The human orbitofrontal cortex, vmPFC, and anterior cingulate cortex effective connectome: emotion, memory, and action

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Abstract

The human orbitofrontal cortex, ventromedial prefrontal cortex (vmPFC) and anterior cingulate cortex are involved in reward processing and thereby in emotion, but are also implicated in episodic memory. To understand these regions better, the effective connectivity between 360 cortical regions and 24 subcortical regions was measured in 172 humans from the Human Connectome Project, and complemented with functional connectivity and diffusion tractography. The orbitofrontal cortex has effective connectivity from gustatory, olfactory, and temporal visual, auditory and pole cortical areas. The orbitofrontal cortex has connectivity to the pregenual anterior and posterior cingulate cortex and hippocampal system, and provides for rewards to be used in memory and navigation to goals. The orbitofrontal and pregenual anterior cortex have connectivity to the supracallosal anterior cingulate cortex which projects to midcingulate and other premotor cortical areas, and provide for action-outcome learning including limb withdrawal or flight or fight to aversive and non-reward stimuli. The lateral orbitofrontal cortex has outputs to language systems in the inferior frontal gyrus. The medial orbitofrontal cortex connects to the nucleus basalis of Meynert and the pregenual cingulate to the septum, and damage to these cortical regions may contribute to memory impairments by disrupting cholinergic influences on the neocortex and hippocampus.

Introduction

It is an aim of much neuroscience to understand better the operation of the human brain in health and disease. To do this, it is important to know the connectivity between different functionally identified areas of the brain (Rolls 2021a). The aim of this investigation is to understand better the connectivity of key areas of the human brain involved in emotion and its disorders including depression, reward value, and motivation: the orbitofrontal cortex, ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (Rolls 2019d, 2019c; Rolls et al. 2020b).

Highlights are: the use of effective connectivity, functional connectivity, and diffusion tractography using the same set of 172 participants in the Human Connectome Project (HCP) imaged at 7T (Glasser et al. 2016b); and the use of the HCP multimodal parcellation atlas (MCP-MMP) that identifies 360 different cortical areas using methods that include cortical structure, functional connectivity, and task-related fMRI (Glasser et al. 2016a; Van Essen and Glasser 2018). One reason why it is important to understand better the connectivity of these regions is that parts of them are targeted for stimulation for the treatment of depression (Riva-Posse et al. 2018; Siddiqi et al. 2021).

The functional context of the connectivity to be investigated here is as follows. The orbitofrontal cortex (OFC) is a key brain region involved in emotion (Rolls 2014a, 2019d). Part of its importance in emotion is that the human orbitofrontal cortex encodes reward value and pleasantness in the medial orbitofrontal cortex, and punishment value, unpleasantness, and non-reward in the lateral orbitofrontal cortex (Grabenhorst and Rolls 2011; Rolls 2019b; Rolls *et al.* 2020b; Rolls et al. 2020d; Rolls 2021b). The anterior cingulate cortex receives inputs from the orbitofrontal cortex (Carmichael and Price 1996; Price 2006; Du et al. 2020; Hsu et al. 2020); and its pregenual part is activated by rewards, and its supracallosal part by non-rewards and punishers (Grabenhorst and Rolls 2011; Rolls 2019c). 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), and may, consistent with this, be involved in linking rewards from the orbitofrontal cortex to emotional behavior (Rolls 2019c; Wan et al. 2020; Rolls et al. 2022c). 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 in the HCP-MMP atlas probably include the pregenual anterior cingulate and area 10 regions (10r, 10v, 10d and 9m) analysed here. The ventromedial prefrontal cortex (vmPFC) is also involved in 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. 2010b, 2010a; Grabenhorst and Rolls 2011), and the effects of damage to it on decision-making (Hornak et al. 2004; Wheeler and Fellows 2008; Fellows 2011; Glascher et al. 2012). A different line of evidence shows also that what is described as the 'ventromedial prefrontal cortex' is involved in episodic memory, as shown by activations and by the effects of brain damage (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; Rolls 2022). It is important to understand the functioning of these regions better, for all are implicated, in different ways, in depression by their different functional connectivity in depression (Cheng et al. 2016; Cheng et al. 2018a; Cheng et al. 2018b; Cheng et al. 2018c; Rolls et al. 2020a).

To understand the function of a brain region, it is very important to know its afferent and efferent connectivity (Rolls 2016b, 2021a). There is a wealth of evidence on this for the orbitofrontal cortex and its connected regions in non-human primates, in which anatomical pathways can be traced (Carmichael and Price 1996; Price 2006, 2007; Saleem et al. 2008; Saleem et al. 2014). However, these methods cannot be applied in humans, and there is a need for a better understanding of the connectivity of each of the orbitofrontal cortex, ventromedial prefrontal cortex, and anterior cingulate cortex in humans, given the great development of these regions in primates compared to rodents, and even in

humans compared to non-human primates (Passingham and Wise 2012; Rolls 2019d; Passingham 2021; Rolls 2021a).

Given this background, one aim of the present investigation was to utilize a new method of measuring effective connectivity in the brain based on a Hopf model which enables the connectivity in both directions between each pair of brain regions to be measured using for example the fMRI BOLD signal (Rolls et al. 2022b). This method has been successfully applied to measure the effective connectivity between hundreds of brain regions (Rolls *et al.* 2022b). This method was complemented by measurement of functional connectivity between the same brain regions, which given that it is based on Pearson correlations, can provide evidence about interactions between brain regions, but not about the direction or causality of effects. It is noted that functional connectivity, measured by correlations in the BOLD signal between pairs of brain regions, does reflect direct connections as shown by combined anatomical and functional connectivity studies in non-human primates, but also reflects indirect effects (Van Essen and Glasser 2018; Van Essen et al. 2019). These methods were complemented by diffusion tractography which can measure direct connections between brain regions using completely different methodology not dependent on the BOLD signal, so can provide independent evidence, though not about the direction of connections nor about effects mediated beyond direct connections. It is important to note that these three approaches provide complementary types of evidence about the connectivity of the brain. Diffusion tractography provides evidence about direct connections between brain regions, but does not provide evidence on the direction of the connections, nor about connectivity beyond direct connections. Functional connectivity provides evidence that reflects correlations of activity between brain regions, and can therefore provide evidence about interactions between brain regions, which could be direct or indirect including common input, and again which does not provide evidence about the direction of the connectivity. Effective connectivity goes beyond functional connectivity by providing evidence about causal interactions between brain regions and about the strengths of the connectivity in each direction between brain regions. In fact, effective connectivity provides a generative model for brain activity, and that is how it is estimated, as described below. In practice, partly probably because effective connectivity reflects causal connectivity and not what could be common input, the effective connectivity measured with the Hopf algorithm utilized here tends to be more sparse than functional connectivity (Rolls *et al.* 2022b). These three approaches thus provide evidence about different aspects of brain connectivity, all important and not identical to each other, and it is a feature that all three are utilized here, all measured in the same participants.

A second aim of this investigation was to utilize the parcellation of the human cerebral cortex provided by the Human Connectome Project atlas (Glasser *et al.* 2016a), which we extended for the present study by including subcortical regions, and by enabling it to be used with standard neuroimaging software such as SPM (Huang et al. 2021a; Huang et al. 2021b; Rolls *et al.* 2022b). This atlas provides unparalleled subdivisions of the human cortex using multimodal methods, with many of the areas having identified functions (Glasser *et al.* 2016a). The multimodal methods used to generate this HCP-MMP v1.0 parcellation included resting state functional connectivity, cortical myelin content and thickness, and task-related fMRI. By combining all these measures to distinguish different cortical areas, and the use of a large number (420) of participants, 360 cortical regions could be identified across the two hemispheres (Glasser *et al.* 2016a). This approach provides better categorization of cortical areas than does for example functional connectivity alone (Power et al. 2011).

Methods

Participants and data acquisition

Multiband 7T resting state functional magnetic resonance images (rs-fMRI) of 184 individuals were obtained from the publicly available S1200 release (last updated: April 2018) of the Human

Connectome Project (HCP) (Van Essen et al. 2013). Individual written informed content was obtained from each participant, and the scanning protocol was approved by the Institutional Review Board of Washington University in St. Louis, MO, USA (IRB #201204036).

Multimodal imaging was performed in a Siemens Magnetom 7T housed at the Center for Magnetic Resonance (CMRR) at the University of Minnesota in Minneapolis. For each participant, a total of four sessions of rs-fMRI were acquired, with oblique axial acquisitions alternated between phase encoding in a posterior-to-anterior (PA) direction in sessions 1 and 3, and an anterior-to-posterior (AP) phase encoding direction in sessions 2 and 4. Specifically, each rs-fMRI session was acquired using a multiband gradient-echo EPI imaging sequence. The following parameters were used: TR = 1000ms, TE = 22.2 ms, flip angle = 45°, field of view = 208 × 208, matrix = 130 × 130, 85 slices, voxel size = 1.6 × 1.6 × 1.6 mm^3, multiband factor = 5. The total scanning time for each session for the rs-fMRI protocol was approximately 16 min with 900 volumes. The timeseries used here thus contained 900 data points for every brain region from the first session. Further details of the 7T rs-fMRI acquisition protocols are given in the HCP reference manual (https://humanconnectome.org/storage/app/media/documentation/s1200/HCP_S1200_Release_Reference_Manual.pdf).

The current investigation was designed to complement investigations of effective connectivity of the hippocampus (Rolls *et al.* 2022b), posterior cingulate cortex (Rolls et al. 2022d), and posterior parietal cortex (Rolls et al. 2022e), and so the same 172 participants with data for the first session of rs-fMRI at 7T were used for the analyses described here (age 22-36 years, 66 males).

Data Preprocessing

The preprocessing was performed by the HCP as described in Glasser et al. (2013), based on the updated 7T data pipeline (v3.21.0, https://github.com/Washington-University/HCPpipelines), including gradient distortion correction, head motion correction, image distortion correction, spatial transformation to the Montreal Neurological Institute space using one step spline resampling from the original functional images followed by intensity normalization. In addition, the HCP took an approach using ICA (FSL's MELODIC) combined with a more automated component classifier referred to as FIX (FMRIB's ICA-based X-noisifier) to remove non-neural spatiotemporal artefact (Smith et al. 2013; Griffanti et al. 2014; Salimi-Khorshidi et al. 2014). This step also used 24 confound timeseries derived from the motion estimation (6 rigid-body parameter timeseries, their backwards-looking temporal derivatives, plus all 12 resulting regressors squared (Satterthwaite et al. 2013) to minimise noise in the data. (The mean framewise displacement was 0.083 ± 0.032 std.) The preprocessing performed by the HCP also included boundary-based registration between EPI and T1w images, and brain masking based on FreeSurfer segmentation. The 'minimally preprocessed' rsfMRI data provided by the HCP 1200 release (rfMRI*hp2000_clean.dtseries) was used in this investigation. The preprocessed data is in the HCP grayordinates standard space and is made available in a surface-based CIFTI file for each participant. With the MATLAB script (cifti toolbox: https://github.com/Washington-University/cifti-matlab), we extracted and averaged the cleaned timeseries of all the grayordinates in each region of the HCP-MMP 1.0 atlas (Glasser *et al.* 2016a), which is a group-based parcellation defined in the HCP grayordinate standard space having 180 brain regions per hemisphere, and is a surface-based atlas provided in CIFTI format. The timeseries were detrended, and temporally filtered with a second order Butterworth filter set to 0.008 – 0.08 Hz.

As is evident from the above, the HCP was extremely careful in its preparation of the timeseries, to minimize any unwanted noise from head motion etc. To address this further, we performed a further analysis with the same 172 participants at 3T which has a 1200 point time series with TR=0.72. In this set of data, it was possible to regress out the framewise displacement, and it was found that this made little difference, in that the functional connectivities with and without regression of frame-wise

displacement were correlated 0.987. The functional connectivities are relevant here, because the effective connectivity is calculated using the functional connectivities and the time-lagged functional connectivities. Frame-wise displacement measures the movement of the head from one volume to the next, and is calculated as the sum of the absolute values of the six realignment estimates (three translation and three rotation parameters) at every timepoint (Power et al. 2012). We also performed cross-validation, and showed that the functional connectivities described here for 172 participants at 7T were correlated 0.944 with those in 845 different HCP participants at 3T. These precautions and cross-validation thus show that the connectivity measurements described here are robust. It is also noted that although signal dropout can be a complication of fMRI in the medial temporal lobe, this is unlikely to differentially influence the regions of interest analyzed here, as they are all close together in the brain (Fig. 1). Further, we checked the temporal signal-to-noise ratio (tSNR) for all brain regions, and that provided evidence that signal dropout was not a problem.

Brain Atlas and Region of Interest Selection

To construct the effective connectivity for the regions of interest in this investigation with other cortical regions of the human brain, we utilised the 7T resting state fMRI data from the HCP, and parcellated this with the surface based HCP-MMP1 atlas which has 360 cortical regions (Glasser *et al.* 2016a). We were able to use the same 172 participants for whom we also had performed diffusion tractography, as described in detail (Huang *et al.* 2021b). The brain regions are shown in Figs. 1 and S1, and a list of the cortical regions in this atlas is provided in Table S1 in the reordered form used in the extended volumetric HCPex atlas (Huang *et al.* 2021a).

