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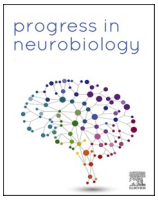

The hippocampus, ventromedial prefrontal cortex, and episodic and semantic memory

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ABSTRACT

The human ventromedial prefrontal cortex (vmPFC)/anterior cingulate cortex is implicated in reward and emotion, but also in memory. It is shown how the human orbitofrontal cortex connecting with the vmPFC and anterior cingulate cortex provide a route to the hippocampus for reward and emotional value to be incorporated into episodic memory, enabling memory of where a reward was seen. It is proposed that this value component results in primarily episodic memories with some value component to be repeatedly recalled from the hippocampus so that they are more likely to become incorporated into neocortical semantic and autobiographical memories. The same orbitofrontal and anterior cingulate regions also connect in humans to the septal and basal forebrain cholinergic nuclei, thereby helping to consolidate memory, and helping to account for why damage to the vMPFC impairs memory. The human hippocampus and vmPFC thus contribute in complementary ways to forming episodic and semantic memories.

1. Introduction

The human hippocampus is involved in episodic memory (Squire and Wixted, 2011; Rosenbaum et al., 2014; Squire et al., 2015; Moscovitch et al., 2016; Gilboa and Marlatte, 2017; Bonnici and Maguire, 2018; McCormick et al., 2018), which is thought to be implemented by association between 'what' and 'where' information in the hippocampal CA3 (Treves and Rolls, 1994; Rolls, 2018a). The orbitofrontal cortex with its connections to the ventromedial prefrontal cortex (vmPFC) and anterior cingulate cortex are together key brain regions involved in reward value and emotion in humans and other primates, as shown by evidence from neuronal recordings, activations by rewards and punishers, and impaired emotion after damage (Rolls, 2019b; 2019c, 2021d; Rolls et al., 2020a). But the vmPFC and related anterior cingulate cortex regions are also implicated (in addition to the hippocampus) in episodic memory, as shown by impairments after damage to the frontal regions (Preston and Eichenbaum, 2013; Rosenbaum et al., 2014; Moscovitch et al., 2016; Gilboa and Marlatte, 2017; Barry et al., 2018; Bonnici and Maguire, 2018; McCormick et al., 2018). The question arises: what is the relation between the orbitofrontal cortex/vmPFC/anterior cingulate cortex system and the hippocampal system in memory?

Here new evidence is described on the connectivity of the human orbitofrontal cortex/vmPFC/anterior cingulate system implicated in reward value and emotion with the hippocampal memory system (Rolls et al., 2022e, 2022f), and that helps to elucidate this important issue in neuroscience as introduced next and then set out in this paper.

First, new evidence (Rolls et al., 2022e, 2022f) shows how reward value and emotional content can reach the human hippocampal memory system and be incorporated into episodic memory. It is proposed that after damage to the vmPFC areas, without this key reward/emotion part of the episodic memory normally stored in the hippocampus, there is an impairment of episodic memory because a key part of it is missing, the reward/emotion component, and further that recall operates less well when a key component normally used in recall is missing.

Second, new evidence also uncovers connections in humans from these anterior cingulate and orbitofrontal cortex regions to the septal nuclei and basal forebrain nucleus of Meynert (Rolls et al., 2022e, 2022f) which contain cholinergic neurons that project to the hippocampus and neocortex respectively (Mesulam, 1990; Zaborszky et al., 2008, 2018). These cholinergic systems are involved in memory consolidation (Hasselmo and Giocomo, 2006; Hasselmo and Sarter, 2011; Rolls et al., 2022e, 2022f), and it is proposed that if the

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orbitofrontal/vmPFC/anterior cingulate cortex system is damaged, then not only is hippocampal episodic memory storage impaired, but so is conversion and consolidation into neocortical long-term semantic memory.

Third, and based on this connectivity in humans, it is proposed that the conversion of episodic to semantic memory (including schemas) is normally facilitated by the episodic event having some value; and that value is signalled by the orbitofrontal cortex/vmPFC/anterior cingulate cortex. The value component can operate in a number of ways, but one is by using the cholinergic mechanism just referred to, and another is by leading to more brain processing of items that have some potential value (signalled by the orbitofrontal cortex system), rather than being lost if the episode is just an everyday event with no reward value.

A highlight of this approach is that it focusses on the evidence from connectivity, neurophysiology, functional neuroimaging, and brain lesion evidence in humans and other primates on the orbitofrontal cortex, vmPFC, and anterior cingulate cortex, which provide the reward value inputs to the hippocampus, for these brain regions are much more developed in primates including humans than rodents (illustrated in Fig. 1) (Vogt, 2009; Rolls, 2019c, 2021a; Passingham, 2021).

2. The orbitofrontal cortex/vmPFC/anterior cingulate cortex system is implicated in reward and emotion

There is a wealth of evidence that the primate including human orbitofrontal cortex, vmPFC, and anterior cingulate cortex (Figs. 1 and 2) are involved in reward and reward-related decision-making (Thorpe et al., 1983; Rolls et al., 1989b, 2020a; O'Doherty et al., 2001; Hare et al., 2008; Rolls and Grabenhorst, 2008; Grabenhorst and Rolls, 2011; Glascher et al., 2012; Rolls, 2014, 2019a, 2019c; Padoa-Schioppa and Conen, 2017; Reber et al., 2017; Schneider and Koenigs, 2017; O'Neill and Schultz, 2018).

The human medial orbitofrontal cortex areas 13 and 11 (Fig. 1) represent reward value on a continuous scale. This is shown at the neuroimaging level in humans to olfactory (Rolls et al., 2003b), pleasant touch (Rolls et al., 2003c; McCabe et al., 2008), food flavour (Kringelbach et al., 2003), warm temperature (Guest et al., 2007; Rolls, 2010), and monetary (O'Doherty et al., 2001; Rolls et al., 2020b) rewards (Grabenhorst and Rolls, 2011; Rolls, 2019a, 2019c; Rolls et al., 2020a; Xie et al., 2021), with foundational evidence from neuronal recordings in macaques (Thorpe et al., 1983; Tremblay and Schultz, 2000;

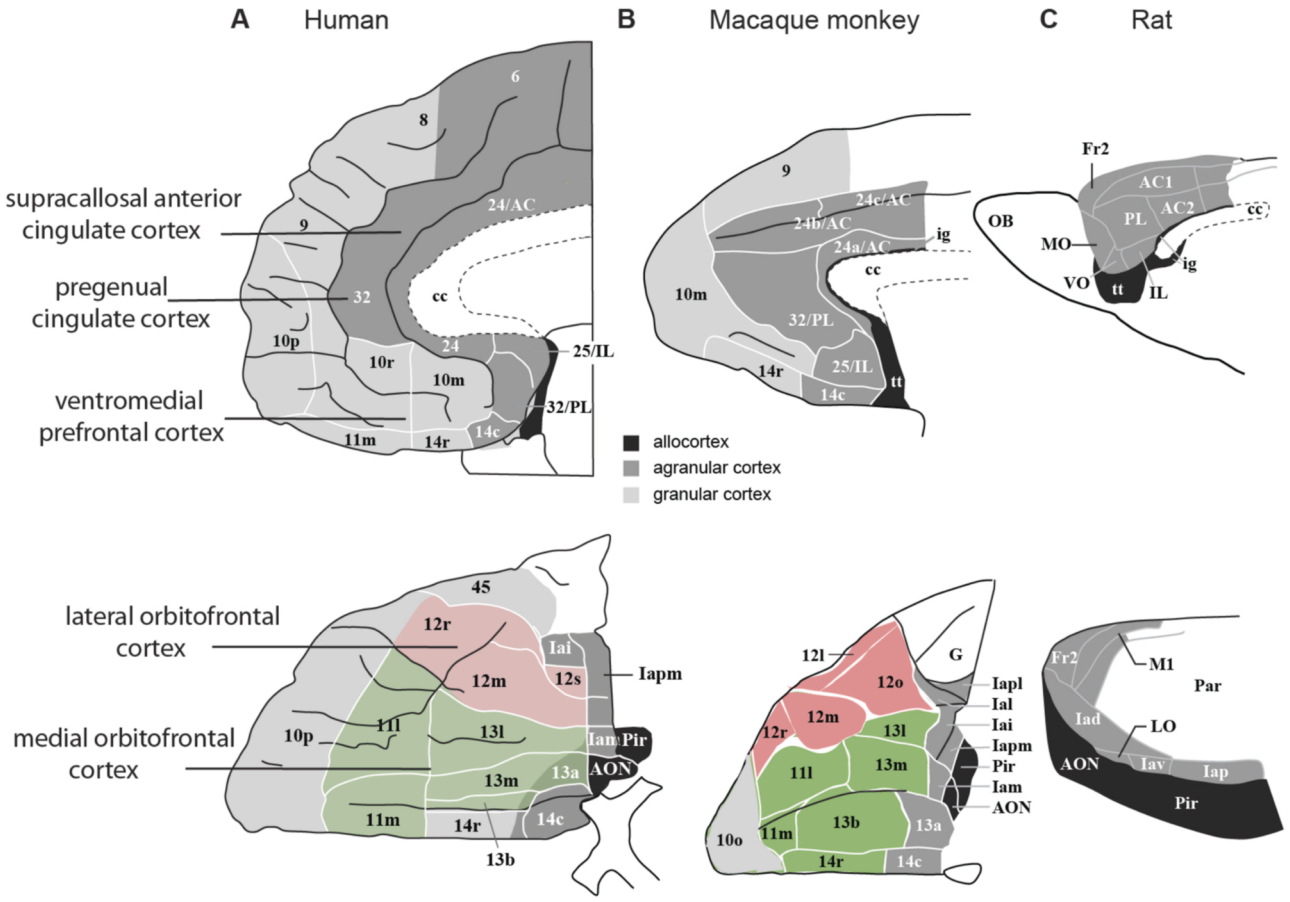

Fig. 1. The orbitofrontal (below) and medial prefrontal including anterior cingulate (above) cortical areas in humans, macaque monkeys, and rats to show the great development of these areas in humans and other primates. (A) Medial (top) and orbital (bottom) areas of the human frontal cortex (Öngür et al., 2003). The medial orbitofrontal cortex is shown in green (areas 13 and 11), and the lateral orbitofrontal cortex in red (area 12). Almost all of the human orbitofrontal cortex except area 13a is granular. Agranular cortex is shown in dark grey. Black shows olfactory regions posterior to the orbitofrontal cortex. The ventromedial prefrontal cortex is the area shown as 10m and below that towards 11m. The anterior cingulate cortex is areas 32 and 24, with the subgenual area 25. The part of area 45 shown is the orbital part of the inferior frontal gyrus pars triangularis, part of Broca's area. (B) Medial (top) and orbital (bottom) areas of the macaque frontal cortex. Conventions as in (B). (C) Medial (top) and lateral (bottom) areas of rat frontal cortex (which is thought to have no granular orbitofrontal cortex equivalent to the primate including human granular orbitofrontal cortex areas 11, 13 and 12 (Passingham and Wise, 2012)). 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: AC, anterior cingulate cortex; AON, anterior olfactory nucleus; cc, corpus callosum; Fr2 second frontal area; Ia, agranular insular cortex; ig, induseum 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
(Adapted from Passingham and Wise, 2012).

