Activity localisation in fMRI

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Why is anatomy important?

- Aim: understand structure-function relationships
- To do this, we need to understand anatomy
  - On a group level, but also on an individual level
- Encourage you to also look at individual subjects
  - Check how consistent effects are/check for outliers
  - Get a better idea of the functional and anatomical interindividual variability
  - Check for associations with macro-anatomical features which might not be apparent on a group level

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Region	BA	Talairach Coordinates x	y	z
R temporoparietal junction (supramarginal gyrus)	22/39/40	56	−36	24
R temporoparietal junction (superior temporal gyrus)	22	55	−53	4
R inferior frontal gyrus	9/44	42	0	22
R inferior frontal gyrus	9/44	53	9	26
R anterior insula	—	43	13	4
L anterior cingulate cortex	24	−7	10	30
L inferior temporal gyrus	37	−47	−46	−24

Macro-anatomy

Micro-anatomy (e.g., cytoarchitectonic Brodmann area [BA])

Coordinates in standard space (e.g., the space of Talairach & Tournoux or the Montreal Neurological Institute [MNI] space)

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Overview

- Introduction to brain anatomy
- Macro-anatomy
  - Anatomical terms and orientations
  - Some anatomical landmarks
  - Interindividual variability
  - Recommended resources
- Micro-anatomy
  - Classic cytoarchitectonic maps
  - The Jülich approach
  - Relation of macro-anatomy and micro-anatomy

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Overview

- Standard space(s)
  - Talairach vs. MNI
  - Normalisation

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A brief introduction to brain anatomy

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Anatomical terms of location

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superior/dorsal

anterior/
rostral

posterior/
caudal

inferior/ventral

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Adapted from: Sobotta, Atlas der Anatomie des Menschen

Anatomical terms!

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superior/dorsal

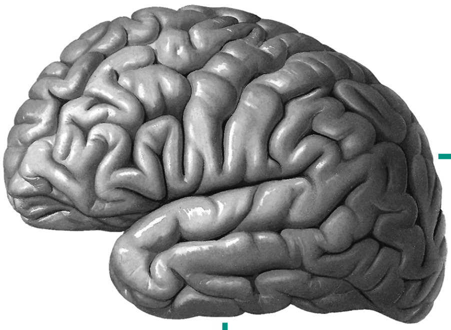
super, above

dorsum, the back

ante,
in front of

anterior/
rostral

rostrum,
the beak



post,
behind

posterior/
caudal

cauda,
the tail

inferior/ventral

infra, below

venter, the belly

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Anatomical planes

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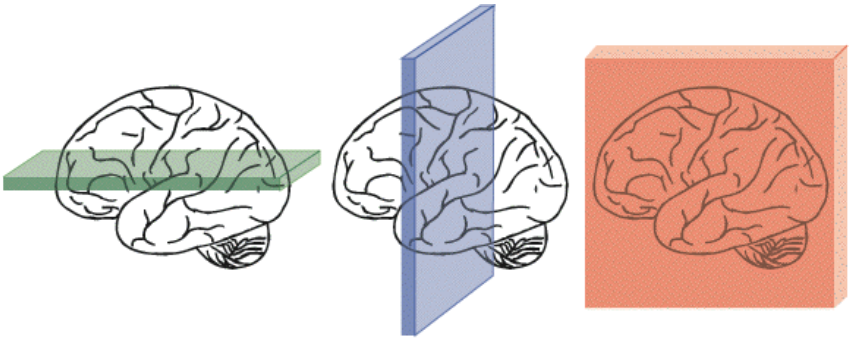

horizontal plane (or axial or transverse) | coronal plane (or frontal) | sagittal plane

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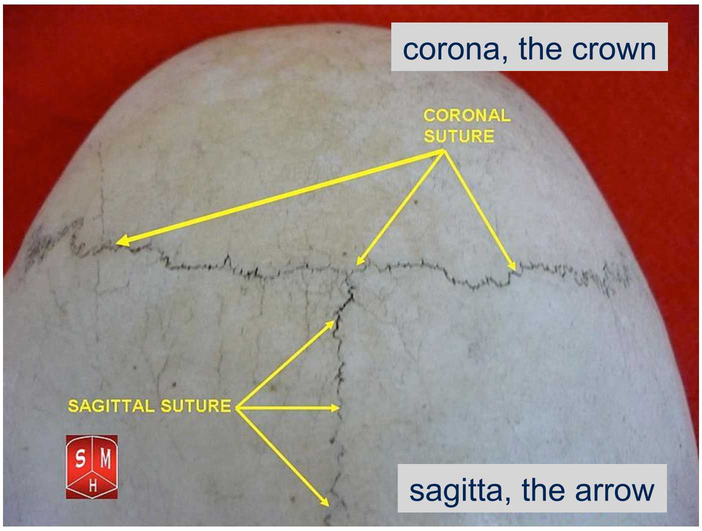