To construct the effective connectivity for the regions of interest in this investigation with subcortical parts of the human brain, we utilised the HCPex atlas (Huang *et al.* 2021a) which combines in volumetric rather than surface-based space HCP's multi-modal parcellation (v1.0), including from it 179 cortical regions per hemisphere except for the hippocampus (Glasser *et al.* 2016a); and 33 subcortical regions per hemisphere including the amygdala, thalamus, putamen, caudate nucleus, nucleus accumbens, globus pallidus, mammillary bodies, septal nuclei and nucleus basalis. To distinguish the subiculum from the hippocampus, we used the subiculum mask provided in the CoBrALab atlas (Winterburn et al. 2013) (see Huang *et al.* 2021a). Thus, the final modified HCPex atlas contained 360 regions which cover the cerebral cortex, and 66 subcortical regions. A list of the cortical regions is provided in Table S1, and coronal slices with the HCP parcellation with labels for each region are provided in Fig. S1 with a more extensive series elsewhere (Huang *et al.* 2021a). The volumetric form of HCPex (Huang *et al.* 2021a) is helpful with many existing types of software such as SPM, though for the very best registration of cortical areas the surface based form of the original HCP atlas (Glasser *et al.* 2016a) has advantages (Coalson et al. 2018; Huang *et al.* 2021a). However, we measured the functional connectivity between the 360 cortical areas in the HCP-MMP v1.0 surface-based atlas (Glasser *et al.* 2016a) and the same areas in the volumetric atlas (Huang *et al.* 2021a), and found that the correlation was 0.94 between the mean functional connectivity matrices averaged across the 172 HCP participants imaged at 7T. This is evidence that the volumetric version (Huang *et al.* 2021a) operates reasonably well for groups of individuals.

In this investigation, the cortical regions of interest (ROIs) included the following regions from the HCP-MMP1 atlas (Glasser *et al.* 2016a), and they were grouped for ease of description into 6 groups. The groups were based on the topography, cytoarchitecture, the correlations between the effective connectivities (Fig. S4), and the functions of these brain areas (Öngür et al. 2003; Vogt 2009; Rolls 2019c, 2019d; Rolls *et al.* 2020b; Rolls 2021a), and on the brain divisions adopted, justified, and used in the HCP-MMP1 (Glasser *et al.* 2016a) and HCPex atlases (Huang *et al.* 2021a). The groups were as follows, with the individual brain regions ordered in a sequence starting with the lateral orbitofrontal cortex, and proceeding medially through the medial orbitofrontal cortex, then moving in

the dorsal direction of the medial aspect of the brain through the pregenual anterior cingulate cortex, some area 10 regions, up to the supracallosal anterior cingulate cortex (see Figs. 1-6): lateral orbitofrontal cortex (47s, 47l, a47r, p47r, 47m); medial orbitofrontal cortex (11l, 13l, OFC, pOFC); subgenual cingulate cortex (25); pregenual anterior cingulate cortex (s32, a24, p24, p32, d32); some closely connected area 10 and related regions (10v, 10r, 10d, 9m); and supracallosal anterior cingulate cortex (a32pr, a24pr, 33pr, p32pr, p24pr). These groups are useful, since they reflect the differences in the effective connectivity of these brain regions, as shown in Figs. 2-6 and in the correlation matrix between the connectivity of these brain regions that is presented in Fig. S5. It is noted that an alternative anatomical terminology for some parts of the supracallosal anterior cingulate cortex is midcingulate cortex (Vogt 2009; Rolls 2019c, 2019a), though in the HCP-MMP atlas the midcingulate cortex consists of regions 23c, 24dd and 24dv (Glasser *et al.* 2016a), with its own set of connectivities (Rolls *et al.* 2022d).

Measurement of effective connectivity

Effective connectivity measures the effect of one brain region on another, and utilizes differences detected at different times in the signals in each connected pair of brain regions to infer effects of one brain region on another. One such approach is dynamic causal modelling, but it applies most easily to activation studies, and is typically limited to measuring the effective connectivity between just a few brain areas (Friston 2009; Valdes-Sosa et al. 2011; Bajaj et al. 2016), though there have been moves to extend it to resting state studies and more brain areas (Frassle et al. 2017; Razi et al. 2017). The method used here (see Rolls *et al.* 2022b) was developed from a Hopf algorithm to enable measurement of effective connectivity between many brain areas, described by Deco et al (2019). A principle is that the functional connectivity is measured at time *t* and time *t* + *tau*, where *tau* is typically 2 s to take into account the time within which a change in the BOLD signal can occur, and then the effective connectivity model is trained by error correction until it can generate the functional connectivity matrices at time *t* and time t + *tau*. Full details of the algorithm and its validation are provided elsewhere (Rolls *et al.* 2022b); a short description is provided next, with a full description in the Supplementary Material.

To infer the effective connectivity, we use a whole-brain model that allows us to simulate the BOLD activity across all brain regions and time. We use the so-called Hopf computational model, which integrates the dynamics of Stuart-Landau oscillators, expressing the activity of each brain region coupled together by the strength of the connectivity in each direction between every pair of brain regions (Deco et al. 2017b). The local dynamics of each brain area (node) is given by Stuart-Landau oscillators which expresses the normal form of a supercritical Hopf bifurcation, describing the transition from noisy to oscillatory dynamics (Kuznetsov 2013). It has been shown that the Hopf whole-brain model successfully simulates empirical electrophysiology (Freyer et al. 2011; Freyer et al. 2012), MEG (Deco et al. 2017a) and fMRI (Kringelbach et al. 2015; Deco *et al.* 2017b; Kringelbach and Deco 2020).

The Hopf whole-brain model can be expressed mathematically as follows:

$$\frac{dx_i}{dt} = \overbrace{\left[a_i - x_i^2 - y_i^2\right]x_i - \omega_i y_i}^{Local\ Dynamics} + \overbrace{G\sum_{j=1}^{N} C_{ij}\left(x_j - x_i\right)}^{Coupling} + \overbrace{\beta\eta_i(t)}^{Gaussian\ Noise} \quad (1)$$

$$\frac{dy_i}{dt} = \left[a_i - x_i^2 - y_i^2\right]y_i + \omega_i x_i + G\sum_{j=1}^{N} C_{ij}\left(y_j - y_i\right) + \beta\eta_i(t) \quad (2)$$

Equations 1 and 2 describe the coupling of Stuart-Landau oscillators through an effective connectivity matrix C. The $x_i(t)$ term represents the simulated BOLD signal data of brain area i. The values of $y_i(t)$ are relevant to the dynamics of the system but are not part of the information read out from the system. In these equations, $\eta_i(t)$ provides additive Gaussian noise with standard deviation β. The Stuart-Landau

oscillators for each brain area *i* express a Hopf normal form that has a supercritical bifurcation at a_i=0, so that if a_i>0 the system has a stable limit cycle with frequency with frequency f_i=$\omega_i/2\pi$ (where ω_i is the angular velocity); and when a_i<0 the system has a stable fixed point representing a low activity noisy state. The intrinsic frequency f_i of each Stuart-Landau oscillator corresponding to a brain area *i* is in the 0.008–0.08Hz band (*i*=1, …, 362). The intrinsic frequencies are fitted from the data, provided here by the averaged peak frequency of the narrowband BOLD signals of each brain region. The coupling term representing the input received in node *i* from every other node *j*, is weighted by the corresponding effective connectivity C_{ij}. The coupling is the canonical diffusive coupling, which approximates the simplest (linear) part of a general coupling function. *G* denotes the global coupling weight, scaling equally the total input received in each brain area. While the oscillators are weakly coupled, the periodic orbit of the uncoupled oscillators is preserved. Details are provided in the Supplementary Material.

The effective connectivity matrix can be derived by optimizing the conductivity of each in order to fit the empirical functional connectivity (FC) pairs and the lagged FC^{tau} pairs. By this, we are able to infer a non-symmetric Effective Connectivity matrix (see Gilson et al (2016)). Note that FC^{tau}, ie the lagged functional connectivity between pairs, lagged at *tau* s, breaks the symmetry and thus is fundamental for our purpose. Specifically, we compute the distance between the model FC simulated from the current estimate of the effective connectivity and the empirical data FC^{emp}, as well as the simulated model FC^{tau} and empirical data FC^{tau_emp} and adjust each effective connection (entry in the effective connectivity matrix) separately with a gradient-descent approach. The model is run repeatedly with the updated effective connectivity until the fit converges towards a stable value.

We can start with the anatomical connectivity obtained with probabilistic tractography from dMRI (which might help the algorithm by utilising as a constraint connections known to be absent in the brain), or with a *C* matrix initialized to zero (which has a potential advantage that it is not influenced by possible errors in the diffusion tractography) as described in the Supplementary Material. The latter method was used here, but in practice the algorithm produced similar results with either method (Rolls *et al.* 2022b). The following procedure is used to update each entry C_{ij} in the effective connectivity matrix

$$C_{ij} = C_{ij} + \varepsilon\left(FC_{ij}^{emp} - FC_{ij} + FC_{ij}^{tau\_emp} - FC_{ij}^{tau}\right) \quad (3)$$

where ϵ is a learning rate constant, and *i* and *j* are the (brain region) nodes. For the implementation, we set *tau* to be 2 s, selecting the appropriate number of TRs to achieve this. The maximum effective connectivity was set to a value of 0.2, and was found between V1 and V2.

Effective Connectome

Whole-brain effective connectivity (EC) analysis was performed between the 24 regions of interest described above and shown in Fig. 1 and the 360 regions defined in the surface-based HCP_MMP1 atlas (Glasser *et al.* 2016a), with the brain regions shown in Table S1 (Huang *et al.* 2021a). This EC was computed from the averaged functional connectivities across the 172 participants. The effective connectivity algorithm was run until it had reached the maximal value for the correspondence between the simulated and empirical functional connectivity matrices at time *t* and *t* + *tau* (see Supplementary Material). The analysis utilized for the subcortical areas the Human Connectome Project multimodal parcellation atlas (Glasser *et al.* 2016a) in a modified form extended to include 66 subcortical areas in volumetric space (Huang *et al.* 2021a). The application of the effective connectivity algorithm used here was validated as described elsewhere (Rolls *et al.* 2022b).

To test whether the vectors of effective connectivities of each of the 24 OFC/vmPFC/ACC ROIs with the 180 cortical regions in the left hemisphere of the HCP-MMP1 atlas were significantly different, the interaction term was calculated for each pair of the 24 ~~hippocampal system~~ ROI effective

connectivity vectors in two-way ANOVAs (each 2 x 180) across the 172 participants, and Bonferroni correction for multiple comparisons was applied.

Functional connectivity

The functional connectivity, which is measured by the Pearson correlation between the BOLD signal in each pair of brain areas, can provide evidence that may relate to interactions between brain regions, while providing no evidence about causal direction-specific effects. A high functional connectivity may in this scenario thus reflect strong physiological interactions between areas, and provides a different type of evidence to effective connectivity.

For comparison with the effective connectivity, the functional connectivity was also measured at 7T with the identical set of participants, data, and filtering of 0.008 – 0.08 Hz. The functional connectivity was measured by the Pearson correlation between the BOLD signal timeseries for each pair of brain regions, and is in fact the FC^{emp} referred to above. A threshold of 0.38 is used for the presentation of the findings in Fig. 5, for this sets the sparseness of what is shown to a level commensurate with the effective connectivity, to facilitate comparison between the functional and the effective connectivity.

Connections shown with diffusion tractography

Diffusion tractography can provide evidence about fibre pathways linking different brain regions with a method that is completely different to the ways in which effective and functional connectivity are measured, so is included here to provide complementary and supporting evidence to the effective connectivity. Diffusion tractography shows only direct connections, so comparison with effective connectivity can help to suggest which effective connectivities may be mediated directly or trans-synaptically. Diffusion tractography does not provide evidence about the direction of connections. Diffusion tractography was performed on the same 172 HCP participants images at 7T with methods described elsewhere (Huang *et al.* 2021b) and not repeated here for conciseness, and is shown here for the orbitofrontal cortex / vmPFC / anterior cingulate cortex areas in Fig. 6.

Results

The effective connectivities to the orbitofrontal cortex and anterior cingulate cortex from other cortical areas in the left hemisphere are shown in Fig. 2. The effective connectivities from the orbitofrontal cortex and anterior cingulate cortex to other cortical areas in the left hemisphere are shown in Fig. 3. The vectors of effective connectivities of each of the 24 OFC/ACC regions of interest (ROIs) with the 180 areas in the HCP atlas both in the left hemisphere were all significantly different from each other (the interaction term in a 2-way ANOVA across the 172 participants was $p<10^{-90}$ for the comparisons between every pair of the 24 ROIs after Bonferroni correction for multiple comparisons). The difference of effective connectivities in the two directions between each pair of brain regions is shown in Fig. 4, as this helps to interpret the relations between brain regions. When considering each group of brain areas in the following, the evidence from the functional connectivity shown in Fig. 5 (which generally supports the effective connectivity but does not provide any measure of directionality), and the diffusion tractography shown in Fig. 6, both for the same 172 HCP participants is taken into account. The different groups of brain regions as set out in the Methods (*Brain Atlas and Region of Interest Selection*) are separated by red lines in the Figures. The functional implications of the results described next are considered in the Discussion, with a synthesis referring to Fig. 7 towards the end of the Discussion.

Lateral orbitofrontal cortex (47s, 47l, a47r, p47r and 47m)

The lateral orbitofrontal cortex areas a47r, p47r and 47m share generally similar effective connectivities from the visual inferior temporal cortex (TE areas); from parts of the parietal cortex (PFm which receives visual and auditory object-level information and IP2 which is visuomotor (Rolls *et al.* 2022e)); from the medial orbitofrontal cortex (11l, 13l, pOFC); from the inferior frontal gyrus regions including IFJ, IFS and BA45; from the dorsolateral prefrontal cortex (8Av, 8BL, a9-46v and p9-46v); and from the frontal pole (a10p, p10p, 10pp) (Fig. 2). 47m (which is relatively medial in this group) also has effective connectivity with the hippocampal system (Hipp, EC, perirhinal, and TF), and with ventromedial prefrontal regions 10r, 10d, and 9m. Although in most cases there are effective connectivities from a47r, p47r and 47m to these other cortical regions (Fig. 3), the effective connectivities are in most cases stronger towards the lateral orbitofrontal, except that the connectivities are stronger from the lateral orbitofrontal cortex towards the set of inferior prefrontal regions including IFJ, IFS, 45 and 44 (Fig. 4). The functional connectivity is generally consistent (Fig. 5), and the diffusion tractography (Fig. 6) provides in addition evidence for connections of these parts of the lateral orbitofrontal cortex with the anterior ventral insular region (AVI), anterior agranular insular complex (AAIC) which may be visceral (Rolls 2016c) and also has taste-olfactory convergence (de Araujo et al. 2003), and the middle insular region (MI) which is somatosensory; and with the piriform (olfactory) cortex. Consistent with this, the frontal opercular areas FOP4 and FOP5 which probably include the insular taste cortex (Fig. S1 (Rolls 2015, 2016c)), have connections with parts of the lateral orbitofrontal cortex (Fig. 6).

