Human Amygdala compared to Orbitofrontal Cortex Connectivity, and Emotion

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Abstract

The amygdala and orbitofrontal cortex have been implicated in emotion. To understand these regions better in humans, their effective connectivity with 360 cortical regions was measured in 171 humans from the Human Connectome Project, and complemented with functional connectivity and diffusion tractography. The human amygdala has effective connectivity from few cortical regions compared to the orbitofrontal cortex: primarily from auditory cortex A5 and the related superior temporal gyrus and temporal pole regions; the piriform (olfactory) cortex; the lateral orbitofrontal cortex 47m; somatosensory cortex; the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal TF; and from the cholinergic nucleus basalis. The amygdala has effective connectivity to the hippocampus, entorhinal and perirhinal cortex; to the temporal pole; and to the lateral orbitofrontal cortex. The orbitofrontal cortex has effective connectivity from gustatory, olfactory, and temporal visual, auditory and pole cortex, and to the pregenual anterior and posterior cingulate cortex, hippocampal system, and prefrontal cortex, and provides for rewards and punishers to be used in reported emotions, and memory and navigation to goals. Given the paucity of amygdalo-neocortical connectivity in humans, it is proposed that the human amygdala is involved primarily in autonomic and conditioned responses via brainstem connectivity, rather than in reported (declarative) emotion.

Introduction

There is much evidence, especially from rodents, that the amygdala is involved in responses to aversive stimuli, and, it has been argued, in emotion (LeDoux, 1994; LeDoux, 1995; LeDoux, 1996; Quirk *et al.*, 1996; Killcross *et al.*, 1997; Rogan *et al.*, 1997; LeDoux, 2000; Johansen *et al.*, 2010). Auditory inputs reach the rodent amygdala from the auditory cortex, and associations can be learned in the lateral amygdala between auditory stimuli such as a tone and an aversive somatosensory stimulus such as an electric shock (LeDoux, 1994; LeDoux, 1995; LeDoux, 1996; Quirk *et al.*, 1996; Rogan *et al.*, 1997; LeDoux, 2000; Johansen *et al.*, 2010), with NMDA receptors involved in this type of associative learning (Davis, 1992, 1994; Davis *et al.*, 1995; Davis, 2006). In the context that pure tone auditory stimuli have been used that do not require cortical processing, it has also been found that there is a "low road" from the medial geniculate nucleus to the lateral amygdala that can be involved in such conditioning (Quirk *et al.*, 1996). Outputs from the amygdala then reach subcortical structures to implement responses to the conditioned aversive stimuli, with outputs from the central nucleus of the amygdala reaching the hypothalamus for conditioned autonomic responses, the central gray in the brainstem for conditioned freezing, and the basal nucleus of Meynert for conditioned cortical arousal; and outputs from the amygdala basal nucleus reaching the ventral striatum for learned incentive effects (Quirk *et al.*, 1996). It has also been shown that the rodent amygdala is involved in conditioned responses to rewarding stimuli (Cador *et al.*, 1989; Everitt *et al.*, 1989; Robbins *et al.*, 1989; Everitt and Robbins, 1992; Cardinal *et al.*, 2002; Everitt *et al.*, 2003). Food preferences are altered after amygdala lesions in rats, because the rats are no longer neophobic (Rolls and Rolls, 1973). Based on evidence of this type, it has been proposed that the amygdala plays a key role in emotion (LeDoux, 1995; LeDoux, 1996; LeDoux, 2000).

In non-human primates, cortical inputs reach the amygdala especially from the inferior temporal visual cortex, superior temporal auditory association cortex (BA22), insular cortex, orbitofrontal cortex, and anterior cingulate cortex (Herzog and Van Hoesen, 1976; Aggleton *et al.*, 1980; Van Hoesen, 1981; Amaral *et al.*, 1992), there are widespread backprojections to the cortex from the amygdala (Amaral *et al.*, 1992), and the amygdala has extensive interconnectivity with the perirhinal, entorhinal, and parahippocampal TF cortex (Stefanacci *et al.*, 1996). In the macaque amygdala, associations between visual stimuli and rewards appear to be learned much less specifically and more slowly than in the orbitofrontal cortex (Sanghera *et al.*, 1979; Wilson and Rolls, 2005; Morrison *et al.*, 2011; Rolls, 2014; Saez *et al.*, 2017; Rolls, 2021d, 2023). Neurons were also discovered in the macaque amygdala that respond to the sight of faces, and these neurons are likely to be involved in social behaviour (Rolls, 1984; Leonard *et al.*, 1985; Gothard *et al.*, 2007) (with similar neurons also in the orbitofrontal cortex (Rolls *et al.*, 2006; Barat *et al.*, 2018)). Further, in macaques some amygdala neurons have activity related to social and economic decision-making (Hernadi *et al.*, 2015; Grabenhorst *et al.*, 2016; Grabenhorst *et al.*, 2019; Grabenhorst and Schultz, 2021).

Given this background, the first aim of the present investigation was to advance understanding of the operation of the human amygdala in emotion by analysing the connectivity of the human amygdala with all cortical regions, and also some subcortical regions. The second aim was to compare the connectivity of the human amygdala with that of a key brain region known to be involved in emotion in humans, the orbitofrontal cortex (Rolls, 2014, 2019b, c; Rolls *et al.*, 2020b; Rolls, 2021a, 2022c, 2023). The third aim is to compare the roles of the amygdala and orbitofrontal cortex in emotion in the light of the new evidence on the connectivity of the human amygdala described in this paper as well as other evidence, and this comparison is provided in the Discussion.

The connectivity of the human amygdala and orbitofrontal cortex was analysed with three methods in the research described here. The first method is effective connectivity 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.*, 2022e). This method has been successfully applied to measure the effective connectivity between hundreds of brain regions (Rolls *et al.*, 2022e). 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. 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. 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.

Another key feature of the present investigation is the use of the Human Connectome Project multimodal parcellation atlas (MCP-MMP) that identifies 360 different cortical areas using methods that include cortical structure (myelin content and cortical thickness), functional connectivity, and task-related fMRI in several different tasks, all used to delineate the boundaries between cortical regions (Glasser *et al.*, 2016a; Van Essen and Glasser, 2018). Another key feature is the analysis of effective connectivity, functional connectivity, and diffusion tractography using the same set of 171 participants in the Human Connectome Project (HCP) imaged at 7T (Glasser *et al.*, 2016b). Another key feature is the use to analyse the connectivity of the amygdala and other subcortical regions of the extended Human Connectome Project atlas HCPex, which adds 66 subcortical regions including the amygdala to the HCP-MMP atlas (Huang *et al.*, 2022).

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.*, 2022e), posterior cingulate cortex (Rolls *et al.*, 2022h), and posterior parietal cortex (Rolls *et al.*, 2022a), and other brain systems (Rolls, 2022a, b; Rolls *et al.*, 2022d, c, b; Rolls *et al.*, 2022f; Rolls *et al.*, 2022g), and so the same 171 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 171 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 171 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 cortical 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 171 participants for whom we also had performed diffusion tractography, as described in detail (Huang *et al.*, 2021). 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.*, 2022).

To construct the effective connectivity for the amygdala and other subcortical regions of interest in this investigation, we utilised the HCPex atlas (Huang *et al.*, 2022) which combines in volumetric rather than surface-based space HCP's multi-modal parcellation (v1.0), including from it 180 cortical regions per hemisphere (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. Details of how the subcortical regions were defined is provided elsewhere (Huang *et al.*, 2022), including the definition of the amygdala which was adapted from the Computational Brain Anatomy Lab Merged Atlas (CoBrALab, https://github.com/CoBrALab/atlases) (Entis *et al.*, 2012; Pipitone *et al.*, 2014). A list of the cortical regions is provided in Table S1 and of the subcortical regions in Table S2, and coronal, sagittal and axial slices with the HCP parcellation with labels for each region are provided in Fig. S1 (Huang *et al.*, 2022). The volumetric form of HCPex (Huang *et al.*, 2022) 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.*, 2022). Accordingly, and to be consistent with previous papers (Rolls *et al.*, 2022d, c, b, a; Rolls *et al.*, 2022f, e; Rolls *et al.*, 2022g), the connectivities shown in the figures in this paper involving only the 360 cortical regions use the surface parcellation, and any connectivity that is with a subcortical region is with the HCPex parcellation.

In this investigation, the cortical regions of interest (ROIs) included the following regions from the HCP-MMP1 (Glasser *et al.*, 2016a) and HCPex (Huang *et al.*, 2022) atlases, where these regions are defined: Amygdala; lateral orbitofrontal cortex (47s, 47l, a47r, p47r, 47m); and medial orbitofrontal cortex (11l, 13l, OFC, pOFC). Although the connectivity of the orbitofrontal cortex has been described in a different paper where it is compared with the connectivity of the ventromedial and anterior cingulate cortex (Rolls *et al.*, 2022f), it is included in the Figures here as a key aim of this paper is to compare the connectivity of the human amygdala with that of the orbitofrontal cortex; and the presentation of the orbitofrontal connectivity is different, in that for example the functional connectivity has been thresholded so that it shows even quite low levels of functional connectivity, to enable what connectivity the amygdala has in humans to be shown.

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.*, 2022e) 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.*, 2022e); 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 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 existing anatomical connection as specified by the Structural Connectivity matrix (measured with tractography (Huang *et al.*, 2021)) 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.*, 2022e). 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 11 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.*, 2022). This EC was computed from the averaged functional connectivities across the 171 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.*, 2022). The application of the effective connectivity algorithm used here was validated as described elsewhere (Rolls *et al.*, 2022e).

To test whether the vectors of effective connectivities of each of the 10 left Amygdala and orbitofrontal cortex 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 11 ROI effective connectivity vectors in two-way ANOVAs (each 2 x 180) across the 171 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 0.25 is used for the presentation of the findings in Fig. 5, to reveal what connectivity the amygdala has in humans, rather than the value of typically 0.4 used in previous investigations (Rolls *et al.*, 2022d, c, b, a; Rolls *et al.*, 2022f, e; Rolls *et al.*, 2022g) which sets the sparseness of the functional connectivity to a level commensurate with the effective connectivity, to facilitate comparison between the functional and the effective connectivity. Part of the aim is to enable even low levels of functional connectivity of the amygdala with other brain regions to be shown.

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 171 HCP participants images at 7T with methods described elsewhere (Huang *et al.*, 2021) and not repeated here for conciseness, and is shown here for the orbitofrontal cortex / amygdala areas in Fig. 6.

Results

The effective connectivities to the amygdala and orbitofrontal cortex (OFC) from cortical areas in the left hemisphere are shown in Fig. 2. The effective connectivities from the amygdala and orbitofrontal cortex to cortical areas in the left hemisphere are shown in Fig. 3. The vectors of effective connectivities of each of the 10 left amygdala and orbitofrontal cortex regions of interest (ROIs) with the 180 areas in the HCP atlas in the left hemisphere were all significantly different from each other (the interaction term in a 2-way ANOVA across the 171 participants was $p<10^{-90}$ for the comparisons between every pair of the 11 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 brain region 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 171 HCP participants, is taken into account.

Amygdala

The effective connectivities from the 180 cortical regions to the left (L) and right (R) human amygdala are shown in Fig. 2. The values provided next are for the left amygdala, but as shown in Fig. 2, the values are very similar for the right amygdala. The strongest effective connectivity is from the hippocampal system, from the hippocampus (0.080), entorhinal cortex (0.024), perirhinal cortex (0.062), and parahippocampal TF (0.017) which is the part of the parahippocampal cortex with connectivity with ventral stream visual cortical regions such as the inferior temporal visual cortex (Rolls *et al.*, 2022c; Rolls *et al.*, 2022e). The amygdala also receives effective connectivity from a group of regions in the anterior superior temporal lobe, A5 (high order auditory association cortex (Rolls *et al.*, 2022g)), and STSda (the cortex in the dorsal anterior bank of the superior temporal sulcus), STGa (the immediately anterior part of the superior temporal gyrus to STSda), and TGd (the immediately anterior dorsal temporal pole) (see Fig. 1). These anterior superior temporal lobe regions are implicated not only in auditory processing including vocalisation, but are also implicated in visual responses to socially relevant stimuli such as face expression and head motion/social gesture by combining information from the ventral and dorsal visual streams (Baylis *et al.*, 1987; Hasselmo *et al.*, 1989a; Hasselmo *et al.*, 1989b) in what is now recognised also in humans as a third visual pathway for processing socially relevant stimuli (Pitcher and Ungerleider, 2021). The human amygdala also receives effective connectivity from the piriform (olfactory) cortex (0.031, Fig. 2). The amygdala also receives effective connectivity from one orbitofrontal cortex region, lateral orbitofrontal cortex 47m (0.007). The amygdala also has very weak effective connectivity (<0.005) from primary somatosensory cortex 3b and motor cortex area 4.

The effective connectivity from the amygdala to the 180 regions in the left cortex is interestingly limited, and most of the cortical regions described above with connectivities to the amygdala do not receive return amygdalo-cortical effective connectivity (Fig. 3). The only moderate effective connectivities from the amygdala are to the hippocampus (0.064), perirhinal cortex (0.037), and temporal pole TGd (0.019); and weakly to the lateral orbitofrontal cortex 47m (0.005). All of these amygdalo-cortical effective connectivities are weaker than the corresponding cortico-amygdala effective connectivities.

The differences of effective connectivities from cortical regions to the amygdala compared to amygdala connectivities to the cortex are shown in Fig. 4. If a connectivity from a cortical region to the amygdala is stronger than the reverse, this shows as red in Fig. 4. This confirms that all the effective connectivities are stronger from cortical regions to the amygdala than vice versa.

As there was effective connectivity of the amygdala with relatively few cortical regions (Figs. 2 and 3), the functional connectivity in Fig. 5 is shown with a low threshold of 0.25, to bring out as much that might be useful as possible, even if it was very weak. The first point is that the functional connectivities of the amygdala with cortical regions are rather sparse compared with the connectivities of the orbitofrontal cortex. What is shown is functional connectivity that is consistent with the effective connectivity, though the low threshold used here for the functional connectivity showing a little more. (For example there is now an indication of some connectivity with PHA1 (medial parahippocampal gyrus) as well as with other parts of the hippocampal system; with A4 and the further superior temporal sulcus regions STSdp and STSva; with temporal pole TGv, temporo-parietal junction TPO1J and parietal PGi which are part of the same STS system involved in semantic representations (Rolls *et al.*, 2022b) and are also activated by faces (Yokoyama *et al.*, 2021); with visual inferior temporal cortex TE1a and with lateral orbitofrontal 47s and well as 47m also activated by faces (Yokoyama *et al.*, 2021); and with a few more somatosensory/motor cortex regions (1, 2, 3a, 3b, 4, 6mp and 6d).