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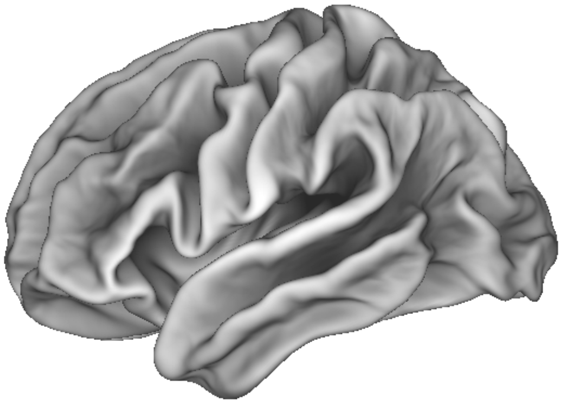
http://en.wikipedia.org/wiki/File:Coronal_suture_2.jpg

Macro-anatomy



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Aims

- How to identify (some) anatomical structures
  - Just a starting point, not enough time to cover all gyri and sulci
  - But mention at least some tips and tricks
  - Some examples: standard brain referred to as MNI152 (more about this later)
- Show examples of interindividual variability
- Examples of structure-function relationships
- Recommend books and online resources for further study
- Recommendations for your study

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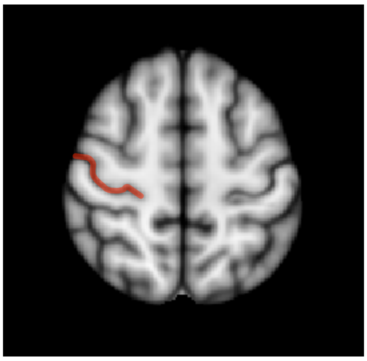
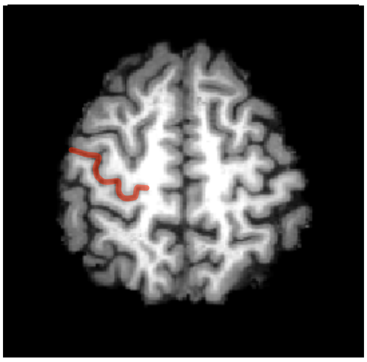
Central sulcus – MNI152

➢ Axial: **omega** or epsilon shape



Central sulcus – individual

➢ Axial: omega or **epsilon** shape



Central sulcus – MNI152

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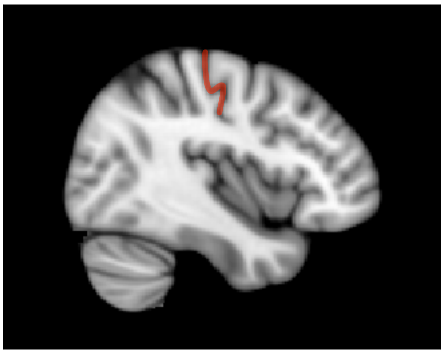
➢ Sagittal: hook



Central sulcus – individual

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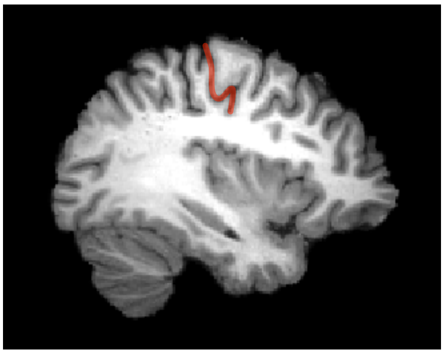
➢ Sagittal: hook



Central sulcus

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- The omega/epsilon and the hook are very reliable features
- Although the exact shape differs considerably across brains, I found that they always work
- Therefore, good starting point for orienting
- Note that these features also represent a functional landmark: they correspond to the motor hand area (Yousry et al., 1997, Brain) → thumb activation from Erno's talk yesterday