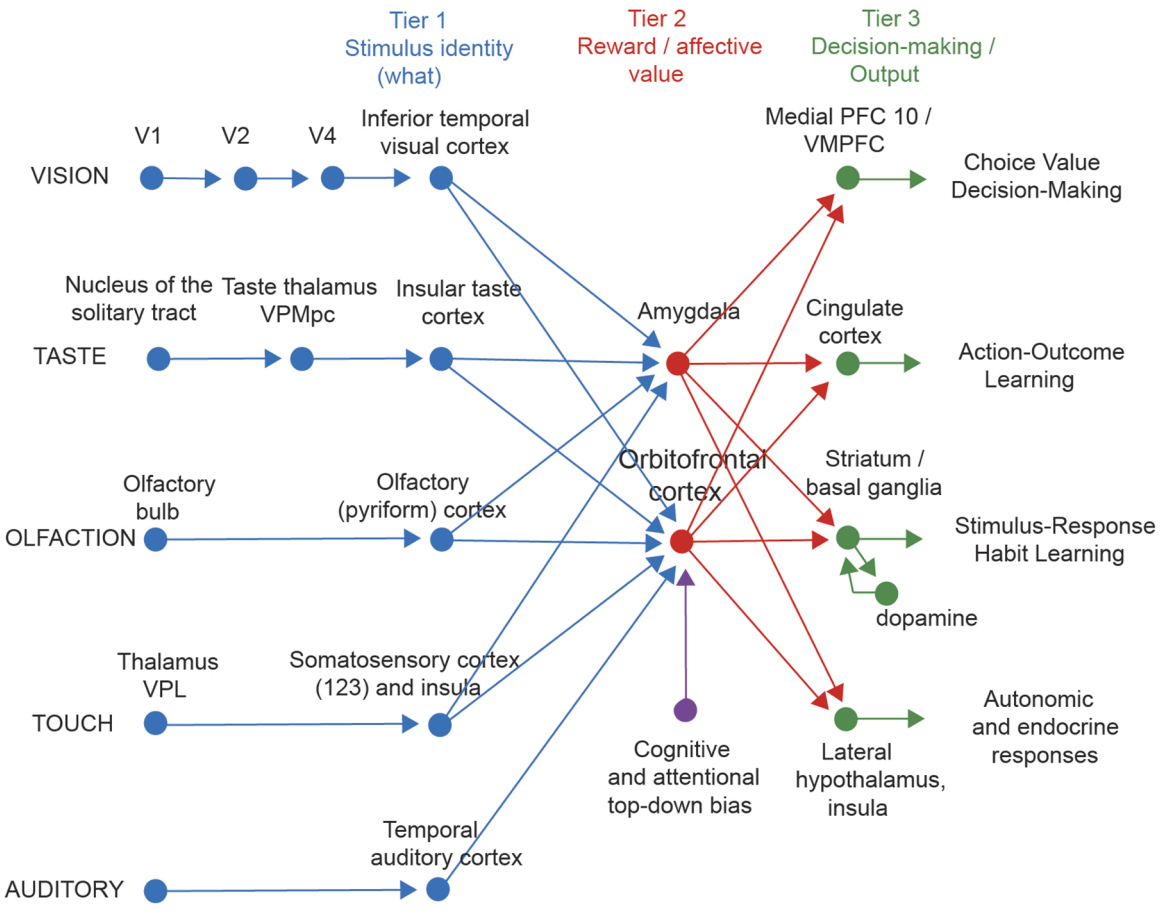

Fig. 2. Schematic diagram showing some of the gustatory, olfactory, visual and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex, in primates. The secondary taste cortex, and the secondary olfactory cortex, are within the orbitofrontal cortex. V1 - primary visual cortex. V4 - visual cortical area V4. Tier 1: the column of brain regions including and below the inferior temporal visual cortex represents brain regions in which 'what' stimulus is present is made explicit in the neuronal representation, but not its reward or affective value which are represented in the next tier of brain regions (Tier 2), the orbitofrontal cortex and amygdala, and in the anterior cingulate cortex. In Tier 3 areas beyond these such as medial prefrontal cortex area 10, choices or decisions about reward value are taken (Rolls, 2008, 2014; Rolls and Deco, 2010). Top-down control of affective reward systems by cognition and by selective attention from the dorsolateral prefrontal cortex is also indicated. Medial PFC 10/VMPFC – ventromedial prefrontal cortex area 10; VPMpc – ventralposteromedial thalamic nucleus, the thalamic nucleus for taste.

Padoa-Schioppa and Conen, 2017; Rolls, 2019a, 2019c; Rolls et al., 2020a). For example, different macaque orbitofrontal cortex neurons represent primary (i.e. unlearned) reinforcers such as taste (Rolls et al., 1989b; Kadohisa et al., 2005; Rolls, 2015), secondary reinforcers such as the smell and sight of food which are learned by association with a primary reinforcer to represent *expected value* (Rolls et al., 1996; Rolls, 2015, 2016c), socially relevant stimuli such as face expression and face identity (Rolls et al., 2006), and non-reward (or non-reward prediction error), generated when an expected reward is not obtained (Thorpe et al., 1983).

The human lateral orbitofrontal cortex area 12 (Fig. 1) represents unpleasant, aversive stimuli (including unpleasant odours (Rolls et al., 2003b), painful touch (Rolls et al., 2003b), and losing or not winning money (O'Doherty et al., 2001; Rolls et al., 2020b; Xie et al., 2021)); and also non-reward, that is, not receiving an expected reward (Grabenhorst and Rolls, 2011; Rolls, 2019a, 2019c; Rolls et al., 2020a, 2020b; Xie et al., 2021). These regions are important in emotion because emotions are states elicited by reward, punishment, and non-reward (Rolls, 2013, 2014, 2018b). Consistent with these discoveries, damage to the orbitofrontal cortex/vmPFC impairs reward-related behaviour including a failure to respond to not receiving an expected reward, and major changes in subjective emotion and emotional behaviour (Rolls et al., 1994; Hornak et al., 2003, 2004; Berlin et al., 2004; Fellows, 2011; Rolls, 2019c, 2021d). In addition, the primate orbitofrontal cortex contains a population of neurons that respond to novel events (Rolls et al., 2005a), and there is complementary evidence for humans (Petrides, 2007). These neurons are likely to play a role in the influence of the orbitofrontal cortex via the cholinergic systems on memory that is described in Section 4.4.

The organisation of reward systems in the primate including human orbitofrontal cortex and its connected areas is summarised in Fig. 2, which shows how the taste, olfactory, visual, somatosensory and auditory inputs reach the orbitofrontal cortex; that before the orbitofrontal cortex is reached, 'what' the stimulus is but not its reward value is represented; that in the orbitofrontal cortex the reward or punishment value of stimuli is represented; and shows the outputs from the orbitofrontal cortex to different action and response systems (Rolls, 2019a, 2019c, 2021a; Rolls et al., 2020a). Value but not actions is represented in the primate orbitofrontal cortex (Thorpe et al., 1983; Padoa-Schioppa and Assad, 2006; Grattan and Glimcher, 2014; Padoa-Schioppa and Conen, 2017; Rolls, 2019a, 2019c). It is noted that this systems-level organisation is very different from that in rodents, in which reward value is mixed with sensory processing from early on in the taste and olfactory systems (Rolls, 2019c, 2021a); in which the visual system is poorly developed (Rolls, 2019c, 2021a); and in which behavioral responses as well as rewards are represented in the rat 'orbitofrontal cortex', though in fact the recordings may have been made in the agranular insular cortex (Wilson et al., 2014; Sharpe et al., 2015).

The human anterior cingulate cortex receives connectivity from the orbitofrontal cortex as shown below. The human pregenual anterior cingulate cortex (shown in Fig. 1a) is activated by many of the same types of reward that activate the medial orbitofrontal cortex, and the supracallosal anterior cingulate cortex by many of the same types of punisher and non-reward as activate the lateral orbitofrontal cortex (Grabenhorst and Rolls, 2011; Rolls et al., 2020b). The functions of the anterior cingulate cortex in value, emotion and action-outcome learning are considered in the context of its connectivity described below.

The 'ventromedial prefrontal cortex' (vmPFC) is a much less well-defined term anatomically, but has been used (Bechara et al., 1999; Mackey and Petrides, 2014; Schneider and Koenigs, 2017; McCormick et al., 2018) to refer to brain regions that probably include the pregenual anterior cingulate cortex and nearby area 10 regions shown in Fig. 1. Moving towards a more precise definition, regions in the Human Connectome Project Multimodal Parcellation (HCP-MMP) atlas (Glasser et al., 2016) that can be included in the vmPFC include 10v, 10r, 10d and 9m; with a broader definition used by some authors (Bonnici and Maguire, 2018; McCormick et al., 2018; Ciaramelli et al., 2019; De Luca et al., 2019) including also the subgenual cingulate cortex area 25 and the pregenual anterior cingulate cortex regions s32, a24, p24, p32, and d32, all of which are shown in Figs. 6–8 (Rolls et al., 2022f). (The HCP-MMP atlas (Glasser et al., 2016; Huang et al., 2022) is used for these definitions because it is based on cortical structure (myelin and cortical thickness), functional connectivity, and task-related fMRI investigations to identify the borders of each region, defining 180 cortical regions in each hemisphere; and because it is used for the new effective connectivity studies referred to in this paper (Rolls et al., 2022a, 2022b, 2022c, 2022d; Rolls et al., 2022e, 2022f, 2022g).) The ventromedial prefrontal cortex (vmPFC) is also involved in reward value and emotion, and may be especially involved in emotion-related decision-making, based on activations in it during reward-related decision-making (Rolls and Grabenhorst, 2008; Rolls et al., 2010a, 2010b; Grabenhorst and Rolls, 2011; Rolls, 2019c), and the effects of damage to it on decision-making (Hornak et al., 2004; Wheeler and Fellows, 2008; Fellows, 2011; Glascher et al., 2012).

