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Anatomy and Function of Four New Cytoarchitectonic Areas in the Human Lateral Orbitofrontal Cortex

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BACKGROUND

The lateral orbitofrontal cortex (lOFC) has been cytoarchitectonically mapped by different authors, resulting in a different number of areas and nomenclature (e.g., BA47[1], Area F*f*[2] or Area 47/12[3]). Most of the maps are two-dimensional, and therefore cannot be directly compared with neuroimaging data.

Functional neuroimaging and co-activational analysis revealed lOFC involvement in memory and reward processing[4]. It receives neuronal input from the sensory systems, the amygdala and the hypothalamus[5].

The present study was designed:

- to investigate the cytoarchitecture of the lOFC using image analysis and a statistically reproducible approach for detecting cytoarchitectonic borders in a sample of ten *post mortem* brains,
- to generate maps which reflect the anatomical intersubject variability in a common reference space,
- to provide cytoarchitectonic probabilistic maps in stereotaxic space as a prerequisite for comparison with in vivo findings,
- to use meta-analysis as an approach to identify functional correlates of the identified areas.

METHODS

- Microstructural analysis of 10 human *post mortem* brains[6]
- Quantitative and statistically reproducible detection of cytoarchitectonic borders in 2D[7]
- Analysis of cytoarchitectonic similarity based on a hierarchical cluster analysis
- Macroanatomical analysis of sulci and gyri
- Calculation of cytoarchitectonic probability maps in the MNI reference space Colin27 and maximum probability maps[8]
- Analysis of co-activational patterns of every lOFC area with meta-analytic connectivity modelling (MACM)[9]
- Functional decoding of all detected lOFC areas with the BrainMap database[10,11]

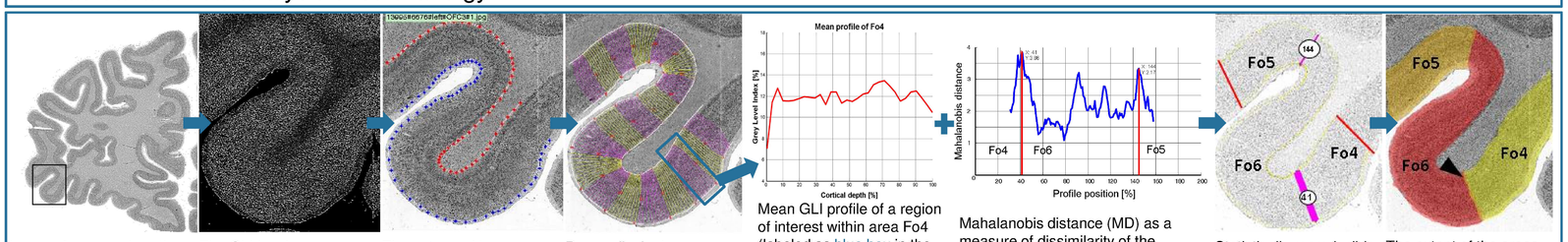
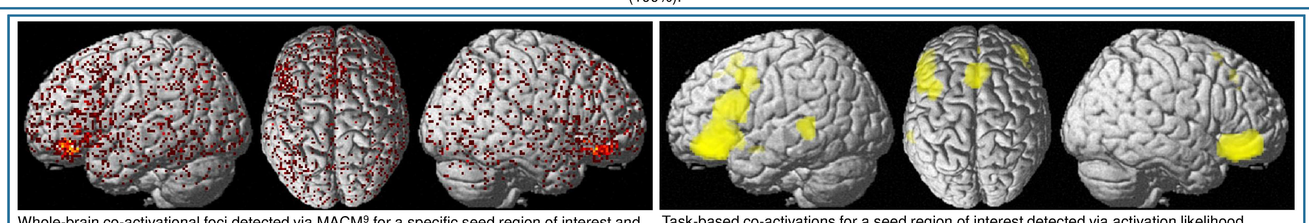


Image of a coronal section (left hemisphere) stained for cell bodies. The GLI has been measured as an estimate of the volume fraction of cell bodies. Levels of volume fraction are shown in different grey levels. The outer and inner contour lines of the cortex are drawn to label the region of interest (ROI). Perpendicular traverses are computed along the cortical ribbon. For each traverse, a GLI-profile is generated of a 10-dimensional feature vector. Mean GLI profile of a region of interest within area Fo4 (labeled as blue box in the previous image). The profile shows laminar changes in cell density from the surface of the cortex (0%) to the white matter boundary (100%). Mahalanobis distance (MD) as a measure of dissimilarity of the laminar patterns of two adjacent blocks of profiles. MD is measured using a sliding window approach. Maximal MD values indicate position of a cortical border. Statistically reproducible delineation of a cortical border between two adjacent structurally diverse cortical areas. The extent of the areas is labeled in the section images over the whole extent of the area, and 3D reconstructed.

