, often with the mouth, and eating of previously rejected items such as meat (Weiskrantz, 1956). These behavioural changes comprise much of the Kluver–Bucy syndrome which is produced in monkeys by bilateral anterior temporal lobectomy (Kluver & Bucy, 1939). In analyses of the bases of these behavioural changes, it has been observed that there are deficits in some types of learning. For example, bilateral ablation of the amygdala in the monkey produced a deficit on learning an active avoidance task (Weiskrantz, 1956). Evidence soon became available that associations between stimuli and positive reinforcers (reward) were also impaired in, for example, serial reversals of a visual discrimination made to obtain food (Jones & Mishkin, 1972). However, when selective lesions are made with a neurotoxin, to damage neurons but not fibres of passage, the effects are more subtle. Using such lesions (made with ibotenic acid) in monkeys, impairments in the processing of food reward value were found, in that when the reward value of one set of foods was devalued by feeding it to satiety [i.e., sensory-specific satiety, a reward devaluation procedure (Rolls, Sienkiewicz, et al., 1989)], the monkeys still chose the visual stimuli associated with the foods with which they had been satiated (Murray & Izquierdo, 2007), so there was some impairment of reward valuation. Consistently, such monkeys showed abnormal patterns of food choice, picking up and eating foods not normally eaten such as meat, and picking up and placing in their mouths inedible objects. In addition, neurotoxic amygdala lesions (as well as orbitofrontal cortex lesions) impaired emotional responses to snakes and human intruders (Murray & Izquierdo, 2007). However, macaques with neurotoxic lesions of the amygdala reveal only mild deficits in social behaviour (Amaral, 2003; Amaral et al., 2003), and this is consistent with the trend for the orbitofrontal cortex to become relatively more important in emotion and social behaviour in primates including humans.

A difference between the effects of selective amygdala lesions and orbitofrontal cortex lesions in monkeys is that selective amygdala lesions have no effect on object reversal learning, whereas orbitofrontal cortex lesions do impair object reversal learning (Murray & Izquierdo, 2007). Further, and consistently, orbitofrontal but not selective amygdala lesions impair instrumental extinction (i.e., macaques with orbitofrontal cortex lesions showed a large number of choices of the previously rewarded object when it was no longer rewarded) (Murray & Izquierdo, 2007). This is consistent with the evidence described in Section 3.3 that the orbitofrontal cortex is important in rapid, one-trial, learning and reversal between visual stimuli and primary reinforcers using both associative and rule-based mechanisms, and its representations of outcome value, expected value, and negative reward prediction error. These contributions of the orbitofrontal cortex are facilitated by its neocortical architecture, which can operate using attractors that are important in many functions including short-term memory, attention, rule-based operation with switching, long-term memory, and decision-making which may help it to compute and utilize non-reward to reset value representations in the orbitofrontal cortex (Deco & Rolls, 2005c; Rolls, 2008c, 2014). The ability to learn very rapidly to alter behaviour when rewards being obtained change is important in emotional and social behaviour, and may be a key computation made possible by the development of the orbitofrontal cortex in primates including humans (Rolls, 2014).

In rats, there is also evidence that the amygdala is involved in behaviour to stimuli learned as being associated with at least classically conditioned reinforcers. We may summarize these investigations in the rat as follows. The central nuclei of the amygdala encode or express Pavlovian S–R (stimulus–response, CS–UR where CS is the conditioned stimulus and UR is the unconditioned response) associations (including conditioned suppression, conditioned orienting, conditioned autonomic and endocrine responses, and Pavlovian-instrumental transfer); and modulate perhaps by arousal the associability of representations stored elsewhere in the brain (Gallagher & Holland, 1994; Holland & Gallagher, 1999). In contrast, the basolateral amygdala (BLA) encodes or retrieves the affective value of the predicted unconditioned stimulus (US), and can use this to influence action–outcome learning via pathways to brain regions such as the nucleus accumbens and prefrontal cortex including the orbitofrontal cortex (Cardinal, Parkinson, Hall, & Everitt, 2002). The nucleus accumbens is not involved in action–outcome learning itself, but does allow the affective states retrieved by the BLA to conditioned stimuli to influence instrumental behaviour by for example Pavlovian-instrumental transfer, and facilitating locomotor approach to food which appears to be in rats a Pavlovian process (Cardinal et al., 2002; Everitt, Cardinal, Parkinson, & Robbins, 2003; Everitt & Robbins, 2013). This leaves parts of the prefrontal and cingulate cortices as strong candidates for action–outcome learning. Consistent with these findings, the acquisition of fear-conditioning in the rat, measured using the fear-potentiated startle test, is impaired by local infusion of the NMDA (*N*-methyl-D-aspartate) receptor antagonist AP5 (which blocks long-term potentiation, an index of synaptic plasticity) (Davis, 1994, 2006). These investigations have now been extended to primates, in which similar effects are found, with ibotenic acid-induced lesions of

the amygdala preventing the acquisition of fear-potentiated startle (Antoniadis, Winslow, Davis, & Amaral, 2009).

3.4.3. *Amygdala neuronal activity*

In the rat, in classical (Pavlovian) conditioning of fear, for some classes of stimulus such as pure tones, the association between the tone and an aversive US (a footshock) is reflected in the responses of neurons in the amygdala (LeDoux, 1995, 2000b). The auditory inputs reach the amygdala both from the subcortical, thalamic, auditory nucleus, the medial geniculate (medial part), and from the auditory cortex. These auditory inputs project to the lateral nucleus of the amygdala (LA), which in turn projects to the central nucleus of the amygdala (Ce) both directly and via the basal (B) and accessory basal nuclei of the amygdala. LeDoux has emphasized the role of the subcortical inputs to the amygdala in this type of conditioning, based on the observations that the conditioning to pure tones can take place without the cortex, and that the shortest latencies of the auditory responses in the amygdala are too short to be mediated via the auditory cortex (LeDoux, 1995, 2000b). This 'low road' from subcortical structures bypassing cortical processing is unlikely to be a route for most emotions in primates including humans (Rolls, 2014), for stimuli requiring complex analysis (e.g., of face identity and expression and gaze) and view, translation, and size invariance require massive cortical computation which is now starting to become understood (Rolls, 2008c, 2012a); and the response latencies of amygdala neurons to such stimuli are longer than those of neurons in the inferior temporal cortex (Rolls, 1984).

There are separate output pathways in the rat from the amygdala for different fear-related classically conditioned responses. Lesions of the lateral hypothalamus (which receives from the central nucleus of the amygdala) blocked conditioned heart rate (autonomic) responses. Lesions of the central gray of the midbrain (which also receives from the central nucleus of the amygdala) blocked the conditioned freezing but not the conditioned autonomic response, and lesions of the stria terminalis blocked the neuroendocrine responses (LeDoux, 2000a).

In primates, the amygdala contains neurons that respond to taste, and oral texture including viscosity, fat texture, and capsaicin, and to somatosensory stimuli (Kadohisa et al., 2005a; Kadohisa, Rolls, & Verhagen, 2005b; Rolls, 1992b, 2000b; Sanghera, Rolls, & Roper-Hall, 1979). These are all potentially primary reinforcers, and these neurons could represent outcome value. Neurons in the primate amygdala also respond to the sight of instrumental reinforcers in a visual discrimination task (Sanghera et al., 1979; Wilson & Rolls, 2005), and to odours. These neurons could signal expected value. However, in reward reversal learning, many amygdala neurons do not reverse their responses (Sanghera et al., 1979; Wilson & Rolls, 2005), and if any reversal is found, it is slow, taking many trials (Paton, Belova, Morrison, & Salzman, 2006; Sanghera et al., 1979; Wilson & Rolls, 2005), whereas orbitofrontal neurons show rule-based reversal in one trial (Thorpe et al., 1983). Further, devaluation by feeding to satiety produced only a partial reduction in responses to taste (Yan & Scott, 1996), and little reduction in responses to visual stimuli associated with food (Sanghera et al., 1979), compared to the complete reduction found for orbitofrontal cortex taste (Rolls, Sienkiewicz, et al., 1989) and visual food (Critchley & Rolls, 1996a) neurons. *Thus by both reversal learning and devaluation measures of neuronal responses, the amygdala in primates appears to make a less important contribution to reward value representations than the orbitofrontal cortex.*

Other amygdala neurons respond to faces (Leonard, Rolls, Wilson, & Baylis, 1985; Rolls, 1992b, 2000b, 2011a; Sanghera et al., 1979), including face expression and identity (Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007), both of which are represented in the inferior temporal cortex areas that project into the amygdala (Hasselmo et al., 1989). The presence of these neurons in the primate amygdala does emphasize that as the amygdala has evolved in primates, it does represent information that becomes highly developed in the primate inferior temporal cortical areas, and that is important for social and emotional responses to individuals, though the orbitofrontal cortex of course also represents similar information (Rolls, Critchley, et al., 2006).