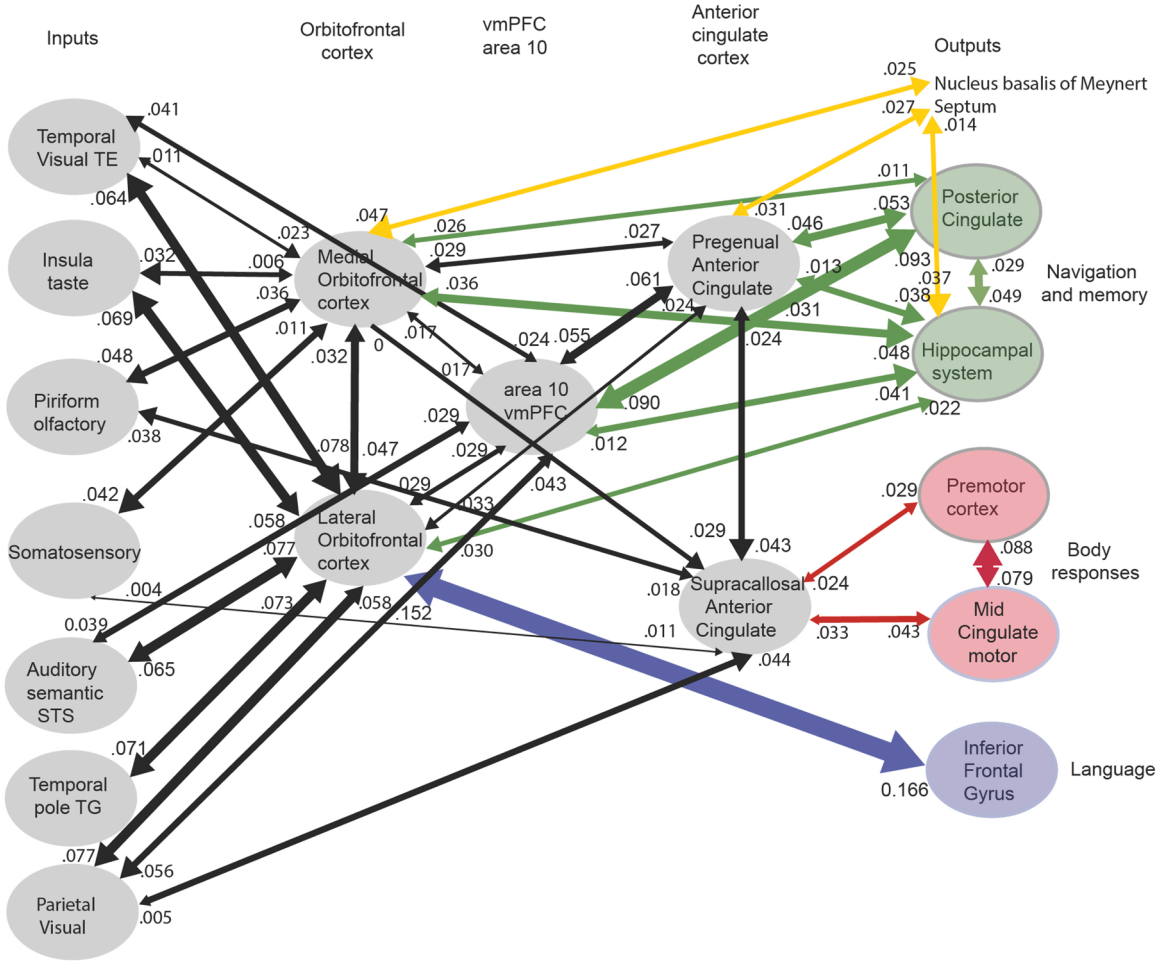

Fig. 3. Effective connectivity of the human orbitofrontal cortex, vmPFC, and anterior cingulate cortex shown in the middle, with inputs on the left and outputs on the right. The effective connectivity was measured in 171 participants imaged at 7 T by the Human Connectome Project, and was measured between the 360 cortical regions in the HCP-multimodal parcellation atlas (Glasser et al., 2016), with subcortical regions using the HCPex atlas (Huang et al., 2022). The effective connectivity measures the effect in each direction between every pair of cortical regions, uses time delays to assess the directionality using a Hopf computational model which integrates the dynamics of Stuart–Landau oscillators in each cortical region, has a maximal value of 0.2, and is described in detail elsewhere (Rolls et al., 2022b, 2022e, 2022f). The width of the arrows is proportional to the effective connectivity in the highest direction, and the size of the arrows reflects the strength of the effective connectivity in each direction. The effective connectivities shown by the numbers are for the strongest link where more than one link between regions applies for a group of brain regions. Effective connectivities with hippocampal memory system regions are shown in green; with premotor/mid-cingulate regions in red; with inferior prefrontal language system in blue; and in yellow to the basal forebrain nuclei of Meynert which contains cholinergic neurons that project to the neocortex and to the septal nuclei which contain cholinergic neurons that project to the hippocampus. The Somatosensory regions include 5 and parietal PF and PFop, which also connect to the pregenual anterior cingulate but are not shown for clarity; the Parietal regions include visual parietal regions 7, PGi and PFm. (From Rolls et al., 2022f) . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

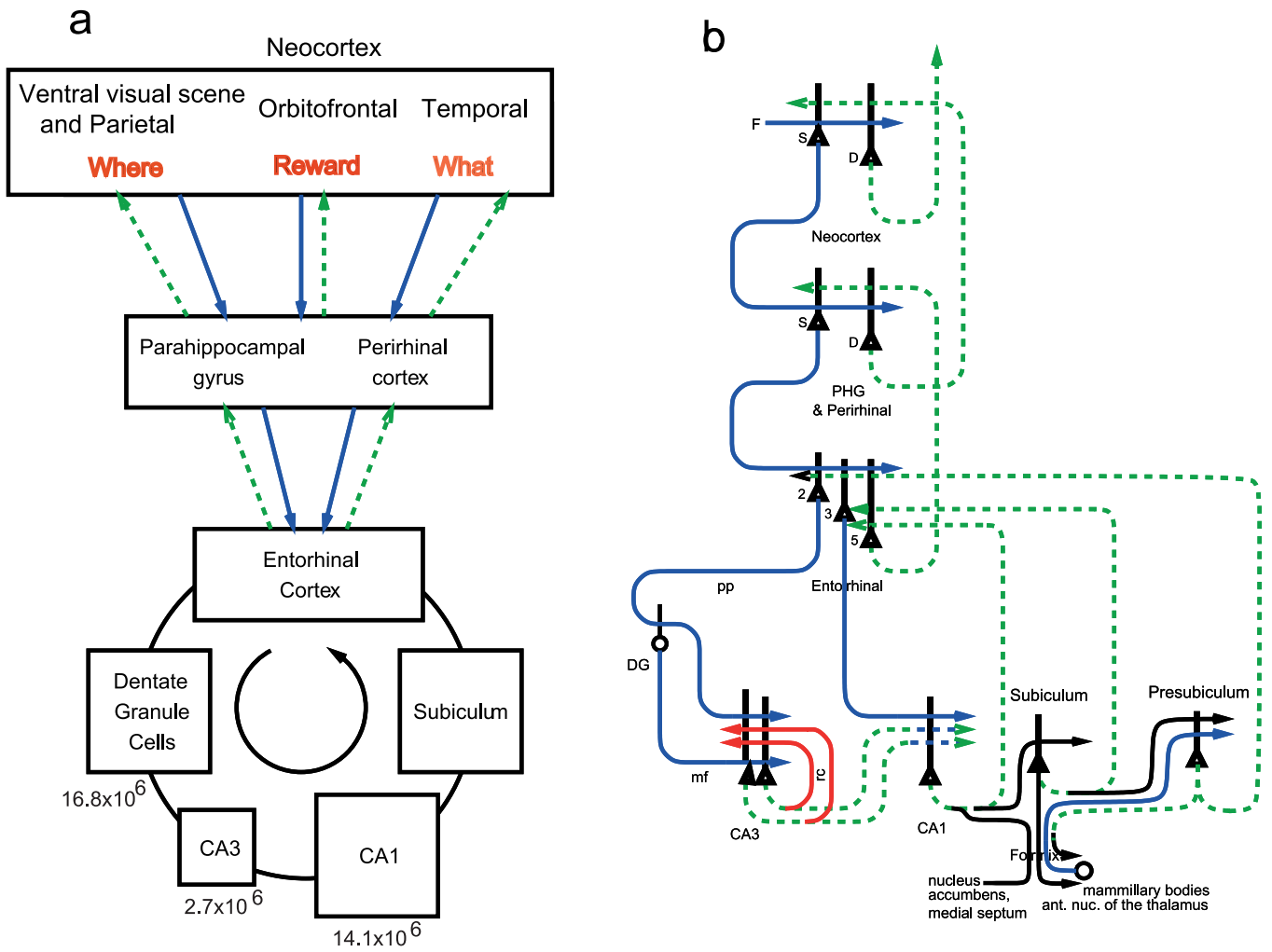

Fig. 4. The human/ primate hippocampus receives neocortical input connections (blue) not only from the 'what' temporal lobe and 'where' ventral visual scene and dorsal parietal systems, but also from the 'reward' prefrontal cortex areas (orbitofrontal cortex, vmPFC, and anterior cingulate cortex) for episodic memory storage; and has return backprojections (green) to the same neocortical areas for memory recall. There is great convergence via the parahippocampal gyrus, perirhinal cortex, and dentate gyrus in the forward connections down to the single network implemented in the CA3 pyramidal cells, which have a highly developed recurrent collateral system (red) to implement an attractor episodic memory by associating the what, where and reward components of an episodic memory. **a:** Block diagram. **b**: Some of the principal excitatory neurons and their connections in the pathways. Time and temporal order are also important in episodic memory, and may be computed in the entorhinal-hippocampal circuitry (Rolls and Mills, 2019). 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 numbers of neurons in different parts of the hippocampal trisynaptic circuit in humans (Rogers Flattery et al., 2020) are shown in (a), and indicate very many dentate granule cells, consistent with expansion encoding and the production of sparse uncorrelated representations prior to CA3 (Rolls, 2016b, 2021b). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. The vmPFC/anterior cingulate cortex system is also implicated in memory

Damage to the human vmPFC can impair memory, especially the ability to retrieve vivid autobiographical and episodic memories (Preston and Eichenbaum, 2013; Rosenbaum et al., 2014; Moscovitch et al., 2016; Gilboa and Marlatte, 2017; Barry et al., 2018; Bonnici and Maguire, 2018; McCormick et al., 2018). There is a reduced frequency of mind-wandering; and a reduced focus on future-oriented thoughts and an increased focus on present-related thought (McCormick et al., 2018; Ciaramelli and Treves, 2019). These patients have an inability to initiate internal reflections, including mental visualizations of extended events. In contrast, patients with hippocampal damage seem able to initiate mental events but they are devoid of visual representations of scenes (Bonnici and Maguire, 2018; McCormick et al., 2018). Hippocampal damage seems to particularly impair the spatial coherence of scenes, whereas vmPFC damage leads to a difficulty constructing scenes in a broader sense, with the prediction of what should be in a scene, and the monitoring or integration of the scene elements being particularly compromised (De Luca et al., 2018). Schemas can be defined as adaptable associative networks of knowledge extracted over multiple similar experiences (and are an important component of long-term semantic memory (van der Linden et al., 2017)), and patients with vmPFC damage appear to have problems in facilitating new encoding by memory schemas, with patients with confabulation (Rosenbaum et al., 2014) having difficulty in reinstating schemas (Ghosh and Gilboa, 2014; Ghosh et al., 2014). The vmPFC is also activated during the learning of new schemas (Gilboa and Marlatte, 2017). (In contrast with the vmPFC, the hippocampus is implicated more in single event memory in which details of the context are encoded (Moscovitch et al., 2016).).