The diffusion tractography in Fig. 6 reveals as is usual ipsilateral and not contralateral connections. Connections are indicated with the hippocampal system (hippocampus, entorhinal and perirhinal cortex); with the pyriform cortex; with temporal pole TGd and TGv; and with a medial orbitofrontal cortex region, pOFC.

The effective connectivities from and to contralateral cortical regions (Figs. S2 and S3) are similar to the ipsilateral effective connectivities (Figs. 2 and 3).

The effective connectivity of the amygdala with other subcortical regions (Fig. 7) indicates strong effective connectivity (0.15) between the left and right amygdala; effective connectivity as high as 0.040 from the nucleus basalis of Meynert to the amygdala, and up to 0.009 from the amygdala to the nucleus basalis of Meynert, with weak effective connectivity from the Left septum.

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

The effective connectivity of one of these regions taken as an example, 47s, is shown schematically in Fig. 9.

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.*, 2022a)); 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, 2016b) 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, 2016b, 2023)), 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 effective connectivity with two regions involved in language (Rolls *et al.*, 2022b). 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.*, 2022b); 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 (Rolls *et al.*, 2022b)) (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 value / punishment / emotion 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, 2019a; Rolls *et al.*, 2020b)).

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 (Rolls *et al.*, 2022b).

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

The effective connectivity of examples for these regions are shown schematically for pOFC in Fig. 10 and for 13l in Fig. 11.

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.*, 2022a); with parts of the posterior cingulate cortex (31pv, 7m, d23ab) related to memory (Rolls *et al.*, 2022h); 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.*, 2022a) (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) (Rolls *et al.*, 2022d). pOFC is the only cortical region 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.*, 2022). Region OFC has effective connectivity directed towards the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA) (Rolls *et al.*, 2022f), which contain dopaminergic neurons. Medial orbitofrontal cortex regions also have effective connectivity directed towards the caudate nucleus and nucleus accumbens (Rolls *et al.*, 2022f).

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) (Rolls *et al.*, 2022f). 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 (Rolls *et al.*, 2022f) 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.

Effective connectivities of the amygdala and orbitofrontal cortex with contralateral cortical areas

The effective connectivities of the amygdala and orbitofrontal 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 regions connect most strongly with the corresponding contralateral cortical region. 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 contralateral effective connectivities are in general weaker than those ipsilaterally.

Subcortical effective connectivities

The subcortical effective connectivities of the 11 Amygdala and orbitofrontal cortex regions are shown in Fig. 7. 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.*, 2022h).

Discussion

The cortical connectivity of the amygdala in humans is very much less than that of the orbitofrontal cortex (Figs. 2-6). We consider now the implications of this, and of the connectivities that the amygdala does have with the cortex (Figs. 2-6, S2-S3) which are summarized in Fig. 8, and with subcortical structures (Fig. 7).

The effective connectivity to the human amygdala from the superior anterior parts of the temporal lobe (STSda, STG, TGd and extending back as far as A5) provides a route for auditory and visual information to reach the amygdala. (The functional connectivity of the amygdala with this set of cortical regions but relatively few others is supported by another investigation (Klein-Flugge *et al.*, 2022), though that did not measure effective connectivity nor utilize the helpful categorisation of cortical areas provided by the HCP-MMP atlas (Glasser *et al.*, 2016a; Huang *et al.*, 2022).) The cortex in the macaque superior temporal sulcus (STS) includes neurons that we discovered respond to face expression and to socially relevant head motion such as turning the head or opening or closing the eyes to make or break social contact (Hasselmo *et al.*, 1989a; Hasselmo *et al.*, 1989b), and there is complementary evidence for humans (Critchley *et al.*, 2000; Freiwald, 2020; Yokoyama *et al.*, 2021) in what has become accepted as a third visual pathway for socially relevant stimuli (Pitcher and Ungerleider, 2021). Consistent with this, neurons in the primate amygdala respond to socially relevant stimuli such as face expression (Rolls, 1984; Leonard *et al.*, 1985) and the social stimuli produced by others (Hernadi *et al.*, 2015; Grabenhorst *et al.*, 2016; Grabenhorst *et al.*, 2019; Grabenhorst and Schultz, 2021). Those anterior superior temporal cortical regions receive connectivity from the inferior temporal cortex part of the ventral visual stream so are likely to include representations of objects as well as faces (Rolls *et al.*, 2022c, b). These anterior superior temporal cortex regions also contain auditory neurons (Baylis *et al.*, 1987), and some neurons respond to combinations of auditory and visual stimuli (Khandhadia *et al.*, 2021) which are likely to be important in decoding the meaning of such social and related stimuli. Given that there is also connectivity in humans from somatosensory and olfactory cortical regions to the amygdala (Fig. 2), these form the inputs needed to associate visual and auditory stimuli with their consequences in the form of primary rewards and punishers such as pleasant or aversive touch and perhaps odour. This system could then be the primate including human equivalent of the auditory to electric shock associative learning system investigated in the rodent amygdala (LeDoux, 1994; LeDoux, 1995; LeDoux, 1996; Quirk *et al.*, 1996; Killcross *et al.*, 1997; Rogan *et al.*, 1997; LeDoux, 2000; Johansen *et al.*, 2010).

But the question then arises of what the outputs are of this stimulus-reward or stimulus-punishment associative system in the amygdala. The paucity of the output connectivity of the amygdala directed to the neocortex in humans (Figs. 3 and 8), with most of the neocortical connectivity being only towards the amygdala without strong backprojections, and different from the orbitofrontal cortex as illustrated in Figs. 9-11, suggests that the amygdala does not have major cortical outputs to lead to actions performed to obtain goals in instrumental learning, which the evidence suggests instead is implemented by the orbitofrontal cortex outputs to the anterior cingulate cortex (Rushworth *et al.*, 2011; Rushworth *et al.*, 2012; Rolls *et al.*, 2022f). An alternative, given the paucity of amygdalo-neocortical connectivity for amygdala output, is that much of the amygdala output is directed to brainstem regions in humans as well as rodents (Fig. 7 and Klein-Flugge *et al.* (2022)) to elicit responses such as autonomic responses, freezing, conditioned cortical arousal elicited via the cholinergic basal nucleus of Meynert, and incentive effects. That would in fact be consistent with the amygdala outputs identified for the rodent auditory-aversive shock system investigated (Quirk *et al.*, 1996). These effects are

conditioned habit responses, and not instrumental goal-directed actions to obtain reinforcers, and the difference is important for understanding behaviour including emotion (Cardinal *et al.*, 2002; Rolls, 2014, 2022c, 2023).

In non-human primates, connections are found between the amygdala and the medial orbitofrontal cortex (including pOFC), both directly and via the mediodorsal nucleus of the thalamus pars magnocellularis (Freese and Amaral, 2009; Price and Drevets, 2010; Timbie *et al.*, 2020). We report consistent data in humans with anatomical connections found between the amygdala and pOFC (Fig. 6), and also between the amygdala and pregenual / subgenual anterior cingulate cortex (Fig. S2). This is interesting in two ways. First, the amygdala, which is evolutionarily old, has anatomical connections with the human posterior orbitofrontal cortex (region pOFC, Fig. 6) which is likely to be the evolutionarily oldest part of the human orbitofrontal cortex (Passingham, 2021). Second, the lack of effective connectivity, and the lower functional connectivity than the low threshold used here for functional connectivity, provides new evidence that these amygdalo-orbitofrontal connections have relatively low functional effects, and are indeed much lower than the effective connectivity of the orbitofrontal cortex with cortical regions (Figs. 2-4), and of the amygdala with the hippocampus and subcortical regions including the septum and basal nucleus of Meynert (Fig. 7).

The paucity of outputs of the amygdala to the neocortex in humans (Figs. 3-6 and 8) also implies that the human amygdala may not be closely involved in human subjective emotions and feelings. That evidence is in fact consistent with what is now believed by those who have worked on the rodent amygdala and auditory to electric shock conditioning, in that interventions such as the use of pharmacological agents that influence amygdala function have little effect on reported human emotions, though they do influence the conditioned responses referred to above (LeDoux, 2012; LeDoux and Pine, 2016; LeDoux, 2017; LeDoux *et al.*, 2018; LeDoux and Daw, 2018; Mobbs *et al.*, 2019; Taschereau-Dumouchel *et al.*, 2022). In addition, damage to the human amygdala may influence some responses, such as which parts of a face are fixated (Adolphs *et al.*, 2005), or learning autonomic responses to a visual stimulus associated with an electric shock (Phelps, 2004; Phelps and LeDoux, 2005; Delgado *et al.*, 2006; Phelps, 2006; Whalen and Phelps, 2009; Schiller *et al.*, 2010), but does not lead to severe changes in emotional behaviour and reported emotional feelings (Aggleton, 1992; Adolphs *et al.*, 1994; Young *et al.*, 1995; Calder *et al.*, 1996; Young *et al.*, 1996; Scott *et al.*, 1997; Adolphs *et al.*, 2002; Adolphs *et al.*, 2005; Spezio *et al.*, 2007; Whalen and Phelps, 2009; Feinstein *et al.*, 2011; Kennedy and Adolphs, 2011; Damasio *et al.*, 2013) that are comparable to those produced by damage to the orbitofrontal cortex (as described below). Indeed, when SM with amygdala damage did fixate faces, the reported emotion was not impaired (Adolphs *et al.*, 2005; Kennedy and Adolphs, 2011). That left LeDoux (and colleagues) (LeDoux, 2012; LeDoux and Pine, 2016; LeDoux, 2017; LeDoux *et al.*, 2018; Mobbs *et al.*, 2019; Taschereau-Dumouchel *et al.*, 2022) with the conundrum: if the amygdala is not involved in reported human emotion, what brain systems are?

The answer to that question, of what brain systems are involved in human emotion, is that the orbitofrontal cortex, together with the regions to which its outputs are directed, the ventromedial prefrontal cortex, anterior cingulate cortex, and language regions (Figs. 3-6 and 9-11 (Rolls *et al.*, 2022b; Rolls *et al.*, 2022f)), are the key brain regions involved in reported (declarative) human emotion (Rolls, 2014, 2019c, 2022c; Rolls *et al.*, 2022b; Rolls *et al.*, 2022f; Rolls, 2023). For example, damage to the human orbitofrontal cortex impairs not only reward-related reversal learning and relates to disinhibited emotional behaviour (Rolls *et al.*, 1994; Berlin *et al.*, 2004; Hornak *et al.*, 2004; Berlin *et al.*, 2005; Fellows, 2011), and the identification of face and vocal emotional expression (Hornak *et al.*, 1996; Hornak *et al.*, 2003; Tsuchida and Fellows, 2012), but damage to the orbitofrontal cortex also reduces the reported subjective experience of emotion (Hornak *et al.*, 2003; Rolls, 2021a). In addition, activations of the human orbitofrontal cortex occur to many emotion / reward-related and punishment-related stimuli (O'Doherty *et al.*, 2001; O'Doherty *et al.*, 2003; Rolls *et al.*, 2003; Grabenhorst and Rolls,

2011; Rolls, 2014, 2019c), and also linearly track the reported subjective pleasure produced by stimuli (Kringelbach *et al.*, 2003; Grabenhorst and Rolls, 2008; Grabenhorst *et al.*, 2008). Further, as shown here, the lateral orbitofrontal cortex does have effective connectivity with a number of language-related regions, including Broca's area (Rolls *et al.*, 2022b; Rolls *et al.*, 2022f). Based on evidence of this type, the human orbitofrontal cortex is the key brain region involved in emotion (including reported, subjectively experienced, emotion) in humans, rather than the amygdala (Rolls, 2014, 2019c, 2021d, 2023), and the evidence on the connectivity of the human amygdala and orbitofrontal cortex described here helps to provide a connectional foundation for this understanding. Indeed, a new concept proposed here is that given the connectivity of some human lateral orbitofrontal cortex regions (e.g. 47l and 47s) with language regions (Rolls *et al.*, 2022b), some of the impulsiveness of humans with orbitofrontal cortex damage and their focus on immediate rewards rather than long-term planning (Rolls *et al.*, 1994) may be related to interruption of language-based planning influences of the reasoning system on the orbitofrontal cortex. Conversely, this connectivity provides a route for reward value and emotion to enter the language-based declarative system in humans and for subjective states to be reported. The amygdala is evolutionarily old, and its role may continue to be largely in linking stimuli to responses such as autonomic responses, freezing, cortical arousal, and effects of incentive stimuli. In contrast, the orbitofrontal cortex is greatly developed in non-human primates and even further in humans (Passingham and Wise, 2012; Rolls, 2019c; Passingham, 2021), with the extensive cortical connectivity with neocortex described here, and related to this great development and neocortical connectivity, may play a key role in human emotion including reported emotional feelings. Further, it is notable that the amygdala has no effective connectivity directed towards dorsolateral and inferior frontal regions of the prefrontal cortex that are implicated in short-term memory functions (Goldman-Rakic, 1996; Miller *et al.*, 2018) and that are even related to language (Rolls *et al.*, 2022d, b), and this prefrontal route (Figs. 9 and 11) may be an important route for activity in the human orbitofrontal cortex to become incorporated into experienced and reported emotional feelings (Rolls, 2008, 2020; Lau, 2022; Rolls, 2023). The orbitofrontal cortex on the other hand has increasing and strong effective connectivity to these lateral prefrontal cortex regions as one moves forward from pOFC to 13l and to 11l (Figs. 2-6, 10 and 11).

