Research report

Functional connectivity of the orbitofrontal cortex, anterior cingulate cortex, and inferior frontal gyrus in humans

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ABSTRACT

Parcellation of the orbitofrontal cortex, anterior cingulate cortex, and inferior frontal gyrus based on their functional connectivity with the whole brain in resting state fMRI with 654 participants was performed to investigate how these regions with different functions in reward, emotion and their disorders are functionally connected to each other and to the whole brain. The human medial and lateral orbitofrontal cortex, the ventromedial prefrontal cortex, the anterior cingulate cortex, and the right and left inferior frontal gyrus have different functional connectivity with other brain areas and with each other; and each of these regions has several parcels with different functional connectivity with other brain areas. In terms of functional connectivity, the lateral orbitofrontal cortex extends especially on the right into the orbital part of the inferior frontal gyrus and provides connectivity with premotor cortical areas. The orbitofrontal cortex, especially the lateral orbitofrontal cortex, has connectivity not only with language-related areas in the inferior frontal gyrus (Broca’s area), but also with the angular and supramarginal gyri. In this context, whereas the connectivity of the orbitofrontal cortex, ventromedial prefrontal cortex, and anterior cingulate cortex is symmetrical, the connectivity of the inferior frontal gyrus triangular and opercular parts is asymmetrical for the right and the left hemispheres. These findings have implications for understanding the neural bases of human emotion and decision-making, and for their disorders including depression.

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1. Introduction

It has been traditional, for historical reasons based on what was technically possible with the light microscope, to divide the cerebral cortex into different areas based on cytoarchitecture and myeloarchitecture (Brodmann, 1909a; Brodmann, 1909b; Henssen et al., 2016; Ongür, Ferry, & Price, 2003; Ongür & Price, 2000; Vogt, 2009; y Cajal, 1995). For example, the primary visual cortex can be identified by its prominent layer 4, with many granule cells involved in processing the massive visual sensory input from the lateral geniculate nucleus. In another example, motor cortex can be identified by its large pyramidal cells in layer 5, involved in sending motor outputs directly to the spinal cord for fine control of the distal extremities such as the fingers. However, an important way in which to define a cortical area is in terms of the functions it performs, which are related to the inputs that it receives and the regions to which it connects (Rolls, 2016a). The implication is that a different way to divide the cortex into different areas is in terms of the connectivity of each brain area with other brain areas.

In this paper we utilize a method to delineate cortical areas based on their functional connectivity with other brain areas, based on the computational concept that the functional subdivisions of the cortex are likely to be related to where they receive connections from, and where they project to (Rolls, 2016a). In essence, the concept is that the cerebral cortex, and the human brain, can be understood in terms of the computations that each brain area performs, based on the inputs that it receives, and where it sends it outputs to (Rolls, 2016a). To achieve this delineation of cortical areas based in their connections with other cortical areas, we measure the functional connectivity of individual voxels in the orbitofrontal cortex and closely related areas the anterior cingulate cortex and inferior frontal gyrus with many different regions of the brain. On the basis of the functional connectivity of each voxel we divide the voxels into different groups or clusters to identify functional subdivisions of voxels within the area being investigated. Functional connectivity refers to correlations between the fMRI BOLD signal in different brain regions, and reflects direct connections between cortical areas as shown by combined anatomical pathways tracing and functional connectivity analyses in macaques, and also some trans-synaptic effects (Van Essen et al., 2019). An advantage of functional connectivity is that it can reveal trans-synaptic effects, and is non-invasive and can be performed in humans.

In the present case, the voxels of interest are in the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the inferior frontal gyrus (IFG), because all of these areas are implicated in different ways in emotion, and in emotional disorders including depression (Cheng et al., 2016; Cheng, Rolls, Qiu, Xie, Lyu, et al., 2018; Cheng, Rolls, Qiu, Xie, Wei, et al., 2018; Cheng, Rolls, Qiu, Yang, et al., 2018; Cheng, Rolls, Ruan, & Feng, 2018; Rolls, 2014, 2018, 2019a, 2019c, 2019d; Rolls, Cheng, Du, et al., 2019; Rolls, Cheng, Gong, et al., 2019). This investigation thus goes beyond a previous parcellation of the orbitofrontal cortex (Kahnt, Chang, Park, Heinzel, & Haynes, 2012) not only in terms of the robustness of the analysis (they utilized results from 13 participants, we utilize results from 654 participants for robustness and generalizability), but also because there is a whole set of connected systems involving the OFC, ACC and IFG that are important in emotion and its disorders, so that it is very important to know how all the subparts of these regions are connected. The current investigation is the first to conduct a parcellation of ACC and IFG together with OFC, in order to show how the subparts of these regions are functionally connected, given the importance of at least parts of these regions for emotion, decision-making, and their disorders. Moreover, in the approach described here, the relations and divisions between areas are based on quantitative measures of correlations between the connectivity of areas (identified with the quantitative approach of cluster analysis) with the rest of the brain, whereas anatomical investigations of sub-networks has been based on a qualitative analysis of network subdivisions (Ongür & Price, 2000; Price, 1999, 2006, 2007).

In the present investigation, the connectivity between each voxel in the areas OFC/ACC/IFG and every AAL3 brain area (Rolls, Huang, Lin, Feng, & Joliot, 2019) was measured by the Pearson correlation between their BOLD signals using resting state functional magnetic resonance imaging (fMRI). The concept here is that in a system in which a task is not being performed, the noise-produced perturbations in the system will influence other nodes in the system according to the strength of the connections between any two nodes in the system. The noise in the system is produced by the almost random (Poisson) times of firing of the neurons in the system for a given mean firing rate (Cabral, Kringlebach, & Deco, 2014; Deco, Rolls, Albantakis, & Romo, 2013; Rolls & Deco, 2010), which in turn can be related to factors such as noise in ion channels (Faisal, Selen, & Wolpert, 2008; Rolls & Deco, 2010). A list of abbreviations of AAL3 areas is provided in Table S1 (see Table 1).