Although the term vmPFC has been used to describe the region implicated in the memory deficits (Bonnici and Maguire, 2018;

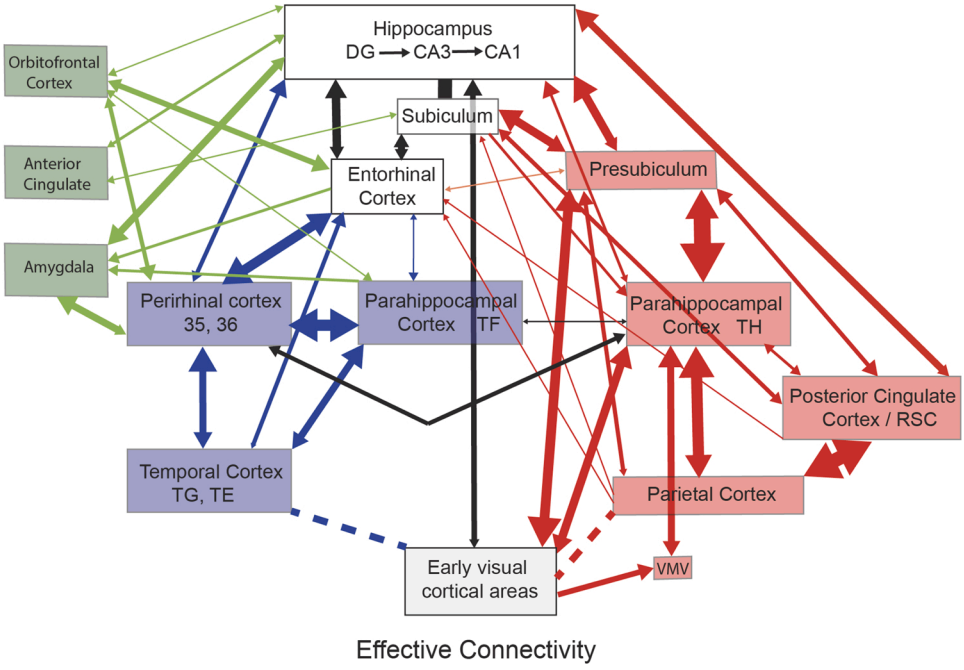

Fig. 5. Effective connectivity of the human hippocampal system with 360 cortical regions in the HCP-multimodal parcellation atlas (Glasser et al., 2016) measured in 172 Human Connectome Project participants at 7 T. The width of the arrows and the size of the arrowheads reflects the strength of the effective connectivity. For areas such as the temporal lobes, the parietal cortex, and the posterior cingulate cortex, there are several subregions in the HCP atlas, and the value of the strongest effectivity connectivity to or from any subarea is shown in this case. Brain regions that are part of the ventral 'what' stream are shown in blue, that are part of the dorsal 'where' or 'action' stream are shown in red, and that involve the orbitofrontal and anterior cingulate cortex reward value stream are in green. The Ventromedial Visual Areas (VMV) and TH include the parahippocampal place/scene area. The early visual areas referred to here include POS1 and ProS. Dashed lines indicate that there are several stages to the connectivity. The summary figure focusses on connectivity of hippocampal system brain regions, and does not show connectivity between other brain systems such as the orbitofrontal cortex and lateral temporal cortex TE and TG. (Modified from Rolls et al., 2022e). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

McCormick et al., 2018), this is not a very precise description, and in fact the overlap of the lesions that produce these problems is in the pregenual anterior cingulate cortex (De Luca et al., 2018), and it is activation in the pregenual and supragenual anterior cingulate cortex that precedes activation of the hippocampus during the recall of remote autobiographical memory (McCormick and Maguire, 2021).

4. The connectivity of the human orbitofrontal cortex, vmPFC, and anterior cingulate cortex, and implications for function in emotion, memory, and action

Given the evidence that the human anterior cingulate cortex and vmPFC are involved in value, reward and in addition in memory, recent evidence on the connectivity of these regions with each other and with the hippocampal memory system is now described, with a summary of the connectivity shown in Fig. 3 (Rolls et al., 2022f). The connectivity was measured in three complementary ways. First effective connectivity was measured, and this reflects the causal (i.e. time-related) effect between every pair of brain regions, and is measured in each direction separately, with the method described elsewhere (Rolls et al., 2022f; e). Second, functional connectivity was measured by the Pearson correlation between the BOLD signal of different brain regions, and this is less selective than effective connectivity in that it can reflect indirect effects such as common input, and does not measure the direction of what reflects interactions between brain regions. Third, the direct connections were measured using diffusion tractography, and this does not provide evidence about the direction of connections. Features of the new evidence (Rolls et al., 2022f; e) are that it was obtained using a large number of Human Connectome Project participants, and the Human Connectome Project Multimodal Parcellation of the cortex which contains 360 cortical regions defined by anatomical characteristics, functional connectivity, and task-related activations (Glasser et al., 2016), to which 66 subcortical areas have been added (Huang et al., 2022).

4.1. Inputs to the orbitofrontal cortex for reward value computation

First, it is shown in Figs. 2 and 3 that the human medial and lateral orbitofrontal cortex between them (and they have effective connectivity with each other) receive taste, somatosensory, olfactory, visual, and auditory inputs that are needed to build the reward and punishment value representations that are found in these regions but much less in the preceding cortical areas that provide these inputs (Rolls, 2016a, 2019a, 2019c, 2021a). Taste and somatosensory inputs provide information about primary reinforcers or outcome value, and the primate orbitofrontal cortex contains visual and olfactory neurons that can learn and reverse in one trial the associations with primary reinforcers and so represent expected value (Thorpe et al., 1983; Rolls et al., 1996), and do represent reward value as shown by experiments in which the reward is devalued by feeding to satiety (Critchley and Rolls, 1996). These neurons also reflect the economic value of the rewards (Padoa-Schioppa and Conen, 2017), and do not reflect actions or behavioural responses (Thorpe et al., 1983; Padoa-Schioppa and Assad, 2006; Grattan and Glimcher, 2014; Rolls, 2019c). This connectivity provides the inputs required by the human orbitofrontal cortex to compute reward value, non-reward, and punishment, and thereby to be fundamental in human emotion (Rolls, 2014, 2019a, 2019c, 2021a).

4.2. Reward value outputs from the orbitofrontal and pregenual anterior cortex, and vmPFC, to the hippocampal memory system

Second, it is indicated in green in Figs. 3 and 8 (Rolls et al., 2022f) that the human medial and lateral orbitofrontal cortex have effective connectivity directed to the hippocampal system (hippocampus, entorhinal cortex, perirhinal cortex) both directly, and via the parts of area 10 in the vmPFC, via the pregenual anterior cingulate cortex, and via the memory-related (posterior) parts of the posterior cingulate cortex (Rolls et al., 2022g). These are the routes by which value/emotion related information can reach the human hippocampal memory system from the orbitofrontal cortex. The information does reach the hippocampus and is incorporated into memory in that some primate hippocampal spatial

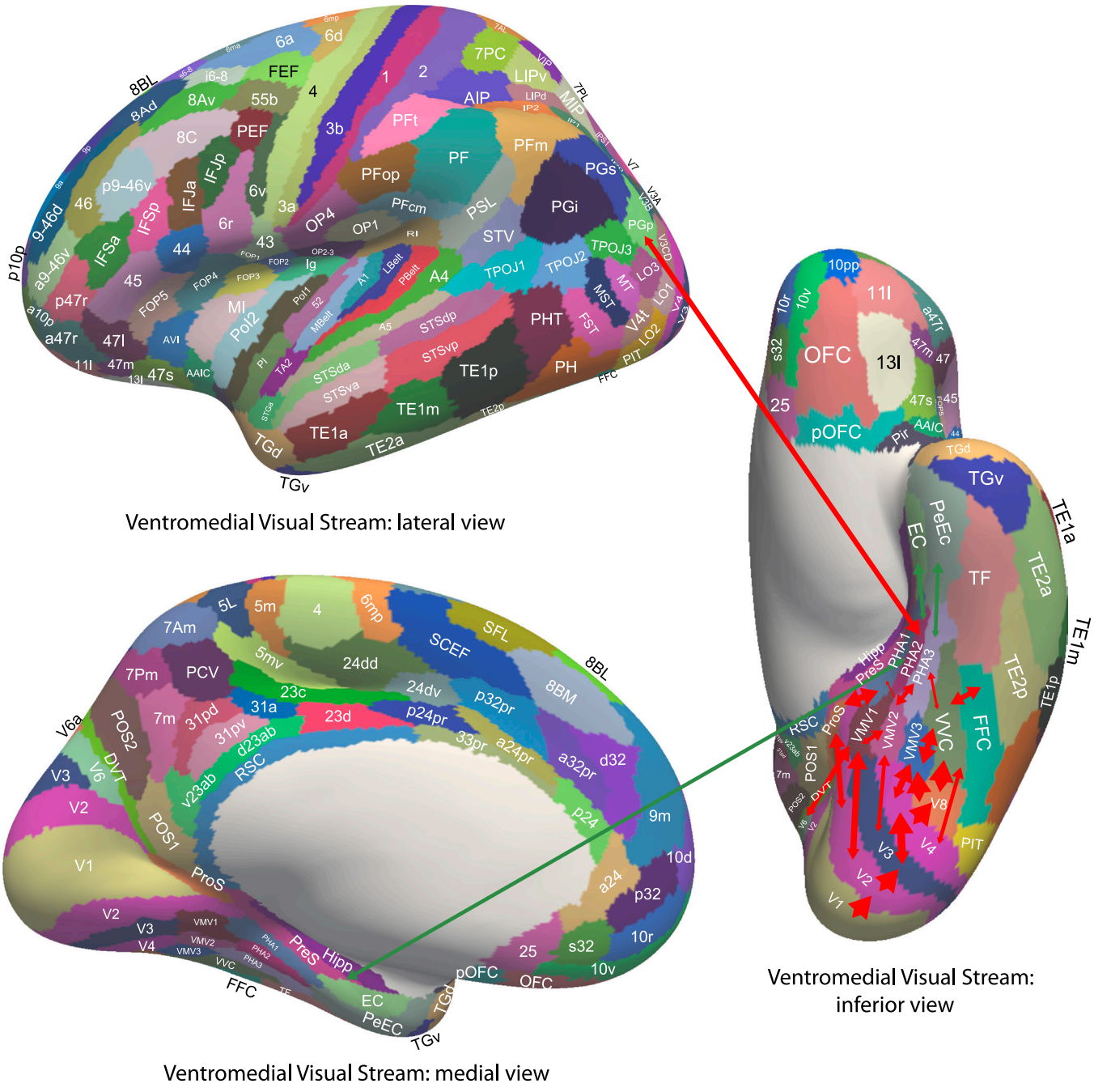

Fig. 6. Effective connectivity of the human Ventromedial Visual Stream which reaches the parahippocampal gyrus PHA1 – PHA3 regions via ventromedial (VMV) and Ventral Visual Complex (VVC) and ProStriate regions: schematic overview. Visual scenes are represented in the anterior parts of VMV and the posterior parts of PHA1 – PHA3 in what is the Parahippocampal Scene Area PSA (sometimes called the Parahippocampal Place Area, PPA). The green arrows show how the Ventromedial Visual Stream provides 'where' input about locations in scenes to the hippocampal memory system from the parahippocampal gyrus PHA1- PHA3 regions (which correspond to TH in macaques). The connectivity from PGp to PHA regions is suggested in the text to be involved in idiothetic update of locations in scenes. The widths of the lines and the size of the arrowheads indicate the magnitude and direction of the effective connectivity. After Rolls et al. (2022d). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

view cells (Rolls et al., 1997a; Robertson et al., 1998; Rolls et al., 1998; Georges-François et al., 1999; Rolls et al., 2005b; Wirth et al., 2017; Rolls and Wirth, 2018; Rolls, 2021a, 2021e, 2022) respond to the reward value of a location viewed in space in a reward-spatial location memory task (Rolls and Xiang, 2005, 2006).