A cautionary note is in order here. Sometimes behavioural and autonomic responses such as changes in heart rate and skin conductance, and freezing or other responses, are used as measures of 'emotion'. Given the points just made, we need to be aware that such responses are not closely related to reported human emotion and are mediated by a different brain system, so may not be fully appropriate measures that relate to human subjectively felt and reported emotions. The instrumental choice of stimuli based on reward value may be a better measure of the value of a good to an animal or human (Rolls, 2022c), but even here we cannot be sure that this always reflects reported consciously felt emotions in humans (Rolls, 2020, 2021c, b, 2022c, 2023). Further, although associations of amygdala functional connectivity with mental disorders have been described (Klein-Flugge *et al.*, 2022), these are associations, and do not show whether the amygdala functional connectivities are caused by or cause the different mental disorders.

The connectivity of the human amygdala to the basal nucleus of Meynert (Fig. 7) which contains cholinergic neurons that provide the cholinergic input to the neocortex (Zaborszky *et al.*, 2008; Zaborszky *et al.*, 2018; Huang *et al.*, 2022) is of considerable interest. Medial orbitofrontal cortex region pOFC is the only cortical area found to have projections to the nucleus basalis of Meynert (Rolls *et al.*, 2022f). Different magnocellular neurons in the macaque basal nucleus of Meynert which are probably cholinergic respond to reinforcing (reward or punishing), or novel, stimuli (Wilson and Rolls, 1990a, b, c), both represented in the orbitofrontal cortex (Rolls *et al.*, 2005; Rolls, 2019b, c). It is now proposed that the amygdala, as well as the more recently evolved human orbitofrontal cortex, may both contribute to cortical arousal, attention, and consolidation of memory in the neocortex given that acetylcholine is

involved in long-term synaptic potentiation (Hasselmo and Sarter, 2011; Newman *et al.*, 2012; Zaborszky *et al.*, 2018) when aversive or rewarding stimuli are encountered, in ways that are described more fully elsewhere (Rolls, 2022b; Rolls *et al.*, 2022f).

The strong effective connectivity of the human amygdala with the hippocampus, entorhinal, and perirhinal cortex, which is a little stronger towards the hippocampal system (Fig. 4), is also of great interest. This connectivity is consistent with what has been described in macaques (Stefanacci *et al.*, 1996). There is corresponding connectivity of the orbitofrontal cortex with the hippocampus (Figs. 2-6 (Rolls *et al.*, 2022f)). It is now proposed here that the amygdala connectivity to the hippocampus implements similar functions to those proposed for the orbitofrontal cortex inputs to the hippocampus, including enabling reward/punishment information to be incorporated into episodic memory, and also enabling any information recalled from episodic memory about rewards and punishers to influence whether that episodic memory is consolidated into neocortical long-term semantic memory, as described in detail elsewhere (Rolls, 2022b). When memories are recalled from the hippocampus to the amygdala, this may enable autonomic and related responses to be produced when memories are retrieved, and this could have adaptive value in preparing the body for action.

In addition to the differences in the connectivity of the human amygdala and orbitofrontal cortex described here, internal differences in their connectivity are likely to contribute to their different computational functions related to emotion. The amygdala has relatively little recurrent collateral excitatory connectivity between its neurons (Millhouse and DeOlmos, 1983), whereas the orbitofrontal cortex, like all neocortex, has highly developed local excitatory recurrent collateral connectivity between its pyramidal cells (Rolls, 2016c, 2021d). These recurrent collaterals are implicated in short-term memory functions, enabling representations to remain active by maintaining the activity of an interconnected set of neurons to continue firing because of the strength of the recurrent collateral synapses of the neurons in each set (Rolls, 2016c, 2021d, 2023). An implication is that memory states related to emotion-provoking stimuli can be maintained using the orbitofrontal cortex but much less by the amygdala. This orbitofrontal cortex recurrent collateral connectivity not only may enable the memory of rewards and punishers received recently to influence future behaviour, but also may enable a mood state to be maintained (e.g. happiness or sadness) that can adaptively influence future behaviour (Rolls, 2014, 2018, 2022c). This functionality may become even more developed especially in humans because the orbitofrontal cortex has reciprocal connectivity with areas such as the angular gyrus involved in language that may implement 'long loop' attractors because of the reciprocal connectivity between these two cortical regions, and thereby contribute to the sad ruminating thoughts that can be a feature of human depression (Cheng *et al.*, 2016; Rolls, 2016a, 2018; Rolls *et al.*, 2020a; Zhang *et al.*, 2023).

One possible limitation of the research described here that care was taken to avoid is that the amygdala might just have generally and overall lower measurable connectivity with other brain regions than do cortical areas, and indeed low values of amygdala functional connectivity have been observed before (Sylvester *et al.*, 2020). Evidence against that possible limitation is that the right and left amygdala have high effective connectivity with each other (Figs. 2-4) ; and that the amygdala does have strong effective connectivity with the hippocampus, and moderate effective connectivity with the entorhinal cortex, perirhinal cortex, parahippocampal TF cortex, A5, STSda, STGa, piriform cortex (Figs 2-3), temporal pole and basal nucleus of Meynert (Figs. 2-4, 7 and S2-S3). Further precautions taken were to use a much lower threshold (0.25) for showing functional connectivity than has been the case for other investigations in this series (typically 0.4) (Rolls *et al.*, 2022d, c, b, a; Rolls *et al.*, 2022f, e; Rolls *et al.*, 2022g; Rolls *et al.*, 2022h), yet even then little more functional connectivity of the amygdala with other cortical regions was found (Fig. 5). Even when the threshold for the functional connectivity was lowered to 0.1, a very low value, no more connectivity of the amygdala with subcortical regions than what is shown for effective connectivity in Fig. 7 was evident. In contrast all

regions of the orbitofrontal cortex had functional connectivity with the striatum (head of caudate or ventral striatum). This does not exclude the possibility that there are more connections anatomically of the human amygdala with the neocortex and subcortical regions, but the evidence described here suggests that if there are others, they are not physiologically very strong, at least in the resting state. This in itself is an interesting issue: the connections traced in macaques may not in all cases have strong effects. For example, in macaques anatomical connections from the amygdala to early cortical visual regions have been described (Amaral *et al.*, 1992; Freese and Amaral, 2005), and connections between the amygdala and V1 were demonstrated anatomically in the present investigation (Fig. 6), but these connections may be functionally weak, for they were not apparent in the physiological measures of effective connectivity (Figs. 2-4), or functional connectivity (Fig. 5). It is possible that more connectivity of the human amygdala with other cortical and subcortical regions would be found if tasks were being performed (cf. Zangemeister *et al.*, 2016), and that can be investigated in future. However, in neurophysiological investigations in macaques (Sanghera *et al.*, 1979; Rolls, 1984; Leonard *et al.*, 1985; Kadohisa *et al.*, 2005a; Kadohisa *et al.*, 2005b; Wilson and Rolls, 2005), the amygdala does not appear to be an especially silent region in a way that might limit its connectivity signatures. Another point is that this research was made possible because of the development of the Human Connectome Project extended atlas with 66 subcortical areas including the amygdala (Huang, Rolls et al (2022)). It was not possible when that atlas was made to reliably include in it a further level of parcellation that would clearly and robustly identify the boundaries with human fMRI data of all the nuclei of the amygdala, so it was not possible in this first investigation of the effective connectivity, functional connectivity, and diffusion tractography of the amygdala with 360 cortical regions in humans to show separately the further connectivities for different amygdala nuclei, and that is a challenge for the future. An alternative to parcellation of different amygdala nuclei from fMRI data in humans is to use clustering of voxel-level functional connectivity of the amygdala, and this shows much connectivity of amygdala nuclei with brainstem nuclei (Klein-Flugge *et al.*, 2022). However, it is possible that if the connectivity of individual amygdala nuclei was investigated in humans, some further cortical connectivities than those described here might become evident.

Conclusions

The research described here shows that the human amygdala has much less effective, and functional, connectivity and anatomical connections with the neocortex than does the orbitofrontal cortex. The direct comparison provided here helps to provide a basis for understanding the different functions of the amygdala vs orbitofrontal cortex in human emotion.

The effective connectivity of the human amygdala indicates that it does receive information about socially relevant visual and auditory stimuli from the anterior superior temporal cortical areas including the temporal pole. The human amygdala also receives information about primary reinforcers such as somatosensory stimuli, and olfactory stimuli. The human amygdala could associate these stimuli to produce responses to aversive and reward visual and auditory stimuli.

Given the paucity of neocortical outputs of the human amygdala, it is suggested, consistent with research in rodents, that key outputs of the human amygdala are to brainstem systems involved in autonomic responses and in behavioural responses such as freezing and perhaps approach responses towards stimuli associated with reward.

Another key output of the amygdala is to the basal forebrain nuclei which contain cholinergic neurons that project to the neocortex, and this potentially enables the human amygdala to play a role in cortical arousal, attention, and memory consolidation in a way comparable to that of the corresponding connectivity from the posterior orbitofrontal cortex (pOFC) to the basal nuclei of Meynert (Rolls, 2022b).

The human amygdala also has strong effective connectivity towards the hippocampus, and this may play a role in enabling aversive and rewarding events to become incorporated into episodic memory, and for autonomic and related responses to be produced when memories are retrieved.

In contrast, the orbitofrontal cortex receives inputs from visual, auditory, somatosensory, taste and olfactory cortical areas, has connectivity to the anterior cingulate cortex involved in action-outcome learning, and has connectivity with prefrontal cortex regions involved in short-term memory, planning, and language, and is involved in reported (declarative) emotions (Rolls, 2023).

The overall implication of the research described here, and of related evidence from the effects of damage to the amygdala, is that the human amygdala in much less important in human reported (declarative) emotion than the orbitofrontal cortex, and that the human amygdala may have a role especially in bodily including autonomic responses to emotion-provoking stimuli, and not in most of the goal-directed behaviours or emotional experiences in which the orbitofrontal cortex is involved. Further discussion of the implications of the connectivity of the orbitofrontal cortex for emotion are provided elsewhere (Rolls, 2022b, c; Rolls *et al.*, 2022f; Rolls, 2023).

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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/).

Author contributions. Edmund Rolls designed and performed the research, and wrote the paper. **Gustavo Deco** provided the effective connectivity algorithm. **Chu-Chung Huang** performed the diffusion tractography and prepared the brain figures with the HCP-MMP labels. **Jianfeng Feng** performed the funding acquisition. All authors approved the paper.

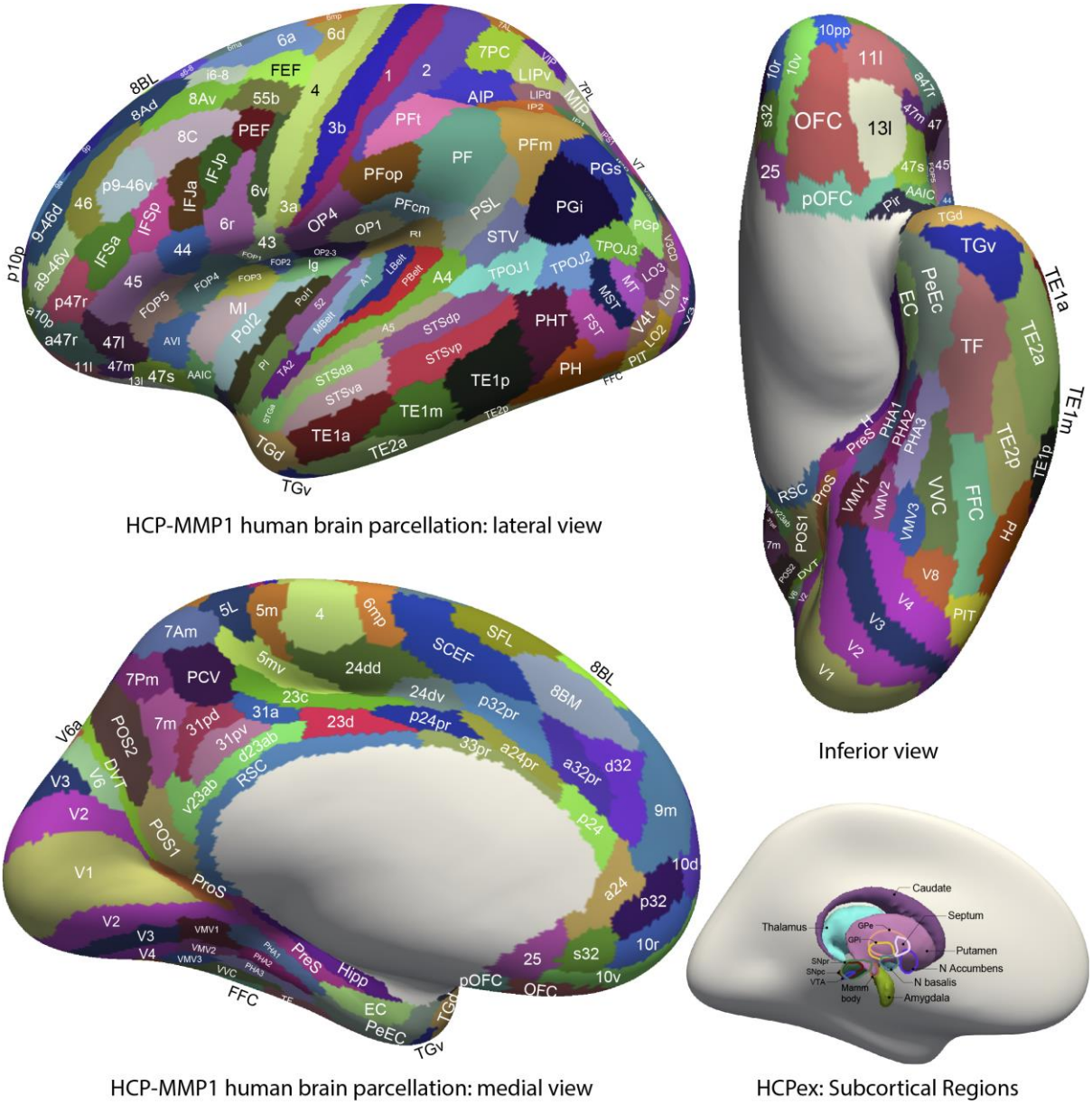

Fig. 1. Regions of interest of the human cortex as defined in the HCP-MMP atlas (Glasser *et al.*, 2016a), and in its extended HCPex version which includes subcortical regions (Huang *et al.*, 2022). The regions are shown on images of the human brain with the sulci expanded sufficiently to allow the regions within the sulci to be shown. The cortical regions investigated are: Lateral orbitofrontal cortex: 47s, 47l, a47r, p47r, 47m. Medial orbitofrontal cortex: 11l, 13l, OFC, pOFC. The subcortical region of interest was the Amygdala. The connectivity of these brain regions with all 360 cortical regions and with subcortical regions as follows was investigated: Putamen; Caudate nucleus; Nucleus accumbens; GPe – globus pallidus pars externa; GPi – globus pallidus pars interna; SNpc – substantia nigra pars compacta; SNpr – substantia nigra pars reticulata; VTA – ventral tegmental area; Mamm body – mammillary bodies; N basalis – forebrain basal magnocellular nucleus of Meynert. Other abbreviations are provided in Tables S1 and S2. (HCPBrainMaster4aSC.eps)