3.4.4. *Amygdala damage in humans*

The greater importance of the orbitofrontal cortex in emotion in humans is emphasized by a comparison with the effects of bilateral amygdala damage in humans, which although producing demonstrable deficits in face processing (Adolphs et al., 2005; Spezio, Huang, Castelli, & Adolphs, 2007), decision-making with linked autonomic deficits (Bechara, Damasio, Damasio, & Lee, 1999; Brand, Grabenhorst, Starcke, Vandekerckhove, & Markowitsch, 2007), and autonomic conditioning (Phelps & LeDoux, 2005), may not (in contrast with the orbitofrontal cortex) produce major changes in emotion that are readily apparent in everyday behaviour (Phelps & LeDoux, 2005; Rolls, 2008c; Seymour & Dolan, 2008; Whalen & Phelps, 2009).

3.5. *The anterior cingulate cortex (ACG)*

The ACC is a limbic structure involved in emotion, with major inputs from structures such as the amygdala and orbitofrontal cortex, and activations that are correlated with the pleasantness or unpleasantness of stimuli. The ACC uses these value (including outcome value) representations in its function with the midcingulate cortex in action–outcome learning. The ACC can be conceived as a system that in primates links the orbitofrontal cortex representations of the value of stimuli (including reward and punisher outcomes) with actions (Rolls, 2014).

3.5.1. *Connections*

The connections of the ACC (Vogt, 2009; Yukie & Shibata, 2009) are illustrated in Fig. 5. The ACC includes area 32, area 25 the subgenual cingulate cortex, and part of area 24. The cortex anterior to the genu (knee, at the front) of the corpus callosum is referred to as the pregenual cingulate cortex. The caudal orbitofrontal cortex and amygdala project to the ACC (Carmichael & Price, 1996; Price, 2006), and especially the orbitofrontal cortex appears to influence the ACC strongly, for activations related to the pleasantness or unpleasantness of many stimuli are present in both (Grabenhorst & Rolls, 2011; Rolls, 2014). It is of interest that the anterior but not

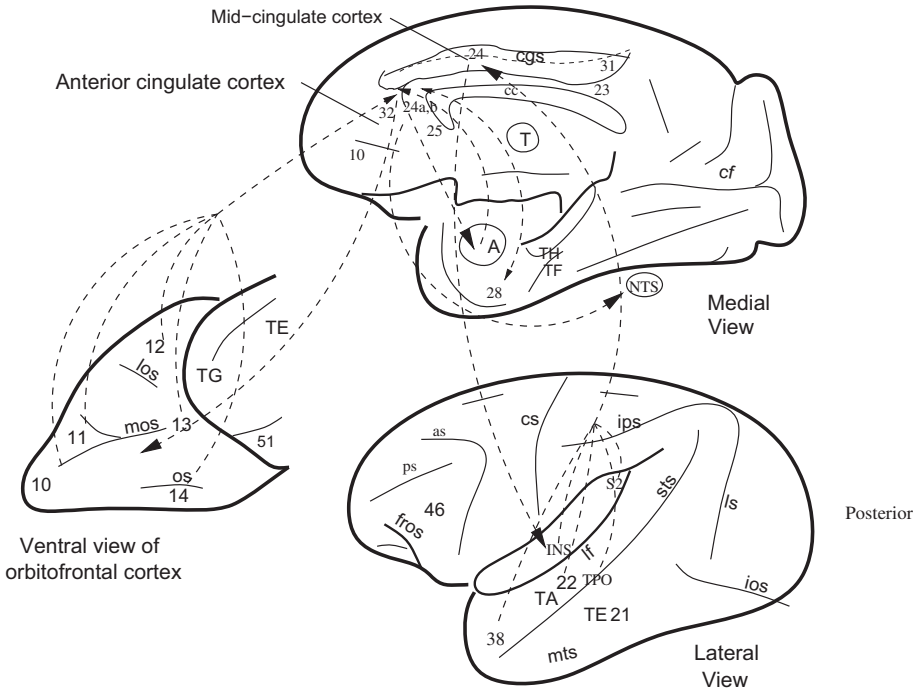

Fig. 5 – Connections of the anterior cingulate (perigenual) and midcingulate cortical areas (shown on views of the primate brain). The cingulate sulcus (cgs) has been opened to reveal the cortex in the sulcus, with the dashed line indicating the depths (fundus) of the sulcus. The cingulate cortex is in the lower bank of this sulcus, and in the cingulate gyrus which hooks above the corpus callosum and around the corpus callosum at the front and the back. The ACC extends from cingulate areas 32, 24a and 24b to subgenual cingulate area 25 [The cortex is called subgenual because it is below the genu (knee) formed by the anterior end of the corpus callosum, cc.]. The perigenual cingulate cortex tends to have connections with the amygdala and orbitofrontal cortex, whereas area 24c tends to have connections with the somatosensory insula (INS), the auditory association cortex (22, TA), and with the temporal pole cortex (38). The midcingulate areas include area 24d, which is part of the cingulate motor area. Abbreviations: as, arcuate sulcus; cc, corpus callosum; cf, calcarine fissure; cgs, cingulate sulcus; cs, central sulcus; ls, lunate sulcus; ios, inferior occipital sulcus; mos, medial orbital sulcus; os, orbital sulcus; ps, principal sulcus; sts, superior temporal sulcus; lf, lateral (or Sylvian) fissure (which has been opened to reveal the insula); A, amygdala; INS, insula; NTS, autonomic areas in the medulla, including the nucleus of the solitary tract and the dorsal motor nucleus of the vagus; TE (21), inferior temporal visual cortex; TA (22), superior temporal auditory association cortex; TF and TH, parahippocampal cortex; TPO, multimodal cortical area in the superior temporal sulcus; 10, medial prefrontal cortex area 10; 12, 13, 11, orbitofrontal cortex; 23, 31, posterior cingulate cortex areas; 28, entorhinal cortex; 38, TG, temporal pole cortex; 51, olfactory (prepyriform and periamygdaloid) cortex.

posterior cingulate cortex receives projections from the amygdala (with a similar trend for the caudal orbitofrontal cortex) (Morecraft & Tanji, 2009; Yukie & Shibata, 2009), consistent with the evidence that there are separate limbic structures including different parts of the cingulate cortex for emotion and memory/spatial function. Having said this, the entorhinal cortex (area 28), the perirhinal cortex area 35/36, and the parahippocampal cortex (areas TF and TH) (areas illustrated in Fig. 6, and providing the gateway to the hippocampus) do have reciprocal connections with the anterior, mid, and posterior cingulate cortex, and the interpretation provided in this paper is that emotional/reward/value information from the anterior cingulate and orbitofrontal cortex may need to be stored in the hippocampus as part of an episodic memory involving spatial and also usually object information; and then subsequently recalled from the hippocampus via the backprojections to the anterior cingulate and orbitofrontal cortex. The ACC also has connections with areas through which it can influence autonomic function, including the anterior insula, hypothalamus, and brainstem autonomic nuclei (Critchley & Harrison, 2013; Vogt & Derbyshire, 2009).

3.5.2. *Activations and neuronal activity*

The orbitofrontal cortex projects to the pregenual cingulate cortex (Carmichael & Price, 1996; Price, 2006), and both these areas have reward and punishment value representations that correlate on a continuous scale with the subjective pleasantness/unpleasantness ratings of olfactory (Anderson et al., 2003; Grabenhorst et al., 2007; Rolls, Critchley, Mason, et al., 1996; Rolls, Kringelbach, et al., 2003), taste (Grabenhorst, Rolls, & Bilderbeck, 2008; Rolls, 2008b; Rolls, Sienkiewicz, et al., 1989; Small et al., 2003), somatosensory (Rolls, O'Doherty, et al., 2003), temperature (Guest et al., 2007), visual (O'Doherty et al., 2003), monetary (Knutson, Rick, Wimmer, Prelec, & Loewenstein, 2007; O'Doherty, Kringelbach, et al., 2001), and social stimuli (Hornak et al.,

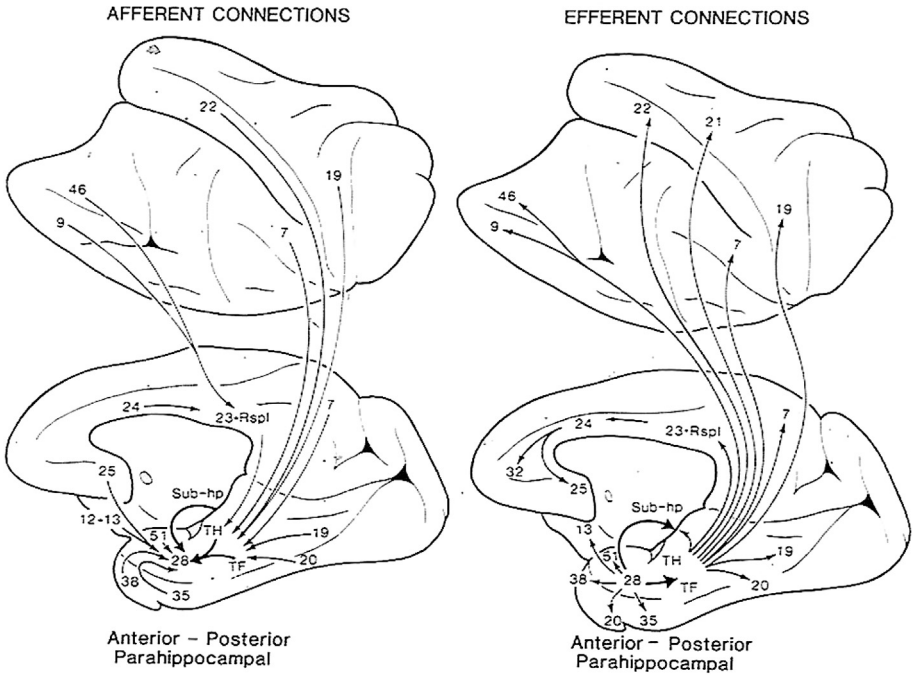

Fig. 6 – Connections of the primate hippocampus with the neocortex (after Van Hoesen, 1982). A medial view of the macaque brain is shown below, and a lateral view is shown inverted above. The hippocampus receives its inputs via the parahippocampal gyrus (areas TF and TH), and the perirhinal cortex (areas 35 and 36), which in turn project to the entorhinal cortex (area 28). The return projections to the neocortex (shown on the right) pass through the same areas. Cortical areas 19, 20, and 21 are visual association areas, 22 is auditory association cortex, 7 is parietal association cortex, and 9, 46, 12, and 13 are areas of frontal association cortex in the prefrontal cortex.