A considerable part of the output of the human medial and lateral orbitofrontal cortex value/emotion system is thus directed towards the hippocampal system for memory (Figs. 3 and 8 (Rolls et al., 2022f)). It is proposed that this connectivity provides a key input about reward/punishment value for the hippocampal episodic memory system, adding to the 'what', 'where', and 'when' information that are also key components of episodic memory. Damage to the vmPFC/anterior cingulate cortex system is likely to contribute to episodic memory impairments produced by damage to these OFC/ vmPFC/ACC regions by impairing a key component of episodic memory, the reward/punishment/emotional value component. Such damage would impair the value information reaching the hippocampal system for storage, and also for later retrieval. Indeed, if one of the possible inputs such as the

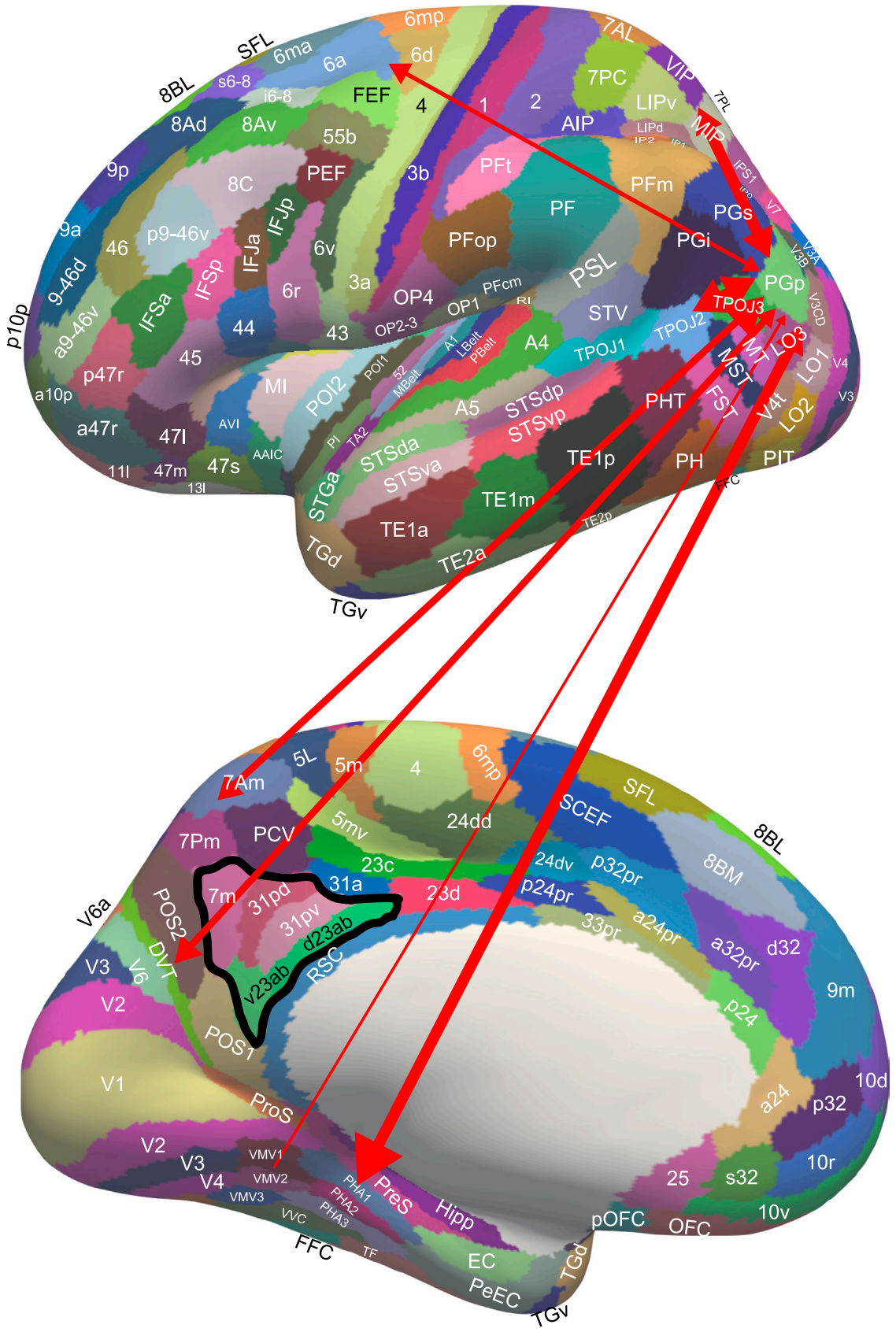

Fig. 7. Effective connectivity of human region PGp. The widths of the lines and the size of the arrowheads indicate the magnitude and direction of the effective connectivity, which are shown in Table S2. PGp has effective connectivity from area 7 and intraparietal regions, and has effective connectivity directed to parahippocampal TH (PHA1–3). It is proposed that this provides a route for visuo-spatial parietal cortex regions involved in spatial coordinate transforms to provide the hippocampal system with information useful in the idiothetic (self-motion) update of hippocampal spatial representations of allocentric space. Consistent with this, PGp also receives from visual scene-related areas DVT and ventromedial visual cortex (VMV2). After Rolls et al. (2022a).

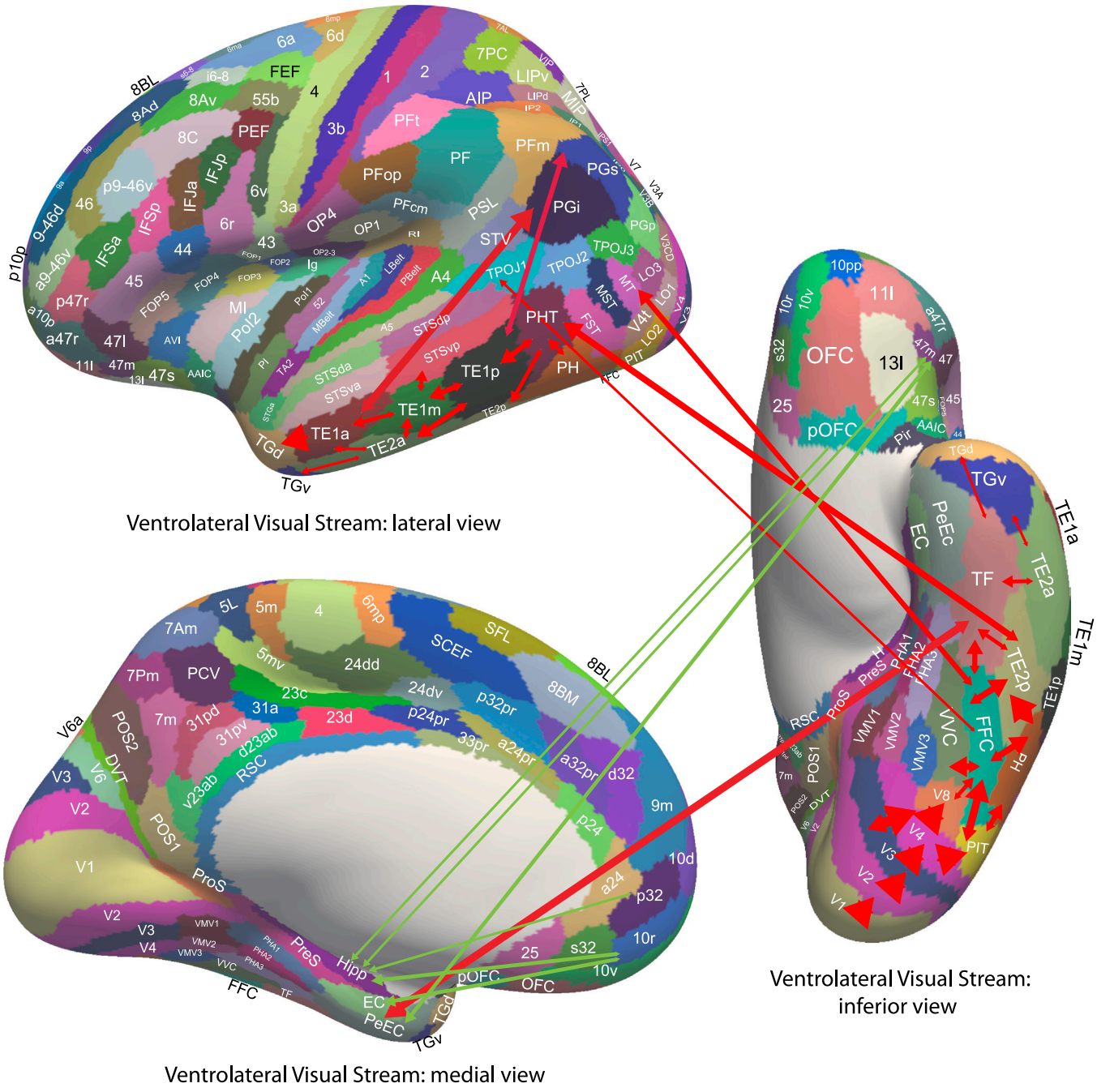

Fig. 8. Effective connectivity of the human Ventrolateral Visual Stream which reaches inferior temporal cortex TE regions in which objects and faces are represented (red arrows): schematic overview. One of the red arrows shows how the Ventrolateral Visual Stream provides 'what' input to the hippocampal memory system via parahippocampal gyrus TF to perirhinal PeEc connectivity from FFC, PH, TE1p, TE2a and TE2p. The green arrows show how reward regions of the orbitofrontal cortex, vmPFC (pOFC, 10r, 10v) and pregenual anterior cingulate (a24 and p32), and punishment/non-reward regions of the lateral orbitofrontal cortex (47m) have effective connectivity with the hippocampus (Hipp), entorhinal cortex (EC), and perirhinal cortex (PeEC). The Ventrolateral Visual Stream also provides input to the semantic language system via TGd and STSvp (Rolls et al., 2022b). The Ventrolateral Visual Stream also has connectivity to the inferior parietal visual area PFm, PGs and PGi as indicated by 2 green arrows. The widths of the lines and the size of the arrowheads indicate the magnitude and direction of the effective connectivity. After Rolls et al. (2022d). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reward input used for hippocampal memory retrieval by completion in the CA3 attractor network was missing, that would be expected to impair memory retrieval (Treves and Rolls, 1991, 1994; Rolls, 2018a, 2021a).

4.3. Reward value outputs from the orbitofrontal and pregenual anterior cortex, and vmPFC, to the hippocampal system to provide the goals for navigation

The hippocampus is also implicated in navigation (O'Keefe and Nadel, 1978; Burgess and O'Keefe, 1996; McNaughton et al., 2006; Miller et al., 2013; Ekstrom et al., 2014; Ekstrom and Isham, 2017; Bellmund et al., 2018; Nau et al., 2018; Rolls and Wirth, 2018; Clark

et al., 2019; Tsitsiklis et al., 2020; Rolls, 2021e). It is proposed that the reward value input from the orbitofrontal/vmPFC/pregenual anterior cortex to the hippocampal and memory-related posterior cingulate cortex (green in Figs. 3 and 8 (Rolls et al., 2022f)) provides important connectivity also required for navigation, and indeed it is a key feature of navigation that it is generally towards goals, usually rewards (Rolls et al., 2022f). Supporting this, neurons in the primate hippocampus encode the locations in viewed scenes at which rewards are located (Rolls and Xiang, 2005), including the goals for navigation (Wirth et al., 2017; Rolls and Wirth, 2018). The information transmitted from the orbitofrontal cortex is about which particular of many possible rewards represented in the orbitofrontal cortex (Rolls, 2014, 2016c, 2019a, 2019c) is the current goal for navigation, so is a high-dimensional vector. The navigation in humans and other primates is proposed to frequently involve navigation from viewed landmark to viewed landmark using spatial view cells (Rolls, 2021e). This is in contrast to what is frequently proposed to be used in rodents, which is path integration from place to place performed by the hippocampus (Burgess and O'Keefe, 1996; McNaughton et al., 1996; Hartley et al., 2014; Edvardsen et al., 2020). Humans might wish to try some navigation themselves with the eyes closed to help to confirm the greatly utility of landmarks in views of spatial scenes in navigation in humans, which are what are encoded by hippocampal and parahippocampal spatial view cells (Rolls, 2022 (in revision)).