Regions 47s and 47l (which tend to be more posterior, and are close to region 45) have rather different effective connectivity which relates these two regions to cortical regions involved in language (Rolls et al. 2022a). For example, 47s and 47l have effective connectivity with superior temporal (STS and STG) auditory association / semantic cortical areas; with the temporal pole TG areas implicated in semantic representations; with the peri-Sylvian language (PSL), STV and TPOJ regions involved in language (Rolls *et al.* 2022a); with the frontal pole (10pp); with the superior frontal language area (SFL); and directed to inferior prefrontal regions including IFJ, IFS, 45 and 44 (Broca's area) (Figs. 2-4). The connectivity of 47s and 47l with the STS/STG regions is not evident in the diffusion tractography (Fig. 6), and may be implemented via the laterally adjacent areas 45 (inferior frontal gyrus pars triangularis) and 44 (inferior frontal gyrus pars opercularis) (both parts of Broca's area), which do have direct connections with these lateral orbitofrontal cortex areas (Fig. 6), and towards which 47s and 47l have strong effective connectivity (Figs. 2-4). Apart from these language-related connectivities, 47s and 47l have connections with other cortical regions that are similar to those of the other parts of the lateral orbitofrontal cortex (a47r, p47r and 47m) with which they also have connectivity, and it is accordingly proposed in the Discussion that 47s and 47l provide access from the orbitofrontal cortex reward / punishment system to language regions for subjective reports of pleasantness, unpleasantness, and affective value.

The lateral orbitofrontal cortex also has some effective (Figs. 2-4) and functional (Fig. 5) connectivity with supracallosal medial prefrontal region 8BM (which is of interest as activations produced by aversive / unpleasant / non-reward stimuli extend into this region (Grabenhorst and Rolls 2011; Rolls 2019c; Rolls *et al.* 2020d)).

A major difference of the connectivity of the lateral orbitofrontal cortex from the other regions considered here is its connectivity with Broca's area (45 and 44) in the inferior frontal gyrus.

Medial orbitofrontal cortex (11l, 13l, OFC, pOFC)

Parts of the medial orbitofrontal cortex (11l, 13l, OFC and pOFC, which are interconnected) have effective connectivity with the taste/olfactory/visceral AAIC; the piriform (olfactory) cortex; the entorhinal cortex (EC); the inferior temporal visual cortex (TE1p, TE2a, TE2p); superior parietal 7Pm; inferior parietal PF which is somatosensory (Rolls *et al.* 2022e); with parts of the posterior cingulate

cortex (31pv, 7m, d23ab) related to memory (Rolls *et al.* 2022d); with the pregenual anterior cingulate cortex (s32, a24, p24, p32, d32) and much less with the supracallosal anterior cingulate cortex (only 33pr); with ventromedial prefrontal 10r, 10d and 9m; with the frontal pole (10pp, p10p, a10p); with lateral orbitofrontal cortex (47m, 47s, a47r); and dorsolateral prefrontal (46 and a9-46v) (Figs. 2 and 3).

The connectivities are stronger towards the medial orbitofrontal cortex for the inferior temporal visual cortex and frontal pole regions, but a number of the other connectivities are stronger away from the medial orbitofrontal cortex (Fig. 4). Region OFC is remarkable for effective connectivities directed towards more cortical regions than other parts of the medial orbitofrontal cortex, including somatosensory cortex regions 5L and 5m; the fusiform face area (FFC) and some other relatively early visual cortical areas; and some parietal areas including PGp, PGs, and some superior parietal parts of 7 and intraparietal areas described elsewhere (Rolls *et al.* 2022e) (Fig. 3). It is regions 11l and 13l that have outputs directed to inferior prefrontal areas (IFS and IFJ regions) and to dorsolateral prefrontal areas 46 and a9-46v (Fig. 3). pOFC is the only cortical area of the 180 regions with effective connectivity directed to the nucleus basalis of Meynert which includes cholinergic neurons that project to the neocortex (Zaborszky et al. 2008; Zaborszky et al. 2018; Huang *et al.* 2021a). Region OFC has effective connectivity directed towards the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA) (Fig. S5), which contain dopaminergic neurons. Medial orbitofrontal cortex regions also have effective connectivity directed towards the caudate nucleus and nucleus accumbens (Fig. S5).

The functional connectivity (Fig. 5) is generally consistent, adding some evidence for interactions with frontal opercular FOP4 which is probably taste related and the somatosensory insula (MI). The diffusion tractography (Fig. 6) provides evidence that medial orbitofrontal cortex regions have direct connections with the anterior agranular insular complex (AAIC) which is probably taste/olfactory/visceral-related and with the piriform cortex (Pir); with the hippocampal system; and with temporal pole TGd.

Overall, the medial orbitofrontal cortex is found in humans to have connectivity with regions at the ends of sensory processing hierarchies that provide evidence for 'what' stimulus is present, including taste, olfactory, visual and somatosensory brain systems; and the part of the posterior parietal cortex that is related to memory; and the hippocampal memory system; and has connectivity also with the pregenual and supracallosal anterior cingulate cortex and lateral orbitofrontal cortex (Fig. 7).

Pregenual anterior cingulate cortex (s32, a24, p24, p32, d32)

As background, the pregenual anterior cingulate cortex is activated by many rewarding stimuli (Grabenhorst and Rolls 2011; Rolls 2019c, 2021a). The effective connectivity to these regions (which are interconnected) as shown in Fig. 2 includes connectivity from medial orbitofrontal cortex regions (pOFC, OFC and 13l) with much less from lateral orbitofrontal cortex regions 47. There is also effective connectivity from the anterior agranular insular complex (AAIC) which is probably taste/olfactory/visceral-related; the hippocampal system (Hipp and presubiculum); with parts of the posterior cingulate cortex (31pv, 31pd, 7m, d23ab, v23ab) related to memory (Rolls *et al.* 2022d); with some ventromedial prefrontal regions (10r, 10v, 10d); and with prefrontal 8Av, 8Ad, 9a and 9p; and (for d32) with the frontal pole. The effective connectivity is stronger to these pregenual cingulate regions from the posterior cingulate, and area 10, regions (Fig. 4). Effective connectivities from the pregenual cingulate cortex to the hippocampal system and the memory-related parts of the posterior cingulate are prominent (Fig. 3). Several of the pregenual anterior cingulate cortex regions have bidirectional connectivity with the septum (Fig. S5) which includes cholinergic neurons that project to the hippocampus (Zaborszky *et al.* 2008; Zaborszky *et al.* 2018; Huang *et al.* 2021a).

The functional connectivity is generally consistent with some additional evidence for interactions with STS regions, and other parts of the posterior cingulate cortex (Fig. 5). The diffusion

tractography (Fig. 6) provides evidence for direct connections of p24 with some posterior cingulate cortex regions and some of the area 10 regions.

Subgenual anterior cingulate cortex area 25

Area 25 has relatively similar effective connectivity to the pregenual anterior cingulate cortex regions, except that 25 does not have effective connectivity with the inferior frontal gyrus and dorsolateral prefrontal cortex regions (Figs. 2-4). The connectivity of region 25 is also similar to that of the medially adjacent (see Fig. 1) pOFC. Region 25 also has some connectivity directed to the hippocampus, and interestingly bidirectional connectivity with the septum (Fig. S5) which includes cholinergic neurons that project to the hippocampus (Zaborszky *et al.* 2008; Zaborszky *et al.* 2018; Huang *et al.* 2021a).

Area 10 and related ventromedial prefrontal cortex regions (10v, 10r, 10d, 9m)

Regions 10v, 10r, 10d and 9m are considered in this group because they are in close proximity to the medial orbitofrontal and pregenual anterior cingulate cortex (Fig. 1), often are co-activated in task-related fMRI and in this respect need to be considered together, and because their effective connectivity has some similarities with the medial orbitofrontal cortex and pregenual anterior cingulate cortex (Fig. 2-4). It is noted that the more frontal pole regions of area 10, in particular a10p, p10p, and 10pp, have different effective connectivity to the regions considered here that is more closely related to language systems (Rolls *et al.* 2022a). As noted earlier, the term 'ventromedial prefrontal cortex' refers to regions that in this HCP-MMP atlas probably include the pregenual anterior cingulate, area 25, and the area 10 regions analysed here.

The effective connectivity of these regions as shown in Figs. 2 and 3 includes effective connectivity with the (auditory/semantic association) cortex in the superior temporal sulcus (STS) and superior temporal gyrus; visual inferior temporal cortex TE, and temporal pole TG; the posterior cingulate cortex (including 31pd, 31pv, 7m, d23ab, and v23ab) with are implicated in memory (Rolls *et al.* 2022d); with the hippocampal memory system (hippocampus and entorhinal cortex EC); anterior cingulate cortex (including especially pregenual areas a24, d32, and p32 to which the connectivity is directed, Figs. 3 and 4), and subgenual cingulate cortex area 25; and the medial orbitofrontal cortex (OFC and pOFC) and lateral orbitofrontal cortex (47m, 47s, 47l).

For these area 10 regions (Fig. 4), the directionality is stronger to than from auditory/semantic (STS) regions (Bonner and Price 2013; Rolls 2021a), hippocampal memory regions (hippocampus, entorhinal cortex), inferior parietal region PGi, some pregenual anterior cingulate cortex regions, and the lateral orbitofrontal cortex (area 47 regions), suggesting that these connectivities are involved more in output from the vmPFC than inputs to it. Conversely, the directionality is stronger from parts of the posterior cingulate cortex to these area 10 regions, suggesting that this as an important pathway for memory-related inputs to reach these area 10 vmPFC regions (Rolls 2022). The diffusion tractography indicates direct connections of these area 10 regions with orbitofrontal cortex and with anterior cingulate cortex regions (Fig. 6).

Supracallosal anterior cingulate cortex (a32pr, a24pr, 33pr, p32pr, p24pr)

Part of the context is that this region is activated by aversive stimuli and non-reward in humans (Grabenhorst and Rolls 2011; Rolls 2019c; Rolls *et al.* 2020d; Rolls 2021a).

As shown in Figs. 2, 3, and S4, these HCP regions have very similar effective connectivity to each other. There is effective connectivity to supracallosal ACC regions from somatosensory cortex 5L, 5mv and PFop (Rolls *et al.* 2022e); from superior parietal 7AL and 7Am; from posterior cingulate 23d which is part of the antero-dorsal visuo-motor part (Rolls *et al.* 2022d); and from the medial orbitofrontal cortex regions 11l, 13l, OFC and pOFC. There is effective connectivity to midcingulate

cortex premotor regions 24dd and 24dv; premotor area 6 and the frontal eye fields FEF; frontal opercular FOP and related opercular somatosensory areas; somatosensory insular regions (e.g. MI, PI, AVI, PoI); and to the Peri-Sylvian Language area (PSL). The supracallosal anterior cingulate cortex thus has outputs to cortical areas involved in limb and body movements.

The functional connectivity (Fig. 5) is consistent with the effective connectivity, and in addition provides evidence for interactions with many early cortical visual areas, with some temporo-parieto-occipital regions (TPO) and the STV related to language (Rolls *et al.* 2022a); and with further posterior cingulate areas such as DVT, PCV and ProS implicated in visuo-motor functions (Rolls *et al.* 2022d). The diffusion tractography provides evidence for direct connections with some of the posterior cingulate cortex regions (Fig. 6).

Effective connectivities of the orbitofrontal cortex, vmPFC, and anterior cingulate cortex with contralateral cortical areas

The effective connectivities of the orbitofrontal cortex, vmPFC, and anterior cingulate cortex from contralateral cortical areas are shown in Fig. S2, and to other contralateral cortical areas in Fig. S3. The predominant pattern of contralateral effective connectivities is that most of the groups of regions connect most strongly with the corresponding contralateral group, and that this holds further for individual cortical regions. The implication of this is that connected cortical areas in hierarchical processing streams connect with each other primarily within the same hemisphere, as shown by comparing Figs. 2 with S2 and 3 with S3, and not between the hemispheres as in Figs. S2 and S3. That is, the contralateral connectivity appears to be mainly, at least for the stronger connectivities, between corresponding cortical regions in the two hemispheres.

The main exceptions are the supracallosal anterior cingulate cortex regions, which do have contralateral connectivity with for example other cortical areas involved in somatomotor function (Fig. S3), which may relate to the necessity of this part of the anterior cingulate cortex involved in action initiation to control actions on both sides of the body.

The contralateral effective connectivities are in general weaker than those ipsilaterally.