2003; Kringelbach & Rolls, 2003; Moll et al., 2006; Spitzer, Fischbacher, Herrnberger, Gron, & Fehr, 2007) (see further Bush, Luu, & Posner, 2000; Grabenhorst & Rolls, 2011; Rolls, 2009a, 2014). Indeed, the pregenual cingulate cortex may be identified inter alia as a tertiary cortical taste area, with single neurons responding to the taste and texture of food (Rolls, 2008b). Moreover, there is very interesting topology, with the activations that are correlated with the pleasantness of stimuli in the pregenual cingulate cortex, and the activations that are correlated with the unpleasantness of stimuli just dorsal and posterior to this, extending back above the genu of the corpus callosum (Grabenhorst & Rolls, 2011; Rolls, 2014).

We may ask why, if the activations in the orbitofrontal cortex and the pregenual cingulate cortex are somewhat similar in their continuous and typically linear representations of reward or affective value (pleasantness ratings), are there these two different areas? A suggestion I make (Rolls, 2014) is that the orbitofrontal cortex is the region that computes the rewards, expected rewards etc., and updates these rapidly when the reinforcement contingencies change, based on its inputs about primary reinforcers from the primary taste cortex (Baylis et al., 1995), the primary olfactory cortex (Carmichael et al., 1994), the somatosensory cortex (Morecraft et al., 1992), etc. The orbitofrontal cortex makes explicit in its representations the reward value, based on these inputs, and in a situation where reward value is not represented at the previous tier, but instead where the representation is about the physical properties of the stimuli, their intensity, etc. (Grabenhorst & Rolls, 2008; Grabenhorst, Rolls, & Bilderbeck, 2008; Grabenhorst et al., 2007; Rolls, 2014; Rolls, Grabenhorst, & Parris, 2008; Rolls, O'Doherty, et al., 2003; Small et al., 2003) (see Fig. 1). The orbitofrontal cortex computes the expected value of previously neutral stimuli, and updates these representations rapidly when the reinforcement contingencies change, as described here. Thus the orbitofrontal cortex is the computer of reward magnitude and expected reward value. It can thus represent outcomes, and expected outcomes, but it does not represent actions such as motor responses or movements (Rolls, 2014). It is suggested that the representations of outcomes, and expected outcomes, are projected from the orbitofrontal cortex to the pregenual cingulate cortex, as the cingulate cortex has longitudinal connections which allow this outcome information to be linked to the information about actions that is represented in the midcingulate cortex, and that the outcome information derived from the orbitofrontal cortex can contribute to action–outcome learning implemented in the cingulate cortex (Rolls, 2008c, 2014; Rushworth, Behrens, Rudebeck, & Walton, 2007; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011). Some of this evidence on action–outcome learning has been obtained in rat lesion studies, and indicates that the costs of actions, as well as the rewards produced by actions, involve the ACC. Although the ACC is activated in relation to autonomic function (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004), its functions clearly extend much

beyond this, as shown also for example by the emotional changes that follow damage to the ACC and related areas in humans (Hornak et al., 2003).

In responding when the reward obtained is less than that expected, the orbitofrontal cortex negative reward prediction error neurons are working in a domain that is related to the sensory inputs being received (expected reward and reward obtained). There are also error neurons in the ACC that respond when errors are made (Niki & Watanabe, 1979), or when rewards are reduced (Shima & Tanji, 1998) (and in similar imaging studies, Bush et al., 2002). Some of these neurons may be influenced by the projections from the orbitofrontal cortex, and reflect a mismatch between the reward expected and the reward that is obtained. However, some error neurons in the ACC may reflect errors that arise when particular behavioural responses or actions are in error, and this type of error may be important in helping an action system to correct itself, rather than, as in the orbitofrontal cortex, when a reward prediction system about stimuli needs to be corrected. Consistent with this, many studies provide evidence that errors made in many tasks activate the anterior/midcingulate cortex, whereas tasks with response conflict activate the superior frontal gyrus (Matsumoto, Matsumoto, Abe, & Tanaka, 2007; Rushworth & Behrens, 2008; Rushworth, Walton, Kennerley, & Bannerman, 2004; Vogt, 2009).

A neuroimaging study in humans illustrates how non-reward/error signals relevant to emotion and social behaviour are found in the ACC. Kringelbach et al. (2003) used the faces of two different people, and if one face was selected then that face smiled, and if the other was selected, the face showed an angry expression. After good performance was acquired, there were repeated reversals of the visual discrimination task. Kringelbach et al. (2003) found that activation of a lateral part of the orbitofrontal cortex and in a dorsal part of the ACC in the fMRI study was produced on the error trials, that is when the human chose a face, and did not obtain the expected reward. An interesting aspect of this study that makes it relevant to human social behaviour is that the conditioned stimuli were faces of different individuals, and the USs were face expressions. Thus the association that was being reversed in this study was between a representation of face identity and a representation of face expression. Moreover, the study reveals that the human orbitofrontal cortex and ACC are very sensitive to social feedback when it must be used to change behaviour (Kringelbach & Rolls, 2003, 2004).

3.5.3. *Effects of ACC lesions in humans*

Cardinal et al. (2002) and Devinsky, Morrell, and Vogt (1995) review evidence that anterior cingulate lesions in humans produce apathy, autonomic dysregulation, and emotional instability.

An investigation in patients with selective surgical lesions has shown that patients with unilateral lesions of the anteroventral part of the ACC and/or medial area 9 were in some cases impaired on voice and face expression identification, had some change in social behaviour (such as inappropriateness, being less likely to notice when other people were angry, not being close to his or her family, and doing things without thinking), and had significant changes in their subjective emotional state (Hornak et al., 2003). Unilateral lesions were sufficient to produce these effects, and there were no strong laterality effects.

The results of Hornak et al. (2003) also confirmed that damage restricted to the orbitofrontal cortex can produce impairments in face and voice expression identification, which may be primary reinforcers. The system is sensitive, in that even patients with unilateral orbitofrontal cortex lesions may be impaired. The impairment is not a generic impairment of the ability to recognize any emotions in others, in that frequently voice but not face expression identification was impaired, and vice versa. This implies some functional specialization for visual versus auditory emotion-related processing in the human orbitofrontal cortex. The results also show that the changes in social behaviour can be produced by damage restricted to the orbitofrontal cortex. The patients were particularly likely to be impaired on emotion recognition (they were less likely to notice when others were sad, or happy, or disgusted); on emotional empathy (they were less likely to comfort those who are sad, or afraid, or to feel happy for others who are happy); on interpersonal relationships (not caring what others think, and not being close to his/her family); and were less likely to cooperate with others; were impatient and impulsive; and had difficulty in making and keeping close relationships. The results also show that changes in subjective emotional state (including frequently sadness, anger and happiness) can be produced by damage restricted to the orbitofrontal cortex (Hornak et al., 2003). In addition, the patients with bilateral orbitofrontal cortex lesions were impaired on the probabilistic reversal learning task (Hornak et al., 2004). The findings overall thus make clear the types of deficit found in humans with orbitofrontal cortex damage, and can be easily related to underlying fundamental processes in which the orbitofrontal cortex is involved as described by Rolls (1999a, 2005), including decoding and representing primary reinforcers, being sensitive to changes in reinforcers, and rapidly readjusting behaviour to stimuli when the reinforcers available change. The implication is that some of the inputs to the ACC which produce similar deficits may come from the orbitofrontal cortex. Consistent with this, unilateral lesions of the ACC (including some of medial area 9) can produce voice and/or face expression identification deficits, changes in social behaviour, and marked changes in subjective emotional state (Hornak et al., 2003).

In summary, the primate including human ACC has connections with other limbic structures such as the amygdala and limbic-related structures such as the caudal orbitofrontal cortex, receives reward and punishment-related information from these brain regions, and appears to be involved in using this reward and punishment information to learn about actions to obtain goals, taking into account the costs of the actions (Grabenhorst & Rolls, 2011; Rolls, 2009a, 2014; Rushworth et al., 2011). Appropriate actions to emotion-provoking stimuli may not be made after ACC damage. The ACC can thus be seen as a limbic structure involved in emotion that forms part of a system with other limbic structures involved in emotion, the amygdala and orbitofrontal cortex. Structures that receive input from these three structures are involved in linking to habit responses (striatum including ventral striatum and

nucleus accumbens), autonomic and endocrine output (insula, hypothalamus, brainstem autonomic nuclei), etc. (Rolls, 2014).