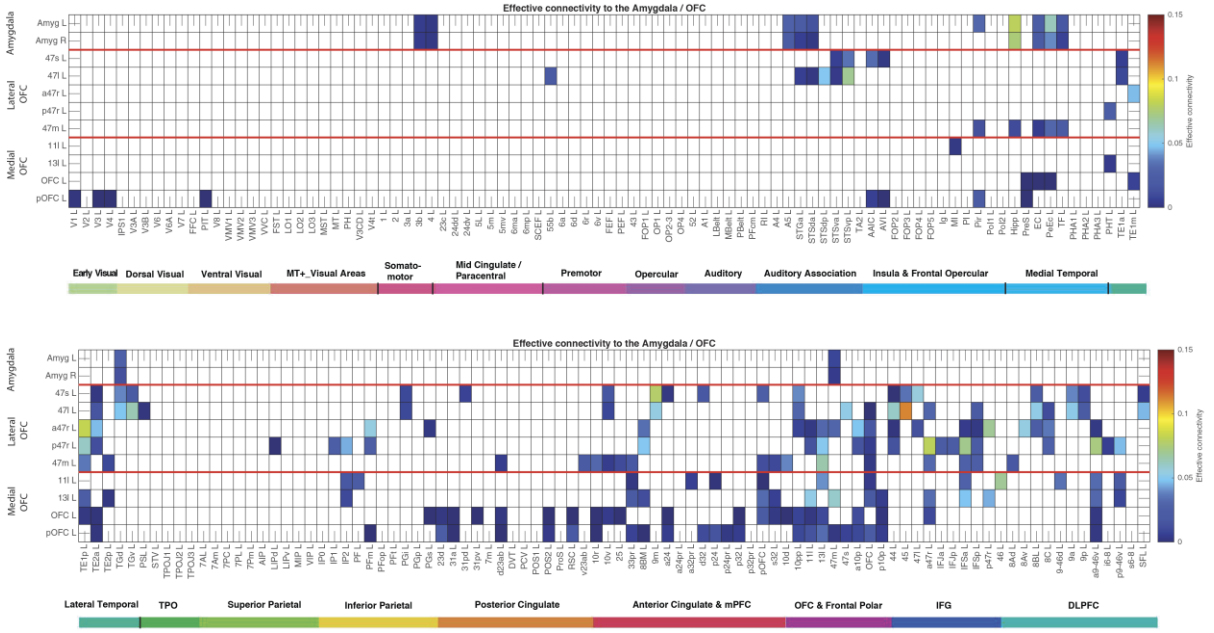

Fig. 2. Effective connectivity to the amygdala and orbitofrontal cortex (OFC) from all 180 cortical regions in the left hemisphere. The effective connectivity is read from column to row. All effective connectivities greater than 0 are shown, and effective connectivities of 0 are shown as a blank. The 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. L – left; R – right. Illustrations of brain regions: Figs. 1 and S1. (ECtoAmyg.eps)

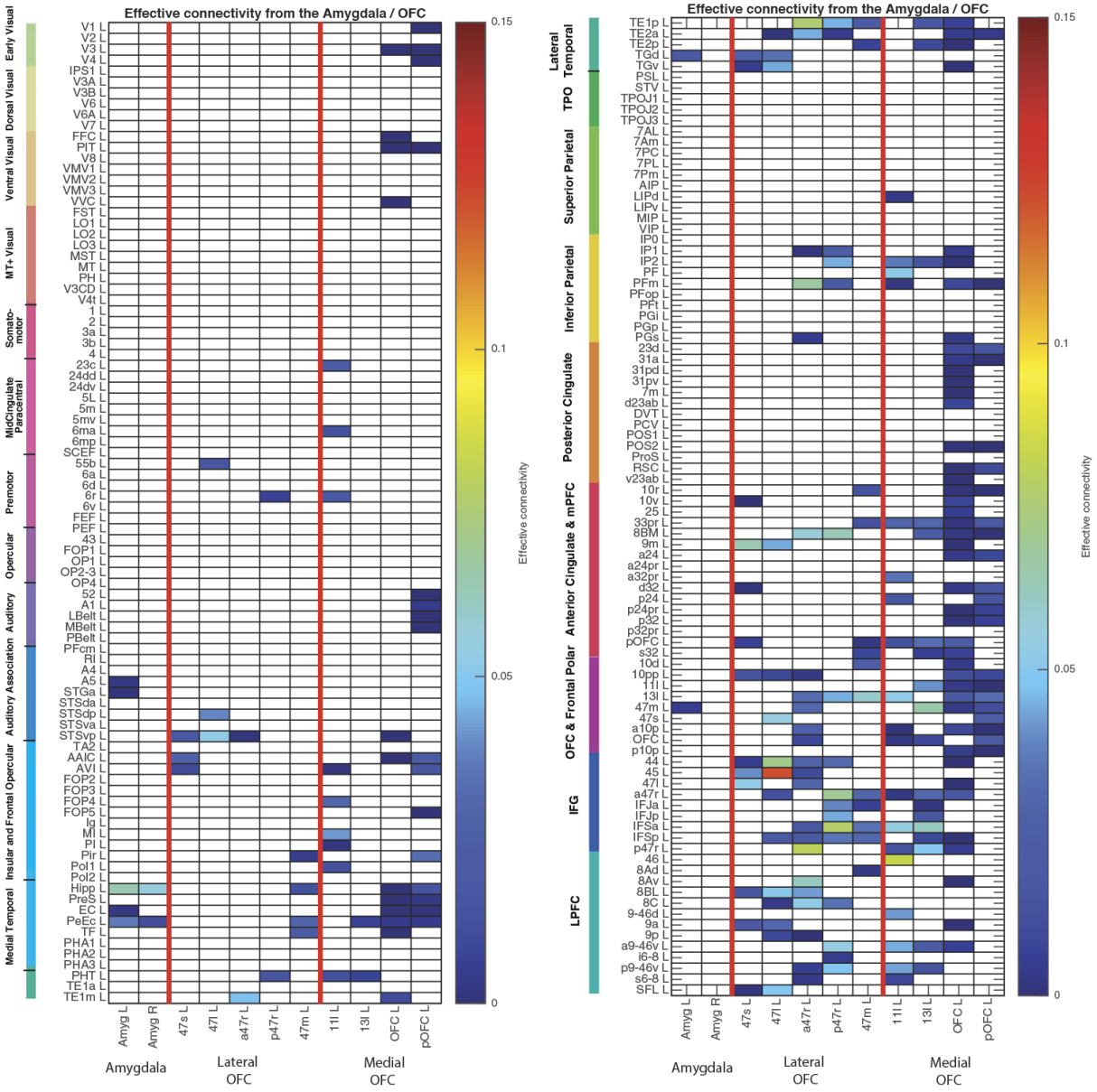

Fig. 3. Effective connectivity from the Amygdala and Orbitofrontal cortex (OFC) to all 180 cortical regions in the left hemisphere. All effective connectivities greater than 0 are shown, and effective connectivities of 0 are shown as a blank. The connectivities to the first set of cortical regions are 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. L – left; R – right. Illustrations of brain regions: Figs. 1 and S1. (ECfromAmyg.eps)

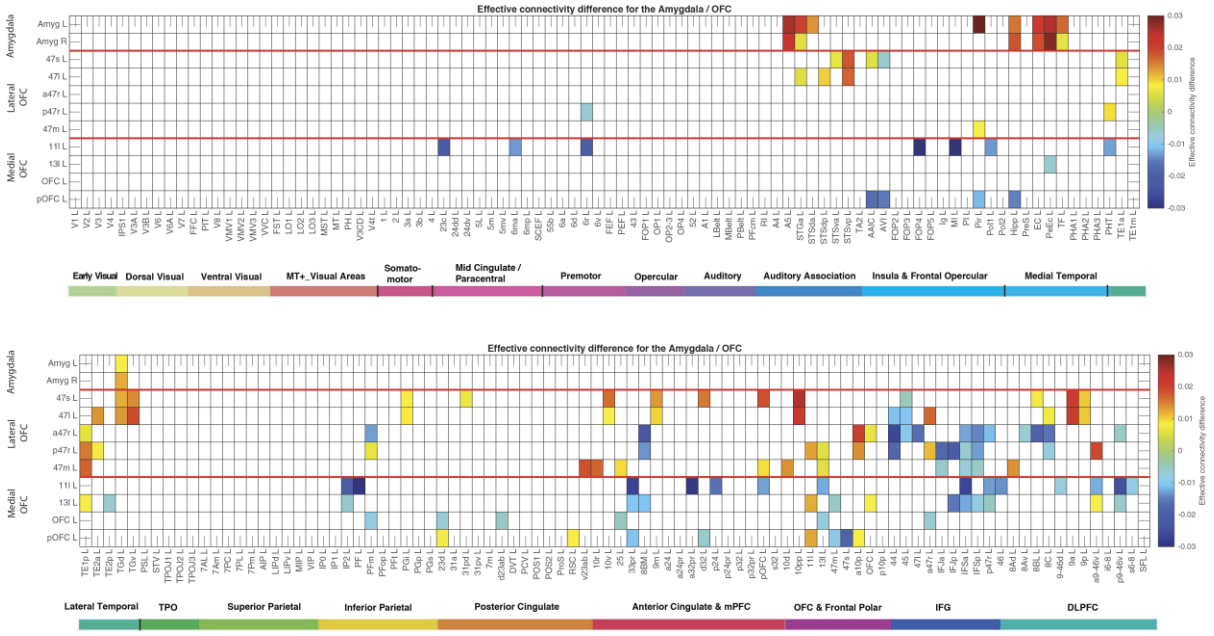

Fig. 4. Difference of the effective connectivity for the amygdala and orbitofrontal cortex with cortical regions. For a given link, if the effective connectivity difference is positive, the connectivity is stronger in the direction column to row. For a given link, if the effective connectivity difference is negative, the connectivity is weaker in the direction from column to row. This is calculated from 171 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. (AmygECdiff.eps)

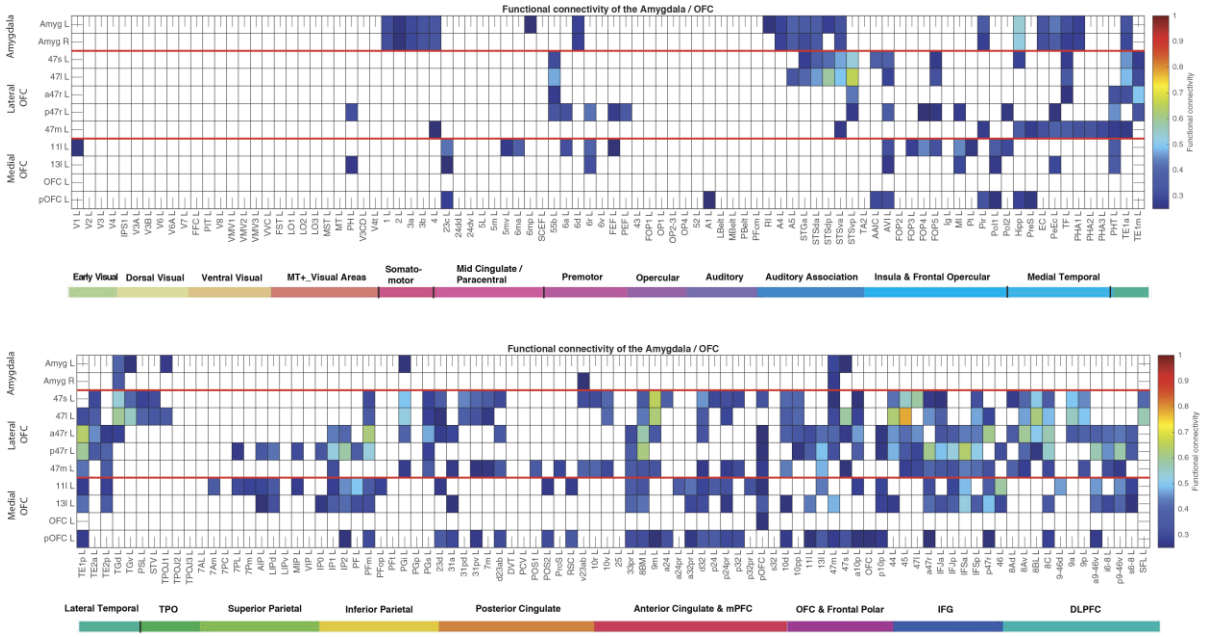

Fig. 5. Functional connectivity between the Amygdala and Orbitofrontal cortex (OFC), and 180 cortical regions in the left hemisphere. Functional connectivities less than 0.25 are shown as blank. The upper figure shows the functional connectivity with the first half of the cortical regions; the lower figure shows the functional connectivity with the second half of the cortical regions. Abbreviations: see Table S1. (AmygFC.eps)