2. Methods

2.1. Participants

There were 254 healthy participants subjects (age: 39.7 ± 15.8, Male/Female: 166/88) from Xinan (First Affiliated Hospital of Chongqing Medical School in Chongqing, China); and there were 400 healthy participants (age: 40.6 ± 21.4, Male/Female: 147/253) from the NKI cohort Nathan Kline Institute—Rockland Sample (NKI-R5) dataset (Nooner et al., 2012). All the functional connectivity-driven parcellations were based on the resting-state fMRI data of the 254 subjects in the Xinan cohort and 400 subjects in NKI cohort to provide a sample of 654 subjects for this parcellation analysis. Exclusion criteria for both groups were as follows: current psychiatric disorders and neurological disorders; substance abuse; and stroke or serious encephalopathy. Of note, all of the subjects did not meet DSM-IV criteria for any psychiatric disorders and did not use any drugs that could affect brain function. The collection of the data used in this study was approved by the Research Ethics Committee of the Brain Imaging Center of Southwest University and First Affiliated Hospital of Chongqing Medical School; and as described elsewhere for the NKI data (Nooner et al., 2012). Informed written consent was obtained from each subject.
Table 1 — Abbreviations. A full list of the automated anatomical labelling atlas 3 areas and their abbreviations is provided in Tables S1 and S2. Those used commonly in the main text are shown next for convenience, together with other abbreviations used.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAL2</td>
<td>automated anatomical labelling atlas 2</td>
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<tr>
<td>AAL3</td>
<td>automated anatomical labelling atlas 3</td>
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<tr>
<td>FC</td>
<td>functional connectivity</td>
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<tr>
<td>MDS</td>
<td>multidimensional scaling</td>
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<tr>
<td>ACCpre</td>
<td>Anterior cingulate cortex, pregenual</td>
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<tr>
<td>ACCsub</td>
<td>Anterior cingulate cortex, subcallosal/subgenual</td>
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<tr>
<td>ACCsup</td>
<td>Anterior cingulate cortex, supracallosal</td>
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<tr>
<td>ANG</td>
<td>Angular gyrus</td>
</tr>
<tr>
<td>HIP</td>
<td>Hippocampus</td>
</tr>
<tr>
<td>IFGoperc</td>
<td>Inferior frontal gyrus, opercular part (BA44)</td>
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<tr>
<td>IFGorb</td>
<td>Inferior frontal gyrus, pars orbitalis (part of BA12)</td>
</tr>
<tr>
<td>IFGtri</td>
<td>Inferior frontal gyrus, triangular part (BA45)</td>
</tr>
<tr>
<td>IPG</td>
<td>Inferior parietal gyrus, excluding supramarginal and angular gyri</td>
</tr>
<tr>
<td>ITG</td>
<td>Inferior temporal gyrus</td>
</tr>
<tr>
<td>MCC</td>
<td>Middle cingulate gyrus</td>
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<tr>
<td>MFG</td>
<td>Middle frontal gyrus</td>
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<tr>
<td>MTG</td>
<td>Middle temporal gyrus</td>
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<tr>
<td>OFCant</td>
<td>Anterior orbital gyrus</td>
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<tr>
<td>OFClat</td>
<td>Lateral orbital gyrus</td>
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<tr>
<td>OFCmed</td>
<td>Medial orbital gyrus</td>
</tr>
<tr>
<td>OFCpost</td>
<td>Posterior orbital gyrus</td>
</tr>
<tr>
<td>OLF</td>
<td>Olfactory cortex (including part of the olfactory tubercle)</td>
</tr>
<tr>
<td>PCC</td>
<td>Posterior cingulate cortex</td>
</tr>
<tr>
<td>PHG</td>
<td>Parahippocampal gyrus</td>
</tr>
<tr>
<td>Rct</td>
<td>Rectus gyrus (BA 14)</td>
</tr>
<tr>
<td>SFG</td>
<td>Superior frontal gyrus, dorsolateral</td>
</tr>
<tr>
<td>SFGmedial</td>
<td>Superior frontal gyrus, medial</td>
</tr>
<tr>
<td>SMA</td>
<td>Supplementary motor area</td>
</tr>
<tr>
<td>SMG</td>
<td>Supramarginal gyrus</td>
</tr>
<tr>
<td>STG</td>
<td>Superior temporal gyrus</td>
</tr>
<tr>
<td>VMPFC</td>
<td>Superior frontal gyrus, medial orbital which is often termed the Ventromedial Prefrontal Cortex</td>
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2.2. Image acquisition and preprocessing

For the Xinan dataset, all the brain images were acquired on a 3.0-T Siemens Trio MRI scanner using a 16-channel whole-brain coil (Siemens Medical, Erlangen, Germany). High-resolution T1-weighted 3D images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (echo time (TE) = 2.52 ms; repetition time (TR) = 1900 ms; inversion time (TI) = 900 ms; flip angle = 9°; slices = 176; thickness = 1.0 mm; resolution matrix = 256 × 256; voxel size = 1 × 1 × 1 mm). For each subject, 242 functional images were acquired with a gradient echo type Echo Planar Imaging (EPI) sequence (echo time (TE) = 30 ms; repetition time (TR) = 2000 ms; flip angle = 90°; slices = 32; slice thickness = 3.0 mm; slice gap = 1 mm; resolution matrix = 64 × 64; voxel size 3.4 × 3.4 × 3 mm). During image acquisition, participants were instructed to keep their eyes closed while keeping their head as still as possible without falling asleep. All participants stayed awake during the MRI imaging as confirmed by the participants after the session.

For the NKI dataset, the resting-state fMRI data used in this study were collected from the publicly available Nathan Kline Institute (NKI)/Rockland sample of the 1000 Functional Connectomes project (fcon_1000.projects.nitrc.org/index/enhanced). Scans were collected using a multiband EPI sequence with the following parameters: repetition time (TR)/echo time (TE) = 650/30 ms, voxel size = 3.0 × 3.0 × 3.0 mm, and 40 slices, covering the whole brain. Individuals’ images were viewed one by one to ensure that the whole brain was covered.