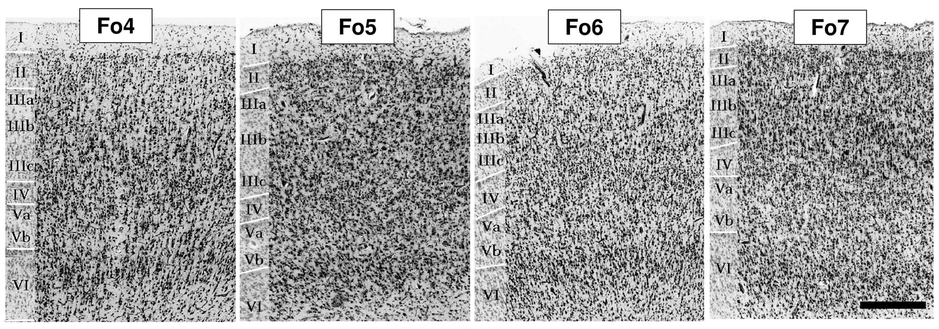


Whole-brain co-activational foci detected via MACM[9] for a specific seed region of interest and projected onto the reference brain in MNI152 space.

Task-based co-activations for a seed region of interest detected via activation likelihood estimation (ALE) and determined with the SPM Anatomy Toolbox.[13]

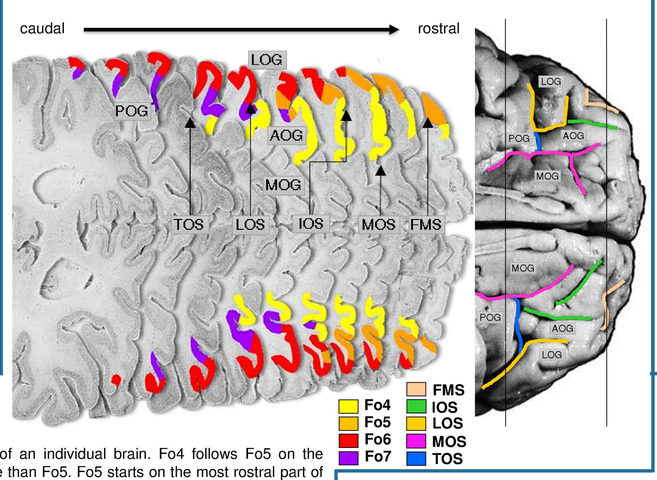
RESULTS

Cytoarchitecture of four new areas in the lOFC



Cytoarchitecture of four identified areas in the lateral OFC. Roman letters indicate respective layers and sublayers. I = molecular layer, II = external granular layer, III = external pyramidal layer (with sublayers a-c), IV = internal granular layer, V = internal pyramidal layer (with sublayers a & b), VI = multiform layer. Scale bar = 500 µm.

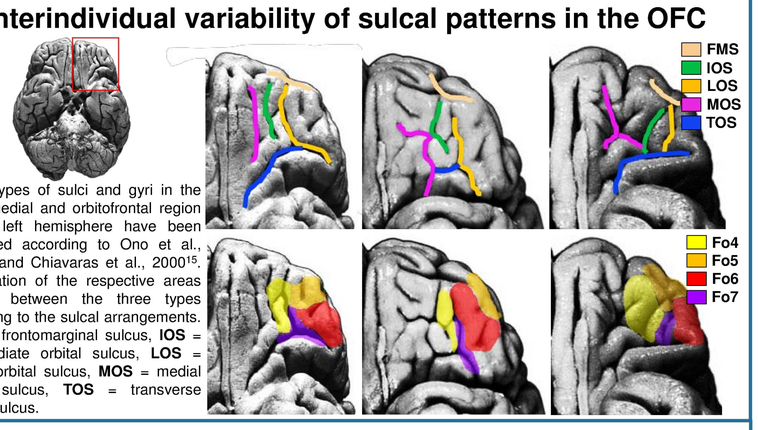
Section sequence of identified areas



Extent of the areas in serial brain sections of an individual brain. Fo4 follows Fo5 on the anterior orbital gyrus. Fo4 has a larger volume than Fo5. Fo5 starts on the most rostral part of the inferior frontal gyrus, at the frontomarginal sulcus, entering the anterior orbital gyrus only shortly. Fo6 occupies the lateral orbital gyrus, separating Fo7 and Fo5 from adjoining areas. Fo7 lies buried in the lateral orbital sulcus between Fo4 and Fo6, terminating in the transverse orbital sulcus.