These three limbic and related structures, the amygdala, orbitofrontal cortex, and ACC, could be thought of as an emotion limbic system, but not *the* limbic system, as different limbic structures related to the hippocampus are involved primarily in episodic memory and related spatial function, and not in emotion. Damage to the emotion limbic system or structures is not described as impairing episodic memory or spatial function.

3.6. *The insular cortex*

The insula has sometimes been lumped in with limbic structures (Catani et al., 2013; Yakovlev, 1948), and parts of it are involved in autonomic/visceral function (Critchley & Harrison, 2013), so it is considered briefly here, and in more detail elsewhere (Rolls, 2014).

3.6.1. *The insular primary taste cortex*

The primary taste cortex is in the dorsal part of the anterior insula and adjoining frontal operculum (Pritchard, Hamilton, Morse, & Norgren, 1986), and this region projects to the orbitofrontal cortex (Baylis et al., 1995). Neurons in the primary taste cortex represent what the taste is (including sweet, salt, sour, bitter, and umami) (Baylis & Rolls, 1991; Rolls, 2009c; Scott et al., 1986; Yaxley et al., 1990), but do not represent reward value in that their responses are not decreased by feeding to satiety (Rolls et al., 1988; Yaxley et al., 1988). Neurons in the insular primary taste cortex do represent oral texture including fat texture (de Araujo & Rolls, 2004; Kadohisa et al., 2005a; Verhagen et al., 2004) and oral temperature (Guest et al., 2007; Kadohisa et al., 2005a; Verhagen et al., 2004). Neurons in the macaque primary taste cortex do not have olfactory responses (Verhagen et al., 2004), and consistently in a human fMRI investigation of olfactory and taste convergence in the brain, it was shown that an agranular more anterior past of the insula does show convergence between taste and odour to represent flavour (de Araujo, Rolls, et al., 2003).

3.6.2. *The visceral/autonomic insular cortex*

A region of the anterior insular cortex just ventral to the primary taste cortex has strong projections to the orbitofrontal cortex (Baylis et al., 1995), and is putatively the visceral/autonomic region of the insula (Critchley & Harrison, 2013). This anterior insular region probably receives inputs from the orbitofrontal cortex and ACC (Price, 2006, 2007), which decode and represent the reward and punishment-related signals that can produce autonomic/visceral responses (Rolls, 2014). It is suggested (Rolls, 2014) that when the anterior insula is activated by emotion-related stimuli and events such as face expressions of disgust (Phillips et al., 1998, 2004) and unfair offers (which are aversive) in an ultimatum game (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003), the activations reflect the effects produced by regions such as the orbitofrontal and anterior cingulate cortices that can produce emotional and autonomic responses, rather than face expression decoding [which is performed elsewhere, in the cortex in the superior temporal sulcus and in the orbitofrontal cortex (Hasselmo et al., 1989; Rolls, 2007b, 2012a, 2011a)] or economic computations. Consistent with this, in a neuroeconomics study with monetary reward, it was found that expected value was negatively correlated with activations in the anterior insula [−38 24 16] in a region that has been implicated in disgust, and interestingly, the activations here were also correlated with the uncertainty of the magnitude of the reward that would be obtained (Rolls, McCabe, et al., 2008). Effectively there was more insula activation in situations that might be described as aversive. This part of the insula has activations that are related to visceral/autonomic function, for example to heart and stomach responses during disgust-associated nausea (Critchley & Harrison, 2013). Further, electrical stimulation in the antero-ventral insula produced feelings related to disgust, including viscero-autonomic feelings (Krolak-Salmon et al., 2003). Moreover, it is of course to be expected, and is the case, that the autonomic output and the corresponding visceral insular activity will be different for different emotional states, e.g., when eating a food versus when reacting to the disgusting bitter taste of quinine or to pain or the sight of aversive or unpleasant stimuli. Menon and Uddin (2010) have suggested that the insula is part of a 'saliency' network. They postulate that the insula is sensitive to salient events, and that its core function is to mark such events for additional processing and initiate appropriate control signals. However, given the inputs to the anterior insula from the orbitofrontal and anterior cingulate cortices, which decode stimuli and events such as rewards, punishers, non-reward, and novel stimuli, it is suggested (Rolls, 2014) that the anterior insula may respond to though not compute such "salient" stimuli and events, and its activation may reflect autonomic and related responses which are of course elicited by these "salient" stimuli. A related point (Rolls, 2014) is relevant to Damasio's somatic marker hypothesis (Damasio, 1996).

3.6.3. *The somatosensory insula*

The mid- and posterior insula has somatosensory representations of the body (Mufson & Mesulam, 1982). A property that may be special about these somatosensory cortical representations is that activations are produced by touch to the body but, in contrast to many other somatosensory cortical areas, not by the sight of touch (McCabe et al., 2008). It was therefore suggested that insular cortex activation thus allows an individual to know that it is touch to the person's body, and not that someone else's body is about to be touched (McCabe et al., 2008). The insular somatosensory cortex may thus provide evidence about what is happening to one's own body (Rolls, 2010a). The same might be said of the insular primary taste cortex, which when activated leaves no doubt that one is tasting, and not seeing someone else tasting. So, in a sense, feelings associated with activations of the insular cortex [and they are: the subjective intensity of taste is linearly related to the activation of the primary taste cortex (Grabenhorst & Rolls, 2008)] do inform one about the state of one's own body, and this relates to Craig's suggestions (Craig, 2009, 2011) about the importance of the insula in interoceptive feelings. However, this does not mean that the insular cortex is necessary for body feelings, and indeed that seems to be ruled out by the finding that a patient with extensive bilateral

damage to the insular cortex reported normal body/emotional feelings (Damasio, Damasio, & Tranel, 2013).

4. A hippocampal limbic system for memory and spatial function

Evidence will be described that the hippocampus and its connected structures are involved in episodic memory, and not in emotion. This is thus a separate system from the amygdala/orbitofrontal cortex/ACC emotional system. Moreover, the computational principles of operation of these two systems are very different.

4.1. *Connections*

The primate hippocampus receives inputs via the entorhinal cortex (area 28) and the highly developed parahippocampal gyrus (areas TF and TH) as well as the perirhinal cortex (area 35/36) from the ends of many processing streams of the cerebral association cortex, including the visual and auditory temporal lobe association cortical areas, the prefrontal cortex, and the parietal cortex (Aggleton, 2012; Amaral, 1987; Amaral et al., 1992; Lavenex, Suzuki, & Amaral, 2004; Rolls, 2008c; Rolls & Kesner, 2006; Suzuki & Amaral, 1994b; Van Hoesen, 1982; Witter, Wouterlood, Naber, & Van Haeften, 2000; Yukie & Shibata, 2009) (see Figs. 6 and 7). The hippocampus is thus by its connections potentially able to associate together object representations (from the temporal lobe visual and auditory cortical areas via entorhinal and perirhinal cortex), and spatial representations (from the parietal cortical areas including the posterior cingulate cortex via parahippocampal areas TF and TH). In addition, the entorhinal cortex receives inputs from the amygdala and the orbitofrontal cortex (Carmichael & Price, 1995a; Pitkanen, Kelly, & Amaral, 2002; Price, 2006; Rolls, 2010b; Stefanacci, Suzuki, & Amaral, 1996; Suzuki & Amaral, 1994a), which thus provide reward-related information to the hippocampus.