Grouping of cortical regions based on the other cortical areas with which they have effective connectivity

The 24 HCP-MMP cortical regions considered here are grouped into 6 groups, the lateral orbitofrontal cortex, the medial orbitofrontal cortex, the subgenual cingulate cortex, the pregenual anterior cingulate cortex, the area 10 ventromedial prefrontal regions, and the supracallosal anterior cingulate cortex, based partly on their topology and cytoarchitecture, and also on their brain divisions in the HCP-MMP1 atlas (Huang *et al.* 2021a). The similarity of their effective connectivities was measured by the Pearson correlation between the effective connectivities of the 24 regions of interest from all 180 cortical areas in the left hemisphere. (This is the correlations between the rows shown in Fig. 2). The resulting correlation matrix is shown in Fig. S4. (The connectivity matrix based on the effective connectivities of the 24 brain regions to other cortical areas was similar but not identical.) Fig. S4 shows that the five regions grouped in the supracallosal anterior cingulate cortex (a23pr, a24pr, 33pr, p32pr, p24pr) have very similar effective connectivities with other cortical regions. The group of area 10 ventromedial prefrontal regions (10r, 10v, 10d, 9m) also have very similar effective connectivities with each other (Fig. S4). For the lateral orbitofrontal cortex, the language-related regions 47s and 47l have very similar effective connectivity to each other. For the medial and lateral orbitofrontal cortex, regions a47r, p47r, 47m, 11l and 13l have somewhat similar connectivities from other brain regions. But apart from this, Fig. S4, together with Figs. 2-4, show that there are considerable differences in the effective connectivities of different regions in the OFC and ACC, underlining the utility of the

parcellation provided in the HCP-MMP1 atlas (Glasser *et al.* 2016a), in that many of its brain regions have, inter alia, differences of connectivity from each other.

Subcortical effective connectivities

The subcortical effective connectivities of the 24 OFC / ACC regions are shown in Fig. S5. Of particular interest are connectivities of the amygdala with the lateral orbitofrontal cortex; of the effective connectivity from the medial orbitofrontal cortex directed towards the substantia nigra pars compacta (SNpc) in which dopamine neurons are found; of the medial orbitofrontal cortex region pOFC the only cortical region with effective connectivity found directed to the nucleus basalis of Meynert which contains cholinergic neurons that project to the neocortex (Zaborszky *et al.* 2008; Zaborszky *et al.* 2018); and of connectivity from pOFC, the pregenual ACC and 10r to the septum which contains cholinergic neurons that project to the hippocampus (Zaborszky *et al.* 2008; Zaborszky *et al.* 2018). These are likely to be important influences on septal neurons, for the only other cortical regions with substantial effective connectivity to the septal region are the hippocampus, subiculum, and v23ab which is part of the posterior cingulate cortex also implicated in episodic memory (Rolls *et al.* 2022d).

Discussion

The main results of this investigation are presented in Figs. 2-7 and are summarized in the abstract. The focus of the discussion is on the implications for function of the effective and functional connectivities and connections described in the Results section. Many of the points made next are based on evidence presented in Figs. 2-7, and a synthesis of the findings is presented towards the end of the Discussion with the summary in Fig. 7.

The lateral orbitofrontal cortex (47s, 47l, a47r, p47r and 47m)

Anterior insular cortex regions such as AAIC, AVI and frontal opercular FOP4 and FOP5 have connectivity/connections with the lateral orbitofrontal cortex (Figs. 2-6), and given that the primary taste cortex is in these anterior insular regions in macaques, this provides a route for taste and oral somatosensory representations (Verhagen et al. 2004; Kadohisa et al. 2005; Rolls 2015, 2016c) to reach the orbitofrontal cortex. Consistent with this, the region with taste neurons in the primate lateral orbitofrontal cortex receives from almost all pyramidal cells in the superficial layers of the insular primary taste cortex (Baylis et al. 1995). Moreover, this anterior insular region is activated by taste in humans (Grabenhorst and Rolls 2008; Grabenhorst et al. 2008a; Rolls 2016c). Further, the texture component of oral signals including viscosity and oral fat texture is represented not only by neurons in the orbitofrontal cortex as well as insula (Rolls et al. 1999; Verhagen et al. 2003; Verhagen *et al.* 2004; Kadohisa *et al.* 2005; Rolls 2015, 2016c; Rolls et al. 2018), but also is revealed by activations to oral fat and other texture signals in the human orbitofrontal cortex where the pleasantness of fat is represented (Grabenhorst et al. 2010b; Rolls 2010; Rolls 2020). The orbitofrontal cortex connectivity with the agranular anterior insular cortex (AAIC) areas may be involved in autonomic/visceral functions (Rolls 2016c; Kleckner et al. 2017) which are activated by rewarding or punishing, that is emotion-provoking (Rolls 2014a, 2018b), stimuli.

The lateral orbitofrontal cortex also has connections with the pyriform (Pir, primary olfactory) cortex which may provide a route for olfactory inputs to reach orbitofrontal cortex areas (Kadohisa *et al.* 2005), and the anterior agranular insular (AAIC / AVI) is an area with taste-olfactory convergence in humans (de Araujo *et al.* 2003). Many olfactory neurons in the primate orbitofrontal cortex alter their responses depending on the taste with which the odor is associated (Critchley and Rolls 1996b; Rolls et al. 1996), and this provides a mechanism for the reward/aversive value and subjective pleasantness of odors to be learned by association with the taste reward value (Rolls and Grabenhorst 2008; Rolls

2019d). Interestingly, pleasant odors are represented in the human medial orbitofrontal cortex, whereas unpleasant odors, which typically have a trigeminal somatosensory component, are represented in the lateral orbitofrontal cortex (Rolls et al. 2003a).

There are also connections of the human lateral orbitofrontal cortex with somatosensory cortical regions (e.g. the middle insula MI in Fig. 6), and this provides a route for the affective (rewarding or punishing) value of touch stimuli to be represented in the human orbitofrontal cortex (Rolls et al. 2003b; McCabe et al. 2008; Rolls 2010).

Visual inputs reach the lateral (and medial) orbitofrontal cortex from the temporal lobe TE areas (Fig. 2) involved in invariant visual object and face representations (Perrett et al. 1982; Rolls 2000; Weiner et al. 2017; Rolls 2021d, 2021a). This provides a route for the reward value of visual stimuli to be represented by neurons in the orbitofrontal cortex, with for example associations between visual stimuli and primary reinforcers such as taste stimuli being learned and reversed in as little as one trial (Thorpe et al. 1983; Rolls *et al.* 1996). Expected reward value is computed in the orbitofrontal cortex in this way (Thorpe *et al.* 1983; Rolls *et al.* 1996; Rolls 2014a, 2021a), and this has been confirmed in macaques (Tremblay and Schultz 2000) and humans (O'Doherty et al. 2002; Rolls et al. 2008c; Rolls *et al.* 2020d). When an expected reward is not obtained, non-reward neurons in the orbitofrontal cortex are activated (Thorpe *et al.* 1983), and this non-reward signal is represented in the human lateral orbitofrontal cortex and supracallosal anterior cingulate cortex (Rolls *et al.* 2020d). Consistent with this, damage to the human orbitofrontal cortex impairs rapid reward reversal, and this makes a great contribution to the emotional changes found in these patients (Rolls et al. 1994; Hornak et al. 2003; Berlin et al. 2004; Hornak *et al.* 2004; Rolls 2019d). The dopamine reward prediction error neurons (Schultz 2017) are likely to receive inputs from the expected reward value and non-reward orbitofrontal cortex neurons, which are together required to compute reward prediction error (Rolls 2017). Consistent with this, region OFC (which has effective connectivity with the lateral orbitofrontal cortex) has effective connectivity directed towards the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA) (Fig. S5), which contain dopaminergic neurons. Medial orbitofrontal cortex regions also have effective connectivity directed towards the caudate nucleus and nucleus accumbens (Fig. S5).

Other visual neurons in the orbitofrontal cortex respond to face expression and gesture which have affective and social signalling value (Rolls et al. 2006), with these inputs probably being received from the regions in the superior temporal sulcus (STS, Figs. 2-5) in which neurons respond to these types of face expression and movement stimuli (Hasselmo et al. 1989a; Hasselmo et al. 1989b; Critchley et al. 2000). Consistent with this, the human lateral orbitofrontal cortex receives inputs from the STS regions (Figs. 2-6), and humans with orbitofrontal cortex damage are impaired at face expression decoding (Hornak et al. 1996; Hornak *et al.* 2003). Auditory neurons that respond for example to vocalization are also found in the orbitofrontal cortex (Rolls *et al.* 2006), and consistent with this auditory neurons are also found in the multimodal STS cortical regions (Baylis et al. 1987) which project to the lateral orbitofrontal cortex (Figs. 2-6), and damage to the human orbitofrontal cortex impairs voice emotional expression processing (Hornak *et al.* 1996; Hornak *et al.* 2003).

The orbitofrontal cortex thus with these inputs can build by associative learning multimodal representations of for example the sight, smell, taste and somatosensory components of objects including foods (Rolls *et al.* 1996; Rolls 2019d, 2021a). In each of these sensory systems in primates including humans the reward or punishment value is represented in the orbitofrontal cortex, but not at the earlier cortical stages of more unimodal processing (Rolls 2019d; Rolls *et al.* 2020b; Rolls 2021a). The conversion to reward/punishment value representations in the orbitofrontal cortex may be achieved at least in part because it allows for example visual inputs to be associated by learning with primary (unlearned) reinforcers such as taste and somatosensory inputs (Rolls *et al.* 1996; Rolls 2014a, 2015, 2019d; Rolls *et al.* 2020b; Rolls 2021a). The representation of reward value in the orbitofrontal cortex at the neuronal level is shown by reward reversal in as little as one trial (Thorpe *et al.* 1983; Rolls *et al.*

1996), reduced firing produced by reward devaluation e.g. during sensory-specific satiety (Rolls et al. 1989; Critchley and Rolls 1996a), and by reflecting economic value (Padoa-Schioppa and Conen 2017). The contribution of the effective connectivity in conjunction with the high resolution HCPex atlas (Glasser *et al.* 2016a; Huang *et al.* 2021a) is that this provides a way for starting to understand the inputs and outputs of each of the 24 regions in the parts of the brain considered here, and should provide a foundation for a better understanding when the same atlas is used for fMRI activation studies.

The investigation also shows that the lateral orbitofrontal cortex has effective connectivity with some language-related areas including areas 44 and 45 (Broca's area), the superior frontal language area (SFL), and with areas in the superior temporal sulcus that may be involved in language (Bornkessel-Schlesewsky et al. 2015; Erickson et al. 2017; Rolls 2021a) (see Figs. 2, 3 and 6). These connectivities, together with the effective connectivities of the lateral orbitofrontal cortex with temporal pole (TG) areas which are implicated in semantic representations (Bonner and Price 2013; DeWitt and Rauschecker 2016; Rolls 2021a), may enable value and emotional representations including pleasantness and unpleasantness to be represented in language, given that activations in the orbitofrontal cortex areas are linearly related to the unpleasantness or pleasantness of stimuli (Grabenhorst and Rolls 2011; Rolls 2019d, 2021a). Indeed, the lateral orbitofrontal cortex may provide a route for reward and punishment value representations to reach language systems so that they can be reported as being subjectively pleasant or unpleasant, and consistent with this, activations in the lateral (and medial) orbitofrontal cortex are linearly related to the subjectively reported pleasantness and unpleasantness of taste, olfactory, tactile and visual stimuli (McCabe and Rolls 2007; Grabenhorst and Rolls 2008; Grabenhorst *et al.* 2008a; McCabe *et al.* 2008; Rolls et al. 2008a; Rolls et al. 2008b; Rolls et al. 2009; Grabenhorst et al. 2010a; Grabenhorst and Rolls 2010; Grabenhorst *et al.* 2010b; Rolls et al. 2010c; Grabenhorst and Rolls 2011). In these language-related functions, regions 47s and 47l may be especially important based on their connectivity with the STS and temporal pole TG regions, with the peri-Sylvian Language area (PSL) and adjacent TPOJ regions, and with the superior frontal language area (SFL) (Figs. 2-5), but most of the lateral orbitofrontal cortex regions have connectivity with language systems as shown by the connectivity of most lateral orbitofrontal cortex regions to regions 44 and 45 (Broca's area) and with the nearby inferior frontal junction (IFJ) and inferior frontal sulcus (IFS) regions (Fig. 3) which are also part of the language system (Rolls *et al.* 2022a).

Effective connectivity was found between the medial and lateral orbitofrontal cortex (Figs. 2-4 and 7), and with both the pregenual and supracallosal cingulate cortices, so these areas do appear to be able to influence each other, and do not operate as separate systems.

It is notable in the context of what follows that the orbitofrontal cortex does not receive effective connectivity from the somato-motor cortical areas 5, 6 and mid-cingulate motor cortex; nor from the posterior cingulate cortex and most parietal cortex areas that implement spatial processing. This is consistent with the evidence that the primate including human orbitofrontal cortex is involved in reward value representations, and not in motor responses or actions (Thorpe *et al.* 1983; Padoa-Schioppa and Assad 2006; Grattan and Glimcher 2014; Rolls 2014a, 2019d, 2019b).

The lateral orbitofrontal cortex does though have outputs directed to the hippocampal memory / navigation system, to the medial orbitofrontal cortex, to parts of area 8 (8BM, 8BL, 8Av), to some of the ventromedial area 10 regions (10r, 10v, 9m), and to parietal PFm (Fig. 3), and to the amygdala (Fig. S5), and these are likely to be important output routes for the lateral orbitofrontal cortex. It is notable that the human amygdala has rather limited effective connectivity with these regions, which is apparent only in part of the lateral orbitofrontal cortex, 47m (Fig. S5). 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; Berlin *et al.* 2004; Hornak *et al.* 2004; Rolls 2019d) 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 2021b; 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 behaviors made to aversive stimuli (Rolls 2014a, 2019d).

Medial orbitofrontal cortex (11l, 13l, OFC, pOFC)

The taste, olfactory, visual and somatosensory inputs to the medial orbitofrontal cortex are somewhat similar to those of the lateral orbitofrontal cortex, and the medial orbitofrontal cortex which has effective connectivity with the lateral orbitofrontal cortex is involved in similar value-related representations and learning, though the medial orbitofrontal cortex represents reward value and has activations correlated with subjective pleasantness (Rolls and Grabenhorst 2008; Grabenhorst and Rolls 2011).