Data preprocessing was performed using DPARSF (Chao-Gan & Yu-Feng, 2010) (http://restfmri.net), which is a toolbox developed for the SPM8 software package. The first 10 echoplanar imaging (EPI) scans were discarded to suppress equilibration effects. The remaining scans of each subject underwent slice timing correction by sinc interpolating volume slices, motion correction for volume to volume displacement, spatial normalization to standard Montreal Neurological Institute (MNI) space using affine transformation and non-linear deformation with a voxel size of 3 × 3 × 3 mm followed by spatial smoothing (8 mm full-width at half-maximum). To remove the sources of spurious correlations, present in resting state blood oxygen level-dependent data, all functional MRI time series underwent band-pass temporal filtering 0.01–0.1 Hz, nuisance signal removal from the ventricles, and deep white matter, and regressing out any effects of head motion using the 24 head motion parameters procedure (Friston, Williams, Howard, Frackowiak, & Turner, 1996). Finally, we implemented additional careful volume censoring (‘scrubbing’) movement correction (Power et al., 2014) to ensure that head motion artefacts do not drive observed effects. The mean framewise displacement was computed with a framewise displacement threshold of .3 mm, and any participants with a value greater than this were excluded. Global signals were not regressed out for reasons described elsewhere (Cheng et al., 2016). For the NKI dataset, the preprocessing used a similar pipeline.

2.3. Definition of region of interest

We selected the orbitofrontal cortex (OFC), inferior frontal gyrus (IFG) and anterior cingulate cortex (ACC) as regions of interest (ROI) using the automated anatomical labelling atlas AAL3 (Rolls, Huang, et al., 2019): Inferior frontal gyrus, opercular part; Inferior frontal gyrus, triangular part; Inferior frontal gyrus pars orbitalis; Superior frontal gyrus, medial orbital; Gyrus rectus; Medial orbital gyrus; Anterior orbital gyrus; Posterior orbital gyrus; Lateral orbital gyrus; Anterior cingulate & paracingulate gyri (which in AAL3 is divided into subgenual, pregenual, and supragenual parts).

2.4. Connectivity-based parcellation

The aim of this study was to parcellate the entire OFC/IFG/ACC into distinct subregions based on their resting-state functional connectivities with the whole brain. Specifically, we
first calculated the Pearson correlation coefficient between the time series in each ROI voxel and all the time series from AAL3 regions (137 brain regions) for each subject. This procedure was repeated for all OFC/IFG/ACC voxels (5515 in total) to obtain a $5515 \times 137$ functional connectivity matrix in which each element $i, j$ of the vector represents the correlation between the $i$th voxel of the OFC/IFG/ACC with the $j$th AAL3 region. Because all the voxels are in MNI space, the functional connectivity of every voxel in the OFC/IFG/ACC with every brain region in the AAL3 atlas could be measured, and the functional connectivity of each voxel with every AAL3 area could be determined based on the average of the functional connectivity across all 654 participants.

Parcellation was performed using a standard k-means clustering algorithm. This method in combination with this distance measure allowed us to compute parcellations with 24 clusters of voxels in which each cluster had a similar pattern of connectivity with the rest of the brain. The number of clusters for this k-means clustering was determined by statistical tests to check that each cluster had significantly different functional connectivity across the 654 participants with at least one AAL3 area. (The details were as follows. We formed a matrix of the 24 parcels $\times 137$ AAL3 areas of the type shown in Fig. 2, but for each of the 654 participants. Then t-tests were performed, with Bonferroni correction for multiple comparisons, to test whether for each of the 24 parcels, at least one of the connectivities with an AAL3 region was significantly different from all other clusters. The large number, 654, of participants in this study contributed to the statistical power of this type of analysis, which has not been possible in any previous investigation.) Factors in the choice of 24 clusters in addition to spatial continuity of voxels in a cluster and statistically significantly different functional connectivity of each cluster with other brain areas, were that with this number of parcels the symmetry of the cluster solution, respectively. Because this measure requires that an ROI (e.g., the OFC) is mirror symmetric (i.e., that each voxel exists in both hemispheres), we only included voxels that are present on both sides and discarded voxels that are present on one side only. A high value indicates that the parcels included in the ROI are similar between the left and right hemispheres, where similarity reflects whether voxels are placed in the same cluster.

The robustness of the parcellation was confirmed by measuring the similarity of the parcellations when the parcellation was repeated a number of times with $k$ close to 24; and the optimal number of clusters was measured by checking that each parcel was composed of spatially contiguous voxels, that none of the parcels contained fewer than 50 voxels, by using the symmetry index as described above, and by using the “variation of information” measure as described above.

**3. Results**

The parcellation based on the resting state fMRI of 654 participants from the NKI and Xian datasets is shown in Fig. 1, with the average functional connectivity (FC) of the voxels of each of the 24 parcels to the AAL3 brain areas shown in Fig. 2. The parcels and their connectivity are as follows. Each of the parcels had connectivity with at least one of the AAL3 areas shown in Fig. 2 that was significantly different at $p = 1.1 \times 10^{-46}$ (Bonferroni corrected). Fig. 3 illustrates the connections of each parcel on surface maps of the brain. Figs. 1–3 are relevant to the next four sections on parcels in each of the orbitofrontal cortex, anterior cingulate cortex, and left and right inferior frontal gyrus. The exact locations of each parcel in MNI space are shown in Fig. S1 in coronal slices.

**3.1. Orbitofrontal cortex**

The orbitofrontal cortex is implicated in reward value representations, in learning and rapidly changing associations between stimuli and reward vs nonreward, and thereby in emotion (Rolls, 2014, 2018, 2019c, 2019d; Rolls, Cheng, & Feng, 2019). The medial orbitofrontal cortex, areas 13 and 11, is especially implicated in reward valuation, and the lateral orbitofrontal cortex in changing associations between stimuli and reward vs non-reward (Rolls, 2014, 2018, 2019c, 2019d; Rolls, Cheng, & Feng, 2019).

The parcels in the left and right orbitofrontal (Fig. 1) are approximately symmetric, and indeed the voxels on the right and left were in the same cluster (or parcel) for the right and the left. Indeed, the symmetry index for the 6 orbitofrontal cortex parcels was .85 (see below).

The group of medial/mid orbitofrontal cortex areas (parcel 2 medial orbitofrontal cortex), posterior orbitofrontal cortex
(parcel 3), and anterior orbitofrontal cortex (parcel 4) are strongly connected with each other (see Fig. 6), and with temporal cortical areas (Figs. 2 and 3A).