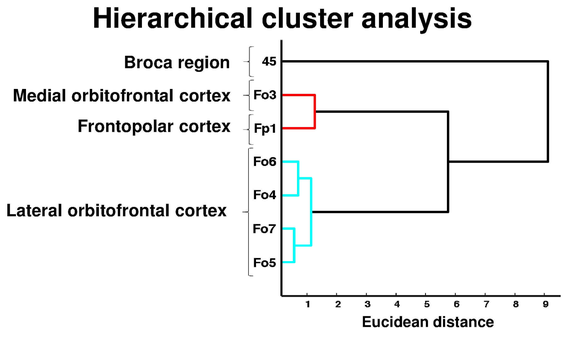
AOG = anterior orbital gyrus, **FMS** = frontomarginal sulcus, **IOS** = intermediate orbital sulcus, **LOG** = lateral orbital gyrus, **LOS** = lateral orbital sulcus, **MOG** = medial orbital gyrus, **MOS** = medial orbital sulcus, **POG** = posterior orbital gyrus, **TOS** = transverse orbital sulcus.

Interindividual variability of sulcal patterns in the OFC



Three types of sulci and gyri in the ventromedial and orbitofrontal region of the left hemisphere have been described according to Ono et al., 1990[14] and Chiavaras et al., 2000[15]. Localization of the respective areas differed between the three types according to the sulcal arrangements. **FMS** = frontomarginal sulcus, **IOS** = intermediate orbital sulcus, **LOS** = lateral orbital sulcus, **MOS** = medial orbital sulcus, **TOS** = transverse orbital sulcus.