The medial orbitofrontal cortex does have effective connectivity with the hippocampal memory system (Figs. 2-7), and it is proposed that this provides a route for value-related information, key in emotion (Rolls 2014b, 2014a), to be incorporated into hippocampal episodic memories, forming a third, affective, component that is added to the 'what' and 'where' components of episodic memory (Rolls *et al.* 2022b). Consistent with and adding to this, the orbitofrontal cortex has effective connectivity with regions of the posterior cingulate cortex (31pv, 7m, d23ab) related to the hippocampal memory system (Rolls *et al.* 2022d). There are thus two routes (direct and via the posterior cingulate cortex) for value representations to become incorporated into episodic memory, and two routes for the affective value to be recalled back into the orbitofrontal cortex during the retrieval of episodic memory.

However, and in addition, pOFC is the only cortical area found to have effective connectivity directed to the nucleus basalis of Meynert, which includes cholinergic neurons that project to the neocortex (Zaborszky *et al.* 2008; Zaborszky *et al.* 2018; Huang *et al.* 2021a) (Figs. S5 and 7). Different magnocellular neurons in the basal nucleus which are probably cholinergic respond to reinforcing (reward or punishing), or novel, stimuli (Wilson and Rolls 1990b, 1990c, 1990a), both represented in the orbitofrontal cortex (Rolls et al. 2005a; Rolls 2019b, 2019d). It is proposed that this medial orbitofrontal cortex system could contribute to some of the memory impairments related to vmPFC damage, by impairing memory consolidation in neocortex to which the basal forebrain cholinergic system projects (Rolls 2022). In addition, it was found here (Figs. S5 and 7) that there is effective connectivity from especially the pregenual ACC, subgenual 25, and 10r to the septum, which contains cholinergic neurons that project to the hippocampus (Zaborszky *et al.* 2008; Zaborszky *et al.* 2018). These ventromedial prefrontal regions are likely to be important influences on septal neurons, for the only other cortical regions found with substantial effective connectivity to the septal region are the hippocampus, subiculum, and v23ab which is part of the posterior cingulate cortex also implicated in episodic memory (Rolls *et al.* 2022d) (Fig. S5). In accordance with this, it is now proposed that the damage in humans to the ventromedial prefrontal cortex regions including the anterior cingulate cortex that impairs episodic memory (McCormick *et al.* 2018; Ciaramelli et al. 2019) arises in part because of the reduced release of acetyl choline to reward / salient stimuli, which may impair LTP (Hasselmo and Sarter 2011; Newman et al. 2012; Zaborszky *et al.* 2018) and thus memory storage (Rolls 2021a, 2022). Indeed, consistent with this, different orbitofrontal cortex neurons respond to rewarding or to punishing stimuli, and others to novel stimuli (Rolls *et al.* 2005a), which is a further type of 'salient' stimulus that may be utilised to enhance memory storage when these rewarding, punishing, or novel stimuli are encountered, which is evolutionarily adaptive. Together, these three processes are it is proposed likely to make major contributions to the memory deficits reported to follow ventromedial prefrontal cortex damage (Bonnici and Maguire 2018; McCormick *et al.* 2018; Ciaramelli *et al.* 2019; McCormick et al. 2020; 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. 1997; 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) is involved in scene processing (Rolls 2021c), and that the cholinergic influence on the hippocampus is likely to be very important in hippocampal functioning including memory storage (Hasselmo and Giocomo 2006; Giocomo and Hasselmo 2007; Hasselmo and Sarter 2011; Newman *et al.* 2012; Zaborszky *et al.* 2018).

Region OFC has (weak) effective connectivity directed towards the substantia nigra pars compacta (SNpc) (Fig. S5), which contains dopaminergic neurons. The dopamine reward prediction error neurons (Schultz 2017) are likely to receive inputs from the expected reward value and non-reward orbitofrontal cortex neurons, which are together required to compute reward prediction error (Rolls 2017). The nucleus accumbens and habenula may provide routes for this influence on dopamine neurons from the orbitofrontal cortex (Rolls 2017). Indeed, medial orbitofrontal cortex regions do have effective connectivity directed towards the nucleus accumbens as well as the caudate nucleus (Fig. S5).

Area 10 and related ventromedial prefrontal cortex regions (10v, 10r, 10d, 9m)

These regions have connectivity with both the medial and lateral orbitofrontal cortex, and are part of what is sometimes termed the ventromedial prefrontal cortex with activations related to reward processing and decision-making (Grabenhorst et al. 2008b; Rolls and Grabenhorst 2008; Rolls *et al.* 2010b, 2010a; Grabenhorst and Rolls 2011), and damage affecting emotion (Hornak *et al.* 2003; Rolls 2021b) and memory (McCormick *et al.* 2018). These vmPFC regions have effective connectivity with the orbitofrontal cortex (Figs. 2, 3 and 7). The vmPFC also has strong effective connectivity with the posterior cingulate cortex, and with the pregenual anterior cingulate cortex, and with the hippocampal system. It thus appears to be related to the memory / spatial system and hippocampus as described below for pregenual anterior cingulate cortex. It also has some effective connectivity with the auditory association STS cortical areas which are also implicated in semantic processing (Bonner and Price 2013; Rolls 2021a; Rolls *et al.* 2022a). These vmPFC regions are also distinguished by little connectivity with the inferior and dorsolateral prefrontal cortex areas that have activity related to short-term memory and executive function (Passingham 2021; Rolls 2021a). Fig. 7 (to be considered further below) summarizes evidence that these vmPFC area 10 regions can be seen as connecting the medial and lateral orbitofrontal cortex with especially the pregenual anterior cingulate cortex and hippocampal memory system. The connectivity of these vmPFC regions is different from pregenual anterior cingulate regions in that there is connectivity with the superior temporal sulcus (STS), temporal pole (TG), and superior frontal language (SFL) regions (Figs. 2-5) implicated in language (Rolls *et al.* 2022a).

Pregenual anterior cingulate cortex (s32, a24, p24, p32, d32) and subgenual cortex (25)

The connectivity to these regions (which are interconnected) includes effective connectivity from medial orbitofrontal cortex regions (pOFC, OFC and 13l) and area 10 vmPFC regions (which are reward-related) with less from lateral orbitofrontal cortex regions 47 (where activations are related to unpleasant or non-reward events) (see Fig. 7), and in line with this, activations in the pregenual cingulate cortex occur to reward-related pleasant stimuli including pleasant odor, flavor, touch, and monetary reward (Grabenhorst and Rolls 2011; Rolls 2019c, 2021a). Effective connectivity is directed to the hippocampal system (hippocampus, entorhinal cortex and presubiculum) (Figs. 3 and 4), and this provides a route for reward-related information to enter the hippocampal system to provide for value-related, affective, information to be part of the hippocampal episodic memory system (Rolls 2018a), and further, to provide the goal towards which navigation occurs (Rolls 2021a). Indeed, it is a fundamental aspect of navigation that it is towards a goal, and the orbitofrontal cortex / anterior cingulate system can provide that goal-related information (Rolls 2022). Consistent with this, some single neurons in the primate hippocampus respond to combinations of spatial view and reward (Rolls and Xiang 2005).

Other outputs of the pregenual anterior cingulate cortex are directed to some area 8 and 9 prefrontal cortical regions, to some parts pf the supracallosal anterior cingulate which in turn have connectivity to premotor areas (see below and Fig. 7), and to area 10 regions considered next (Fig. 3), and this connectivity could be related to learning associations between actions and the rewards or punishers associated with the actions (Noonan *et al.* 2011; Rushworth *et al.* 2012), for which the pregenual anterior cingulate (and medial orbitofrontal cortex) would provide the reward or goal representation. Consistent with this, individuals with high functional connectivity between the medial orbitofrontal and pregenual anterior cingulate cortex are strongly reward-driven, in that they are more likely to be sensation seekers and to take risks in order to obtain goals (Rolls 2019c; Wan *et al.* 2020; Rolls *et al.* 2022c).

The subgenual cingulate cortex area 25 has relatively similar connectivity to the other pregenual anterior cingulate regions except with prefrontal regions. Area 25 has strong connectivity directed to the septal nuclei (Figs. S5 and 7).

Supracallosal anterior cingulate cortex (a32pr, a24pr, 33pr, p32pr, p24pr)

These regions do receive inputs from the orbitofrontal cortex (e.g. from 11l, 13l, OFC and pOFC) and pregenual cingulate cortex (Figs. 2 and 7), and thus receive value-related representations, but are rather different from many of the other brain groups considered here in having in addition connectivity from many somatosensory and visuo-motor regions: somatosensory cortex 5L, 5mv and inferior parietal PFop (Rolls *et al.* 2022e); superior parietal 7AL and 7Am; and from 23d and related parts of the antero-dorsal visuo-motor part of the posterior cingulate cortex (Rolls *et al.* 2022d). This group of regions is also different in having outputs to midcingulate cortex premotor regions 24dd and 24dv; premotor area 6 and the frontal eye fields FEF; frontal opercular FOP and related opercular somatosensory areas; somatosensory insular regions (e.g. MI, PI, AVI, PoI); and to the Peri-Sylvian Language area (PSL) (Figs. 3 and 7). The supracallosal anterior cingulate cortex thus has outputs to cortical areas involved in limb and body movements. This set of connectivities suggest that this is the key part of the anterior cingulate cortex that is related to learning associations between actions and the rewards or punishers associated with the actions (Noonan *et al.* 2011; Rushworth *et al.* 2012). For this, the orbitofrontal cortex inputs provide it is proposed the reward/punishment representation, and the connectivity with somatosensory and premotor regions the required evidence about actions just performed and the required outputs to especially limb and body systems. The findings that this brain region is activated primarily by punishers and non-reward (Grabenhorst and Rolls 2011; Rolls 2019c; Rolls *et al.* 2020d; Rolls 2021a) may be that limb and body movements which utilise premotor cortical output regions are often made to avoid aversive stimuli. In contrast, the reward-related pregenual anterior cingulate cortex was proposed above to be en route for navigation-based systems, which are utilised generally to obtain rewards or goals. *This may be a fundamental concept about differences between the pregenual and supracallosal anterior cingulate cortex*. Indeed, this is a useful extension to the action-reward outcome theory of the cingulate cortex (Rolls 2019c), in that it provides evidence that there are two types of output to action from the anterior cingulate cortex, one from the pregenual anterior cingulate cortex to the hippocampal system important for reward-guided action in space and navigation; and another from the supracallosal anterior cingulate cortex important for mainly limb and body movements learned to avoid punishing reinforcers. This is an interesting result that is produced by this research.

It is noted that non-reward in for example a reward reversal task activates not only the supracallosal anterior cingulate cortex regions described here, but also more dorsal regions (Kringelbach and Rolls 2003; Grabenhorst and Rolls 2011; Rolls *et al.* 2020d) that include 8BM and that may also be treated as part of the supracallosal anterior cingulate cortex, and to which the lateral orbitofrontal cortex projects (as shown in Figs. 2-4).

Interhemispheric effective connectivity

The contralateral connectivity of most of the 24 brain regions investigated here appears to be mainly, at least for the stronger connectivities, between corresponding cortical regions in the two hemispheres (compare Figs. 2 and 3 with S2 and S3). This is a mode of connectivity that minimizes connection lengths and therefore brain size by connecting hierarchical processing streams within each hemisphere (Rolls 2021a), and restricting contralateral connectivity to exchange activity at a similar level of processing between the two hemispheres. It is now proposed that this is an important property of connectivity within the bi-hemispheric brain, though there are exceptions, as shown for example by the connectivity of the supracallosal anterior cingulate cortex to a number of contralateral premotor cortical regions as described in the Results.

Translational implications for understanding emotional disorders and individual differences

The connectivity with the medial orbitofrontal cortex that is characteristic of all the pregenual / subgenual anterior cingulate cortex regions is of interest in relation to depression, for the electrical stimulation in these regions (sometimes described as 'subcallosal') that may reduce depression (Hamani et al. 2011; Lujan et al. 2013; Mayberg et al. 2016; Riva-Posse *et al.* 2018; Siddiqi *et al.* 2021) may act in part it is proposed here by activating the medial orbitofrontal cortex, which is known to be a key brain region related to reward processing and to depression (Rolls 2018b, 2019d, 2019b; Rolls *et al.* 2020b). In this context, it is useful to remember that the mid-orbitofrontal cortex is a key brain site in macaques in which electrical stimulation of the brain produces reward (Rolls et al. 1980; Rolls *et al.* 2020b). Relating to this, it has been found that the efficacy of subcallosal electrical stimulation for depression is related to the status of the medial orbitofrontal cortex (Elias et al. 2021b), and the stimulation also decreased activity in the supracallosal anterior cingulate cortex (Elias et al. 2021a), in which aversive and non-reward stimuli are represented (Grabenhorst and Rolls 2011; Rolls *et al.* 2020d).

In the context of depression, it has been found that patients with depression have lower functional connectivity of the reward-related medial orbitofrontal cortex with a number of brain regions including the medial temporal lobe memory system, and not only is this likely to be related to the anhedonia of depression, but the lower connectivity is not normalized by treatment with modern antidepressant drugs (Cheng *et al.* 2016; Cheng *et al.* 2018a; Cheng *et al.* 2018b; Cheng *et al.* 2018c; Rolls *et al.* 2020a). An implication is that it could be useful to search for drugs that increase the activity or connectivity of the medial orbitofrontal cortex to help treat depression. In contrast the functional connectivity of the non-reward related lateral orbitofrontal cortex with a number of brain regions is higher in depression (Cheng *et al.* 2016; Cheng *et al.* 2018a; Cheng *et al.* 2018b; Cheng *et al.* 2018c; Rolls *et al.* 2020a), and this is consistent with the theory of depression that a component of depression is increased sensitivity to non-reward, and hence increased sadness (Rolls 2016a, 2018b). Consistent with this, it has been shown in adolescents at risk for depression that there is decreased sensitivity of the medial orbitofrontal to reward, and increased sensitivity of the lateral orbitofrontal cortex to non-reward (not winning) in the monetary incentive delay task (Xie et al. 2021). Most of these investigations were with the automated anatomical labelling atlas with 94 cortical areas defined mainly by topology (Rolls et al. 2015; Rolls et al. 2020c), and it is a priority to obtain evidence now using the HCP-MMP atlas and the connectivity described here, for this will provide much more detailed evidence about the brain regions that have different functionality in depression. For example, is the connectivity of the orbitofrontal cortex with the parietal regions involved in body image and self representations (Rolls *et al.* 2022e) different in depression, relating it is suggested to the low self-esteem that can occur in depression?