The medial orbitofrontal cortex (parcel 2) has high FC with the anterior and posterior OFC, with the OLF area, and with the gyrus rectus, and its connectivity with the lateral OFC (AAL3 areas OFClat and IFGorb) is smaller (Figs. 2 and 3A). It also has moderate FC with the inferior temporal visual cortex, and with the nucleus accumbens.

The posterior orbitofrontal cortex (parcel 3) has high FC with the anterior and medial OFC, and with the gyrus rectus, and it has some connectivity with the lateral OFC (OFClat and IFGorb2) and inferior frontal gyrus pars triangularis (Figs. 2 and 3A). It also has moderate FC with the parahippocampal gyrus, hippocampus, the posterior mid- and inferior-temporal cortex and fusiform gyrus, the insula, and the mid-cingulate cortex. Parcel 3 (posterior OFC) is thus notable in having moderate FC with a large number of other brain areas, and is
in the graph theory sense a hub. Parcels 2 and 3 have high FC with the OLF region, which is a region at the posterior border of the OFC where it adjoins the olfactory cortex/tuber.

The anterior orbitofrontal cortex (parcel 4) has high FC with the posterior and medial OFC, and its connectivity with the lateral OFC (OFClat and IFGorb2) is relatively low. It also has high FC with inferior parietal cortex, and anterior inferior temporal cortex, and the middle frontal gyrus (MFG) (Figs. 2 and 3A). It has notably low connectivity with the posterior cingulate cortex, parahippocampal gyrus and hippocampus. The gyrus rectus (parcel 1) has high FC with the anterior, medial and posterior OFC (parcels 2–4), and OLF, and its connectivity with the lateral OFC (OFClat and IFGorb2) is also considerable (Figs. 2 and 3A). It also has high FC with the angular gyrus, middle temporal gyrus, with other prefrontal cortical areas including FrontalMedorb (or VMFPC), and with the ACCpre and ACCsub and ACCpost but not ACCsup. It has low connectivity with the insula.

The posterior part of the lateral orbitofrontal cortex (parcel 5) has very high FC with IFGorb2, high with the IFGtri but low with IFGoperc, and moderate FC with superior frontal, the ventromedial prefrontal cortex (VMFPC, AAL3 area Frontal-MedOrb), gyrus rectus, posterior OFC, OLF, middle and posterior cingulate, hippocampus, parahippocampal gyrus, left angular gyrus, all temporal cortical areas, the ACCpre and ACCsub but not ACCsup (Figs. 2 and 3A). This parcel is larger on the right as shown in coronal slices Fig. 1 (right 128 voxels, left 115), and the AAL3 area OFClat is larger on the right than the left. (Similarly, parcel 8, the connected and related orbital part of the inferior frontal gyrus, is larger on the right than the left (171 vs 46 voxels).) This is consistent with the lateral orbitofrontal cortex and inferior frontal gyrus areas pars orbitalis areas being larger on the right, compared to the left where they may be reduced in size to accommodate the larger inferior frontal gyrus areas that are part of Broca’s area on the left.

The anterior part of the lateral orbitofrontal cortex (parcel 6) has very high FC with IFGorb2, high with the IFGtri but low with IFGoperc, gyrus rectus, very high with lateral OFC, left angular gyrus, and mid and inferior temporal gyri. Parcel 6 has overlap with AAL3 area OFClat (Figs. 2 and 3A).

The lateral orbitofrontal cortex areas, and the gyrus rectus, are notable in having moderate FC with the angular gyrus. The anterior cingulate cortex receives information from the orbitofrontal cortex, and is implicated in learning associations between actions and reward versus punishment outcomes (Rolls, 2019; Rushworth, Kolling, Sallet, & Mars, 2012).

The anterior cingulate cortex parcel 14 which is supracallosal and posterior has high FC with IFGoperc but not IFGtri, and moderate FC with other prefrontal areas, supplementary motor area, insula, midcingulate, supramarginal gyrus, putamen, pallidum, superior temporal, ACCsup (where this parcel is located). These two supracallosal ACC parcels are notable in having moderate FC with the supramarginal gyrus (Figs. 2 and 3B).

The pregenual anterior cingulate cortex (parcel 12) has high FC with FrontalSupMed, FrontalMedOrb, Superior Frontal Gyrus, OFCpost, midcingulate, post cingulate, left angular, and ACCpre (where this parcel is located), ACCsub, and ACCsup (Figs. 2 and 3B).

The ventromedial prefrontal cortex (upper part, parcel 11, which includes the subcallosal anterior cingulate cortex) has high FC with ACCsub (where this parcel is located), with ACCpre which is higher than ACCsup, superior frontal, OLF, FrontalSupMed, FrontalMedOrb or VMFPC (especially high), rectus, posterior cingulate with some mid-cingulate, nucleus accumbens, hippocampus, left angular gyrus (Figs. 2 and 3B).

The ventromedial prefrontal cortex (middle part, parcel 10) has high FC with superior frontal, OLF, SFGmedial, Frontal-MedOrb (i.e., VMFPC where this parcel is located), rectus, OFCpost, posterior cingulate, hippocampus and parahippocampal cortex, angular bilaterally, precuneus, middle temporal, temporal pole, ACCsub and ACCpre but not ACCsup (Figs. 2 and 3B).

The ventromedial prefrontal cortex (lower part, parcel 9, which includes part of the gyrus rectus) has very similar FC to parcel 10 except for lower FC with ACCsub and ACCpre, but higher FC with angular, and rectus (Figs. 2 and 3B). This fits with parcels 10 and 9 being important areas in reward and memory with links to language.

Parcels 9–12 in the ACCpre and VMFPC are notable in having moderate FC with the angular gyrus and with anterior parts of the temporal lobe (Fig. 3B).

### 3.3. Left lateral inferior frontal gyrus

The left inferior frontal gyrus is part of Broca’s area and is implicated in language production (Amunts & Zilles, 2012).