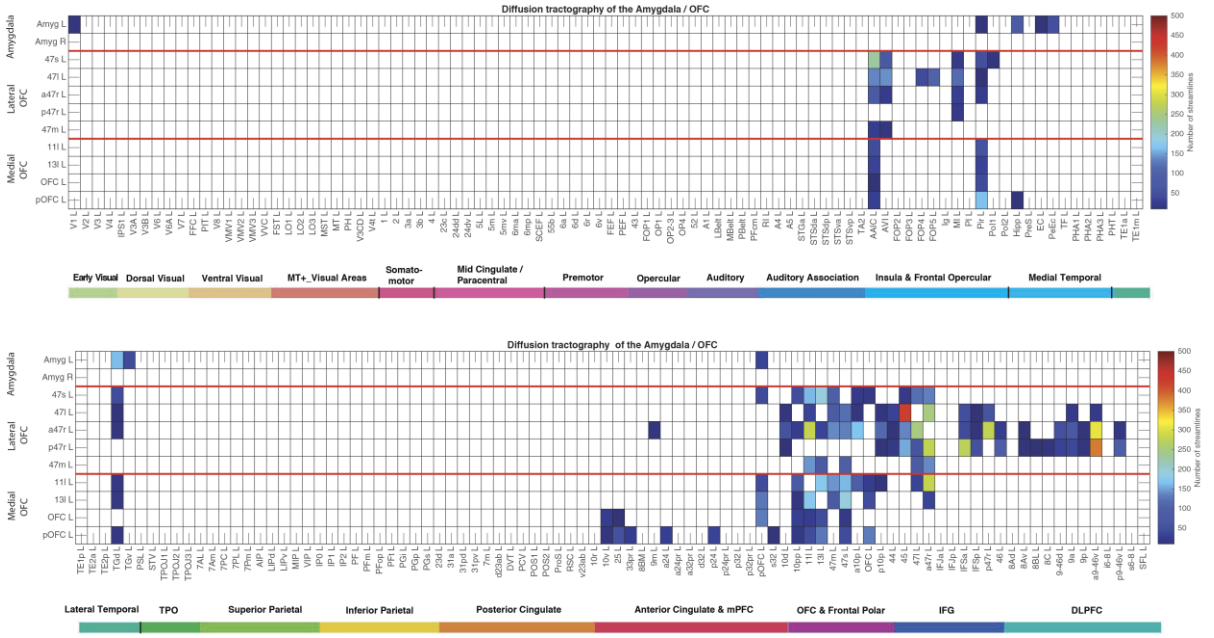

Fig. 6. Connections between the Amygdala plus Orbitofrontal cortex (OFC) and 180 cortical regions in the left hemisphere as shown by diffusion tractography using the same layout as in Figs. 2, 4 and 5. The number of streamlines shown was thresholded at 10 and values less than this are shown as blank.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

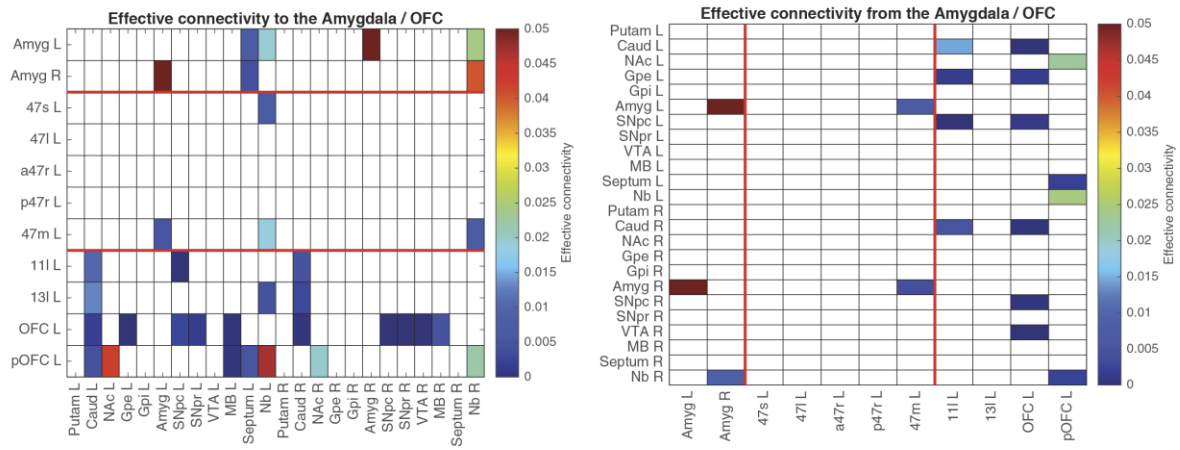

Fig. 7. Effective connectivity TO (left) the Amygdala and orbitofrontal cortex from subcortical regions; and FROM (right) the Amygdala and Orbitofrontal cortex regions to subcortical regions defined in the HCPex atlas (Huang *et al.*, 2022). The effective connectivity is read from column to row. Abbreviations: Putam – putamen; Caud – caudate nucleus; NAc – nucleus accumbens; GPe – globus pallidus pars externa; GPi – globus pallidus pars interna; Amyg – amygdala; SNpc – substantia nigra pars compacta; SNpr – substantia nigra pars reticulata; VTA – ventral tegmental area; MB – mammillary bodies; Nb – forebrain basal magnocellular nucleus of Meynert; L – left; R – right. Other abbreviations are shown in Table S1. (AmygSubcort.eps)

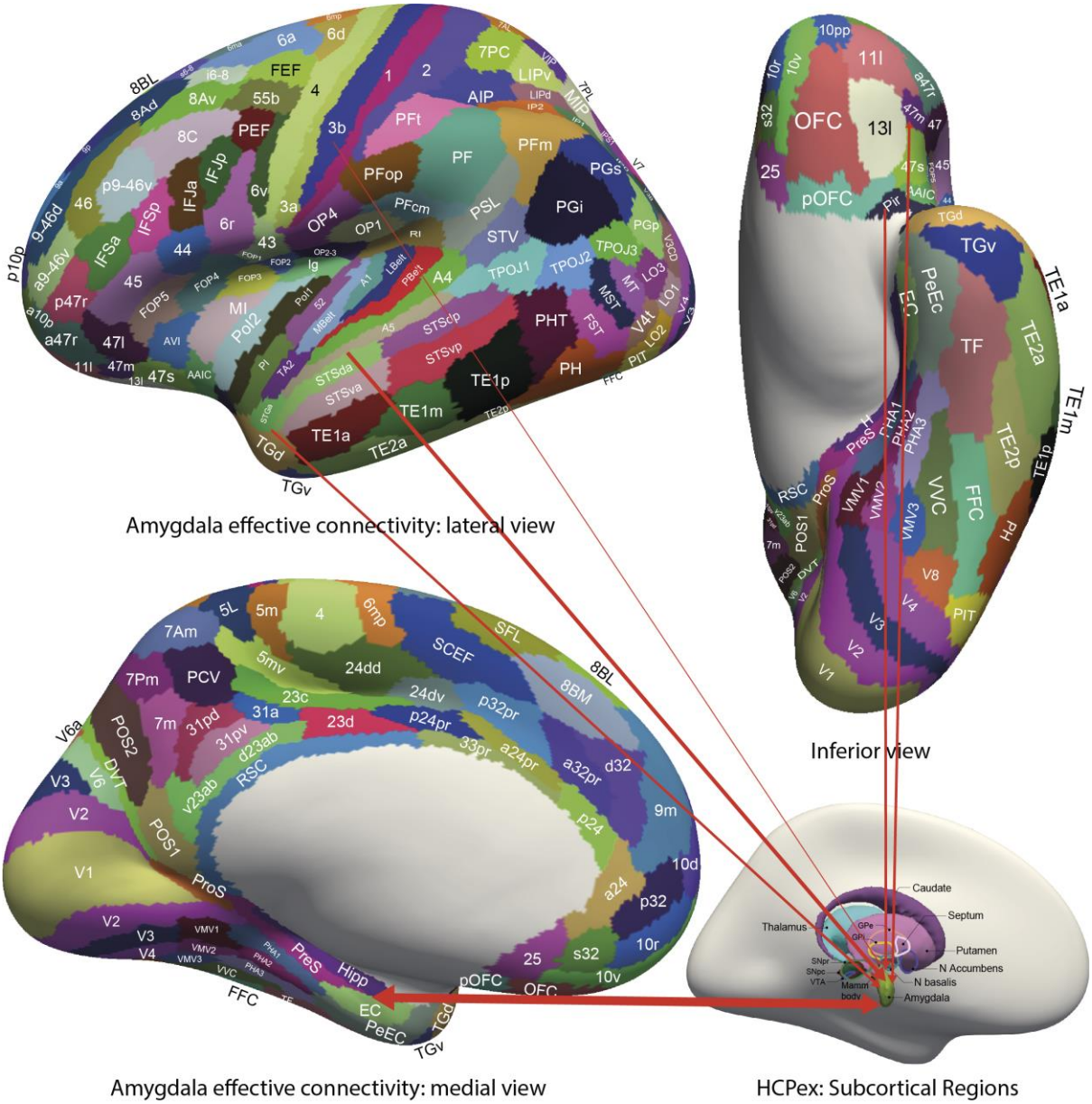

Fig. 8. Effective connectivity of the human amygdala: schematic diagram. The width of the arrows reflects the effective connectivity with the size of the arrowheads reflecting the connectivity in each direction. The connectivity from most cortical areas (STGa and TGd, STSda and A5, and pyriform olfactory cortex) is only towards the amygdala. The connectivity with the hippocampal system (Hipp, entorhinal cortex EC, and perirhinal cortex PeEc) is in both directions. The abbreviations are listed in Tables S1 and S2. (AmygECbrain.eps)

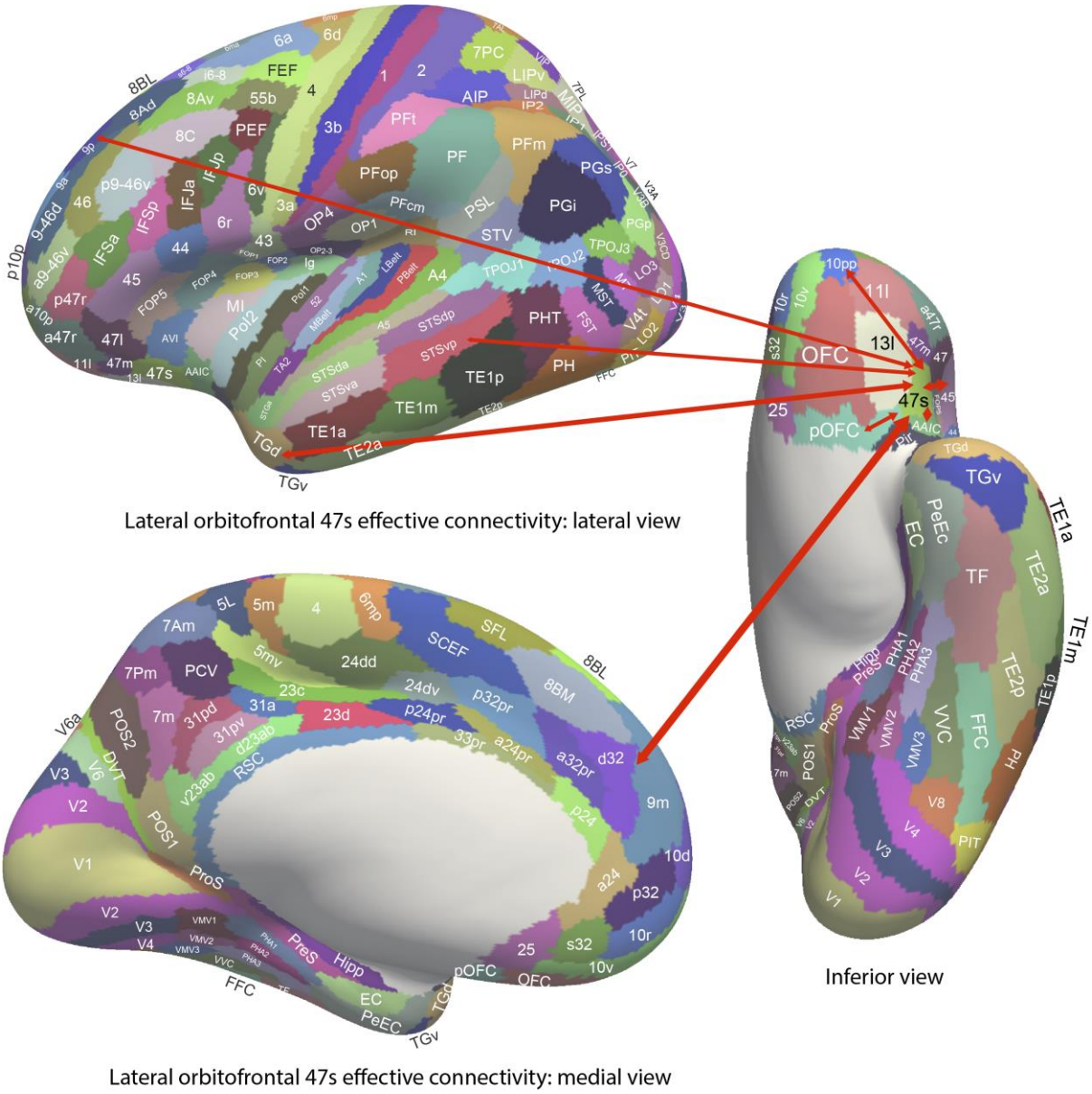

Fig. 9. Effective connectivity of the human lateral orbitofrontal cortex region 47s: schematic diagram. The width of the arrows reflects the effective connectivity with the size of the arrowheads reflecting the connectivity in each direction. Some arrows reflect effective connectivity of several related regions: taste cortex AVI and putative visceral cortex AAIC; supracallosal anterior cingulate and medial prefrontal d32 and 9m; dorsal prefrontal 9a, 9p and 8BL; TGv and TGv. The abbreviations are listed in Tables S1 and S2. (LatOFC47s.eps)