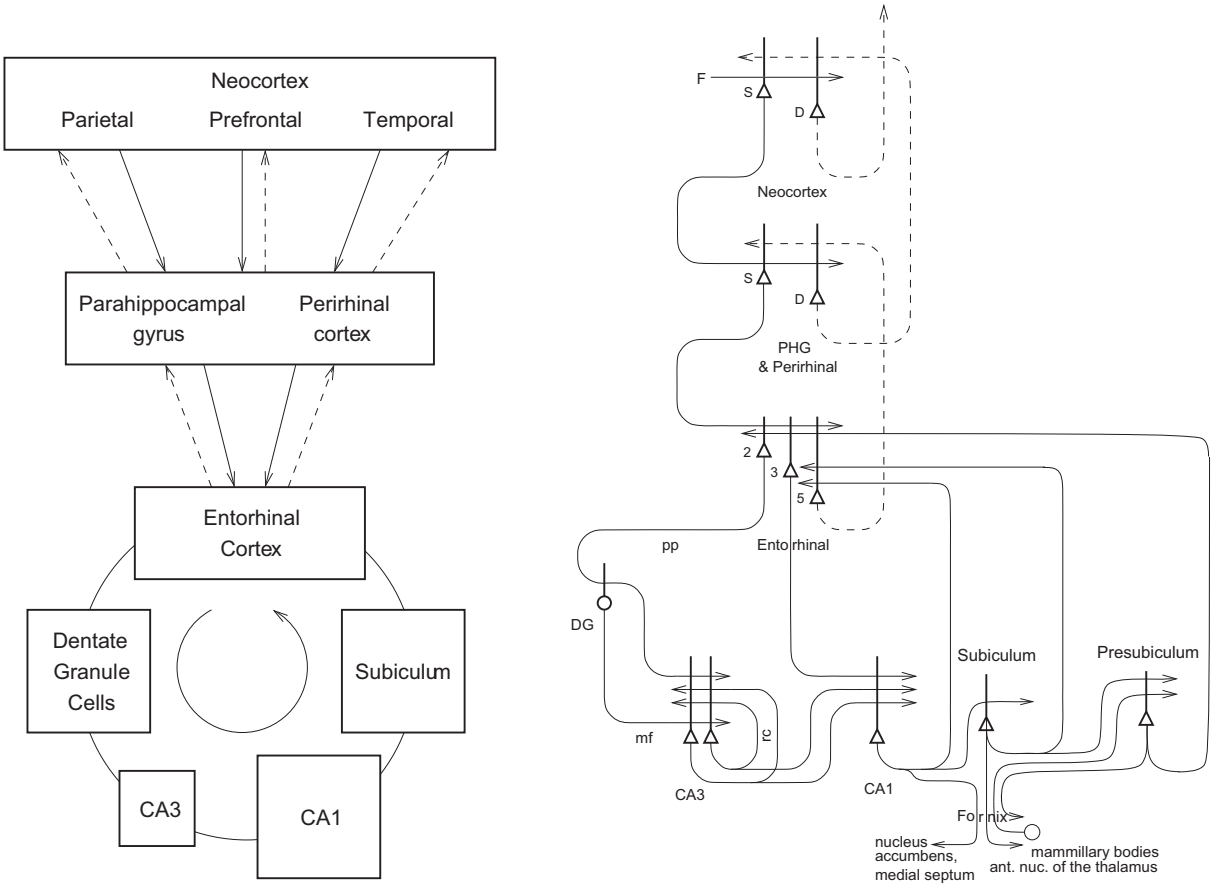

Fig. 7 – Forward connections (solid lines) from areas of cerebral association neocortex via the parahippocampal gyrus and perirhinal cortex, and entorhinal cortex, to the hippocampus; and backprojections (dashed lines) via the hippocampal CA1 pyramidal cells, subiculum, and parahippocampal gyrus to the neocortex. There is great convergence in the forward connections down to the single network implemented in the CA3 pyramidal cells; and great divergence again in the backprojections. Left: block diagram. Right: more detailed representation of some of the principal excitatory neurons in the pathways. Abbreviations: D, deep pyramidal cells; DG, dentate granule cells; F, forward inputs to areas of the association cortex from preceding cortical areas in the hierarchy; mf, mossy fibres; PHG, parahippocampal gyrus and perirhinal cortex; pp, perforant path; rc, recurrent collateral of the CA3 hippocampal pyramidal cells; S, superficial pyramidal cells; 2, pyramidal cells in layer 2 of the entorhinal cortex; 3, pyramidal cells in layer 3 of the entorhinal cortex. The thick lines above the cell bodies represent the dendrites.

The primary output from the hippocampus to neocortex originates in CA1 and projects to subiculum, entorhinal cortex, and parahippocampal structures (areas TF–TH) as well as prefrontal cortex (Delatour & Witter, 2002; van Haeften, Baksteen-Bulte, Goede, Wouterlood, & Witter, 2003; Van Hoesen, 1982; Witter, 1993) (see Figs. 6 and 7). These are the pathways that are likely to be involved in the recall of information from the hippocampus. There are other outputs (Rolls & Kesner, 2006), including subicular complex connections to the orbitofrontal cortex and ACC, and even direct connections from CA1 to the orbitofrontal cortex and ACC (Price, 2006; Vogt & Pandya, 1987; Yukie & Shibata, 2009), which are likely it is suggested to be involved in the recall of emotional and reward-related components of episodic memory; and subicular complex projections to the posterior cingulate cortex (Vogt & Pandya, 1987; Yukie & Shibata, 2009), which are likely it is suggested to be involved in the recall of spatial components of episodic memory.

In addition, there are subcortical connections that form Papez' circuit (Papez, 1937). The subiculum (subicular complex) projects via the fornix to the mammillary bodies (Fig. 7), which then project via the mammillo-thalamic tract to the anterior thalamic nuclei, which project most strongly to the posterior cingulate cortex (Shibata & Yukie, 2009), which in turn via the cingulum projects back towards the hippocampus via the parahippocampal cortex (Yukie & Shibata, 2009). The fornix also conveys the cholinergic input from the septal nuclei, classed as limbic structures, to the hippocampus, and this must be taken into account when considering the effects on memory of damage to the hippocampus, for acetylcholine facilitates synaptic modification and regulates recurrent collateral efficacy in the CA3 system (Giocomo & Hasselmo, 2007; Rolls, 2010b).

4.2. *Effects of hippocampal system damage in primates including humans*

In humans, episodic memory, the memory of a particular episode, requires the ability to remember particular events, and to distinguish them from other events, and is impaired by damage to the hippocampal system. An event consists of a set of items that occur together, such as seeing a particular object or person's face in a particular place. An everyday example might be remembering where one was for dinner, who was present, what was eaten, what was discussed, and the time at which it occurred. The spatial context is almost always an important part of an episodic memory (Dere, Easton, Nadel, & Huston, 2008), and it may be partly for this reason that episodic memory is linked to the functions of the hippocampal system, which is involved in spatial processing and memory. A famous case, is that of H.M., who after surgery for epilepsy that removed bilaterally parts of the temporal lobe including parts of the hippocampus could no longer form memories of events that occurred after the damage (anterograde amnesia), but could recall memories of events prior to the hippocampal damage (Corkin, 2002), and similar impairments are found in other patients with damage to the hippocampus and connected structures (Squire & Wixted, 2011). Indeed, section of the fornix in humans, at one time a side effect of surgery on a third ventricle cyst, produces similar amnesia (Gaffan & Gaffan, 1991), as can damage to the mammillary body/mammillo-thalamic tract/anterior nucleus of the thalamus pathway (see Aggleton, 2012). In humans, functional neuroimaging shows that the hippocampal system is activated by allocentric spatial processing and episodic memory (Burgess, 2008; Burgess, Maguire, & O'Keefe, 2002; Chadwick, Hassabis, Weiskopf, & Maguire, 2010; Hassabis et al., 2009).

Damage to the hippocampus or to some of its connections such as the fornix in monkeys produces deficits in learning about the places of objects and about the places where responses should be made (Buckley & Gaffan, 2000). For example, macaques and humans with damage to the hippocampal system or fornix are impaired in object-place memory tasks in which not only the objects seen, but where they were seen, must be remembered (Burgess et al., 2002; Crane & Milner, 2005; Gaffan, 1994; Gaffan & Saunders, 1985; Parkinson, Murray, & Mishkin, 1988; Smith & Milner, 1981). Posterior parahippocampal lesions in macaques impair even a simple type of object-place learning in which the memory load is just one pair of trial-unique stimuli (Malkova & Mishkin, 2003) (It is further predicted that a more difficult object-place learning task with non-trial-unique stimuli and with many object-place pairs would be impaired by neurotoxic hippocampal lesions.). Further, neurotoxic lesions that selectively damage the primate hippocampus impair spatial scene memory, tested by the ability to remember where in a scene to touch to obtain reward (Murray, Baxter, & Gaffan, 1998). Also, fornix lesions impair conditional left–right discrimination learning, in which the visual appearance of an object specifies whether a response is to be made to the left or the right (Rupniak & Gaffan, 1987). A comparable deficit is found in humans (Petrides, 1985). Fornix sectioned monkeys are also impaired in learning on the basis of a spatial cue which object to choose (e.g., if two objects are on the left, choose object A, but if the two objects are on the right, choose object B) (Gaffan & Harrison, 1989a). Monkeys with fornix damage are also impaired in using information about their place in an environment. For example, there are learning impairments when which of two or more objects the monkey had to choose depended on the position of the monkey in the room (Gaffan & Harrison, 1989b).

More recently, Lavenex et al. have described deficits produced by hippocampal damage in monkeys performing allocentric spatial memory tasks (Banta Lavenex & Lavenex, 2009). One such task involved freely moving in an environment using allocentric spatial room cues to remember the locations of inverted cups that contained food. This is a food reward – allocentric place association task. In contrast, the perirhinal cortex, area 35, with its connections to inferior temporal cortex areas involved in object perception (Rolls, 2008c, 2012a), is involved in recognition memory (Buckley, 2005), and indeed contains neurons related to long-term familiarity memory (Hölscher, Rolls, & Xiang, 2003; Rolls, 2008c; Rolls, Franco, & Stringer, 2005).

Rats with hippocampal lesions are also impaired in using environmental spatial cues to remember particular places (Cassaday & Rawlins, 1997; Jarrard, 1993; Kesner, Lee, & Gilbert, 2004; Kesner, Morris, & Weeden, 2012; Martin, Grimwood, & Morris, 2000; O'Keefe & Nadel, 1978), to utilize

spatial cues or to bridge delays (Kesner, 1998; Kesner et al., 2004; Kesner & Rolls, 2001; Rawlins, 1985; Rolls & Kesner, 2006), to perform object-place memory (Kesner et al., 2012; Rolls & Kesner, 2006), or to perform relational operations on remembered material (Eichenbaum, 1997).