In the inferior frontal gyrus, pars triangularis, Parcel 15 (which is bilateral, and at the top of the IFG) has high FC with Middle Frontal Gyrus, IFGtri (where this parcel is located), IFGorb (bilaterally, part of the lateral orbitofrontal cortex), left fusiform, inferior parietal, posterior temporal areas, with the supramarginal and angular cortex, and with the caudate and putamen (Figs. 2 and 3D).

In the inferior frontal gyrus, pars triangularis (area 45), Parcel 18 (on the left only) has high FC with superior and middle frontal gyrus, IFGtri (where the parcels is located), IFGorb (especially high on the left) and lateral orbitofrontal cortex; angular, part of the supramarginal, and inferior parietal cortices; supplementary motor area; the medial superior frontal gyrus (FrontalSupMed); the posterior orbitofrontal cortex; gyrus rectus; and many temporal lobe cortical areas including especially anteriorly and the middle temporal gyrus (Figs. 2 and 3D).

In the inferior frontal gyrus, pars triangularis and opercularis, Parcel 17 (on the left only) has high FC with precentral, middle Frontal Gyrus, IFGtri and IFGoperc, IFGorb (especially left), supplementary motor area, OFCant (on the left), left insula, left fusiform, supramarginal gyrus, and posterior inferior temporal (Figs. 2 and 3D).
Fig. 3 – A. Surface maps showing the connectivity of each parcel. A. For the orbitofrontal cortex. B. For the anterior cingulate cortex. C. For the inferior frontal gyrus right and symmetric parcels. D. For the inferior frontal gyrus left asymmetric parcels. The functional connectivities have been thresholded at 0.3.
In the inferior frontal gyrus, pars opercularis, Parcel 16 has high FC with precentral and postcentral, IFGoperc (of which it is a part), Rolandic operculum, Supplementary Motor area, insula bilaterally (very high), mid-cingulate, supramarginal (high FC bilaterally), putamen, pallidum (Figs. 2 and 3D).

In the inferior frontal gyrus, pars orbitalis parcel 7 (which is bilateral) has high FC with IFGorb (where it is located), the supracallosal part of the anterior cingulate cortex and the mid-cingulate cortex, IFGtri and IFGoperc, supplementary motor area, insula, cingulate mid, Supramarginal left and right (but not angular gyrus), putamen, pallidum, and superior temporal (Figs. 2 and 3D).

In the inferior frontal gyrus, pars orbitalis parcel 8 (which is bilateral) has high FC with IFGorb (where it is located); notably with the lateral orbitofrontal cortex (OFClat), anterior cingulate cortex supracallosal part, and the mid cingulate cortex; IFGtri; OFCpost; supplementary motor area;insula; supramarginal gyrus bilaterally, mid- and superior temporal areas, and superior medial frontal cortex (Figs. 2 and 3D).

### 3.4 Right lateral inferior frontal gyrus

The right inferior frontal gyrus is implicated in some types of behavioral inhibition including some types of impulsivity (Aron, Robbins, & Foldrack, 2014; Deng et al., 2017). The right inferior frontal gyrus may especially convey information from non-reward systems in the lateral orbitofrontal cortex and orbital part of the inferior frontal gyrus to premotor areas (Rolls, 2019c; Rolls, Cheng, Du, et al., 2019; Rolls, Cheng, & Feng, 2019).

IFGtri (posteriorly) Parcel 19 has high FC with IFGorb (where it is located); notably with the lateral orbitofrontal cortex (OFClat), anterior cingulate cortex supracallosal part, and the mid cingulate cortex; IFGtri; OFCpost; supplementary motor area;insula; supramarginal gyrus bilaterally, mid- and superior temporal areas, and superior medial frontal cortex (Figs. 2 and 3C).

IFGtri (and IFGorb) Parcel 20 has high FC with IFGtri and IFGorb (where it is located), Middle FG, IFG opercular (area 44, right), OFCpost (right), supramarginal (right), posterior superior and middle temporal (right), with the inferior parietal cortex, and with the right supramarginal cortex (Figs. 2 and 3C).

### 3.5 Graphical representation of the connectivity

The result of multidimensional scaling (MDS) on the correlation matrix of Fig. 2 is shown in Fig. 4. The distance in this space reflects how different the connectivity is of each parcel. This diagram is complemented by Fig. 5 which shows by the thickness and colour of the lines the strength of the functional connectivity between the different parcels, shown in this case on a view of the brain. It is also complemented by Fig. 6 which shows the functional connectivities between the parcels as a matrix. The description that follows refers to the MDS space in Fig. 4, but reference to Figs. 5 and 6 will also be useful.

The OFC areas OFCmedial, OFCposterior, and OFCanterior are close together. Interestingly, the IFG triangular superior parcel (15) is close to these OFC areas.

The lateral OFC areas (6 and 5) are somewhat separated from these medial OFC areas, and interestingly the gyrus rectus (1) is close to these lateral OFC areas. The IFG orbital parcel 8 is not very close to parcels 5 and 6, and IFG orbital parcel 7 is closer to the other IFG areas.

The VMPFC parcels 9, 10 and 11 are well separated from other parcels, with VMPFC inferior (9) closest to OFC areas, and VMPFC superior (11) closest to ACC pregenual (12). The subgenual/subcallosal cingulate cortex will be within parcel 11.

The three ACC parcels are well spread out from other nodes, and from each other. It is notable that the ACC supracallosal anterior parcel is not close to the OFC lateral parcels, even though both represent punishers and non-reward (Rolls, 2019c, 2019d). This is probably because the ACC supracallosal areas have connectivity with movement-related areas.

The IFG parcels are in a region of the right of the MDS space in Fig. 4, with, interestingly, parcel 17 IFG triangular superior L and parcel 18 IFG triangular superior R relatively close to the medial OFC areas in parcels 2, 3 and 4.

### 3.6 Correlations between the connectivity of the parcels

The correlations between the 24 different parcels defined by their functional connectivity with all areas in the AAL3 atlas (Rolls, Huang, et al., 2019) are shown in Fig. 6. First, it should be made clear that all the parcels are statistically different, in that the least significant p value for the difference of a functional connectivity of any two parcels with an AAL3 brain area...
Fig. 6 shows that Parcels 1–7 are correlated with each other. These are the orbitofrontal cortex parcels. Parcels 9–13 are correlated with each other, as are the VMPFC and ACC parcels, with the exception of the most posterior supracallosal ACC parcel. The correlation matrix shows that parcel 22, a small parcel at the junction of VMFFC and ACC, should be included with this group. Parcels 15–24 (except for 22) form a third group, all involving inferior frontal gyrus areas. Fig. 6 shows that parcel 7 in the IFG orbital part correlates with this IFG group, whereas parcel 8 also in the IFG orbital part correlates only partly with the IFG group, and partly with the OFC group.