The findings that the medial orbitofrontal cortex has effective connectivity directed to the nucleus basalis of Meynert and the pregenual cingulate to the septum (Figs. 7 and S5) leads to the hypothesis that damage to the orbitofrontal cortex and anterior cingulate cortex may contribute to memory impairments (McCormick *et al.* 2018) by disrupting cholinergic influences on the neocortex and hippocampus from the basal nucleus and septum respectively. This has implications for understanding the impairments in patients that follow brain damage to the medial orbitofrontal cortex, vmPFC, and anterior cingulate cortex regions. It also has implications for understanding the effects of electrical stimulation of these medial orbitofrontal and pregenual anterior cingulate cortical regions, for such electrical stimulation is likely to produce enhanced attention, alertness and memory because of actions of these cholinergic systems on the neocortex and hippocampus (Hasselmo and Sarter 2011). It is proposed here that this could contribute to the possible beneficial effects of electrical stimulation of these anterior cingulate and related cortical regions in depression (Elias *et al.* 2021a; Elias *et al.* 2021b). To understand how these influences normally operate, it has been discovered that different neurons in the nucleus basalis are activated by rewarding, punishing, or novel stimuli (Rolls *et al.* 1980; Wilson and Rolls 1990b, 1990c, 1990a), which are represented in the orbitofrontal cortex (Thorpe *et al.* 1983; Rolls *et al.* 1989; Critchley and Rolls 1996a; Rolls *et al.* 1996; Rolls *et al.* 2005a; Rolls 2019b, 2019d). These cholinergic neurons may thus strobe cortical areas at times when it may be especially important to store new memories (Rolls and Deco 2015; Rolls 2021a). This same cholinergic system is implicated in the effects of normal aging on memory (Rolls and Deco 2015).

The connectivity of the orbitofrontal cortex and anterior cingulate cortex described here is also useful in understanding personality differences better. For example, sensation-seeking is related to high connectivity between medial orbitofrontal cortex and anterior cingulate regions (Wan *et al.* 2020), and so is risk-taking (Rolls *et al.* 2022c), implying that a component of both is sensitivity to reward and its link to action systems. The same applies to understanding difficulties in the control of food intake, with higher body weight related to higher functional connectivity of the medial orbitofrontal cortex (Rolls et al. 2021), which again provides evidence that differences in the functioning or connectivity of the brain regions described here can be related to individual differences. Even understanding these differences may help in treatment (Rolls 2018b).

Evaluation of the methodology

The use of the HCP-MMP surface atlas (Glasser *et al.* 2016a) was very helpful, in providing 360 cortical areas. This level of resolution was very helpful in resolving the connections between brain regions. For example, with this level of resolution it was possible to show that two regions (47s and 47l) of the five in the lateral orbitofrontal cortex have connectivity with the auditory (and possibly semantic) areas in the cortex in the superior temporal sulcus, with the superior frontal language area (SFL), and with the temporal pole (TG areas, also implicated in semantic representations (Rolls 2021a)); that pOFC is the main cortical area with effective connectivity to the (cholinergic) basal forebrain nucleus of Meynert which by releasing acetyl choline in the cortex may facilitate memory storage (Rolls and Deco 2015; Rolls 2022); that different parts of the orbitofrontal cortex / vmPFC / anterior cingulate cortex system have connectivity with different parts of the inferior frontal gyrus and dorsolateral prefrontal cortex areas (Figs. 2-4) suggesting that these different lateral prefrontal regions implement different types of short-term / working memory; and that the effective connectivity with contralateral brain regions can be primarily to regions as small as those defined in the HCP-MMP atlas (Figs. S2 and S3). This provides great support for the strategy used in the HCP-MMP atlas to define many different cortical regions (Glasser *et al.* 2016a).

At the same time, the effective connectivities described here show that some grouping of regions defined in the HCP-MMP can be made based on their connectivity to help understand function. For example, 47s and 47l have similar effective connectivity; and the regions grouped into the

supracallosal anterior cingulate cortex have similar effective connectivity to each other (see Figs. 2, 3 and S4).

The use of the Hopf effective connectivity algorithm (Rolls *et al.* 2022b) was also very helpful in that it provides evidence on the direction of influence (which diffusion tractography and functional connectivity do not), which is important in understanding brain function such as hierarchical processing, memory storage vs recall, top-down attention, etc (Deco and Rolls 2005; Rolls 2016b, 2021a). Although in many of the effective connectivity links analyzed there were bidirectional effects, the connectivities were frequently stronger in one direction (see Fig. 4, and as is expected in cortical systems (Rolls 2016b, 2021a)). For example, effective connectivities tended to be stronger from visual and other sensory cortical areas to the orbitofrontal cortex than in the return direction. In another example, effective connectivities tended to be stronger from the orbitofrontal cortex, vmPFC and anterior cingulate cortex to the hippocampal system used for storage than in the backprojection direction used for memory recall, which is consistent with theoretical understanding (Rolls 2016b, 2021a). In another example, effective connectivities from the supracallosal anterior cingulate cortex to motor cortical areas tended to be stronger than in the reverse direction, consistent with the hypothesis that the supracallosal anterior cingulate cortex can drive motor output. In some cases, the effects in each direction were very different. For example, medial orbitofrontal cortex region 11l has considerable effective connectivity (0.029) to the supracallosal anterior cingulate cortex regions a32pr, 33pr, with no return effective connectivity. (Note that what is shown in Fig. 7 for connectivity in different directions shows the strongest connectivity among several links, so is not representative of the differences in effective connectivity for individual links.)

The Hopf effective connectivity algorithm has been validated in a number of ways. First, in a cross-validation design, with a data split of the 172 participants into two groups, the effective connectivities in the two groups were correlated 0.98 (Rolls *et al.* 2022b). Second, the effective connectivities between early visual cortical areas were as predicted with stronger effective connectivities in the forward direction V1 to V2 to V3 to V4 than in the reverse direction (Huang *et al.* 2021b). Third, the functional connectivities in the dataset (Fig. 5) were what is expected given the effective connectivities measured by the Hopf algorithm. Fourth, the measured effective connectivities with each hemisphere (i.e. ipsilaterally) were stronger than the effective connectivities between the hemispheres (i.e. contralaterally, see Figs. 2 and 3 vs S2 and S3)), as expected. Nevertheless, there may be limitations of the Hopf algorithm, in that the effective connectivity of the algorithm can generate the empirically measured functional connectivities at time t and $t+tau$ with a correlation of in the order of 0.8 (whereas 1.0 would be better). Moreover, although the effective connectivities measured by the algorithm can generate the functional connectivities at time t and $t+tau$, this may not be a unique set of effective connectivities that generate the functional connectivities.

The actual values of the effective connectivity measure used here are scaled to a maximum value of 0.2, but for most of these regions are considerably lower than that. The reason for this is that the effective connectivity between early visual areas V1 to V2 is very strong, and that sets the maximum value across all cortical areas (Rolls *et al.* 2022b). The Hopf effective connectivity algorithm is non-linear, and sets to zero effective connectivities that do not contribute to the generation of the optimal t and $t+tau$ functional connectivity matrices in the generative model. The non-zero effective connectivity values are those that are involved in generating the optimal functional connectivity matrices. Their reliability is indicated by the cross-validation in which with a data split of the 172 participants into two groups, the effective connectivities in the two groups were correlated 0.98 (Rolls *et al.* 2022b).

Comparison with neuroanatomical investigations in macaques

A brief comparison with neuroanatomical findings in macaques (Carmichael et al. 1994; Carmichael and Price 1995a; Carmichael and Price 1995b; Carmichael and Price 1996; Ongür and Price

2000; Price 2006; Barbas 2007; Saleem *et al.* 2008; Vogt 2009; Mackey and Petrides 2010; Saleem *et al.* 2014; Pandya et al. 2015; Garcia-Cabezas and Barbas 2017; van Heukelum et al. 2020) is provided here, for they provide support in many cases for the evidence described here for humans. It is noted that the lateral orbitofrontal cortex of macaques, area 12, is known as 12/47 in humans, and as 47 in the HCP-MMP1 atlas (Glasser *et al.* 2016a; Huang *et al.* 2021a) used here. For example, taste inputs reach the orbitofrontal cortex from the insular primary taste cortex (Baylis *et al.* 1995), olfactory inputs from the pyriform cortex (Carmichael *et al.* 1994), visual inputs from the inferior temporal visual cortex (especially TEav) and the cortex in the superior temporal sulcus (STSf/v) (to both medial OFC 11 and 13 and lateral OFC 12) (Saleem *et al.* 2008), and somatosensory inputs from the frontal operculum and insula (Saleem *et al.* 2008). Connections with the amygdala in macaques are mainly with lateral orbital areas 12o, 12m, and 12l and medial wall areas 24a,b and 32. A 'medial network' (which includes the anterior cingulate cortex and area 14) has connections with the rostral superior temporal gyrus (STGr) and the dorsal bank of the superior temporal sulcus (STSd); and with the hippocampus, entorhinal cortex and posterior cingulate cortex (Carmichael and Price 1996; Saleem *et al.* 2008).

Synthesis

The new findings for humans described here are now incorporated into a synthesis with reference to the summary of effective connectivity in Fig. 7. Part of the background is that the human orbitofrontal cortex encodes reward value and pleasantness in the medial orbitofrontal cortex, and punishment value, unpleasantness, and non-reward in the lateral orbitofrontal cortex (Grabenhorst and Rolls 2011; Rolls 2019b; Rolls *et al.* 2020b; Rolls 2021b). The pregenual anterior cingulate cortex is activated by rewards, and the supracallosal anterior cingulate cortex is activated by non-rewards and punishers (Grabenhorst and Rolls 2011; Rolls 2019c; Rolls *et al.* 2020d). For the following text, citations to the relevant literature are provided in the earlier part of the Discussion, and are not repeated here for clarity unless this is especially useful.

1. Fig. 7 shows how a large part of the output of the medial and lateral orbitofrontal cortex is directed towards the hippocampal system for memory and navigation. Navigation is generally towards goals, usually rewards, and it is proposed that this connectivity provides the goals for navigation. It is also 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.

2. The routes from the orbitofrontal cortex to the hippocampal memory / navigation system are both direct, and via the ventromedial area 10 regions (10r, 10d, 10v and 9m), pregenual anterior cingulate cortex, and the memory-related parts of the posterior cingulate cortex (Fig. 7).

3. The medial and lateral orbitofrontal 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 2019d, 2019b, 2021a). Taste and somatosensory inputs provide information about primary reinforcers or outcome value, and the 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.

4. Two regions of the lateral orbitofrontal cortex, 47l and 47s, are especially connected with language systems in the temporal pole (TG), cortex in the superior temporal sulcus (STS), and inferior frontal gyrus including Broca's area 45 and 44 (Rolls *et al.* 2022a). This provides a route for subjective reports to be made about the pleasantness or unpleasantness of stimuli and events.

5. The pregenual anterior cingulate cortex differs from the orbitofrontal cortex in receiving inputs from the motor-related supracallosal anterior cingulate cortex. Consistent with this, reward / punishment value is represented in the orbitofrontal cortex but not movements, whereas the pregenual anterior cingulate cortex may relate more to actions.

6. However, 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 2019c), the part of the anterior cingulate cortex that is most likely to be involved in action-outcome learning is the supracallosal anterior cingulate cortex, which has strong effective connectivity with somato-motor areas involved in actions, but which as shown in Fig. 7 receives 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.

7. The ventromedial prefrontal area 10 regions (10r, 10d, 10v) with the closely related 9m have effective connectivity with not only medial and lateral orbitofrontal cortex regions, but also with regions in the STS involved in semantic and auditory processing, so may provide a medial route into language systems. These vmPFC regions are linked into the hippocampal memory / navigation system that is guided by goals, rather than the supracallosal body action system.

8. Part of the importance of the orbitofrontal cortex and pregenual anterior cingulate and vmPFC regions in memory is likely to be that especially the pregenual anterior cingulate cortex and subgenual region 25 provide inputs to the septum, in which cholinergic neurons are present that project to the hippocampus and play important roles in memory storage in the hippocampal system. Further, the pOFC region is the only cortical region found with effective connectivity to the basal forebrain nucleus of Meynert in which cholinergic neurons are found that project to the neocortex, and which are likely to be involved in memory consolidation in the neocortex. Damage to these key OFC and pregenual anterior cingulate inputs to the septum and nucleus basalis are likely to be a key component of the memory problems produced by damage to the OFC / vmPFC / pregenual anterior cingulate cortex region (Rolls 2022).

Conclusions

Until now, much of our understanding of the connectivity of the human orbitofrontal cortex, vmPFC, and anterior cingulate cortex has been based on important neuronal tract-tracing studies in macaques (Ongür and Price 2000; Price 2006; Saleem *et al.* 2008; Saleem *et al.* 2014). Indeed, previously an attempt was made at a synthesis of the connectivity of the human medial prefrontal and orbitofrontal cortex based on anatomical studies in macaques (Ongür and Price 2000), but it did not link closely to how the system might operate. Indeed, the present study goes beyond earlier studies in many ways. First, it is performed in humans, and there has been considerable development of the human orbitofrontal cortex, vmPFC, and anterior cingulate cortex compared to the macaque (Öngür *et al.* 2003; Vogt 2009; Passingham and Wise 2012; Vogt 2019; van Heukelum *et al.* 2020; Passingham 2021). Second, the present study is based on multimodal parcellation of these and all other cortical regions into 360 regions in humans (Glasser *et al.* 2016a) which enables human MRI studies to be easily mapped (Huang *et al.* 2021a) into a connectivity space using this HCP-MMP parcellation as described here.