It is notable that emotional changes, reward-related learning and reversal impairments, and devaluation impairments of stimuli are not produced by damage to this hippocampal system. This is further evidence for one of the theses of this paper, that we should no longer be considering the operation of limbic and related structures as being part of a single limbic system. There is a double dissociation of functions, with the orbitofrontal/amygdala/ACC limbic system being involved in emotion but not episodic memory, and the hippocampal system being involved in memory but not in emotion.

4.3. *Neuronal representations in the primate hippocampus*

The systems-level neurophysiology of the hippocampus shows what information could be stored or processed by the hippocampus. To understand how the hippocampus works it is not sufficient to state just that it can store information – one needs to know what information. The systems-level neurophysiology of the primate hippocampus has been reviewed by Rolls and Xiang (2006), and a summary is provided here because it provides a perspective relevant to understanding the function of the human hippocampus that is somewhat different from that provided by the properties of place cells in rodents, which have been reviewed elsewhere (Jeffery, Anderson, Hayman, & Chakraborty, 2004; Jeffery & Hayman, 2004; McNaughton, Barnes, & O'Keefe, 1983; Muller, Kubie, Bostock, Taube, & Quirk, 1991; O'Keefe, 1984).

4.3.1. *Spatial view neurons in the primate hippocampus*

We have shown that the primate hippocampus contains spatial cells that respond when the monkey looks at a certain part of space, for example at one quadrant of a video monitor while the monkey is performing an object-place memory task in which he must remember where on the monitor he has seen particular images (Rolls, 1999c; Rolls, Miyashita, et al., 1989). Approximately 9% of hippocampal neurons have such spatial view fields, and approximately 2.4% combine information about the position in space with information about the object that is in that position in space (Rolls, Miyashita, et al., 1989). The representation of space is for the majority of hippocampal neurons in allocentric not egocentric coordinates (Feigenbaum & Rolls, 1991). These spatial view cells can be recorded while monkeys move themselves round the test environment by walking (or running) on all fours (Georges-François, Rolls, & Robertson, 1999; Robertson, Rolls, & Georges-François, 1998; Rolls, Robertson, & Georges-François, 1997; Rolls, Treves, Robertson, Georges-François, & Panzeri, 1998). These hippocampal 'spatial view neurons' respond significantly differently for different allocentric spatial views and have information about spatial view in their firing rate, but do not respond differently just on the basis of eye position, head direction, or place (Georges-François et al., 1999). If the view details are obscured by curtains and darkness, then some spatial view neurons (especially those in CA1 and less those in CA3) continue to respond when the monkey looks towards the spatial view field, showing that these neurons can be updated for at least short periods by idiothetic (self-motion) cues including eye position and head direction signals (Robertson et al., 1998; Rolls, Treves, Foster, & Perez-Vicente, 1997).

4.3.2. *Object-place neurons in the primate hippocampus*

A fundamental question about the function of the primate including human hippocampus in relation to episodic memory is whether object as well as allocentric spatial information is represented. To investigate this, Rolls, Xiang, and Franco (2005) made recordings from single hippocampal formation neurons while macaques performed an object-place memory task that required the monkeys to learn associations between objects, and where they were shown in a room. Some neurons (10%) responded differently to different objects independently of location; other neurons (13%) responded to the spatial view independently of which object was present at the location; and some neurons (12%) responded to a combination of a particular object and the place where it was shown in the room. These results show that there are separate as well as combined representations of objects and their locations in space in the primate hippocampus. This is a property required in an episodic memory system, for which associations between objects and the places where they are seen, are prototypical. The results thus show that a requirement for a human episodic memory system, separate and combined neuronal representations of objects and where they are seen "out there" in the environment, are present in the primate hippocampus (Rolls, Xiang, et al., 2005).

What may be a corresponding finding in rats is that some rat hippocampal neurons respond on the basis of the conjunction of location and odour (Wood, Dudchenko, & Eichenbaum, 1999). Results consistent with our object-place neurons in primates are that Diamond et al. have now shown using the vibrissa somatosensory input for the 'object' system, that rat hippocampal neurons respond to object-place combinations, objects, or places, and there is even a reward-place association system in rats (Itskov, Vinnik, & Diamond, 2011) similar to that in primates described below. This brings the evidence from rats closely into line with the evidence from primates of hippocampal neurons useful for object-place episodic associative memory.

Spatial view cells and object-place cells, are also present in the parahippocampal areas (Georges-François et al., 1999; Robertson et al., 1998; Rolls, Robertson, et al., 1997; Rolls, Treves, et al., 1998; Rolls, Xiang, et al., 2005). There are back-projections from the hippocampus to the entorhinal cortex and thus to parahippocampal areas, and these back-projections could enable the hippocampus to influence the spatial representations found in the entorhinal cortex and parahippocampal gyrus. On the other hand, some of the spatial functions may be provided for in these parahippocampal areas, which will in turn influence the hippocampus. However, it is argued below that the hippocampus may be able to make a special contribution to event or episodic memory, by enabling in the CA3 network with its very widespread recurrent collateral connections an association

between any one item with any other item to form an arbitrary association to represent an event.

4.3.3. *Recall-related neurons in the primate hippocampus*

It has been possible to investigate directly, neurophysiologically, the hippocampal recall process in primates (Rolls & Xiang, 2006). We used a visual object-place memory task because this is prototypical of episodic memory. It has been shown that a one-trial odour-place recall memory task is hippocampal-dependent in rodents (Day, Langston, & Morris, 2003). We designed a one-trial object-place recall task, in which the whole memory was recalled from a part of it. Images of new objects were used each day, and within a day the same objects were used, so that with non-trial unique objects within a day, the recall task is quite difficult.

Recordings were made from 347 neurons in the hippocampus of a macaque performing the object-place recall task. The following types of neurons were found in the task (Rolls & Xiang, 2006).

One type of neuron had responses that occurred to one of the objects used in the task. A number of these neurons had activity that was related to the recall process. For example, one type of single neuron had activity that was greater to object one when it was shown, but also when the object was no longer visible, and the macaque was touching the recalled location of that object. Thus while the location was being recalled from the object, this type of neuron continued to respond as if the object was present, that is it kept the representation of the object active after the object was no longer visible, and the place to touch was being recalled. Sixteen of the neurons responded in this way (Rolls & Xiang, 2006). None of these neurons had differential responses for the different places used in the object-place recall task.

A second type of neuron had responses related to the place (left or right) in which an object was shown. This type of neuron responded more for example when an object was shown in the left position (P1) than in the right position (P2) on the screen. Interestingly, when the recall object was shown later in the trial in the top centre of the screen, the neuron also responded as if the left position (P1) was being processed on trials on which the left position had to be recalled. Thus this type of neuron appeared to reflect the recall of the position on the screen at which the object had been represented. Thirteen neurons had differential responses to the different places P1 and P2, and continued to show place-related activity in the recall part of the task (Rolls & Xiang, 2006). The new finding is that 13 of the neurons had place-related responses when a place was being recalled by an object cue. The recording sites of the object and of the place neurons were within the hippocampus proper (Rolls & Xiang, 2006). The mean firing rate of the population of responsive neurons to the most effective object or place was 7.2 ± .6 spikes/sec (±sem), and their mean spontaneous rate was 3.2 ± .6 spikes/sec.

These findings (Rolls & Xiang, 2006) are the first we know in the primate hippocampus of neuronal activity that is related to recall. It is particularly interesting that the neurons with continuing activity to the object after it had disappeared in the recall phase of the task could reflect the operation of the object-place recall process that is hypothesized to take place in the CA3 cells. By continuing to respond to the object while the place is being recalled in the task, the object-related neurons could be part of the completion of the whole object-place combination memory from an autoassociation or attractor process in CA3 (Rolls & Kesner, 2006). Consistent with these findings, and with the computational theory, it has now been reported that human hippocampal neurons are activated during recall (Gelbard-Sagiv, Mukamel, Harel, Malach, & Fried, 2008).

The neurons with recall-related activity in the object-place recall task also provide neurophysiological evidence on the speed of association learning in the hippocampal formation. Given that this is a one-trial object-place recall task, with the association between the object and its place being made in stages 1 and 2 of each trial, it is clear that it takes just one trial for the object-place associations to be formed that are relevant to the later recall on that trial (Rolls & Xiang, 2006). This is the speed of learning that is required for episodic memory, and this neurophysiological evidence shows that this type of rapid, one-trial, object-place learning is represented in the primate hippocampus (Rolls, 2010b).

4.3.4. *Reward-place neurons in the primate hippocampus*

The primate anterior hippocampus (which corresponds to the rodent ventral hippocampus) receives inputs from brain regions involved in reward processing such as the amygdala and orbitofrontal cortex (Aggleton, 2012; Pitkanen et al., 2002). To investigate how this affective input may be incorporated into primate hippocampal function, Rolls and Xiang (2005) recorded neuronal activity while macaques performed a reward-place association task in which each spatial scene shown on a video monitor had one location which if touched yielded a preferred fruit juice reward, and a second location which yielded a less preferred juice reward. Each scene had different locations for the different rewards. Of 312 hippocampal neurons analysed, 18% responded more to the location of the preferred reward in different scenes, and 5% to the location of the less preferred reward (Rolls & Xiang, 2005). When the locations of the preferred rewards in the scenes were reversed, 60% of 44 neurons tested reversed the location to which they responded, showing that the reward-place associations could be altered by new learning in a few trials. The majority (82%) of these 44 hippocampal reward-place neurons tested did not respond to object-reward associations in a visual discrimination object-reward association task. Thus the primate hippocampus contains a representation of the reward associations of places "out there" being viewed, and this is a way in which affective information can be stored as part of an episodic memory, and how the current mood state may influence the retrieval of episodic memories. There is consistent evidence that rewards available in a spatial environment can influence the responsiveness of rodent place neurons (Hölscher, Jacob, & Mallot, 2003; Tabuchi, Mulder, & Wiener, 2003).