For comparison with what is shown in Fig. 6, we also directly measured the functional connectivity between the 24 parcels by using the correlation between the BOLD signals for every pair of parcels. The BOLD signal for each parcel was measured by taking the average of the BOLD signal across all voxels within each parcel. The resulting functional correlation matrix was very similar to that shown in Fig. 6, and indeed the correlation between the two correlation matrices was .91. This shows that the functional connectivity measured directly from the BOLD signal correlations between the 24 OFC/ACC/IFG parcels was similar to that measured from the correlations between the BOLD signal in each of the 24 parcels with all AAL3 areas. An almost identical result was obtained when the functional connectivity directly measured using the BOLD signal from the 24 parcels was compared to that measured from the correlations between the BOLD signal in each of the 24 parcels with all AAL3 areas except AAL3 areas in the OFC/ACC/IFG. These results are consistent with the functional connectivities measured between the 24 parcels in the orbitofrontal cortex/anterior cingulate cortex/inferior frontal gyrus reflecting both connectivity between the 24 parcels, and the connectivity of each of the parcels with other brain areas.

Fig. 5 – A. Similarity of different parcels in the orbitofrontal cortex, anterior cingulate cortex, and inferior frontal gyrus based on the functional connectivity (FC) of each parcel with the other parcels that is illustrated in Fig. 6. The color of the edges and their thickness represents the strength of the functional connectivity. The color of the parcel nodes indicates the brain region: orbitofrontal cortex - red; anterior cingulate and ventromedial prefrontal cortex - green; inferior frontal gyrus - yellow. The two parcels that are asymmetric in the left inferior frontal gyrus are placed on the left of the brain (looking down on a view of the orbitofrontal cortex). B. The similarity (Correlation) based on the functional connectivity of each parcel with the whole brain (i.e., all AAL3 areas).
and right IFG are placed into different parcels. Right do not have similar connectivity, so the voxels in the left contrast, for the IFG, several of the parcels on the Left and are clustered together by k-means into the same parcel. In functional connectivity with other brain areas, and therefore and ACC, voxels in the left and right hemispheres have similar and widespread areas of the temporal lobe cortex; the para-lateral orbitofrontal cortex have interesting connectivity with (Grabenhorst 2019d). Many rewards are represented in this region (Grabenhorst & Rolls, 2011; Rolls, 2019c, 2019d). Two parcels in the inferior frontal gyrus, pars orbitalis (8 and 7 especially on the right) have strong connectivity with the lateral orbitofrontal cortex and also with a number of movement related areas (the supplementary motor area, insula, midcingulate and supracallosal anterior cingulate, supra-marginal left and right). These inferior frontal gyrus pars orbitalis areas may relate the lateral orbitofrontal cortex to brain areas involved in movement initiation.

Third, parcels in the ventromedial prefrontal cortex parcels (9, 10 and 11) and the pregenual anterior cingulate cortex (parcel 12) have connectivity with the angular gyrus, with anterior parts of the temporal lobe (Fig. 3B); with the orbitofrontal cortex; and with the parahippocampal gyrus and hippocampus, posterior cingulate cortex and precuneus all of which are implicated in memory (Rolls, 2016a; 2019c, 2019d). This fits with these areas being important in reward, decision-making, and memory, with interesting links to language (Rolls, 2016a, 2019c, 2019d).

Fourth, in the supracallosal anterior cingulate cortex, parcels 13 and 14 have connectivity with the mid-cingulate cortex, supplementary motor area and basal ganglia; with the inferior frontal gyrus pars opercularis (BA 44) rather than with pars triangularis (BA45); and with the supramarginal gyrus (BA 40) rather than the angular gyrus (BA 39). These supracallosal anterior cingulate areas activated by punishers and non-reward (Rolls, 2016a, 2019c, 2019d) are thus more closely related to the brain areas involved in the initiation of movements, and perhaps to somatosensory function and phonology in which the marginal gyrus is implicated.

Fifth, the left inferior frontal gyrus, pars triangularis (area 45), and pars opercularis (area 44) involved in language as part of Broca’s area and with functional connectivity with the angular, supramarginal, and inferior parietal cortices, with anterior (area 45) and posterior (area 44) temporal cortical areas also interestingly had some functional connectivity with the orbitofrontal cortex, and may thereby provide a route for some orbitofrontal cortex areas to link to language systems.

4. Discussion

4.1. The connectivity and some of the implications

The findings of this parcellation of the orbitofrontal cortex, anterior cingulate cortex, and inferior frontal gyrus based on the functional connectivity with the whole brain include the following.

First, three parcels (2–4) located mainly in areas 13 and 11 in the medial/mid orbitofrontal cortex had strong connectivity with each other, and moderate connectivity with posterior to mid-temporal cortical areas and insula (which are likely to provide visual, auditory and taste inputs), with the cingulate cortex (which are likely to provide outputs to action-outcome systems), and with the parahippocampal gyrus and hippocampus (which are related to memory) (Rolls, 2016a, 2019c, 2019d). Many rewards are represented in this region (Grabenhorst & Rolls, 2011; Rolls, 2019c, 2019d).

Second, two parcels (5 and 6) located mainly in area 12 the lateral orbitofrontal cortex have interesting connectivity with the left angular gyrus which is related to language, as well as with widespread areas of the temporal lobe cortex; the parahippocampal gyrus and hippocampus; and with the triangular part of the inferior frontal gyrus (which may provide for outputs), as well as with the supracallosal anterior cingulate cortex. Many punishers and non-reward are represented in this region (Grabenhorst & Rolls, 2011; Rolls, 2019c, 2019d).
However, more importantly, the functional connectivity parcellation provides information about connectivity, which the cytoarchitecture does not, and the connectivity is considered next using the evidence provided in Figs. 2–6. The following discussion focuses on some of the key differences between the different parcels, using the functional connectivity values in Fig. 2. In Fig. 2, the strongest FCs provide an indication of the AAL3 region(s) where the parcel is located, because there is typically high FC of the voxels within an AAL3 region.