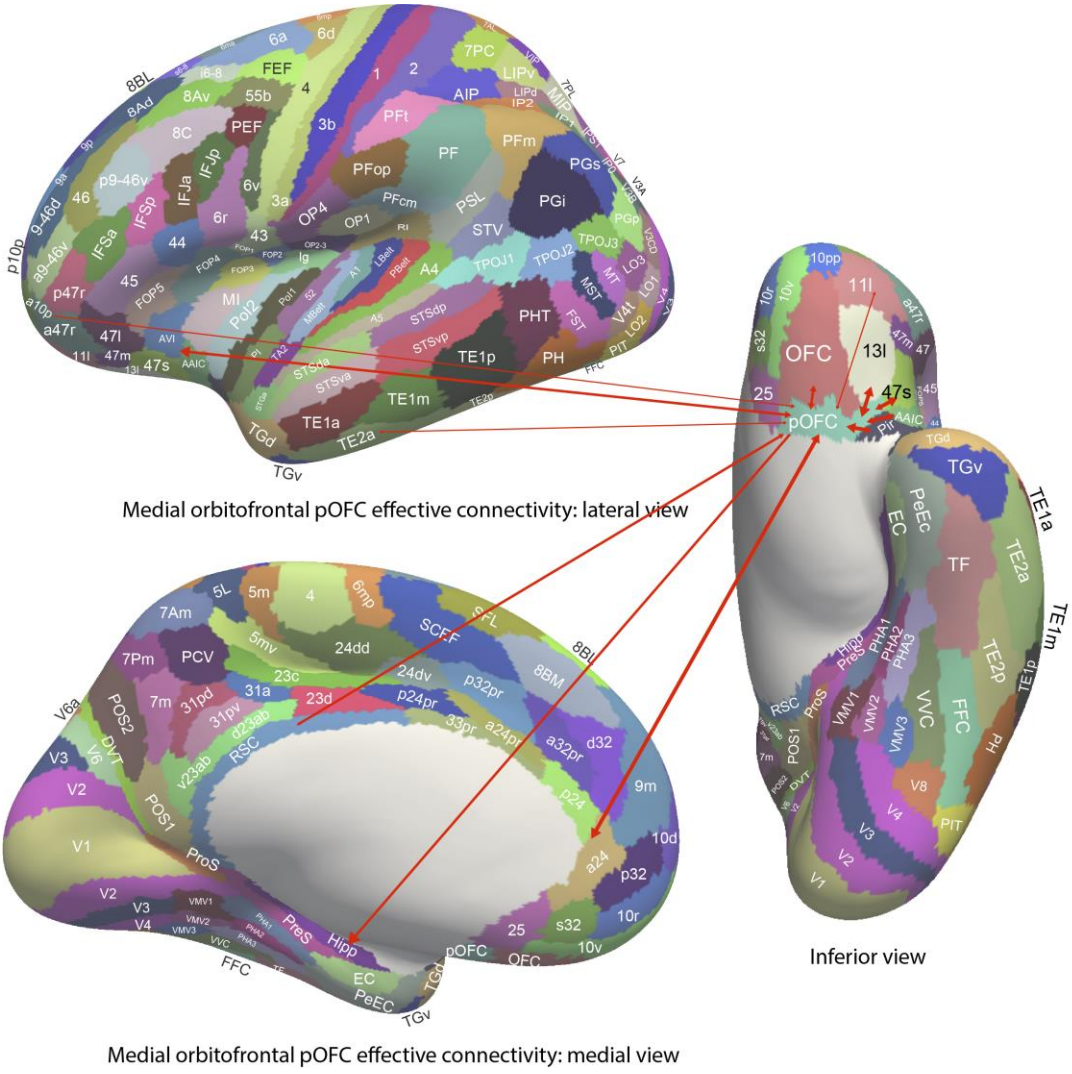

Fig. 10. Effective connectivity of the human medial orbitofrontal cortex region pOFC: schematic diagram. The width of the arrows reflects the effective connectivity with the size of the arrowheads reflecting the connectivity in each direction. One arrow in some cases reflects effective connectivity with several related regions: pregenual anterior cingulate a24, p24 and d32; RSC and 23d; frontal pole a10p and p10p. Effective connectivity is shown of pOFC with pyriform (olfactory) cortex Pir, taste cortex AVI and putative visceromotor cortex AAIC, inferior temporal cortex TE2a, pregenual anterior cingulate cortex; and to the hippocampus Hipp. The abbreviations are listed in Table S1. (MedOFCpOFC.eps)

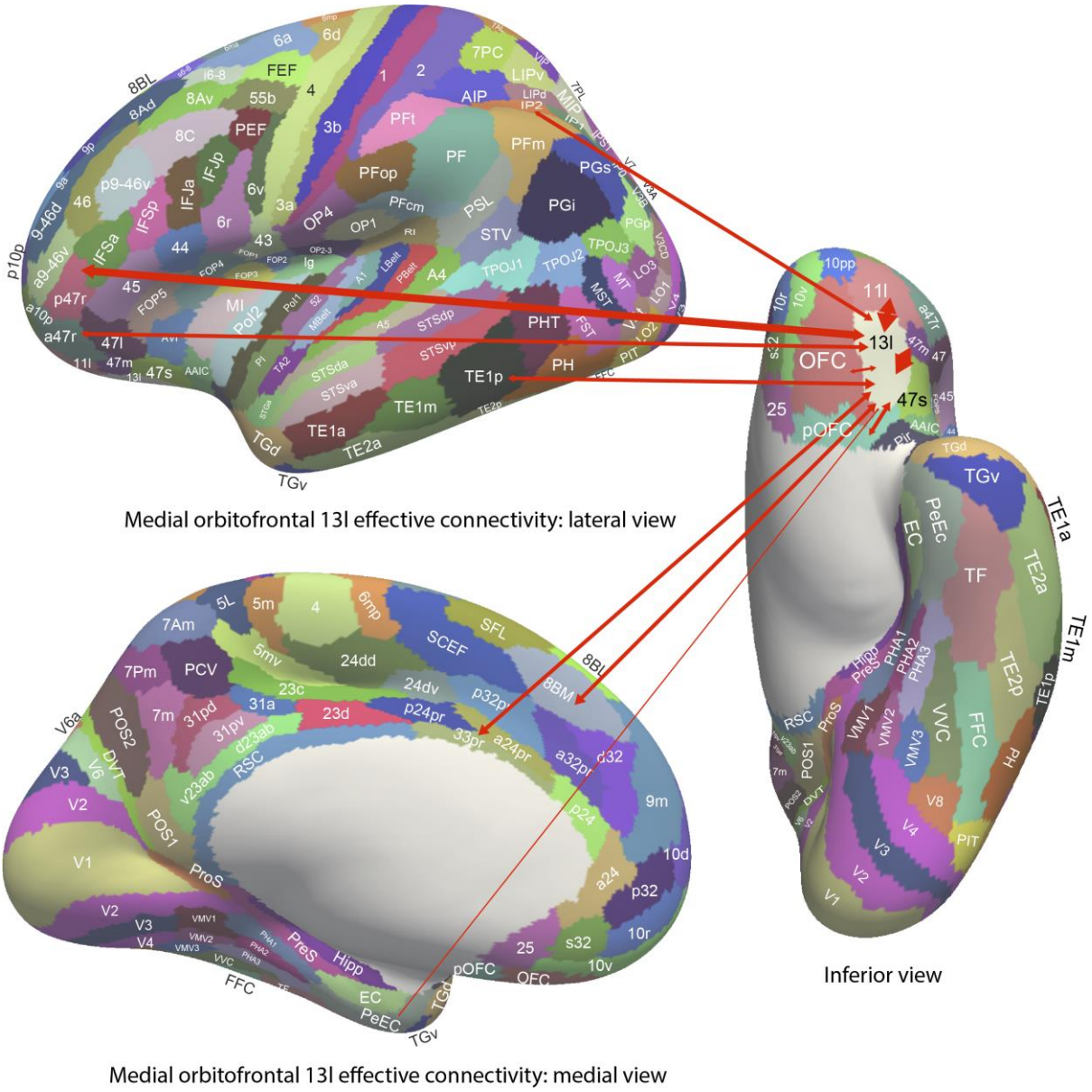

Fig. 11. Effective connectivity of the human medial orbitofrontal cortex region 11l: schematic diagram. The width of the arrows reflects the effective connectivity with the size of the arrowheads reflecting the connectivity in each direction. One arrow reflects effective connectivity with several related regions: IFSa, a9-46v, p9-46v, and p47r. Inputs are shown to 13l from inferior temporal cortex TE1p; with other orbitofrontal cortex regions; with many lateral prefrontal cortex regions; and from 13l to the perirhinal cortex. The abbreviations are listed in Table S1. (MedOFC13l.eps)

References

Adolphs, R., Tranel, D., Damasio, H. and Damasio, A. (1994) Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* **372,** 669-672.

Adolphs, R., Baron-Cohen, S. and Tranel, D. (2002) Impaired recognition of social emotions following amygdala damage. *J. Cogn. Neurosci.* **14,** 1264-1274.

Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P. and Damasio, A. R. (2005) A mechanism for impaired fear recognition after amygdala damage. *Nature* **433,** 68-72.

Aggleton, J. P., Burton, M. J. and Passingham, R. E. (1980) Cortical and subcortical afferents to the amygdala in the rhesus monkey (Macaca mulatta). *Brain Res.* **190,** 347-368.

Aggleton, J. P. (1992) The functional effects of amygdala lesions in humans: a comparison with findings from monkeys. In: *The Amygdala*. pp. 485-503. Ed. J. P. Aggleton. Wiley-Liss: New York.

Amaral, D. G., Price, J. L., Pitkanen, A. and Carmichael, S. T. (1992) Anatomical organization of the primate amygdaloid complex. In: *The Amygdala*. pp. 1-66. Ed. J. P. Aggleton. Wiley-Liss: New York.

Bajaj, S., Adhikari, B. M., Friston, K. J. and Dhamala, M. (2016) Bridging the gap: Dynamic Causal Modeling and Granger Causality analysis of resting state functional magnetic resonance imaging. *Brain Connect* **6,** 652-661.

Barat, E., Wirth, S. and Duhamel, J. R. (2018) Face cells in orbitofrontal cortex represent social categories. *Proc. Natl. Acad. Sci. U. S. A.* **115,** E11158-E11167.

Baylis, G. C., Rolls, E. T. and Leonard, C. M. (1987) Functional subdivisions of the temporal lobe neocortex. *J. Neurosci.* **7,** 330-342.

Berlin, H., Rolls, E. T. and Kischka, U. (2004) Impulsivity, time perception, emotion, and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain* **127,** 1108-1126.

Berlin, H., Rolls, E. T. and Iversen, S. D. (2005) Borderline Personality Disorder, impulsivity and the orbitofrontal cortex. *Am. J. Psychiatry* **162,** 2360-2373.

Cador, M., Robbins, T. W. and Everitt, B. J. (1989) Involvement of the amygdala in stimulus-reward associations: interaction with the ventral striatum. *Neuroscience* **30,** 77-86.

Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R. and Etcoff, N. L. (1996) Facial emotion recognition after bilateral amygdala damage: differentially severe impairment of fear. *Cogn. Neuropsychol.* **13,** 699-745.

Cardinal, N., Parkinson, J. A., Hall, J. and Everitt, B. J. (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and Biobehavioural Reviews* **26,** 321-352.

Cheng, W., Rolls, E. T., Qiu, J., Liu, W., Tang, Y., Huang, C. C., Wang, X., Zhang, J., Lin, W., Zheng, L., Pu, J., Tsai, S. J., Yang, A. C., Lin, C. P., Wang, F., Xie, P. and Feng, J. (2016) Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression. *Brain* **139,** 3296-3309.

Coalson, T. S., Van Essen, D. C. and Glasser, M. F. (2018) The impact of traditional neuroimaging methods on the spatial localization of cortical areas. *Proc. Natl. Acad. Sci. U. S. A.* **115,** E6356-E6365.

Critchley, H., Daly, E., Phillips, M., Brammer, M., Bullmore, E., Williams, S., Van Amelsvoort, T., Robertson, D., David, A. and Murphy, D. (2000) Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study. *Hum. Brain Mapp.* **9,** 93-105.

Damasio, A., Damasio, H. and Tranel, D. (2013) Persistence of feelings and sentience after bilateral damage of the insula. *Cereb. Cortex* **23,** 833-846.

Davis, M. (1992) The role of the amygdala in conditioned fear. In: *The Amygdala*. pp. 255-305. Ed. J. P. Aggleton. Wiley-Liss: New York.

Davis, M. (1994) The role of the amygdala in emotional learning. *Int. Rev. Neurobiol.* **36,** 225-266.

Davis, M., Campeau, S., Kim, M. and Falls, W. A. (1995) Neural systems and emotion :the amygdala's role in fear and anxiety. In: *Brain and Memory: Modulation and Mediation of Neuroplasticity*. Eds. J. L. McGaugh, N. M. Weinberger, G. Lynch. Oxford University Press: New York.

Davis, M. (2006) Neural systems involved in fear and anxiety measured with fear-potentiated startle. *Am. Psychol.* **61,** 741-756.

De Araujo, I. E., Rolls, E. T., Kringelbach, M. L., McGlone, F. and Phillips, N. (2003) Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. *Eur. J. Neurosci.* **18,** 2059-2068.

Deco, G., Cabral, J., Woolrich, M. W., Stevner, A. B. A., van Hartevelt, T. J. and Kringelbach, M. L. (2017a) Single or multiple frequency generators in on-going brain activity: A mechanistic whole-brain model of empirical MEG data. *Neuroimage* **152,** 538-550.

Deco, G., Kringelbach, M. L., Jirsa, V. K. and Ritter, P. (2017b) The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. *Sci. Rep.* **7,** 3095.

Deco, G., Cruzat, J., Cabral, J., Tagliazucchi, E., Laufs, H., Logothetis, N. K. and Kringelbach, M. L. (2019) Awakening: Predicting external stimulation to force transitions between different brain states. *Proceedings of the National Academy of Sciences* **116,** 18088-18097.

Delgado, M. R., Olsson, A. and Phelps, E. A. (2006) Extending animal models of fear conditioning to humans. *Biol. Psychol.* **73,** 39-48.

Entis, J. J., Doerga, P., Barrett, L. F. and Dickerson, B. C. (2012) A reliable protocol for the manual segmentation of the human amygdala and its subregions using ultra-high resolution MRI. *Neuroimage* **60,** 1226-1235.

Everitt, B. and Robbins, T. W. (1992) Amygdala-ventral striatal interactions and reward-related processes. In: *The Amygdala*. pp. 401-430. Ed. J. P. Aggleton. Wiley: Chichester.

Everitt, B., Cardinal, R. N., Parkinson, J. A. and Robbins, T. W. (2003) Impact of amygdala-dependent mechanisms of emotional learning. *Ann. N. Y. Acad. Sci.* **985,** 233-250.