4.4. Connectivity of the orbitofrontal cortex to the basal nucleus of Meynert and of the anterior cingulate cortex to the septal nuclei for cholinergic memory consolidation

The medial orbitofrontal cortex (pOFC region) is the only cortical region in humans found to have effective connectivity directed to the basal forebrain magnocellular nucleus of Meynert (yellow in Fig. 3 (Rolls et al., 2022f)), which contains cholinergic neurons that project to the neocortex in humans (Mesulam, 1990; Zaborszky et al., 2008, 2018). The human pregenual anterior cingulate cortex (with subgenual 25 and 10r) in humans has effective connectivity directed to the septal nuclei (yellow in Fig. 3 (Rolls et al., 2022f)), which contains cholinergic neurons that project to the hippocampus in humans (Mesulam, 1990; Zaborszky et al., 2008, 2018). These pregenual anterior cingulate regions are likely to be important influences on septal neurons, for the only other cortical regions found with substantial effective connectivity to the human septal region (Rolls et al., 2022f) are the hippocampus, subiculum, and v23ab which is part of the posterior cingulate cortex also implicated in episodic memory (Rolls et al., 2022g). In accordance with this, it is proposed that the damage in humans to the orbitofrontal and anterior cingulate cortex regions that impairs episodic memory (McCormick et al., 2018; Ciaramelli et al., 2019) arises in part because of the reduced release of acetylcholine to reward/punishing/salient stimuli, which may impair long-term synaptic potentiation and thus memory storage in both the hippocampus and neocortex (Hasselmo and Giocomo, 2006; Giocomo and Hasselmo, 2007; Hasselmo and Sarter, 2011; Newman et al., 2012; Zaborszky et al., 2018; Rolls, 2021a).

Indeed, it is known that different magnocellular neurons in the basal nucleus which are probably cholinergic respond to reinforcing (rewarding, or punishing), or novel, stimuli (Wilson and Rolls, 1990a, 1990b, 1990c), all represented in the orbitofrontal cortex (Rolls et al., 2005a; Rolls, 2019a, 1990c). Cholinergic activation by these types of 'salient' stimuli can be utilised to enhance memory storage when these rewarding, punishing, or novel stimuli are encountered, which is evolutionarily adaptive by facilitating memory storage when rewarding, punishing, or novel environmental situations are encountered (Rolls and Deco, 2015; Rolls, 2021a).

In terms of the different effects of vmPFC and hippocampal damage on mind-wandering (McCormick et al., 2018; Ciaramelli and Treves, 2019), it is to be expected that damage to the orbitofrontal cortex region will impair neocortically mediated effects because the pOFC region has effective connectivity to the nucleus basalis which in turns connects to neocortical regions where it influences cortical excitability, learning, and thereby semantic memory consolidation (Fig. 3) (Rolls et al., 2022f). vmPFC lesions that influence the cholinergic nucleus basalis to neocortex system would thus be expected to impair long-term memory consolidation and remote memory including the use and development of schemata. The view proposed here is therefore that there is not a major memory system/network in the vmPFC that processes schemata, but that instead the vmPFC can modulate the use and generation of such schemata because of alteration of neocortical function produced by altering the nucleus basalis input to the neocortex. The normal function of this pOFC to nucleus basalis system is proposed, based on the above evidence, to release acetyl choline into the neocortex to facilitate its storage and processing functions when rewarding, punishing, or novel stimuli are encountered, which are important times when consolidation of memory in the neocortex may be useful, to facilitate the memory and semantic processing about those events. In contrast, as expected, damage to the hippocampus impairs mind-wandering about events in 'recent' memory (in the order of the last 6 months) (McCormick et al., 2018; Ciaramelli and Treves, 2019), and if vmPFC damage extends to the pregenual anterior cingulate cortex this hippocampal episodic memory system may also be impaired, because the pregenual anterior cingulate cortex has effective connectivity to the cholinergic septal region, as does the hippocampus, and this system is expected to in a comparable way modulate when the hippocampus stores episodic memory (Fig. 3) (Rolls et al., 2022f).

There are thus three memory-related influences of the orbitofrontal and pregenual anterior cingulate cortex uncovered by the effective connectivity in humans: (1) reward as a component of hippocampal episodic memory, and cholinergic influences both on (2) the neocortex and (3) on the hippocampus driven by the orbitofrontal and pregenual anterior cingulate cortex (Rolls et al., 2022f). Together, these three processes are it is proposed likely to make major contributions to the memory deficits reported to follow ventromedial prefrontal cortex damage in humans (Bonnici and Maguire, 2018; McCormick et al., 2018, 2020; Ciaramelli et al., 2019; Ciaramelli and Treves, 2019; McCormick and Maguire, 2021). Although it has been suggested that scene processing types of computation are affected by ventromedial prefrontal cortex damage (De Luca et al., 2019), this might be expected given that the hippocampus with its spatial view neurons (Rolls et al., 1997a; Robertson et al., 1998; Georges-François et al., 1999; Rolls and Xiang, 2005; Rolls et al., 2005b; Rolls and Xiang, 2006; Wirth et al., 2017; Rolls and Wirth, 2018; Tsitsiklis et al., 2020; Rolls, 2022) is involved in scene processing (Rolls, 2021e), and that the cholinergic influence on the hippocampus is likely to be very important in hippocampal functioning including memory storage because acetylcholine facilitates synaptic long-term potentiation and reduces during that time the relative efficacy of the CA3 recurrent collateral synapses to help emphasise new rather than existing memories (Hasselmo and Giocomo, 2006; Giocomo and Hasselmo, 2007; Hasselmo and Sarter, 2011; Newman et al., 2012; Zaborszky et al., 2018; Rolls, 2021a).

4.5. Connectivity of the supracallosal anterior cingulate cortex from the orbitofrontal cortex and with somato-premotor cortical systems implicates it in action-outcome learning

It has further been found that the human supracallosal anterior cingulate cortex, which is activated by aversive stimuli and non-reward (Rolls and Grabenhorst, 2008; Grabenhorst and Rolls, 2011; Rolls et al., 2020b), has effective connectivity with somatosensory and premotor cortical areas including the midcingulate premotor cortex (red in Fig. 3 (Rolls et al., 2022f), consistent with earlier evidence (Vogt, 2009, 2016)). It also has effective connectivity with the medial orbitofrontal cortex and pregenual anterior cingulate cortex (Fig. 3 (Rolls et al., 2022f)). In the context that the anterior cingulate cortex is implicated in learning associations between actions and the rewards or punishers

associated with the actions (Noonan et al., 2011; Rushworth et al., 2012; Rolls, 2019b), it has been proposed that the part of the anterior cingulate cortex that is most likely to be involved in action-outcome learning is the supracallosal anterior cingulate cortex, given its strong effective connectivity with somato-motor areas involved in actions, and its inputs from the medial orbitofrontal cortex and pregenual anterior cingulate cortex that it is proposed provide the reward/punishment 'outcome' signals necessary for action-outcome learning (Rolls et al., 2022f). Consistent with this, the 'dorsal anterior cingulate cortex' in humans is implicated in reward-guided actions (Scholl et al., 2017).

It is very interesting to see that in humans the different parts of the anterior cingulate cortex have different connectivity and functionality, as shown in Fig. 3 (Rolls et al., 2022f). The pregenual anterior cingulate cortex which is mainly reward-related has outputs directed to the hippocampal system where value information can be stored as part of episodic memories and can provide the goals for navigation. In contrast, the punishment/non-reward related supracallosal anterior cingulate cortex has somato-premotor connectivity though also receives orbitofrontal cortex value information, which can guide actions as in action-outcome learning, but which may also be useful in limb and body movements to avoid or withdraw from aversive stimuli.

5. Human hippocampal system circuitry for episodic memory: 'what', 'where', 'when', and reward value

New evidence on the connectivity of the human hippocampus (Huang et al., 2021; Ma et al., 2022; Rolls et al., 2022d, 2022e) and how it relates to the orbitofrontal and anterior cingulate cortex reward/punishment/emotion system and the amygdala (Rolls et al., 2022f) helps to elucidate how the human hippocampus operates in the storage and recall of episodic memory, as described next.

5.1. Hippocampal system circuitry for the storage of episodic memory: 'what', 'where', 'when', and reward value

The architecture of the primate including human hippocampal episodic memory system is shown in Fig. 4, with some important new additions described next. The classic view is that spatial or 'where' representations from the parietal cortex, and object and face or 'what' representations from the temporal cortex, are brought together in a single network formed by the CA3 cells in the hippocampus (Rolls, 1989, 2016a; Rolls and Treves, 1994; Treves and Rolls, 1994, 2018a, 2021a). This enables any 'what' and any 'where' representation to be associated together in the CA3 network. The association is implemented by the highly developed recurrent collateral CA3 connections that run throughout the hippocampus (Kondo et al., 2009) and form an autoassociation or attractor network (Rolls and Treves, 1994; Treves and Rolls, 1994; Kesner and Rolls, 2015; Rolls, 2018a, 2021a). This enables arbitrary associations to be formed for episodic memory of what happened where at a particular time when the synapses were associatively modified to form the 'what' – 'where' episodic memory. At least part of the time and temporal order information needed for the 'when' component of episodic memory may be computed in the entorhinal-hippocampal circuitry using competitive learning (Rolls and Mills, 2019) to convert slow temporal changes in the firing rate of neurons in the lateral entorhinal cortex (Tsao et al., 2018) into time cells in the hippocampus (Kraus et al., 2013; Eichenbaum, 2017; Sugar and Moser, 2019).

Adding now to this classic 'standard' view, Figs. 4 and 8 emphasize that the human hippocampal system also receives inputs about reward (and punishment) value from the orbitofrontal cortex/vmPFC/anterior cingulate cortex, which enable the reward value/emotional components also to be part of an episodic memory. Consistent with this, reward value is important in memory in humans, with better hippocampal system memory if rewards are involved and if reward sensitivity is high (Frank et al., 2019); and with the human ventrolateral prefrontal (inferior prefrontal) cortex implicated in selecting goal-relevant information in working memory (Blumenfeld and Ranganath, 2019; Rolls et al., 2022c). Similarly, rewards can facilitate spatial learning in the rodent hippocampus (Michon et al., 2021), and there is evidence that the anterior hippocampus (ventral in rodents) is more involved in reward/salience encoding, and the posterior (dorsal in rodents) is more involved in spatial coding (Preston and Eichenbaum, 2013; Moscovitch et al., 2016). It is very adaptive to be able to remember where we have seen different types of reward in the environment, so that we can find them in future.

The effective connectivity of the hippocampal system in humans (Fig. 5 (Rolls et al., 2022e), complemented by functional connectivity (Ma et al., 2022) and diffusion tractography (Huang et al., 2021)) shows how the hippocampus has widespread connectivity with visual system areas involved in 'where' representations (red in Fig. 5, including the ventral visual stream parahippocampal cortex scene area shown in Fig. 6 (Rolls et al., 2022d) and the dorsal visual stream parietal cortex stream shown in Fig. 7 (Rolls et al., 2022d)); and ventral visual stream areas involved in 'what' (object and face) representations shown in Fig. 8 (Rolls et al., 2022d) (blue in Fig. 5, including the anterior temporal, perirhinal and parahippocampal TF). The human parahippocampal TH regions include visual scene areas such as the parahippocampal place (or scene) area (Epstein and Kanwisher, 1998; Kamps et al., 2016; Sulpizio et al., 2020; Natu et al., 2021), and in primates contains spatial view cells that provide a route to hippocampal spatial view cells that encode locations in viewed scenes (Rolls et al., 1997a; Robertson et al., 1998; Georges-François et al., 1999; Rolls and Xiang, 2005; Rolls et al., 2005b; Rolls and Xiang, 2006; Rolls and Wirth, 2018; Rolls, 2022). In humans, the (more lateral and anterior) TF parahippocampal area is connected with the ventral temporal lobe 'what' system that provides inputs to the hippocampal system (blue in Fig. 5 (Rolls et al., 2022e) and see also Fig. 8 (Rolls et al., 2022d)).