4.3. Relation to areas implicated in language

One aspect of interest is with respect to areas implicated in language. The connectivity of the angular gyrus (on the left especially) is high with parcels in the angular gyri (18); and VMPFC/ACC (9, 10, 11, 12), gyrus rectus (1), and lateral orbitofrontal cortex (5 and 6). The connectivity of the supramarginal gyrus (mostly bilaterally) is high with parcels in the inferior frontal gyrus (7, 16, 17, 18, 19, 20), and with the supracallosal anterior cingulate cortex posterior part (14) and ACC pregenual parcel 12. A very interesting finding shown in Fig. 4 is that the inferior frontal gyrus areas (IFG) implicated in language (especially on the left) are quite close to orbitofrontal cortex areas (e.g., the anterior and posterior orbitofrontal cortex) in the multidimensional space, and relatively far from the ventromedial prefrontal cortex (VMPFC) and the anterior cingulate cortex (ACC). This provides interesting evidence for a close relationship between what is represented in the orbitofrontal cortex and language. Consistent with this, cognitive inputs at the language level can bias reward representations of odour, taste and flavour in the orbitofrontal cortex (de Araujo, Rolls, Velazco, Margot, & Cayeux, 2005; Grabenhorst, Rolls, & Bilderbeck, 2008); and the reported subjective pleasantness of many rewarding stimuli, including taste, flavor, and somatosensory stimuli is linearly related to the activations of the medial/mid orbitofrontal cortex (Grabenhorst, D’Souza, Parris, Rolls, & Passingham, 2010; Grabenhorst, Rolls, & Parris, 2008; Grabenhorst, Rolls, Parris, & D’Souza, 2010).

4.4. Symmetry

Second, the orbitofrontal parcels are remarkably symmetric across the midline (Similarity Index .85), whereas in line with the lateralization of language and the importance of the inferior frontal gyrus in language (Amunts & Zilles, 2012; Clos, Amunts, Laird, Fox, & Eickhoff, 2013), the inferior frontal gyrus is asymmetric (SI = .27). The symmetry of the orbitofrontal connectivity (and therefore parcellation) is consistent with the findings that there is little evidence for strong lateralization of activations of the orbitofrontal cortex in task-related fMRI, with some differences in individual studies not generally found when large numbers of studies are considered (Grabenhorst & Rolls, 2011). Interestingly, the anterior cingulate cortex has a high SI of .94, reflecting great symmetry in the voxel-level connectivity of the right and left anterior cingulate, an area that receives reward value information from the orbitofrontal cortex, and is then involved in learning actions to obtain the rewards signaled by the orbitofrontal cortex (Rolls, 2019a).

4.5. Functional regions of the orbitofrontal cortex

Third, there is much evidence for a hedonic map in the orbitofrontal cortex, with many rewards and subjectively pleasant stimuli represented in the medial orbitofrontal cortex, and many unpleasant stimuli and non-rewards represented in the lateral orbitofrontal cortex (Grabenhorst & Rolls, 2011; Rolls, 2019c). This applies for example to monetary reward and loss (O’Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Xie et al., 2019), olfactory stimuli (Rolls, Kringelbach, & de Araujo, 2003), and not winning in a reversal task indicating that reversal should occur (Kringelbach & Rolls, 2003). Does
the connectivity of the medial/mid orbitofrontal cortex differ from that of the lateral orbitofrontal in any way that may illuminate this? One difference is that the medial orbitofrontal cortex areas tend to have high functional connectivity with the pregenual anterior cingulate cortex in both of which rewards are represented. In contrast, the lateral orbitofrontal cortex including AAL3 areas such as OFC lat and the inferior frontal gyrus orbital part has high functional connectivity with the supracallosal anterior cingulate cortex, in both of which unpleasant stimuli and non-reward are represented (Rolls, Cheng, Gong, et al., 2019). From Fig. 2, differences in the FC of the medial OFC (parcels 2, 3, and 4) from the lateral OFC (parcels 5 and 6) are as follows. The lateral OFC has higher FC with the inferior frontal gyrus, SFGmedial, ACCpost, angular gyrus, and mid-temporal cortex. Parcel 6 (lateral OFC, anterior parcel) has low FC with the ACCsub and Pre, but parcel 5 posteriorly does not. Parcels 7 and 8 in the orbital part of the inferior frontal gyrus have high FC with the supracallosal part of the anterior cingulate cortex, IFGopercular, SFGmedial, SMA, caudate, putamen and pallidum, insula, and supramarginal gyrus. Parcels 7 and 8 may thus relate to unpleasantness (because of the association with the supracallosal anterior cingulate cortex), and in line with this, have high FC with the insula, the anteroventral part of which is related to autonomic function and much of it to somato-sensory function. Parcels 7 and 8 can thus be considered as a lateral part of the orbitofrontal cortex, connecting with the supracallosal part of the anterior cingulate cortex, both involved in punishers and non-reward, consistent with a more detailed analysis (Rolls, Cheng, Gong, et al., 2019). The medial OFC has high FC with the inferior parietal cortex, and low with the angular gyrus. 

The main parcels with high functional connectivity with the insula are in the IFGtri, IFGoperc, IFGorb and ACCsup, with the OFCpost having some connectivity. This may reflect the insula being used as part of a visceromotor region for outputs to autonomic function (Rolls, 2016b).