Third, the present study goes beyond anatomical studies in macaques by providing a measure of the physiological effect of one brain region on another, which depends on factors beyond whether an anatomical pathway is present by taking into account factors such as synaptic strength, and the site of termination of neurons on the dendrites which is an important difference between forward and backprojection pathways in the cerebral cortex (Markov et al. 2014a; Markov et al. 2014b; Rolls 2016b, 2021a). Fourth, the effective connectivity measure used here provides evidence about the relative strengths of the connectivity in both directions separately (see Figs. 2-4). Moreover, effective connectivity is measured by a causal, generative, model (Rolls *et al.* 2022b), and in this respect goes beyond functional connectivity which reflects correlations. Fifth, the current approach is leading to new concepts about the organization of the orbitofrontal cortex, vmPFC and anterior cingulate cortex. These are described above, and include the points that connectivity from the medial orbitofrontal cortex to the pregenual anterior cingulate cortex provides a route for actions in external viewed space to be linked with rewards via connectivity to the posterior cingulate cortex, parietal areas, and hippocampus; and from the supracallosal anterior cingulate cortex for body responses to be made to punishing or rewarding stimuli via its connections to somatomotor areas such as area 6, 5 and the mid-cingulate motor cortex; and that parts of the lateral orbitofrontal cortex area 47 and parts of the ventromedial area 10 regions have connectivity to language-related cortical areas.

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Conflict of interest. The authors have no competing interests to declare.

Data and code availability. The data are available at the HCP website http://www.humanconnectome.org/. Code for the Hopf effective connectivity algorithm is available at https://github.com/decolab/Effective-Connectivity--Hopf.

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Ethical Permissions. No data were collected as part of the research described here. The data were from the Human Connectome Project, and the WU-Minn HCP Consortium obtained full informed consent from all participants, and research procedures and ethical guidelines were followed in accordance with the Institutional Review Boards (IRB), with details at the HCP website (http://www.humanconnectome.org/).

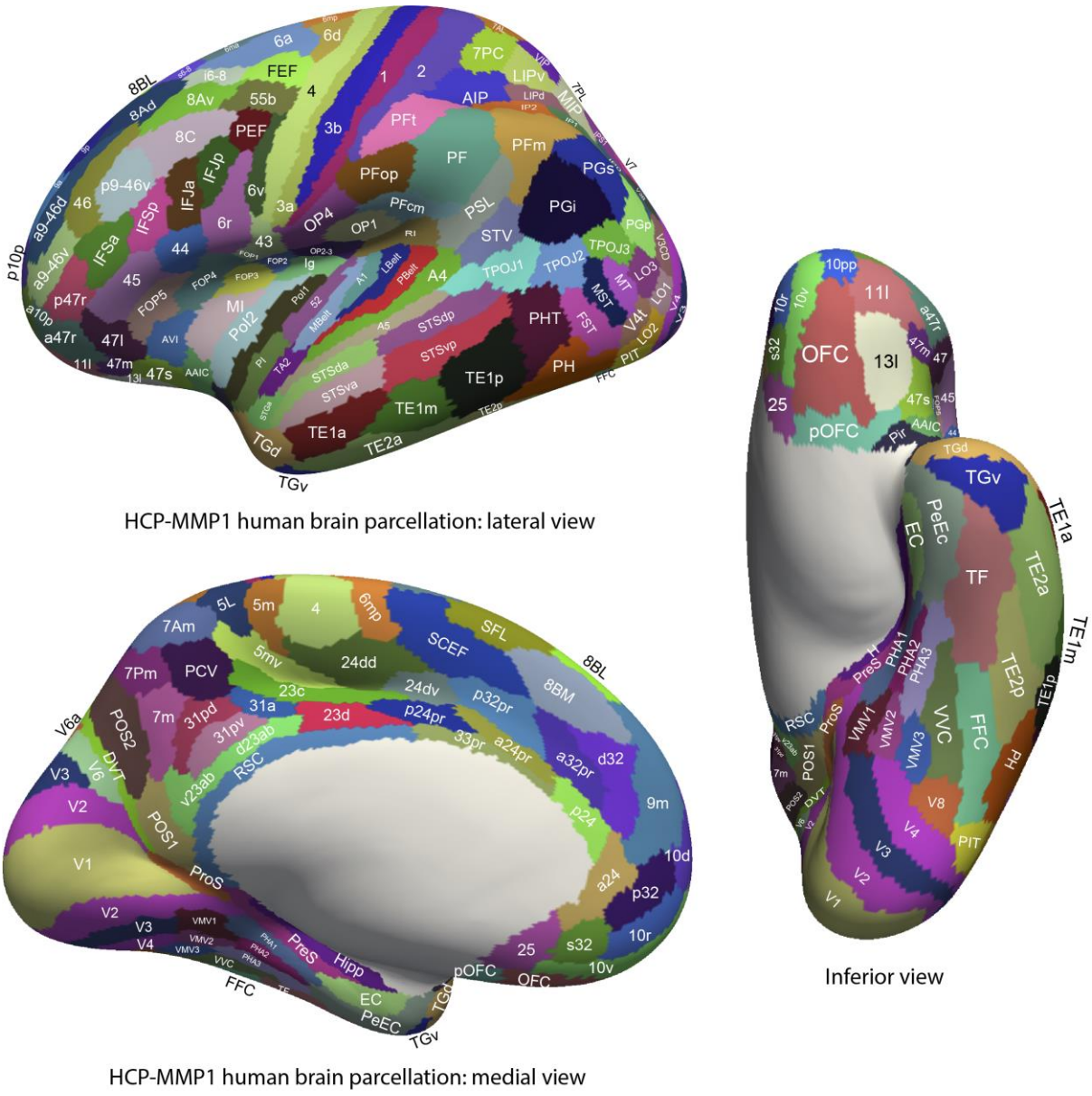

Fig. 1. Regions of interest of the human cortex as defined in the HCP-MMP atlas (Glasser *et al.* 2016a), and in its extended version HCPex (Huang *et al.* 2021a). The regions are shown on images of the human brain with the sulci expanded sufficiently to allow the regions within the sulci to be shown. The regions investigated are: Lateral orbitofrontal cortex: 47s, 47l, a47r, p47r, 47m. Medial orbitofrontal cortex: 11l, 13l, OFC, pOFC. Subgenual cingulate cortex: 25. Pregenual anterior cingulate cortex: s32, a24, p24, p32, d32. Area 10: 10v, 10r, 10d, 9m. Supracallosal anterior cingulate cortex: a32pr, a24pr, 33pr, p32pr, p24pr. Abbreviations are provided in Table S1. (HCPBrainMaster4a.eps)

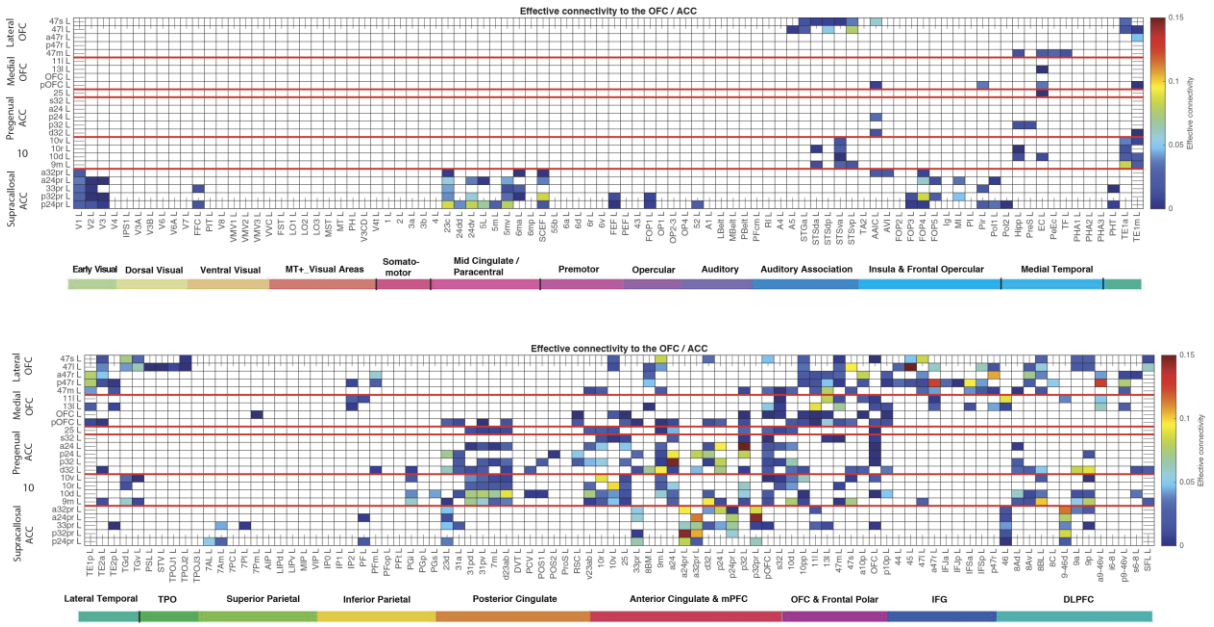

Fig. 2. Effective connectivity to the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) from all 180 cortical regions in the left hemisphere. The area 10 group consists of 10v, 10r, 10d and 9m, and are included here because they are close to and have somewhat similar connectivity to the pregenual ACC group, and are part of what is sometimes termed the ventromedial prefrontal cortex. The effective connectivity is read from column to row. All effective connectivities greater than 0 are shown, and effective connectivities of 0 are shown as a blank. The connectivities from the first set of cortical regions are shown above, and from the second set below. All effective connectivity maps are scaled to show 0.15 as the maximum, as this is the highest effective connectivity found between this set of brain regions. The effective connectivity algorithm for the whole brain is set to have a maximum of 0.2, and this was for connectivity between V1 and V2. Abbreviations: see Table S1; 25 – subgenual cingulate cortex. Illustrations of brain regions: Figs. 1 and S1. (ECtoOFC2.eps)

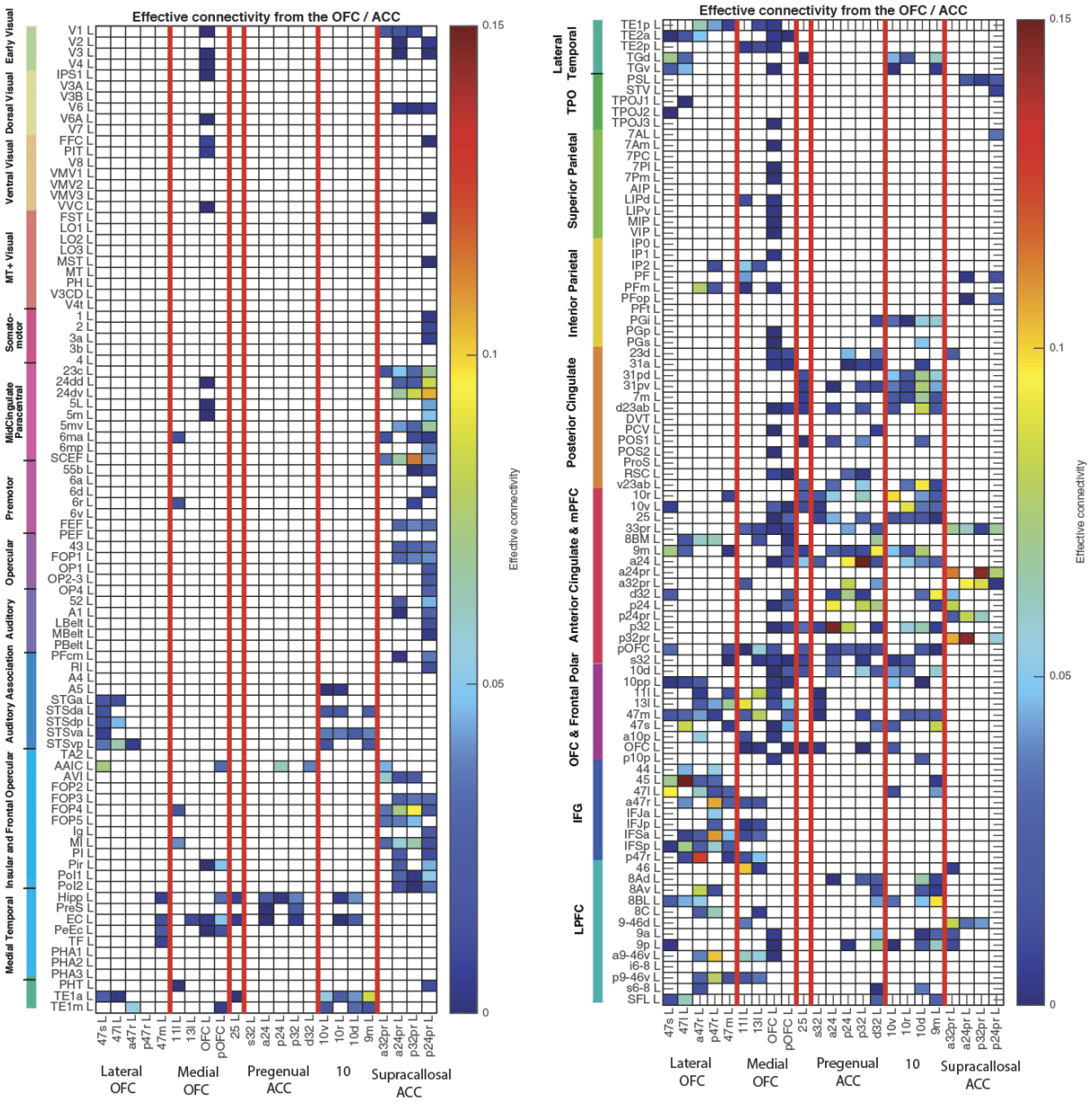

Fig. 3. Effective connectivity from the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) to all 180 cortical regions in the left hemisphere. All effective connectivities greater than 0 are shown, and effective connectivities of 0 are shown as a blank. The connectivities to the first set of cortical regions are shown on the left, and to the second set on the right. The effective connectivity is read from column to row. Conventions as in Fig. 2. Abbreviations: see Table S1; 25 – subgenual cingulate cortex. (ECfromOFC2.eps)