Everitt, B. J., Cador, M. and Robbins, T. W. (1989) Interactions between the amygdala and ventral striatum in stimulus-reward assiciation: studies using a second order schedule of sexual reinforcement. *Neuroscience* **30,** 63-75.

Feinstein, J. S., Adolphs, R., Damasio, A. and Tranel, D. (2011) The human amygdala and the induction and experience of fear. *Curr. Biol.* **21,** 34-38.

Fellows, L. K. (2011) Orbitofrontal contributions to value-based decision making: evidence from humans with frontal lobe damage. *Ann. N. Y. Acad. Sci.* **1239,** 51-58.

Frassle, S., Lomakina, E. I., Razi, A., Friston, K. J., Buhmann, J. M. and Stephan, K. E. (2017) Regression DCM for fMRI. *Neuroimage* **155,** 406-421.

Freese, J. L. and Amaral, D. G. (2005) The organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *J. Comp. Neurol.* **486,** 295-317.

Freese, J. L. and Amaral, D. G. (2009) Neuroanatomy of the primate amygdala. In: *The Human Amygdala*. pp. 3-42. Eds. P. J. Whalen, E. A. Phelps. Guilford: New York.

Freiwald, W. A. (2020) The neural mechanisms of face processing: cells, areas, networks, and models. *Curr. Opin. Neurobiol.* **60,** 184-191.

Freyer, F., Roberts, J. A., Becker, R., Robinson, P. A., Ritter, P. and Breakspear, M. (2011) Biophysical mechanisms of multistability in resting-state cortical rhythms. *J. Neurosci.* **31,** 6353-6361.

Freyer, F., Roberts, J. A., Ritter, P. and Breakspear, M. (2012) A canonical model of multistability and scale-invariance in biological systems. *PLoS Comput. Biol.* **8,** e1002634.

Friston, K. (2009) Causal modelling and brain connectivity in functional magnetic resonance imaging. *PLoS Biol.* **7,** e33.

Gilson, M., Moreno-Bote, R., Ponce-Alvarez, A., Ritter, P. and Deco, G. (2016) Estimation of directed effective connectivity from fMRI functional connectivity hints at asymmetries in the cortical connectome. *PLoS Comput. Biol.* **12,** e1004762.

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J. R., Van Essen, D. C., Jenkinson, M. and Consortium, W. U.-M. H. (2013) The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage* **80,** 105-124.

Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C. F., Jenkinson, M., Smith, S. M. and Van Essen, D. C. (2016a) A multi-modal parcellation of human cerebral cortex. *Nature* **536,** 171-178.

Glasser, M. F., Smith, S. M., Marcus, D. S., Andersson, J. L., Auerbach, E. J., Behrens, T. E., Coalson, T. S., Harms, M. P., Jenkinson, M., Moeller, S., Robinson, E. C., Sotiropoulos, S. N., Xu, J., Yacoub, E., Ugurbil, K. and Van Essen, D. C. (2016b) The Human Connectome Project's neuroimaging approach. *Nat. Neurosci.* **19,** 1175-1187.

Goldman-Rakic, P. S. (1996) The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philosophical Transactions of the Royal Society B* **351,** 1445-1453.

Gothard, K. M., Battaglia, F. P., Erickson, C. A., Spitler, K. M. and Amaral, D. G. (2007) Neural responses to facial expression and face identity in the monkey amygdala. *J. Neurophysiol.* **97,** 1671-1683.

Grabenhorst, F. and Rolls, E. T. (2008) Selective attention to affective value alters how the brain processes taste stimuli. *Eur. J. Neurosci.* **27,** 723-729.

Grabenhorst, F., Rolls, E. T. and Bilderbeck, A. (2008) How cognition modulates affective responses to taste and flavor: top down influences on the orbitofrontal and pregenual cingulate cortices. *Cereb. Cortex* **18,** 1549-1559.

Grabenhorst, F. and Rolls, E. T. (2011) Value, pleasure, and choice in the ventral prefrontal cortex. *Trends Cogn. Sci.* **15,** 56-67.

Grabenhorst, F., Hernadi, I. and Schultz, W. (2016) Primate amygdala neurons evaluate the progress of self-defined economic choice sequences. *Elife* **5,** e18731.

Grabenhorst, F., Baez-Mendoza, R., Genest, W., Deco, G. and Schultz, W. (2019) Primate amygdala neurons simulate decision processes of social partners. *Cell* **177,** 986-998 e915.

Grabenhorst, F. and Schultz, W. (2021) Functions of primate amygdala neurons in economic decisions and social decision simulation. *Behav. Brain Res.* **409,** 113318.

Griffanti, L., Salimi-Khorshidi, G., Beckmann, C. F., Auerbach, E. J., Douaud, G., Sexton, C. E., Zsoldos, E., Ebmeier, K. P., Filippini, N., Mackay, C. E., Moeller, S., Xu, J., Yacoub, E., Baselli, G., Ugurbil, K., Miller, K. L. and Smith, S. M. (2014) ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. *Neuroimage* **95,** 232-247.

Hasselmo, M. E., Rolls, E. T. and Baylis, G. C. (1989a) The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey. *Behav. Brain Res.* **32,** 203-218.

Hasselmo, M. E., Rolls, E. T., Baylis, G. C. and Nalwa, V. (1989b) Object-centred encoding by face-selective neurons in the cortex in the superior temporal sulcus of the monkey. *Exp. Brain Res.* **75,** 417-429.

Hasselmo, M. E. and Sarter, M. (2011) Modes and models of forebrain cholinergic neuromodulation of cognition. *Neuropsychopharmacology* **36,** 52-73.

Hernadi, I., Grabenhorst, F. and Schultz, W. (2015) Planning activity for internally generated reward goals in monkey amygdala neurons. *Nat. Neurosci.* **18,** 461-469.

Herzog, A. G. and Van Hoesen, G. W. (1976) Temporal neocortical afferent connections to the amygdala in the rhesus monkey. *Brain Res.* **115,** 57-69.

Hornak, J., Rolls, E. T. and Wade, D. (1996) Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia* **34,** 247-261.

Hornak, J., Bramham, J., Rolls, E. T., Morris, R. G., O'Doherty, J., Bullock, P. R. and Polkey, C. E. (2003) Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain* **126,** 1691-1712.

Hornak, J., O'Doherty, J., Bramham, J., Rolls, E. T., Morris, R. G., Bullock, P. R. and Polkey, C. E. (2004) Reward-related reversal learning after surgical excisions in orbitofrontal and dorsolateral prefrontal cortex in humans. *J. Cogn. Neurosci.* **16,** 463-478.

Huang, C.-C., Rolls, E. T., Hsu, C.-C. H., Feng, J. and Lin, C.-P. (2021) Extensive cortical connectivity of the human hippocampal memory system: beyond the "what" and "where" dual-stream model. *Cereb. Cortex* **31,** 4652-4669.

Huang, C. C., Rolls, E. T., Feng, J. and Lin, C. P. (2022) An extended Human Connectome Project multimodal parcellation atlas of the human cortex and subcortical areas. *Brain Struct Funct* **227,** 763-778.

Johansen, J. P., Tarpley, J. W., LeDoux, J. E. and Blair, H. T. (2010) Neural substrates for expectation-modulated fear learning in the amygdala and periaqueductal gray. *Nat. Neurosci.* **13,** 979-986.

Kadohisa, M., Rolls, E. T. and Verhagen, J. V. (2005a) The primate amygdala: neuronal representations of the viscosity, fat texture, temperature, grittiness and taste of foods. *Neuroscience* **132,** 33-48.

Kadohisa, M., Rolls, E. T. and Verhagen, J. V. (2005b) Neuronal representations of stimuli in the mouth: the primate insular taste cortex, orbitofrontal cortex, and amygdala. *Chem. Senses* **30,** 401–419.

Kennedy, D. P. and Adolphs, R. (2011) Reprint of: Impaired fixation to eyes following amygdala damage arises from abnormal bottom-up attention. *Neuropsychologia* **49,** 589-595.

Khandhadia, A. P., Murphy, A. P., Romanski, L. M., Bizley, J. K. and Leopold, D. A. (2021) Audiovisual integration in macaque face patch neurons. *Curr. Biol.* **31,** 1826-1835 e1823.

Killcross, S., Robbins, T. W. and Everitt, B. J. (1997) Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala. *Nature* **388,** 377-380.

Klein-Flugge, M. C., Jensen, D. E. A., Takagi, Y., Priestley, L., Verhagen, L., Smith, S. M. and Rushworth, M. F. S. (2022) Relationship between nuclei-specific amygdala connectivity and mental health dimensions in humans. *Nat Hum Behav*.

Kringelbach, M. L., O'Doherty, J., Rolls, E. T. and Andrews, C. (2003) Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cereb. Cortex* **13,** 1064-1071.

Kringelbach, M. L., McIntosh, A. R., Ritter, P., Jirsa, V. K. and Deco, G. (2015) The rediscovery of slowness: exploring the timing of cognition. *Trends Cogn. Sci.* **19,** 616-628.

Kringelbach, M. L. and Deco, G. (2020) Brain states and transitions: insights from computational neuroscience. *Cell Rep* **32,** 108128.

Kuznetsov, Y. A. (2013) *Elements of applied bifurcation theory*. Springer Science and Business Media: New York.

Lau, H. (2022) *In Consciousness We Trust: the cognitive neuroscience of conscious experience*. Oxford University Press: Oxford.

LeDoux, J. (2012) Rethinking the emotional brain. *Neuron* **73,** 653-676.

LeDoux, J., Brown, R., Pine, D. and Hofmann, S. (2018) Know thyself: well-being and subjective experience. *Cerebrum* **2018,** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6353121/.

LeDoux, J. E. (1994) Emotion, memory and the brain. *Sci. Am.* **270,** 32-39.

LeDoux, J. E. (1995) Emotion: clues from the brain. *Annu. Rev. Psychol.* **46,** 209-235.

LeDoux, J. E. (1996) *The Emotional Brain*. Simon and Schuster: New York.

LeDoux, J. E. (2000) Emotion circuits in the brain. *Annu. Rev. Neurosci.* **23,** 155-184.

LeDoux, J. E. and Pine, D. S. (2016) Using neuroscience to help understand fear and anxiety: a two-system framework. *Am. J. Psychiatry* **173,** 1083-1093.

LeDoux, J. E. (2017) Semantics, Surplus Meaning, and the Science of Fear. *Trends Cogn. Sci.* **21,** 303-306.

LeDoux, J. E. and Daw, N. D. (2018) Surviving threats: neural circuit and computational implications of a new taxonomy of defensive behaviour. *Nat. Rev. Neurosci.* **19,** 269-282.

Leonard, C. M., Rolls, E. T., Wilson, F. A. W. and Baylis, G. C. (1985) Neurons in the amygdala of the monkey with responses selective for faces. *Behav. Brain Res.* **15,** 159-176.

Miller, E. K., Lundqvist, M. and Bastos, A. M. (2018) Working Memory 2.0. *Neuron* **100,** 463-475.

Millhouse, O. E. and DeOlmos, J. (1983) Neuronal configuration in lateral and basolateral amygdala. *Neuroscience* **10,** 1269-1300.

Mobbs, D., Adolphs, R., Fanselow, M. S., Barrett, L. F., LeDoux, J. E., Ressler, K. and Tye, K. M. (2019) Viewpoints: Approaches to defining and investigating fear. *Nat. Neurosci.* **22,** 1205-1216.

Morrison, S. E., Saez, A., Lau, B. and Salzman, C. D. (2011) Different time courses for learning-related changes in amygdala and orbitofrontal cortex. *Neuron* **71,** 1127-1140.

Newman, E. L., Gupta, K., Climer, J. R., Monaghan, C. K. and Hasselmo, M. E. (2012) Cholinergic modulation of cognitive processing: insights drawn from computational models. *Front. Behav. Neurosci.* **6,** 24.

O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J. and Andrews, C. (2001) Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat. Neurosci.* **4,** 95-102.

O'Doherty, J., Winston, J., Critchley, H., Perrett, D., Burt, D. M. and Dolan, R. J. (2003) Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. *Neuropsychologia* **41,** 147-155.

Passingham, R. E. (2021) *Understanding the Prefrontal Cortex: selective advantage, connectivity and neural operations*. Oxford University Press: Oxford.

Passingham, R. E. P. and Wise, S. P. (2012) *The Neurobiology of the Prefrontal Cortex*. Oxford University Press: Oxford.

Phelps, E. A. (2004) Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr. Opin. Neurobiol.* **14,** 198-202.

Phelps, E. A. and LeDoux, J. E. (2005) Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* **48,** 175-187.

Phelps, E. A. (2006) Emotion and cognition: insights from studies of the human amygdala. *Annu. Rev. Psychol.* **57,** 27-53.

Pipitone, J., Park, M. T., Winterburn, J., Lett, T. A., Lerch, J. P., Pruessner, J. C., Lepage, M., Voineskos, A. N., Chakravarty, M. M. and Alzheimer's Disease Neuroimaging, I. (2014) Multi-atlas segmentation of the whole hippocampus and subfields using multiple automatically generated templates. *Neuroimage* **101,** 494-512.

Pitcher, D. and Ungerleider, L. G. (2021) Evidence for a third visual pathway specialized for social perception. *Trends Cogn. Sci.* **25,** 100-110.

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L. and Petersen, S. E. (2012) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* **59,** 2142-2154.

Price, J. L. and Drevets, W. C. (2010) Neurocircuitry of mood disorders. *Neuropsychopharmacology* **35,** 192-216.

Quirk, G. J., Armony, J. L., Repa, J. C., Li, X. F. and LeDoux, J. E. (1996) Emotional memory: a search for sites of plasticity. *Cold Spring Harb. Symp. Quant. Biol.* **61,** 247-257.

Razi, A., Seghier, M. L., Zhou, Y., McColgan, P., Zeidman, P., Park, H. J., Sporns, O., Rees, G. and Friston, K. J. (2017) Large-scale DCMs for resting-state fMRI. *Netw Neurosci* **1,** 222-241.

Robbins, T. W., Cador, M., Taylor, J. R. and Everitt, B. J. (1989) Limbic-striatal interactions in reward-related processes. *Neurosci. Biobehav. Rev.* **13,** 155-162.