The larger extent of the lateral orbitofrontal cortex areas found in parcels 5 and 6 on the right, and the parcels in or near the orbital part of the inferior frontal gyrus on the right (8 and 20, see Fig. S1) are of especial interest, for these areas on the right are implicated in depression, in that voxels in parts of these regions have high functional connectivity in depression with the angular gyrus, temporal cortex, the precuneus, and the posterior cingulate cortex (Cheng et al., 2016; Cheng, Rolls, Qiu, Xie, Wei, et al., 2018; Cheng, Rolls, Qiu, Yang, et al., 2018; Rolls, Cheng, Du, et al., 2019). These findings are consistent with the hypothesis that increased attractor-related activity in the lateral orbitofrontal cortex non-reward system contributes to depression (Rolls, 2016c, 2018; Rolls, Cheng, & Feng, 2019), and that the right inferior frontal gyrus provides a route to premotor systems for behavioral output that relates to depression (Rolls, Cheng, Du, et al., 2019). The right inferior frontal gyrus is further implicated in routes to action, in that this system is activated in the stop-signal task (Deng et al., 2017), and damage to the right inferior frontal gyrus in humans impairs behavioral inhibition in the stop-signal task (and in this sense increases response-related impulsivity) (Aron et al., 2014). If these lateral orbitofrontal and inferior frontal gyrus regions have increased connectivity and are overactive in depression, then behavioral output to action systems may be diminished with too much inhibition of behavior; and if these regions are damaged, behavior may be insufficiently stopped resulting in a type of impulsiveness (Rolls, 2019c; Rolls, Cheng, Du, et al., 2019; Rolls, Cheng, & Feng, 2019).

4.6. Comparison with connections in the macaque

Comparison of the functional connectivity between the different parcels shown in Figs. 5B and 6, and the anatomical connections of the orbitofrontal cortex and anterior cingulate in the macaque shown in Fig. 19 of Carmichael and Price (1996), indicates the following. (Carmichael and Price identified medial prefrontal networks, which included the anterior cingulate cortex, and orbital networks.) In humans, parcels 2, 3, and 4 form one network for the medial orbitofrontal cortex. For the lateral orbitofrontal cortex, parcels 5 and 6 are part of a network which includes gyrus rectus and left inferior frontal gyrus pars triangularis (18) and inferior frontal gyrus pars orbitalis (8). Another network includes parcels in the ventromedial prefrontal cortex and the pregenual and subgenual anterior cingulate cortex (9,10,11,12) and posterior lateral orbitofrontal cortex (5). Another network includes the right and bilateral inferior frontal gyrus areas (7, 8, 15, 16, 19, 20, 24), which notably include parcel 8 in IFGorb. Last, the left inferior frontal gyrus (parcels 17 and 18) connect to other IFG regions, OFC lat (5,6) and IFGorb (8). In the macaque Carmichael and Price (1996) investigated the OFC and ACC, and did not include the inferior frontal gyrus, or of course any connectivity with language areas, which was so interesting in the human functional connectivity. In an ‘orbital prefrontal’ network they showed a number of subregions in the medial orbitofrontal cortex BA areas 13 and 11 with connections with subregions in the lateral orbitofrontal cortex BA area 12. In contrast, in humans the medial and lateral orbitofrontal networks were more separate, and the lateral orbitofrontal cortex continues round the inferior prefrontal convexity to include at least inferior frontal gyrus orbital part especially on the right. Carmichael and Price (1996) identified a macaque ‘medial prefrontal network’ which included the anterior cingulate cortex, but did not distinguish pregenual from supracallosal parts of the ACC which have quite different functional connectivity in humans, and also showed connectivity with a single VMpFC region (BA 10 m) rather than the several VMpFC subregions identified here in humans.

We further note that the present investigation goes beyond that of Kahnt et al. (2012), by including in the parcellation in addition to the orbitofrontal cortex, for the first time also the anterior cingulate cortex and medial prefrontal cortex, so that we could directly compare the functional connectivity of these nearby regions with other brain areas (Fig. 2), and with each other (Fig. 6), because all are implicated in different ways in emotion and action (Rolls, 2019b, 2019c, 2019d; Rolls, Cheng, & Feng, 2019); and by including 654 participants compared to 13.

In conclusion, the new findings described here include the following. First, in areas BA 13 and 11 in the medial/mid orbitofrontal cortex had strong connectivity with each other, and moderate connectivity with posterior to mid-temporal...
cortical areas and insula (which are likely to provide visual, auditory and taste inputs), with the cingulate cortex (which are likely to provide outputs to action-outcome systems), and with the parahippocampal gyrus and hippocampus (which are related to memory). Second, parcels in area BA 12 the lateral orbitofrontal cortex have connectivity with the left angular gyrus, as well as with the temporal lobe cortex; the parahippocampal gyrus and hippocampus; and with the triangular part of the inferior frontal gyrus (which may provide for outputs), as well as with the supracallosal anterior cingulate cortex. Parcels in the inferior frontal gyrus, pars orbitalis have strong connectivity with the lateral orbitofrontal cortex and with movement-related areas, and may provide a route from the lateral orbitofrontal cortex to brain areas involved in movement initiation. Third, parcels in the ventromedial prefrontal cortex and pregenual anterior cingulate cortex have connectivity with the orbitofrontal cortex; angular gyrus; temporal lobe, parahippocampal gyrus and hippocampus, posterior cingulate cortex and precuneus. This fits with these areas being important in reward, decision-making, and memory, with interesting links to language. Fourth, the supracallosal anterior cingulate cortex has connectivity with the orbitofrontal cortex and movement-related areas, so may provide a route to movement from the orbitofrontal cortex. Fifth, the left inferior frontal gyrus involved in language has functional connectivity with the orbitofrontal cortex and may thereby provide a route for some orbitofrontal cortex areas to link to language systems.

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No part of the study procedures was pre-registered prior to the research being conducted. We report in this paper how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study, in the Methods section. The neuroimaging data from NKI is publicly available at http://fcon.1000.projects.nitrc.org/indi/pro/nki.html. The conditions of the ethics approval for the neuroimaging data from Chongqing Medical School do not permit public archiving of those individual anonymised MRI data. Readers seeking information about those data should contact the author Dr. Wei Cheng at the Institute of Science and Technology for Brain-inspired Intelligence, Fudan University, Shanghai, 200433, PR China. Email: wcheng@fudan.edu.cn. Specifically, requestors must meet the following conditions to obtain the data: completion of a formal data sharing agreement. The code used in the study used standard functions available in Matlab™ and SPM, and is archived at https://osf.io/zbqn7/. J.F. is also supported by Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZJLab.

Declaration of Competing Interest
None of the authors declares a conflict of interest.

CRediT authorship contribution statement

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Supplementary data

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