Fig. 5 summarizes the orbitofrontal and anterior cingulate effective connectivity bringing value information to the hippocampus, but also shows the effective connectivity with the amygdala, which is directed more strongly away from the hippocampus to the amygdala, rather than the reverse which is typical of the neocortical regions. Further, it is notable that the human amygdala has rather limited effective connectivity with the orbitofrontal and anterior cingulate cortex regions, with effective connectivity of the amygdala detected only with lateral orbitofrontal cortex region 47m (Rolls et al., 2022f). This may relate to the greater importance of the orbitofrontal cortex than the amygdala in emotion including subjective emotion in humans, as shown by for example the effects of brain damage to the orbitofrontal cortex (Rolls et al., 1994; Hornak et al., 2003, 2004; Berlin et al., 2004; Rolls, 2019c) vs amygdala for which the effects appear to be much less profound in humans (Whalen and Phelps, 2009; LeDoux, 2012; LeDoux et al., 2018; Rolls, 2021d; Taschereau-Dumouchel et al., 2022). It is also of interest that the amygdala effective connectivity in humans is with the lateral orbitofrontal cortex, for both are especially involved in behaviours made to aversive stimuli (Rolls, 2014, 2019c; LeDoux and Daw, 2018).

New investigations on visual pathways in the human brain (Rolls et al., 2022d) facilitated by the use of the Human Connectome Project multimodal parcellation atlas (Glasser et al., 2016) and the analysis of effective (i.e. directed, causal) connectivity lead to some further new concepts. There is a 'ventromedial visual pathway' that leads from V1 > V2 > V4 to a set of ventromedial visual regions VMV1–3 which then connect to PHA1–3, which is the medial parahippocampal gyrus, corresponding to macaque TH (Fig. 6). The human parahippocampal place area (PPA) (Epstein and Kanwisher, 1998; Epstein, 2005, 2008; Epstein and Julian, 2013; Kamps et al., 2016; Epstein and Baker, 2019; Sulpizio et al., 2020; Natu et al., 2021) is found in PHA1–3 where is adjoins VMV1–3 (Sulpizio et al., 2020). (Use of the description 'scene areas', e.g. PSA or Parahippocampal Scene Area instead of PPA for 'parahippocampal place area' is preferred for this area, because macaque parahippocampal spatial view cells respond to viewed locations in scenes, not to the place where the individual is located (Robertson et al., 1998; Rolls et al., 1998; Georges-François et al., 1999; Rolls, 2022), and

the human neuroimaging evidence just cited is consistent with scene responsiveness, not the place where the participant being imaged is located.) It is proposed that scene representations are built using combinations of ventral visual stream features that when overlapping in space are locked together by associative learning and can form a continuous attractor network to encode a visual scene (Rolls and Stringer, 2005; Stringer et al., 2005; Rolls et al., 2008, 2022a) using spatial view cells (Rolls et al., 1997a; Robertson et al., 1998; Rolls et al., 1998; Georges-François et al., 1999; Wirth et al., 2017; Rolls and Wirth, 2018; Tsitsiklis et al., 2020; Rolls, 2022) in the parahippocampal scene (or place) area referred to above, which in turn connects to the hippocampus to provide the 'where' component of episodic memory (Rolls et al., 2022e). The green arrow in Fig. 6 shows how the Ventromedial Visual Stream provides 'where' input about locations in scenes to the hippocampal memory system from the parahippocampal gyrus PHA1-PHA3 regions. A new concept is that the ventromedial visual pathway, a ventral visual stream pathway encoding combinations of visual features, is thus a key system in humans for providing 'where' representations for the hippocampal memory system (Rolls et al., 2022d).

There is however effective connectivity from parietal cortex regions to the parahippocampal scene area, as illustrated in Figs. 6 and 7. Strong effective connectivity is directed from inferior parietal region PGp to the parahippocampal scene area (PSA) in PHA1–3 (Figs. 6 and 7) (Rolls et al., 2022a). PGp receives its inputs from parietal area 7 regions and intraparietal regions (Rolls et al., 2022a) involved in visual motion analysis and in coordinate transforms from retinal to head-based and then to world-based (allocentric) coordinates (Snyder et al., 1998; Salinas and Sejnowski, 2001; Rolls, 2020a). These coordinate transforms are fundamental for self-motion update of scene representations, so that the spatial view neurons in the parahippocampal scene area can represent where in a scene the individual is looking independently of eye position, head direction, and even the place of the head in the environment, when the view details are obscured or in the dark (Robertson et al., 1998; Rolls, 2020a, 2022). Given these two lines of evidence, it is proposed that the parietal cortex has the role of idiothetic update of the scene representations in the PSA and thereby in the hippocampus (Rolls et al., 2022a, 2022d). Thus the hypothesis is that the 'where' scene representations in the human ventromedial visual stream are built by combinations of ventral stream spatial features, and the viewed position in the scene is updated by coordinate transforms to the allocentric level of scenes (Rolls, 2020a) by the parietal cortex inputs to the PSA (Rolls et al., 2022a, 2022d).

It is emphasized in this approach that the 'path integration' that is required for idiothetic update in humans and other primates involves eye position as well head direction etc and takes place in the dorsal visual system regions in the cortex in the intraparietal sulcus and area 7 (Rolls, 2020a). A real problem with hypothesizing that path integration of any type occurs within the hippocampus is that the energy landscape of any continuous attractor representation of place or spatial view in the hippocampus that utilised idiothetic update (Stringer et al., 2002, 2005; Rolls and Stringer, 2005) would be so distorted by association with the 'what' and reward information used for episodic memory that it would be very poor at path integration, as the energy landscape would be too bumpy because of the associations (cf. Spalla et al., 2021).

To add to the recently developing understanding of human hippocampal system inputs, Fig. 8 shows the ventrolateral visual stream in humans progressing via V1 > V2 > V4 > FFC (which contains representations of faces, objects and even words in the visual word form area laterally) > the anterior temporal lobe TE regions where invariant representations of objects are faces are built (Rolls et al., 2022d). This pathway provides 'what' inputs to the hippocampal memory system via parahippocampal area TF, which is lateral and anterior to the parahippocampal scene area in PHA1–3 (Fig. 8) (Rolls et al., 2022d). Fig. 8 also illustrates some of the reward-related inputs to the hippocampal system with green arrows. In more detail, key discoveries about this ventrolateral visual system leading to the anterior inferior temporal visual cortex (IT) are that IT neurons code for objects and not their reward value (Rolls et al., 1977); that some neurons code for faces (Perrett et al., 1979, 1982); that IT neurons use sparse distributed encoding for face identity (Baylis et al., 1985; Rolls et al., 1997c) with relatively independent information provided by populations of neurons (Rolls et al., 1997b; Treves et al., 1999; Rolls and Treves, 2011); that feature combinations in the correct spatial position encode faces and objects (Perrett et al., 1982; Desimone et al., 1984); and that IT neurons have representations of objects that are invariant with respect to transforms including retinal position (Gross et al., 1985; Tovee et al., 1994), size and contrast (Rolls and Baylis, 1986), spatial frequency (Rolls et al., 1985) and in some cases to view (Hasselmo et al., 1989; Booth and Rolls, 1998). For natural vision, in complex natural scenes IT neurons respond primarily to the object being fixated (Sheinberg and Logothetis, 2001; Rolls et al., 2003a; Aggelopoulos and Rolls, 2005) by reducing their receptive field size (Rolls et al., 2003a) which simplifies the interpretation of the output of IT (Rolls, 2021a) by structures such as the orbitofrontal cortex which implements object-reward association learning (Thorpe et al., 1983; Rolls et al., 1996) and the hippocampal system which implements object-scene location learning (Rolls et al., 2005b). The 'what' information to the hippocampal memory system (via TF and in some cases perirhinal or entorhinal cortex) is tapped from this ventrolateral object/face visual stream from the FFC, PH, PHT, TE2p, TE1p, TE2a and TGd to the hippocampal system (Rolls et al., 2022d). Moreover, it was discovered that IT neurons can learn rapidly to represent new objects without disturbing representations of previously learned objects (Rolls et al., 1989a). Results consistent with these discoveries and principles of operation have been reported (Freiwald et al., 2009; Rust and DiCarlo, 2010; Tsao, 2014; Freedman, 2015; Aparicio et al., 2016; Freiwald, 2020; Arcaro and Livingstone, 2021).

5.2. *Hippocampal system circuitry for the recall of episodic memory back to the neocortex: 'what', 'where', 'when', and reward value*

How the hippocampal system illustrated in Fig. 4 operates computationally during learning to associate together reward as well as 'what' and 'where' information in the CA3 network and later recall the information back to the neocortical regions has been developed into a quantitative analytic theory (Treves and Rolls, 1992, 1994; Kesner and Rolls, 2015; Rolls, 2016b, 2018a, 2021a, 2021b). To this we can now add reward value/emotional representations in the orbitofrontal and anterior cingulate cortex and vmPFC, given what is shown in Figs. 4, 5 and 8 (Rolls et al., 2022f). Once information is recalled back from the hippocampal episodic memory system to the neocortex, the recalled information may be used to help build new neocortical semantic representations in the ways considered below. But first the recall process itself from the hippocampus to the neocortex is described.

The theory and model of the recall of information from the hippocampus to the neocortex uses the backprojection pathways (Van Hoesen, 1982; Lavenex and Amaral, 2000) shown in green in Fig. 4 (Rolls, 1989, 2018a; Rolls and Treves, 1994; Treves and Rolls, 1994). The concepts are that during the learning of an episodic memory, the forward inputs to the hippocampus lead to learning between CA3 neurons disjunctive for object and place and reward (Rolls, 2021a, 2021b); that CA1 uses competitive learning to recode into representations that may be conjunctive and thus useful for recall (Rolls, 2021b); and that neurons are then activated at each stage in the backprojection paths until the neocortical neurons are reached by the backprojections (Rolls and Treves, 1994; Treves and Rolls, 1994; Rolls, 2018a, 2021a; b). In Fig. 4b, the forward connecting neurons at each cortical stage from the neocortex to the hippocampus are shown in blue; and the backprojecting neurons are shown in dashed green lines. Details on this and much other connectivity of the neocortex are described elsewhere (Rolls, 2016a, 2021a). The multistage backprojection hierarchy allows expansion of neuron numbers from stage to stage so that the CA1 neurons can

indirectly access large parts of the neocortex without too many synapses per neuron (>10,000) at any one stage (Treves and Rolls, 1994). These active backprojections terminate in layer 1 of the neocortex, on neurons in for example the inferior temporal visual cortex that encode a particular face (using sparse distributed encoding (Rolls and Treves, 2011)). The active backprojection synapses on the active neocortical neurons then modify by associative learning, in what is formally a pattern association computation (Rolls, 2021a, 2021c). The backprojection signals become associated with other components of the episodic memory, such as viewed locations represented in the parahippocampal scene areas (Sulpizio et al., 2020; Huang et al., 2021; Rolls, 2021a; Rolls et al., 2022a, 2022e, 2022g), and rewards in the orbitofrontal cortex, pregenual anterior cingulate cortex and vmPFC (Rolls et al., 2020a). Later, during hippocampal recall of an episodic memory, the backprojection neurons because of their modified synapses activate the same neocortical neurons in different neocortical areas that were activated during the formation of the episodic memory. Once recalled into activity in different neocortical areas specialising in different types of representation (faces, objects, spatial views, actions, semantic memories in the anterior temporal lobe, etc) (Treves and Rolls, 1994; Rolls, 2021a), the neocortex can then participate in the formation of new semantic memories in the anterior temporal lobe and connected cortical regions (Rolls et al., 2022b), as described later.