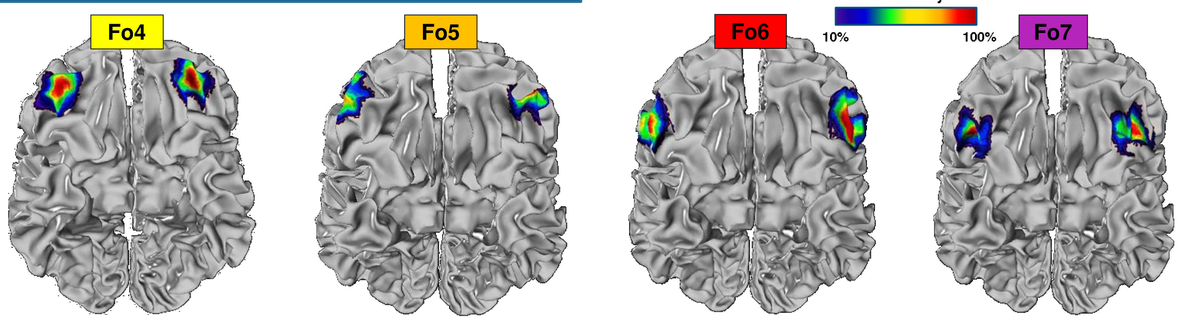
Hierarchical cluster analysis



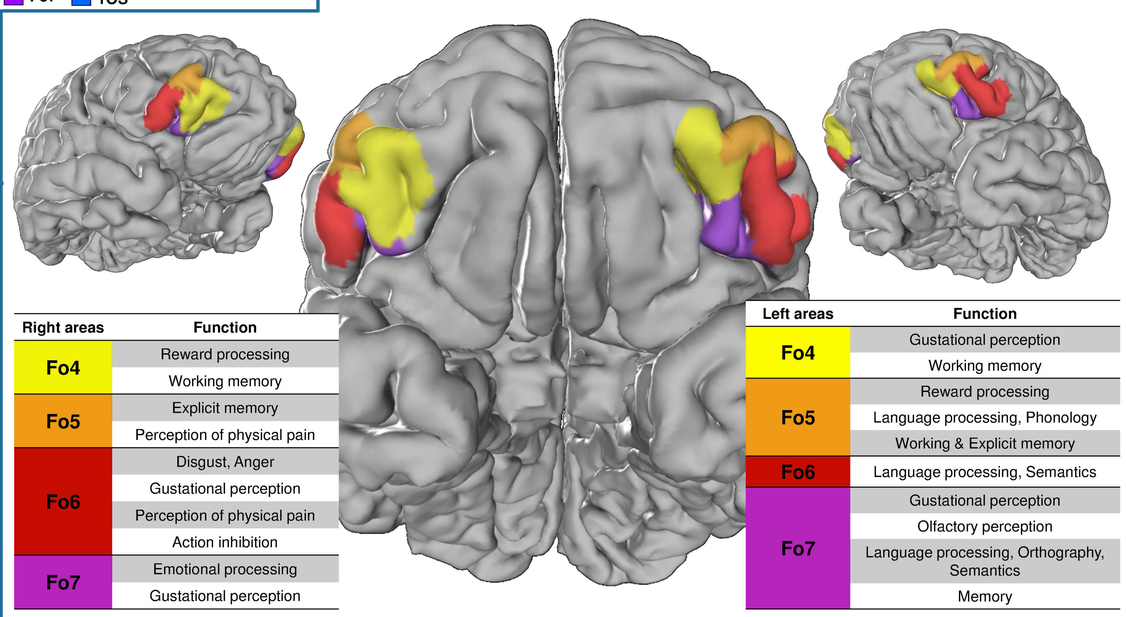
High structural simmilarity between Fo5 & Fo7, also Fo4 & Fo6 revealing lateral clustering of the four new lOFC areas, based on higher granularity in Fo5 & Fo7 as well as a more striate appearance in Fo4 & Fo6. Frontal pole area **Fp1**, medial OFC area **Fo3** and Broca area **45** show an increasing structural dissimilarity compared to the lOFC areas.

Probability maps in stereotaxic MNI space

Continuous probability maps of areas Fo4, Fo5, Fo6 & Fo7 revealing their location and extent in the stereotaxic MNI reference brain 'Colin27', ranging from high (**red** = 100% = 10 out of 10 brains) to low (**blue** = 10% = 1 out of 10 brains) probable appearance in ten analyzed brains according to the interindividual variability of areal extents.



Maximum probability map & Functional decoding



Right areas	Function
Fo4	Reward processing
	Working memory
Fo5	Explicit memory
	Perception of physical pain
Fo6	Disgust, Anger
	Gustational perception
	Perception of physical pain
	Action inhibition
Fo7	Emotional processing
	Gustational perception

Left areas	Function
Fo4	Gustational perception
	Working memory
Fo5	Reward processing
	Language processing, Phonology
	Working & Explicit memory
Fo6	Language processing, Semantics
Fo7	Gustational perception
	Olfactory perception
	Language processing, Orthography, Semantics
	Memory

Maximum probability map of identified areas Fo4, Fo5, Fo6 & Fo7 superimposed onto the MNI reference brain 'Colin27'. Threshold = 0,4. Areas were smoothed prior to final image creation. Additional functional decoding of every lOFC area in both hemispheres was calculated using the BrainMap database[10,11].

CONCLUSIONS

- **Microanatomy**: Identification of our new cortical areas Fo4, Fo5, Fo6 & Fo7 based on differences in the cytoarchitecture. Partial overlap with a region previously being described as BA47 by Brodmann[1].
- Predominantly high cell density in the deep parts of layer III, weak layer IV and separation of layer V into two sublayers V_a and V_b according to cytoarchitectonic analysis.
- Clustering of areas Fo4 + Fo6 versus Fo5 + Fo7 based on structural differences in granularity, lamination and greater pyramidal cells in layer IIIc in areas Fo5 + Fo7.
- **Macroanatomy**: Detection of three different sulcal patterns, with diversely distributed medial, lateral and transverse orbital sulci and therefore changing arrangements of the four new areas.
- **Mapping**: Calculation of cytoarchitectonic probabilistic maps and the Maximum Probability Map in the MNI reference brain 'Colin27' as well as MNI152.
- The maps are publicly available in the atlas of the Human Brain Project and the JuBrain Cytoarchitectonic atlas (QR codes).
- **Meta-Analysis**: Detection of co-activational clustering according to MACM analysis, with areas of the inferior parietal lobule, the frontal pole and medial orbital cortex as well as Broca areas 44 and 45, centromedial and laterobasal amygdaloid nuclei and hippocampal area CA1.
- All areas are involved in cognitive processing and emotional evaluation of sensory input. Areas Fo5, Fo6 & Fo7 participate in language processing in the left hemisphere.

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