Rogan, M. T., Staubli, U. V. and LeDoux, J. E. (1997) Fear conditioning induces associative long-term potentiation in the amygdala. *Nature* **390,** 604-607.

Rolls, E. T. and Rolls, B. J. (1973) Altered food preferences after lesions in the basolateral region of the amygdala in the rat. *J. Comp. Physiol. Psychol.* **83,** 248-259.

Rolls, E. T. (1984) Neurons in the cortex of the temporal lobe and in the amygdala of the monkey with responses selective for faces. *Hum. Neurobiol.* **3,** 209-222.

Rolls, E. T., Hornak, J., Wade, D. and McGrath, J. (1994) Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J. Neurol. Neurosurg. Psychiatry* **57,** 1518-1524.

Rolls, E. T., O'Doherty, J., Kringelbach, M. L., Francis, S., Bowtell, R. and McGlone, F. (2003) Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. *Cereb. Cortex* **13,** 308-317.

Rolls, E. T., Browning, A. S., Inoue, K. and Hernadi, S. (2005) Novel visual stimuli activate a population of neurons in the primate orbitofrontal cortex. *Neurobiol. Learn. Mem.* **84,** 111-123.

Rolls, E. T., Critchley, H. D., Browning, A. S. and Inoue, K. (2006) Face-selective and auditory neurons in the primate orbitofrontal cortex. *Exp. Brain Res.* **170,** 74-87.

Rolls, E. T. (2008) Emotion, higher order syntactic thoughts, and consciousness. In: *Frontiers of Consciousness*. pp. 131-167. Eds. L. Weiskrantz, M. K. Davies. Oxford University Press: Oxford.

Rolls, E. T. (2014) *Emotion and Decision-Making Explained*. Oxford University Press: Oxford.

Rolls, E. T. (2015) Taste, olfactory, and food reward value processing in the brain. *Prog. Neurobiol.* **127-128,** 64-90.

Rolls, E. T. (2016a) A non-reward attractor theory of depression. *Neurosci. Biobehav. Rev.* **68,** 47-58.

Rolls, E. T. (2016b) Functions of the anterior insula in taste, autonomic, and related functions. *Brain Cogn.* **110,** 4-19.

Rolls, E. T. (2016c) *Cerebral Cortex: Principles of Operation*. Oxford University Press: Oxford.
Rolls, E. T. (2018) *The Brain, Emotion, and Depression*. Oxford University Press: Oxford.
Rolls, E. T. (2019a) The cingulate cortex and limbic systems for emotion, action, and memory. *Brain Struct Funct* **224,** 3001-3018.
Rolls, E. T. (2019b) The orbitofrontal cortex and emotion in health and disease, including depression. *Neuropsychologia* **128,** 14-43.
Rolls, E. T. (2019c) *The Orbitofrontal Cortex*. Oxford University Press: Oxford.
Rolls, E. T. (2020) Neural computations underlying phenomenal consciousness: a Higher Order Syntactic Thought theory. *Frontiers in Psychology (Consciousness Research)* **11,** 655.
Rolls, E. T., Cheng, W. and Feng, J. (2020a) The orbitofrontal cortex: reward, emotion, and depression. *Brain Communications* **2,** fcaa196.
Rolls, E. T., Vatansever, D., Li, Y., Cheng, W. and Feng, J. (2020b) Rapid rule-based reward reversal and the lateral orbitofrontal cortex. *Cerebral Cortex Communications* **1,** doi: 10.1093/texcom/tgaa1087.
Rolls, E. T. (2021a) The neuroscience of emotional disorders. In: *Handbook of Clinical Neurology: Disorders of Emotion in Neurologic Disease*. pp. 1-26. Eds. K. M. Heilman, S. E. Nadeau. Elsevier: Oxford.
Rolls, E. T. (2021b) A neuroscience levels of explanation approach to the mind and the brain. *Front. Comput. Neurosci.* **15,** 649679.
Rolls, E. T. (2021c) Mind causality: a computational neuroscience approach. *Front. Comput. Neurosci.* **15,** 70505.
Rolls, E. T. (2021d) *Brain Computations: What and How*. Oxford University Press: Oxford.
Rolls, E. T. (2022a) Hippocampal spatial view cells for memory and navigation, and their underlying connectivity in humans. *Hippocampus***,** doi: 10.1002/hipo.23467.
Rolls, E. T. (2022b) The hippocampus, ventromedial prefrontal cortex, and episodic and semantic memory. *Prog. Neurobiol.* **217,** 102334.
Rolls, E. T. (2022c) Emotion, motivation, decision-making, the orbitofrontal cortex and the amygdala. *Emot. Rev.*
Rolls, E. T., Deco, G., Huang, C.-C. and Feng, J. (2022a) The human posterior parietal cortex: effective connectome, and its relation to function. *Cereb. Cortex***,** doi: 10.1093/cercor/bhac1266.
Rolls, E. T., Deco, G., Huang, C.-C. and Feng, J. (2022b) The human language effective connectome. *Neuroimage* **258,** 119352.
Rolls, E. T., Deco, G., Huang, C.-C. and Feng, J. (2022c) Multiple cortical visual streams in humans. *Cereb. Cortex***,** doi: 10.1093/cercor/bhac1276.
Rolls, E. T., Deco, G., Huang, C.-C. and Feng, J. (2022d) Prefrontal and somatosensory-motor cortex effective connectivity in humans. *Cereb. Cortex***,** doi: 10.1093/cercor/bhac1391.
Rolls, E. T., Deco, G., Huang, C. C. and Feng, J. (2022e) The effective connectivity of the human hippocampal memory system. *Cereb. Cortex* **32,** 3706-3725.
Rolls, E. T., Deco, G., Huang, C. C. and Feng, J. (2022f) The human orbitofrontal cortex, vmPFC, and anterior cingulate cortex effective connectome: emotion, memory, and action. *Cereb. Cortex***,** doi: 10.1093/cercor/bhac1070.
Rolls, E. T., Rauschecker, J. P., Deco, G., Huang, C.-C. and Feng, J. (2022g) Auditory cortical connectivity in humans. *Cereb. Cortex***,** in review.
Rolls, E. T., Wirth, S., Deco, G., Huang, C.-C. and Feng, J. (2022h) The human posterior cingulate, retrosplenial and medial parietal cortex effective connectome, and implications for memory and navigation. *Hum. Brain Mapp.***,** doi: 10.1002/HBM.26089.
Rolls, E. T. (2023) *Brain Computations and Connectivity*. Oxford University Press: Oxford.
Rushworth, M. F., Noonan, M. P., Boorman, E. D., Walton, M. E. and Behrens, T. E. (2011) Frontal cortex and reward-guided learning and decision-making. *Neuron* **70,** 1054-1069.
Rushworth, M. F., Kolling, N., Sallet, J. and Mars, R. B. (2012) Valuation and decision-making in frontal cortex: one or many serial or parallel systems? *Curr. Opin. Neurobiol.* **22,** 946-955.
Saez, R. A., Saez, A., Paton, J. J., Lau, B. and Salzman, C. D. (2017) Distinct roles for the amygdala and orbitofrontal cortex in representing the relative amount of expected reward. *Neuron* **95,** 70-77 e73.

Salimi-Khorshidi, G., Douaud, G., Beckmann, C. F., Glasser, M. F., Griffanti, L. and Smith, S. M. (2014) Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. *Neuroimage* **90,** 449-468.

Sanghera, M. K., Rolls, E. T. and Roper-Hall, A. (1979) Visual responses of neurons in the dorsolateral amygdala of the alert monkey. *Exp. Neurol.* **63,** 610-626.

Satterthwaite, T. D., Elliott, M. A., Gerraty, R. T., Ruparel, K., Loughead, J., Calkins, M. E., Eickhoff, S. B., Hakonarson, H., Gur, R. C., Gur, R. E. and Wolf, D. H. (2013) An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage* **64,** 240-256.

Schiller, D., Monfils, M. H., Raio, C. M., Johnson, D. C., Ledoux, J. E. and Phelps, E. A. (2010) Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature* **463,** 49-53.

Scott, S. K., Young, A. W., Calder, A. J., Hellawell, D. J., Aggleton, J. P. and Johnson, M. (1997) Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature* **385,** 254-257.

Smith, S. M., Beckmann, C. F., Andersson, J., Auerbach, E. J., Bijsterbosch, J., Douaud, G., Duff, E., Feinberg, D. A., Griffanti, L., Harms, M. P., Kelly, M., Laumann, T., Miller, K. L., Moeller, S., Petersen, S., Power, J., Salimi-Khorshidi, G., Snyder, A. Z., Vu, A. T., Woolrich, M. W., Xu, J., Yacoub, E., Ugurbil, K., Van Essen, D. C., Glasser, M. F. and Consortium, W. U.-M. H. (2013) Resting-state fMRI in the Human Connectome Project. *Neuroimage* **80,** 144-168.

Spezio, M. L., Huang, P. Y., Castelli, F. and Adolphs, R. (2007) Amygdala damage impairs eye contact during conversations with real people. *J. Neurosci.* **27,** 3994-3997.

Stefanacci, L., Suzuki, W. A. and Amaral, D. G. (1996) Organization of connections between the amygdaloid complex and the perirhinal and parahippocampal cortices in macaque monkeys. *J. Comp. Neurol.* **375,** 552-582.

Sylvester, C. M., Yu, Q., Srivastava, A. B., Marek, S., Zheng, A., Alexopoulos, D., Smyser, C. D., Shimony, J. S., Ortega, M., Dierker, D. L., Patel, G. H., Nelson, S. M., Gilmore, A. W., McDermott, K. B., Berg, J. J., Drysdale, A. T., Perino, M. T., Snyder, A. Z., Raut, R. V., Laumann, T. O., Gordon, E. M., Barch, D. M., Rogers, C. E., Greene, D. J., Raichle, M. E. and Dosenbach, N. U. F. (2020) Individual-specific functional connectivity of the amygdala: A substrate for precision psychiatry. *Proc. Natl. Acad. Sci. U. S. A.* **117,** 3808-3818.

Taschereau-Dumouchel, V., Michel, M., Lau, H., Hofmann, S. G. and LeDoux, J. E. (2022) Putting the "mental" back in "mental disorders": a perspective from research on fear and anxiety. *Mol. Psychiatry* **27,** 1322-1330.

Timbie, C., Garcia-Cabezas, M. A., Zikopoulos, B. and Barbas, H. (2020) Organization of primate amygdalar-thalamic pathways for emotions. *PLoS Biol.* **18,** e3000639.

Tsuchida, A. and Fellows, L. K. (2012) Are you upset? Distinct roles for orbitofrontal and lateral prefrontal cortex in detecting and distinguishing facial expressions of emotion. *Cereb. Cortex* **22,** 2904-2912.

Valdes-Sosa, P. A., Roebroeck, A., Daunizeau, J. and Friston, K. (2011) Effective connectivity: influence, causality and biophysical modeling. *Neuroimage* **58,** 339-361.

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E., Yacoub, E., Ugurbil, K. and Consortium, W. U.-M. H. (2013) The WU-Minn Human Connectome Project: an overview. *Neuroimage* **80,** 62-79.

Van Essen, D. C. and Glasser, M. F. (2018) Parcellating cerebral cortex: how invasive animal studies inform noninvasive mapmaking in humans. *Neuron* **99,** 640-663.

Van Hoesen, G. W. (1981) The differential distribution, diversity and sprouting of cortical projections to the amygdala in the rhesus monkey. In: *The Amygdaloid Complex*. pp. 77-90. Ed. Y. Ben-Ari. Elsevier: Amsterdam.

Whalen, P. J. and Phelps, E. A. Eds (2009) *The Human Amygdala*. Guilford: New York.

Wilson, F. A. W. and Rolls, E. T. (1990a) Learning and memory are reflected in the responses of reinforcement-related neurons in the primate basal forebrain. *J. Neurosci.* **10,** 1254-1267.

Wilson, F. A. W. and Rolls, E. T. (1990b) Neuronal responses related to reinforcement in the primate basal forebrain. *Brain Res.* **509,** 213-231.

Wilson, F. A. W. and Rolls, E. T. (1990c) Neuronal responses related to the novelty and familiarity of visual stimuli in the substantia innominata, diagonal band of Broca and periventricular region of the primate. *Exp. Brain Res.* **80,** 104-120.

Wilson, F. A. W. and Rolls, E. T. (2005) The primate amygdala and reinforcement: a dissociation between rule-based and associatively-mediated memory revealed in amygdala neuronal activity. *Neuroscience* **133,** 1061-1072.

Yokoyama, C., Autio, J. A., Ikeda, T., Sallet, J., Mars, R. B., Van Essen, D. C., Glasser, M. F., Sadato, N. and Hayashi, T. (2021) Comparative connectomics of the primate social brain. *Neuroimage* **245,** 118693.

Young, A. W., Aggleton, J. P., Hellawell, D. J., Johnson, M., Broks, P. and Hanley, J. R. (1995) Face processing impairments after amygdalotomy. *Brain* **118,** 15-24.

Young, A. W., Hellawell, D. J., Van De Wal, C. and Johnson, M. (1996) Facial expression processing after amygdalotomy. *Neuropsychologia* **34,** 31-39.

Zaborszky, L., Hoemke, L., Mohlberg, H., Schleicher, A., Amunts, K. and Zilles, K. (2008) Stereotaxic probabilistic maps of the magnocellular cell groups in human basal forebrain. *Neuroimage* **42,** 1127-1141.

Zaborszky, L., Gombkoto, P., Varsanyi, P., Gielow, M. R., Poe, G., Role, L. W., Ananth, M., Rajebhosale, P., Talmage, D. A., Hasselmo, M. E., Dannenberg, H., Minces, V. H. and Chiba, A. A. (2018) Specific basal forebrain-cortical cholinergic circuits coordinate cognitive operations. *J. Neurosci.* **38,** 9446-9458.

Zangemeister, L., Grabenhorst, F. and Schultz, W. (2016) Neural basis for economic saving strategies in human amygdala-prefrontal reward circuits. *Curr. Biol.* **26,** 3004-3013.

Zhang, B., Rolls, E. T., Wang, X., Xie, C., Cheng, W. and Feng, J. (2023) Dissociable roles of medial and lateral orbitofrontal cortex in major depression: pathophysiology and treatments.