4.3.5. *Grid cells in the entorhinal cortex*

The entorhinal cortex contains grid cells, which have high firing in the rat in a two-dimensional spatial grid as a rat traverses an environment, with larger grid spacings in the ventral entorhinal cortex (Fyhn, Molden, Witter, Moser, & Moser, 2004; Hafting, Fyhn, Molden, Moser, & Moser, 2005). This may be a system optimized for path integration (McNaughton, Battaglia, Jensen, Moser, & Moser, 2006) which

may self-organize during locomotion with longer time constants producing more widely spaced grids in the ventral entorhinal cortex (Kropff & Treves, 2008). How are the grid cell representations, which would not be suitable for association of an object or reward with a place to form an episodic memory, transformed into a place representation that would be appropriate for this type of episodic memory? We have demonstrated how this could be implemented by a competitive network (Rolls, 2008c) in the dentate gyrus which operates to form place cells, implemented by each dentate granule cell learning to respond to particular combinations of entorhinal cortex cells firing, where each combination effectively specifies a place, and this has been shown to be feasible computationally (Rolls, Stringer, & Elliot, 2006).

In primates, there is now evidence that there is a grid cell like representation in the entorhinal cortex, with neurons having grid-like firing as the monkey moves the eyes across a spatial scene (Killian, Jutras, & Buffalo, 2012). Similar competitive learning processes may transform these entorhinal cortex 'spatial view grid cells' into hippocampal spatial view cells, and may help with the idiothetic (produced in this case by movements of the eyes) update of spatial view cells (Robertson et al., 1998). The presence of spatial view grid cells in the entorhinal cortex of primates (Killian et al., 2012) is of course predicted from the presence of spatial view cells in the primate CA3 and CA1 regions (Georges-François et al., 1999; Robertson et al., 1998; Rolls, 2008c; Rolls, Robertson, et al., 1997; Rolls, Treves, et al., 1998; Rolls & Xiang, 2006). Further support of this type of representation of space being viewed 'out there' rather than where one is located as for rat place cells is that neurons in the human entorhinal cortex with spatial view grid-like properties have now been described (Jacobs et al., 2013).

4.3.6. *Neuronal representations of space 'out there' for episodic memory, and parietal inputs to the hippocampus*

These discoveries show that the primate hippocampus contains neurons that represent space 'out there' being viewed, and reflect during learning associations of these viewed locations with objects and with rewards. This is fundamental to human episodic memory. Humans can in one trial remember where in a room or locality they have seen an object or reward, even though they may never have visited and been at the location. This functionality could not be implemented by rat place cells, which respond to the location where the rat is located.

The representations of space 'out there' which are very important in primate hippocampal function show how important the primate parietal cortical areas and the posterior cingulate cortex are in providing inputs to the hippocampus, for the parietal cortex receives inputs from the dorsal ('where') visual system, and in areas such as the retrosplenial cortex, contains representations of landmarks and spatial scenes (Auger & Maguire, 2013). These areas connect to the hippocampus via parahippocampal areas such as TF and TH (Yukie & Shibata, 2009), in which, consistently, spatial view neurons are found (Georges-François et al., 1999; Robertson et al., 1998; Rolls, 2008c; Rolls, Robertson, et al., 1997; Rolls, Treves, et al., 1998; Rolls & Xiang, 2006).

Macaque hippocampal neurons have little response to objects or faces or rewards such as food or punishers such as saline (Rolls & Xiang, 2006), even when the monkey is performing an object-reward task (Rolls & Xiang, 2005). Thus the hippocampus does not appear to be involved in emotion. It is only when rewards must be associated with their spatial context that primate hippocampal neurons become involved (Rolls & Xiang, 2005). The hippocampus is thus seen as a limbic structure in which space is very important as a typical component of episodic memory, and as a structure in which is a reward or emotional state as part of the episodic/single event memory, can then be stored as part of the episodic memory, and later recalled when the episodic memory is recalled. Episodic memory must be able to incorporate emotional states and rewards, and the way that this occurs in terms of connectivity, neuronal responses, and learning in hippocampal networks is proposed clearly in this paper.

4.4. *Neural network computations in the hippocampus for episodic memory*

A computational theory of how the hippocampus implements episodic memory has been developed in stages and described elsewhere (Rolls, 1987, 1989a, 1989b, 1989c, 1990a, 1990b, 1991, 1995b, 1996b, 2007a, 2008c, 2010b, 2013b, 2013c; Rolls & Deco, 2010; Rolls & Kesner, 2006; Rolls & Treves, 1998; Rolls, Tromans, & Stringer, 2008; Treves & Rolls, 1991, 1992, 1994). Here I wish to show that hippocampal operation is computationally very different from that involved in emotion, providing further support for the thesis that there is no single limbic system. There are at least two separate systems, performing very distinct types of computation.

In outline, the theory describes quantitatively how the hippocampal system illustrated in Fig. 7 operates to implement episodic memory, and the later recall of a whole episodic memory from any part. The CA3 recurrent collateral system operates as a single attractor or autoassociation memory network to enable rapid, one-trial, associations between any spatial location (place in rodents, or spatial view in primates) and an object or reward, and to provide for completion of the whole memory during recall from any part. The theory is extended to associations between time and object or reward to implement temporal order memory, also important in episodic memory. The dentate gyrus performs pattern separation by competitive learning to produce sparse representations, producing for example neurons with place-like fields from entorhinal cortex grid cells. The dentate granule cells produce by the very small number of mossy fibre connections to CA3 a randomizing pattern separation effect important during learning but not recall that separates out the patterns represented by CA3 firing to be very different from each other, which is optimal for an unstructured episodic memory system in which each memory must be kept distinct from other memories. The direct perforant path input to CA3 is quantitatively appropriate to provide the cue for recall in CA3, but not for learning. The CA1 recodes information from CA3 to set up associatively learned backprojections to neocortex to allow subsequent retrieval of information to neocortex, providing a quantitative account of the large number of hippocampo-neocortical and neocortical–neocortical backprojections.

The theory shows how object information could be recalled in the inferior temporal visual cortex, spatial information in

parietal allocentric spatial areas such as the retrosplenial cortex, and reward and emotional information in areas that receive as well as send inputs to the hippocampus, the orbitofrontal cortex, amygdala, and ACC. Fundamental in this computation is the autoassociation in the CA3 network, for this enables different components of an episodic memory (typically one being spatial, and others including as the case may be object, face, and reward/emotional value information) to be associated together, and then for the whole of the memory to be recalled in CA3 from any one of the components. [The operation of autoassociation or attractor networks is described elsewhere (Hertz, Krogh, & Palmer, 1991; Hopfield, 1982; Rolls, 2008c; Rolls & Treves, 1998).]. After completion in the CA3 autoassociation network, the backprojections to the neocortex allow for recall of the neuronal activity in each cortical area that was active during the original storage of the episodic memory (Rolls, 2008c; Treves & Rolls, 1994).

This functionality, of storing a multicomponent memory rapidly in an unstructured way, recalling the whole memory from any part, and then recalling the activity that was present in each high-order cortical area providing inputs to the hippocampus (Rolls, 2008c, 2010b, 2013b) (see Fig. 7), is completely different from the operations of other limbic structures involved in emotion (the "emotion limbic system"), as described next. The difference also helps to account for the different connectivities of the two systems, with the emotion system being primarily feedforward (Fig. 1), while the hippocampal limbic system provides for feedback, both for recall within the CA3 autoassociation network itself, and from the hippocampus back to high-order cortical areas (Fig. 7).

5. Different computations for the 'emotional limbic system' from those in the 'memory limbic system'

The circuitry involved in emotion in primates is shown schematically in Fig. 1.

It is crucial that the representation of primary (unlearned) reinforcers becomes explicit, i.e., in terms of reward value, in the orbitofrontal cortex. In the case of taste, my hypothesis is that genetic encoding of pathways is used to implement this (Rolls, 2014), with molecular specification of the synapses in the pathways from the genetically encoded taste receptors (Chandrashekar, Hoon, Ryba, & Zuker, 2006; Chaudhari & Roper, 2010), continuing through to the orbitofrontal cortex, so that sweet in a receptor is encoded as the identity of sweet taste in the insular primary taste cortex, and as the reward value of a sweet taste in the orbitofrontal cortex.

The main type of learning required in the emotion system is then pattern association between a previously neutral stimulus such as a round object, and a primary reinforcer such as taste, pleasant touch, or pain. The architecture and operation of a pattern associator are shown in Fig. 8, with details provided elsewhere (Rolls, 2008c, 2014; Rolls & Treves, 1998). This is a feedforward operation. The conditioned stimulus, e.g., the visual stimulus, becomes associated with the US (e.g., the taste). However, the opposite can not occur, the visual stimulus can not be retrieved from the taste. This is a feedforward operation. It is completely different from the completion of a memory enabled by the autoassociation network in the hippocampus (Rolls, 2013b). The pattern association operation enables expected value to be computed from outcome value (Rolls, 2008c, 2014).