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Central sulcus

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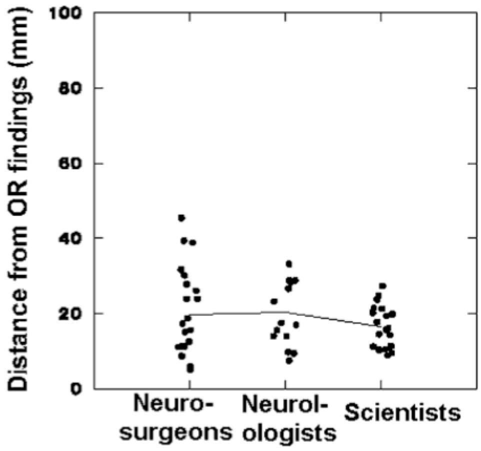

Fig. 1. The distance of the predictions of "expert judges" of the location of the cortical hand sensory area from the true location as determined from intraoperative studies. The three groups were not significantly different.

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Towle et al., 2003, Neuroimage

From central sulcus – MNI152

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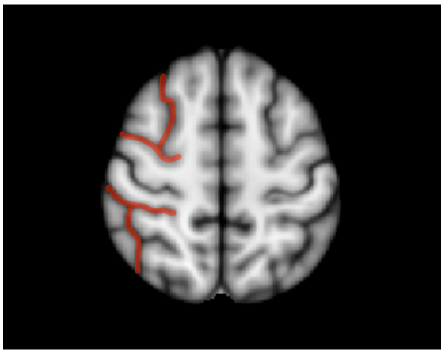
- Superior frontal sulcus/superior precentral sulcus
- Intraparietal sulcus/postcentral sulcus



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Lateral frontal lobe – MNI152

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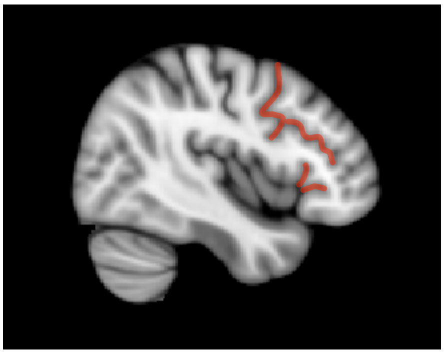
- Inferior precentral sulcus/inferior frontal sulcus
- Ascending and horizontal ramus of the Sylvian fissure



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Tip

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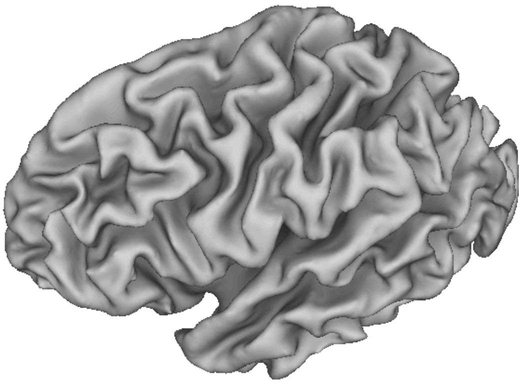
- Create surface reconstructions (Freesurfer, Caret)
  - It's hard to express how much easier understanding the macro-anatomy of a brain becomes
  - Try it!



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Tip

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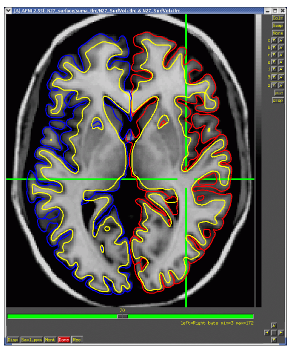
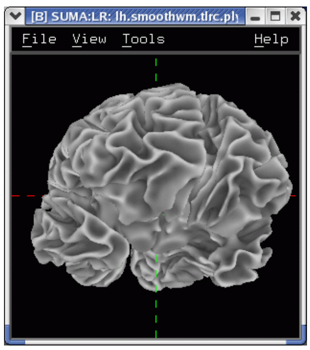
- If possible, use a tool that allows the display of vol-ume and surface simultaneously (e.g., AFNI/SUMA)