This original theory of memory recall from the hippocampus to the neocortex (Rolls, 1989) was developed into quantitative analytic form in which the capacity of the recall process was specified in terms of the numbers of backprojection synapses onto each neocortical neuron (Rolls and Treves, 1994; Treves and Rolls, 1994), and modelled computationally (Rolls, 1995). The processing speed in the forward and backward connecting pathways from the neocortex to the hippocampus and back to the neocortex is sufficiently fast for this process to be realised (Rolls, 2021a). The theory has received support (McClelland et al., 1995), with emphasis in their discussion on CA1 as a stage at which backprojection synapses are modified. Our quantitative theory of the recall of information from the hippocampus back to the neocortex (Rolls and Treves, 1994; Treves and Rolls, 1994) can now be extended to the case where whole spatial scenes are retrieved back to the neocortex. The extension follows the analysis showing how a large number of charts or equivalently scenes can be stored in the hippocampus (Battaglia and Treves, 1998), for the same analysis can be applied to the heterosynaptic multistage pattern association backprojection system to the neocortex as to a single attractor network in CA3 (Treves and Rolls, 1994). A similar extension can probably be made from the analysis of temporal sequences of events in a single network (Spalla et al., 2021) to the multistage back-projection system to the neocortex from the hippocampus.

It is an important concept that the information in the neocortex is not organised just in the unstructured form of hippocampal episodic memory where components are associated together just because they occur at the same time, but instead are restructured and reorganised into a form in which the information is more knowledge (McClelland et al., 1995) or schema (Wang and Morris, 2010) based. For example, what happens in a single episode such as part of a particular journey can be used to develop semantic knowledge such as a map with information about the relative locations of different places and the attributes of each place. The recall of information from the hippocampus to the neocortex is more than consolidation of the information in the same unstructured time-stamped hippocampal form. New proposals are described next for how reward components originating in the orbitofrontal cortex, anterior cingulate cortex and vmPFC may be important not only for hippocampal system episodic memories, but also in facilitating the formation of new neocortical semantic memories.

6. A link between reward-related processing of the vmPFC/anterior cingulate cortex, episodic memory, and semantic memory

6.1. The roles of value in the consolidation of episodic events into semantic and schema memory

One of the great puzzles of the hippocampal episodic memory system is that hippocampal damage impairs not only episodic memory (the memory for particular events at a particular place and time), but also the learning of new semantic memories, that is knowledge about the world, facts, etc. Already existing semantic memory may show little impairment. A well-known example is that HM, who had bilateral medial temporal lobe damage which included large parts of the hippocampus, could not learn his way to his new house after the bitemporal surgery, but could remember his way to the house he lived in before the surgery. He could never learn who his doctors were (Corkin, 2002). There is much consistent evidence that hippocampal damage can impair new semantic learning (Duff et al., 2019). Why is the hippocampal episodic memory system so importantly involved in learning new semantic information? The new findings on the connectivity of the orbitofrontal cortex/vmPFC/anterior cingulate cortex system with the hippocampus (Rolls et al., 2022f) considered above lead to a new proposal.

During our daily lives, hundreds of events occur to us. We see many people and objects in many places. Some of these events will be associated with some value representation, for example if one of the people is a close friend, who perhaps tells us something useful about a scientific experiment. Most of the daily episodic events will have no value association. In any case, many of these episodic events are stored 'on the fly' in unstructured form in the hippocampus.

Later, when we are not faced with a barrage of incoming information in different episodes, we may have time to reflect on the events of the day. During that recall, the object/people and spatial but also value representations will be recalled by the hippocampus, with activation of neocortical areas that originally provide the object/person, spatial, and value information to the hippocampus for episodic memory storage as described above. If the recalled episodic memory during this time of reflection contains no value component, that is, is not useful to us, or is not very novel as signalled by the orbitofrontal cortex (Rolls et al., 2005a, 2020a; Rolls, 2019a, 2019c), we are likely to think no more about those 'insignificant' events with no value/novelty association. However, if there is a reward/punishment/emotional/novelty component, then we are likely to keep thinking about the whole episode, and what we might learn from that episodic event. It is argued that the prolonged reflection on, and thinking about, episodic events with value associations, is key to learning new semantic memories which are only likely to be formed if they have some utility as reflected in orbitofrontal cortex/vmPFC processing. In reflecting on the episodic events, we try to incorporate them into our knowledge base, including schemas (van der Linden et al., 2017) and adjust our knowledge base as necessary, that is, to learn new semantic information in neocortical areas such as the anterior temporal lobe, temporo-parietal junction, and angular gyrus (Bonner and Price, 2013; van der Linden et al., 2017; Rolls, 2021a; Rolls et al., 2022b).

The proposal thus is that if an episodic event has a value component (including a potential value component) as signalled by the vmPFC/anterior cingulate cortex/orbitofrontal cortex, then that value information is likely to make us process the recalled episodic events deeply, and incorporate new information from the hippocampal episodic event into our neocortical knowledge/semantic memory. Evidence supporting this approach is that the depth of processing makes a large difference to how well a memory is encoded and stored (Craik and Tulving, 1975; Xue, 2018). Indeed, I propose that one key factor that influences the depth of processing and the storage of memory, and its conversion into a semantic representation with depth, is the reward value associated with the event, which reflects the utility of that event for long-term memory

storage. I propose that the depth of processing tends to remain shallow for daily events with no reward value or emotional component, and that if the event has reward value, we are far more likely to think about the ramifications of the event in depth, and to make use of the event in developing semantic representations and schemas. This provides a clear and testable hypothesis about how episodic memory can be so important in forming new semantic memories; and indeed accords the orbitofrontal cortex/vmPFC/pregenual anterior cingulate cortex a key role in influencing how the operation of episodic memory is related to the formation of new semantic memories, by allowing value to influence the processing and thereby the consolidadtion. Further support for the approach is that there is increasing acceptance that the vmPFC 'helps refine hippocampal representations to form efficient concept spaces that are tuned based on goal relevance' (Morton and Preston, 2021).

6.2. The roles of value in the consolidation of episodic events into autobiographical memory

Autobiographical memory may be formed in a similar way, by incorporating episodic events recalled from the hippocampal system with some value in relation to the self into a form of a narrative account of oneself that is built like a semantic set of memories about the self, and that is stored in brain regions such as the anterior temporal lobe and temporo-parietal junction. In more detail, vmPFC and hippocampal lesions can both impair autobiographical memory, but in different ways, with the hippocampus especially involved in vivid visual representations of scenes (Bonnici and Maguire, 2018; McCormick et al., 2018; Ciaramelli et al., 2019). Semantic and episodic information are both utilized in constructing autobiographical memory (Cubelli et al., 2020): "autobiographical memory is thus not a collection of episodes; it includes semantic information, like the name of our grandparents or our childhood home address. Autobiographical memory encompasses schemata and abstract representations of events and people" (Cubelli et al., 2020). It is proposed here and indeed predicted that a contribution of the vmPFC/anterior cingulate cortex to autobiographical memory is the vivid component of autobiographical memory that relates to the recall of the emotional contents of an autobiographical memory to the orbitofrontal cortex/vmPFC/anterior cingulate cortex system. Part of the grounds for this proposal is that patients with orbitofrontal cortex/vmPFC/anterior cingulate cortex surgical lesions report that the subjective emotional content of what they experience is flattened (Hornak et al., 2003). Thus autobiographical memories are now proposed to include: 1) semantic components (for example information about one's friends during one's educational years, information about one's educational achievements, and information about the places where one has lived and visited); 2) together with information about particular events that happened at a particular place and time with what and whom (which the hippocampus may especially contribute to and make vivid); and 3) together with information about the reward, non-reward, punishing and goal-related aspects of recalled memories (which the orbitofrontal cortex/vmPFC/anterior cingulate cortex may especially contribute to and make vivid, and which may appear to have an organising role because of the goal-related information). Consistent with this, medial prefrontal areas are implicated in autobiographical memory (McCormick et al., 2018, 2020), and part of the reason suggested here for this is that many autobiographical memories have a value component to them, with importance to the self. The semantic component of autobiographical memory is supported by the evidence that brain regions such as the anterior temporal lobe involved in semantic memory (Bonner and Price, 2013; Rolls, 2021a; Rolls et al., 2022b) are also implicated by the effects of brain damage in autobiographical memory (Maguire et al., 2010). The role of representations of the self in episodic and autobiographical memory can also be related to the posterior cingulate component (Rolls et al., 2022g) of the circuitry described here, for the connected medial parietal cortex regions are implicated in the sense of self (Cavanna and Trimble, 2006; Freton et al., 2014; Hebscher et al., 2018; Rolls et al., 2022a), and epilepsy and electrical stimulation of the posterior cingulate cortex can produce a sense of self-dissociation in which there is a "distorted awareness of the position of the body in space and feeling as if the person had temporarily become an outside observer to his own thoughts, his "me" having become a separate entity that was listening to different parts of his brain speak to each other" (Parvizi et al., 2021).

6.3. Reward value may facilitate memory storage in many animals

The approach taken here to the relation between episodic memory, semantic memory, and reward value, is in contrast to the proposal that somehow sleep is a good time to recall information from hippocampal episodic memory and, somehow have that usefully incorporated into useful new neocortical semantic knowledge structures during sleep (Wilson and McNaughton, 1994; Wilson, 2002). The proposal here is that if episodic recall happens during waking, then this may allow in humans thinking about how the recalled episodic event information may contribute to the restructuring of semantic memory and schemata using thought correction processes (Rolls, 2020b). Further, although the concept described above refers to rumination in humans being encouraged by reward-related episodic memory components, reward value could play a role in the consolidation of some episodic memories in non-humans, for if the recalled memory includes a reward component, this could add to the 'what' and 'where' components of a recalled episodic memory, and lead to a larger backprojection signal to neocortex, contributing to better consolidation into long-term memory. A reward value or novelty component could also facilitate memory storage and long-term consolidation in non-humans as well as in humans via influences of reward-related brain regions on the cholinergic systems and thereby on the neocortex and hippocampus.

7. Conclusions

The reward/punishment value system in the human orbitofrontal cortex and regions to which it projects including the vmPFC and pregenual anterior cingulate cortex has effective connectivity with the hippocampus, and provides an important value/emotion-related component of episodic memory used by the hippocampus in addition to 'what', 'where', and 'when' components.

Damage to the human vmPFC and anterior cingulate cortex may impair episodic memory implemented by the hippocampal system because it impairs this important component, value information. That may leave the memory system less anchored in goals, and therefore perhaps thinking less about the future.

Damage to the human orbitofrontal cortex, pregenual anterior cingulate cortex, and vmPFC may also impair activation of brain regions to which they connect, the basal forebrain cholinergic system which connects to the neocortex, and the cholinergic medial septal nuclei which project to the hippocampus, and thereby impair memory consolidation in the neocortex and hippocampus, leading to weaker memories, and thereby to confabulation, a key memory change that follows the medial prefrontal damage.

The value/utility component of hippocampal episodic memory representations dependent on the human orbitofrontal cortex/vmPFC/pregenual anterior cingulate cortex may influence the extent to which value-related episodic memories are repeatedly recalled and used in further processing. Greater depth of processing driven by an orbitofrontal cortex/vmPFC/pregenual anterior cingulate cortex value component of a recalled hippocampal episodic event memory is more likely to activate neocortical semantic representations and schemas which then are modified to incorporate new evidence from the episodic event. It is proposed that this is an important way in which the formation or correction of semantic memories depends on the operation of the hippocampal episodic memory system including its value component.

Declaration of competing interest

None.

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