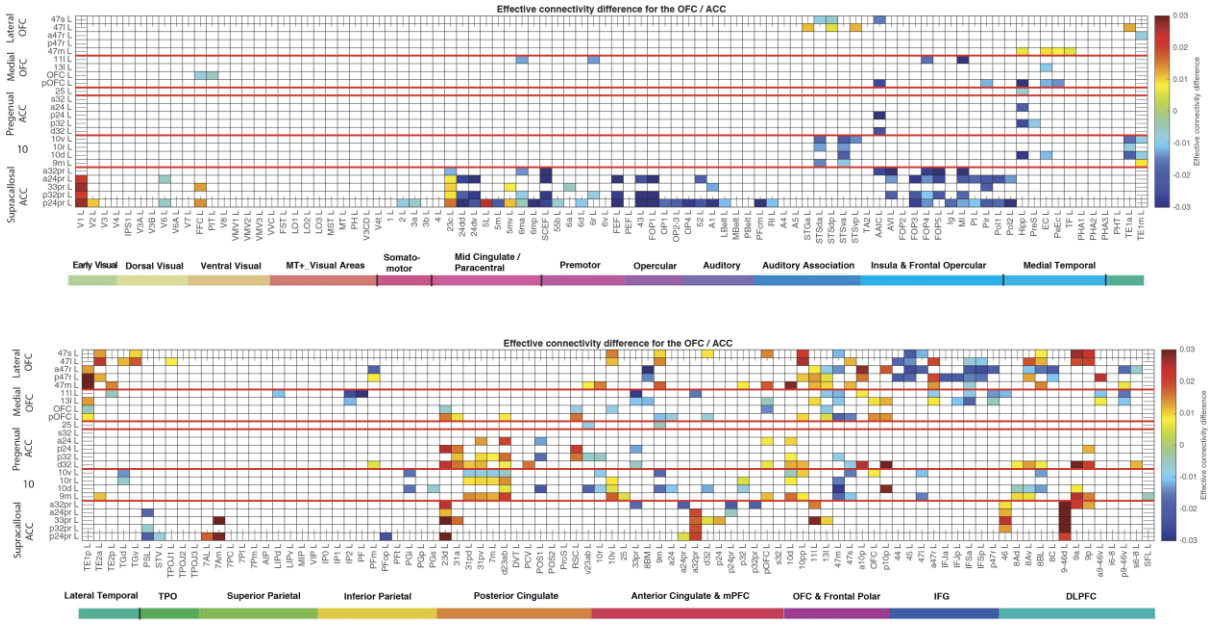

Fig. 4. Difference of the effective connectivity for the orbitofrontal cortex / anterior cingulate cortex system with cortical regions. For a given link, if the effective connectivity difference is positive, the connectivity is stronger in the direction column to row. For a given link, if the effective connectivity difference is negative, the connectivity is weaker in the direction from column to row. This is calculated from 172 participants in the HCP imaged at 7T. The threshold value for any effective connectivity difference to be shown is 0.005. The abbreviations for the brain regions are shown in Table S1, and the brain regions are shown in Figs. 1 and S1. The effective connectivity difference for the first set of cortical regions is shown above; and for the second set of regions below. (OFCECdiff2.eps)

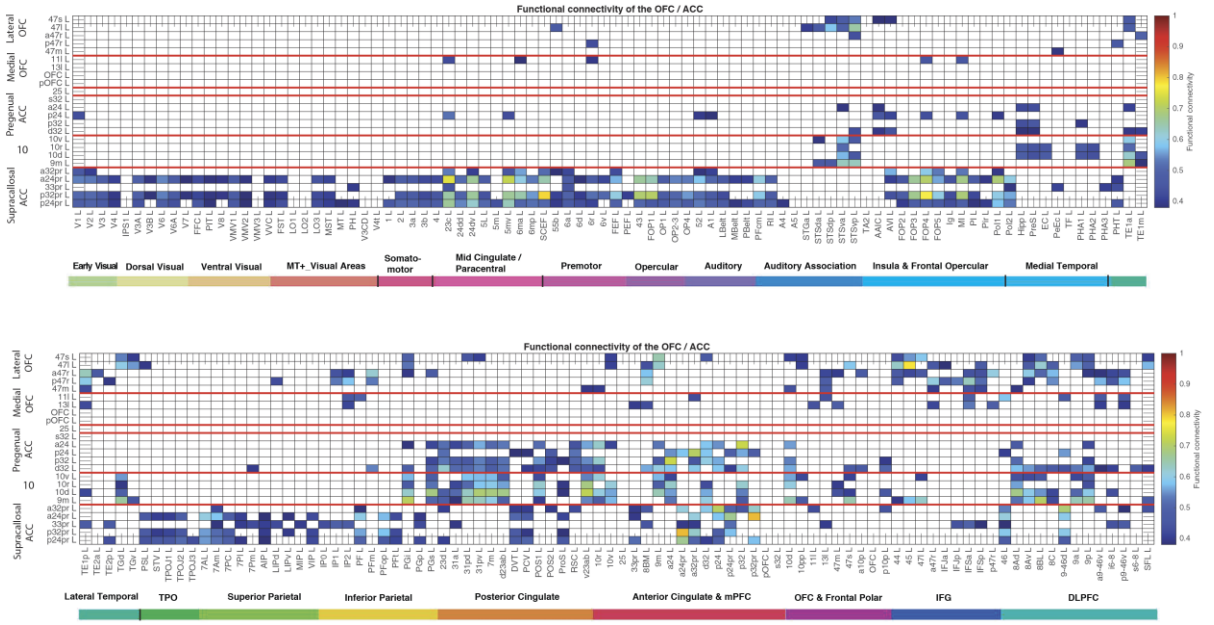

Fig. 5. Functional connectivity between the Orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) and 180 cortical regions in the left hemisphere. Functional connectivities less than 0.38 are shown as blank. The upper figure shows the functional connectivity with the first half of the cortical regions; the lower figure shows the functional connectivity with the second half of the cortical regions. Abbreviations: see Table S1; 25 – subgenual cingulate cortex. (FC_OFC2.eps)

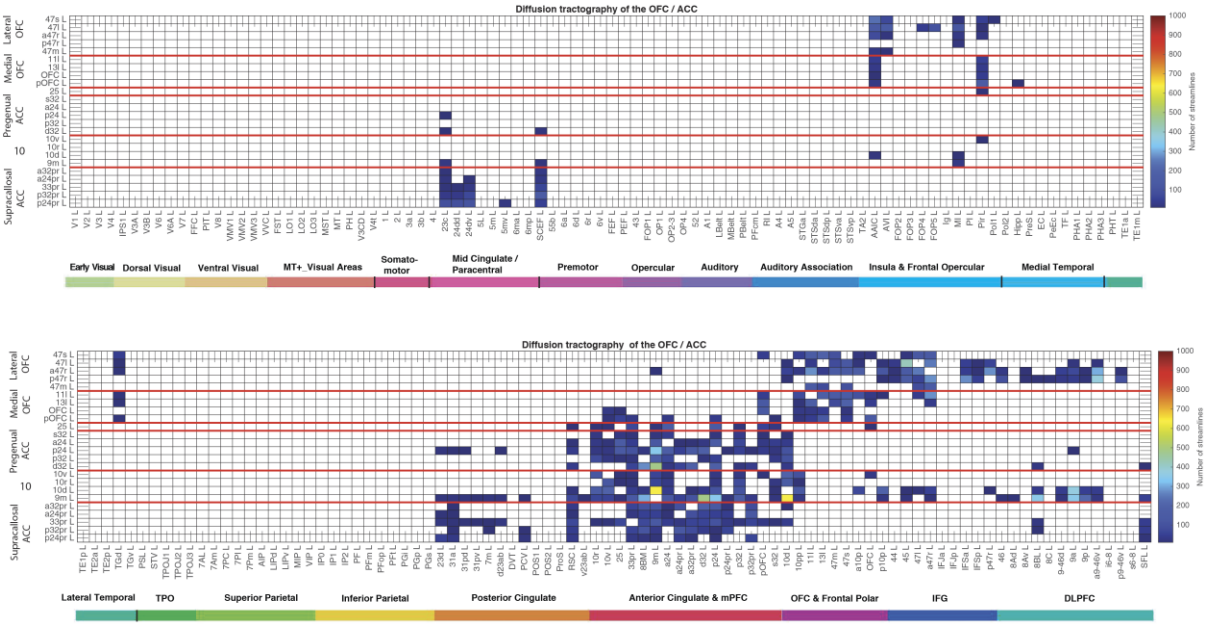

Fig. 6. Connections between the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) and 180 cortical regions in the left hemisphere as shown by diffusion tractography using the same layout as in Figs. 2, 4 and 5. The number of streamlines shown was thresholded at 10 and values less than this are shown as blank. Abbreviations: 25 – subgenual cingulate cortex and Table S1. (SC_OFC2.eps)

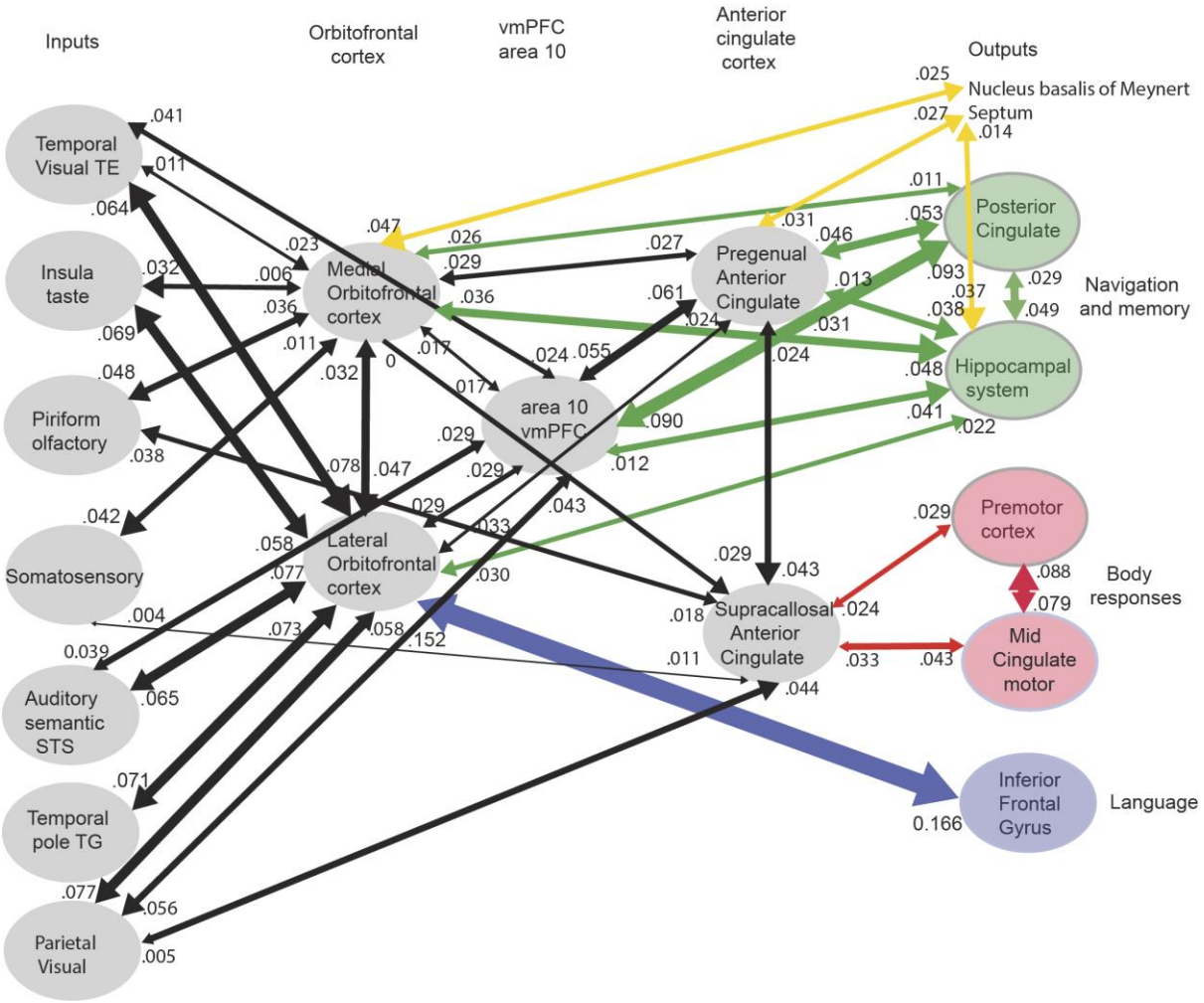

Fig. 7. Synthesis of the effective connectivity of the orbitofrontal cortex, vmPFC, and anterior cingulate cortex shown in the middle, with inputs on the left and outputs on the right. The regions included for each of the 5 central ellipses are as defined in the text, and are separated by red lines in Figs. 2-6. 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 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. The connectivity with dorsolateral prefrontal cortex is shown in Figs. 2-6 and is not included here for clarity. Connectivity is shown for the five groups in the centre of the Figure, and does not include for example connectivity between somatosensory and premotor cortical regions. (OFCconns3.eps)

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