In computing emotion-related value representations, inputs about the properties of primary reinforcers and objects are required, not inputs about space. That is why the inputs to the emotional system are from sensors such as those involved in taste, touch and pain, and are from the ventral visual system where objects that can have these properties are represented. This dominance of the ventral ('what') visual system as providing the inputs for emotion and value decoding is strongly to be contrasted with the episodic memory system, in which where, and when, events happened is important, with input therefore required from the parietal spatial/dorsal visual systems. The orbitofrontal cortex is in a sense one end of the 'what' processing systems, and does not know about space or actions (Rolls, 2014). As we have seen the amygdala is in primates to some extent a secondary player to the orbitofrontal cortex, though involved in at least some classically conditioned responses to stimuli that produce emotions.

The orbitofrontal cortex (but not the amygdala) goes even beyond though the pattern associator computation illustrated in Fig. 8, and can involve a one-trial, rule-based, change of reward-related behaviour. For example, if one visual stimulus suddenly becomes no longer associated with reward, the orbitofrontal cortex system can immediately switch to another visual stimulus, even though that stimulus has previously been associated with punishment (Thorpe et al., 1983). An integrate-and-fire neuronal network mechanism that utilises the positive reward prediction error neurons found in the orbitofrontal cortex has been described and simulated (Deco & Rolls, 2005c). An attractor network keeps the current rule active, and biases appropriately the conditional reward neurons found in the orbitofrontal cortex (Rolls, 2014). The positive reward prediction error neurons, themselves showing continuous firing in an attractor, then quench the rule attractor, so that another rule attractor population of neurons can emerge because it is less adapted than the recently firing rule neurons. The whole network operates well, and simulates and provides an account for several types of neuron found in the orbitofrontal cortex (Deco & Rolls, 2005c; Rolls, 2014).

The value representations computed in the orbitofrontal cortex are then transmitted to the ACC so that with outcomes represented now in the ACC, and with connections moving back towards the midcingulate cortex, action–outcome learning can be implemented. For action–outcome learning, a representation of an action that has just been made is required, and this is present in midcingulate cortex areas. The action must be remembered, perhaps for several seconds, until the outcome is received. The memory of the action, I hypothesize, is provided for by an attractor network in the mid/ACC. Associations can then be learned by pattern association learning in the mid/ACC between the actions and the outcomes. Often the whole process may be facilitated by the learning of associations between the conditioned stimulus, the expected value representation, and the action–outcome pairing represented in the mid/ACC. The special role in this scenario for the anterior and midcingulate cortex is then to bring actions into the processing, and the costs of performing

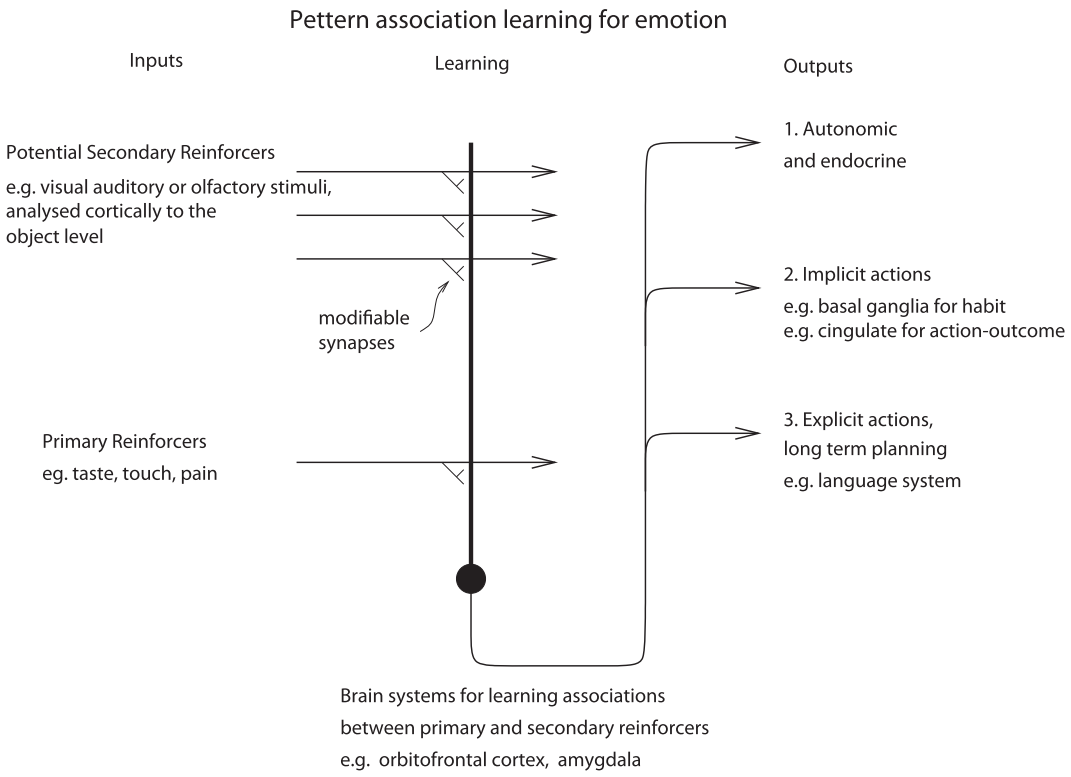

Fig. 8 – Pattern association networks for emotion-related learning. Primary reinforcers drive the neurons with unmodifiable synapses, to make the neurons respond to primary reinforcers such as taste, pleasant touch, or pain, for different neurons. If a visual, auditory, or olfactory stimulus occurs just before or at the same time as the primary reinforcer, the synapses with simultaneous pre- and post-synaptic activity increase in strength by associative (Hebbian) learning, as reflected in long-term potentiation. After learning, presentation of the visual, auditory, or olfactory stimulus now produces firing of the neuron, even in the absence of any primary reinforcer. Thus for example the taste can be recalled by the sight of food, and the sight of food has become a secondary, learned, reinforcer. Different pattern association networks in different brain regions may be involved in producing the different types of output response, including autonomic responses, and freezing, habit, or goal-directed behaviour.

actions, so that appropriate instrumental, goal-directed, actions can be performed to emotion-provoking stimuli represented in terms of reward value (Rolls, 2014).

6. Conclusions: separate limbic structures or systems for emotion and for memory, but no single limbic system

The concept of a (single) limbic system has been shown to be outmoded, in that anterior limbic and related structures involved in emotion can operate independently, and by different computational principles, from the hippocampal memory system. Instead, the anatomical, neurophysiological, functional neuroimaging, and neuropsychological evidence described shows that anterior limbic and related structures including the orbitofrontal cortex and amygdala are involved in emotion, reward valuation, and reward-related decision-making (but not memory), with the value representations transmitted to the ACC for action–outcome learning. In this 'emotion limbic system' feedforward pattern association networks learn associations between visual, olfactory and auditory stimuli with primary reinforcers such as taste, touch, and pain. In primates including humans this learning can be very rapid and rule-based, with the orbitofrontal cortex overshadowing the amygdala in this learning important for social and emotional behaviour. The cortical inputs to this limbic system come in primates from areas that represent 'what' object is present, including inferior temporal cortical areas towards the end of the ventral visual system, and the anterior insular taste cortex and somatosensory cortical areas.

The complementary anatomical, neurophysiological, functional neuroimaging, and neuropsychological evidence described shows that the hippocampus and limbic structures to which it is connected including the posterior cingulate cortex and the fornix-mammillary body-anterior thalamus-posterior cingulate circuit are involved in episodic or event memory, but not emotion. This 'hippocampal system' receives information from neocortical areas about spatial location including parietal cortex areas towards the end of the dorsal visual system, and about objects and faces from the temporal cortical visual areas towards the end of the ventral visual system, and can associate this information together by autoassociation in the CA3 region of the hippocampus which

involves feedback in the recurrent collateral system. The hippocampal memory system can later recall the whole of this information in the CA3 region from any component, a feedback process, and can recall that information back to neocortical areas, again a feedback (to neocortex) recall process. The nature of the computation in this hippocampal system is thus very different from the feedforward pattern association involved in stimulus-reward association learning in the emotion system (Rolls, 2013b). Emotion and reward signals can enter the hippocampal memory system from the orbitofrontal cortex, amygdala and ACC (Rolls, 2014; Rolls & Xiang, 2005), and can be recalled back to the orbitofrontal cortex, amygdala and ACC during memory recall (Smith, Stephan, Rugg, & Dolan, 2006), as emotion can provide a component of episodic memory.

Thus, the emotional and hippocampal networks or 'limbic systems' operate by different principles, and operate independently of each other except insofar as emotional state may be part of an episodic memory. The concept of a single limbic system may no longer appropriately reflect how the brain operates. Instead, separate systems, which might be designated the emotional limbic system and the episodic memory hippocampal system, are present in the brain, and the separate and different principles of their operation have been described here and elsewhere (Rolls, 2008c, 2010b, 2013b, 2014).

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