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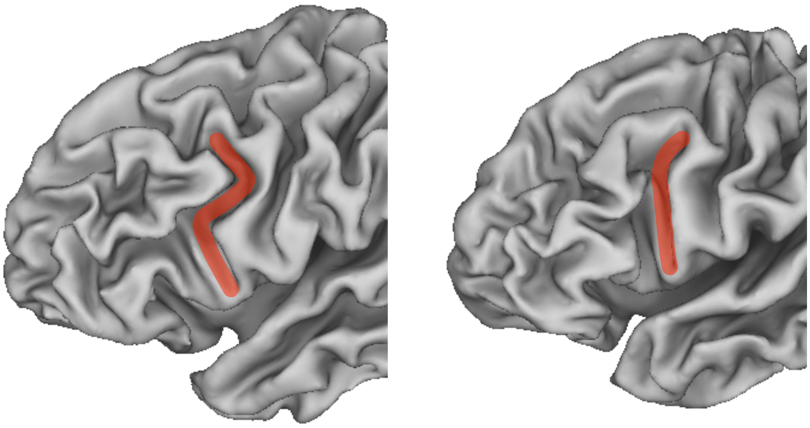
Never underestimate inter-individual variability



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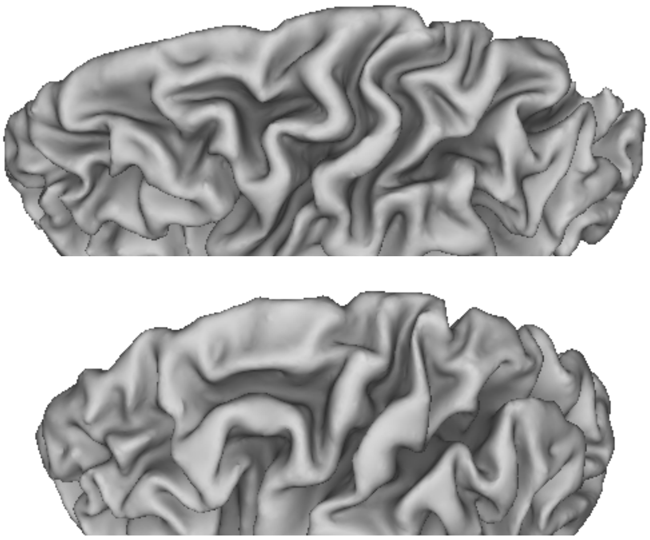
Never underestimate inter-individual variability



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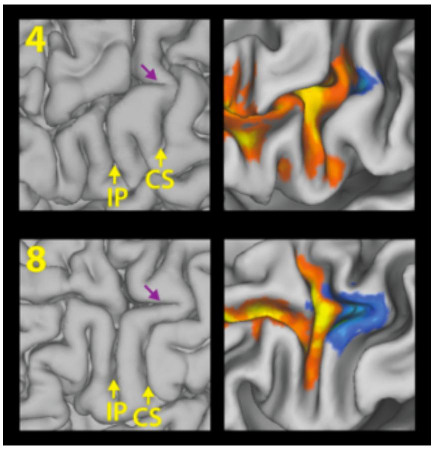
Structure-function relationships

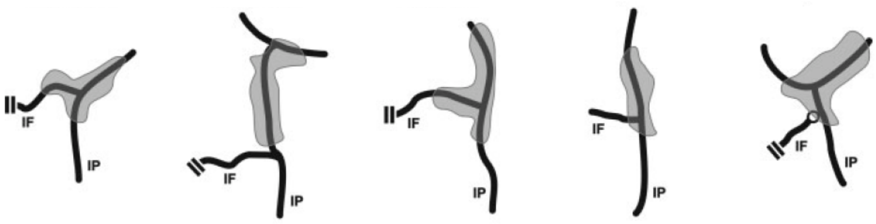
- Posterior branch of inferior precentral sulcus (purple arrow) as a landmark for the inferior frontal eye field (blue)



Derrfuss et al. (2012), Neuroimage

Structure-function relationships

- Task-switching activations consistently located at dorsal part of inferior precentral sulcus at the junction with the inferior frontal sulcus (so-called inferior frontal junction area, IFJ)



IF = inferior frontal sulcus, IP = inferior precentral sulcus

Derrfuss et al. (2009), Hum Brain Mapp

Structure-function relationships

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- Frontal eye fields/dorsal premotor cortex: Amiez et al. (2006, J Neurosci)
- Cingulate motor areas: Amiez & Petrides (2012, Cereb Cortex)
- Feedback-related activity in midcingulate cortex: Amiez et al. (2013, J Neurosci)
- V5/hMT: Dumoulin et al. (2000, Cereb Cortex), Malikovic et al. (2007, Cereb Cortex)
- Anterior fusiform face area (FFA-2): Weiner et al. (2014, Neuroimage)

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Books

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- Focus on neuroanatomy
  - Petrides (2011). The human cerebral cortex – $200
    - MR + surface reconstruction (latter not so useful…)
    - Brain in standard space
    - Very detailed information about sulci/gyri
    - Not a lot information about interindividual variability
  - Ono et al. (1990). Atlas of the cerebral sulci – $235
    - Fixated brains
    - Focus on interindividual variability

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Books

- Mai et al. (2007). Atlas of the human brain (3rd ed.) – $176 (http://www.thehumanbrain.info)
  - Standard space
  - Macroscopic part: MR, fixated head, schematic drawings
  - Microscopic part: myelin stains, schematic drawings
  - Detailed information on subcortical structures, but not so much on cortical gyri/sulci
- Duvernoy (1999). The human brain (2nd ed.) – out of print
  - MR and fixated brain photographed from 5 different angles
  - Photographs of very high quality

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Books

- Damasio (2005), Human brain anatomy in computerized images (2nd ed.) – $103
  - MR
  - Not so useful (focus on differently angled cutting planes)

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Books/Articles

- Focus on neuroanatomy and function
  - Mai & Paxinos (2011). The human nervous system (3rd ed.) – $199
  - Nieuwenhuys et al. (2007). The human central nervous system (4th ed.) – $72
- Devlin, J. T., & Poldrack, R. A. (2007). In praise of tedious anatomy. Neuroimage, 37, 1033-1041.
- Destrieux et al. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage, 53, 1-15.

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Online resources

- http://www.anatomie-amsterdam.nl/sub_sites/anatomie-zenuwwerking/123_neuro/start.htm
- http://www.thehumanbrain.info/
- http://human.brain-map.org/static/brainexplorer
- http://www9.biostr.washington.edu/da.html (looks terrible, but has some useful content)
- https://www.msu.edu/~brains/brains/human/
- But really nothing overwhelming… (let me know if you find something really useful)

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Recommendations

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- Check anatomical atlasses (plural, if possible)
- I tend not to trust automatic labelling tools (including the AAL atlas in SPM)
- But: if you have no idea where you are, use automatic labelling tool first and then anatomical atlasses
- Use surface reconstructions and overlay activations onto these (in particular for single subjects)
- Do not hesitate to report multiple structures for activations encompassing more than one structure
- Include figures that clearly demonstrate the locations of activations

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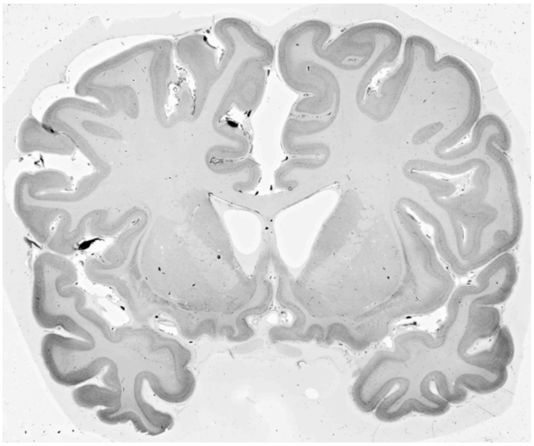
Micro-anatomy



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Aims

- Highlight shortcomings of classical cyto-architectonic maps
- Explain creation of the Jülich probabilistic cyto-architectonic maps
- Discuss limitations of the Jülich approach
- Briefly show how to access these maps in FSL (Peter will cover the SPM anatomy toolbox in more detail in the afternoon session)
- Discuss the relationship of micro-anatomy and macro-antomy
- Recommendations for your study

Disclaimer

- Focus on **cyto**-architectonics (Greek kytos, the cell)
- Other methods
  - Myelin staining
  - Receptor architectonics

Classic cyto-architectonic maps

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➢ How many cortical areas are there?
- Bailey and von Bonin (1951): about 10
- Campbell (1905): about 20
- Brodmann (1909): about 40
- Elliot Smith (1907) [myelin]: about 50
- von Economo & Koskinas (1925): about 100
- Oskar and Cécile Vogt (1919) [myelin]: about 200

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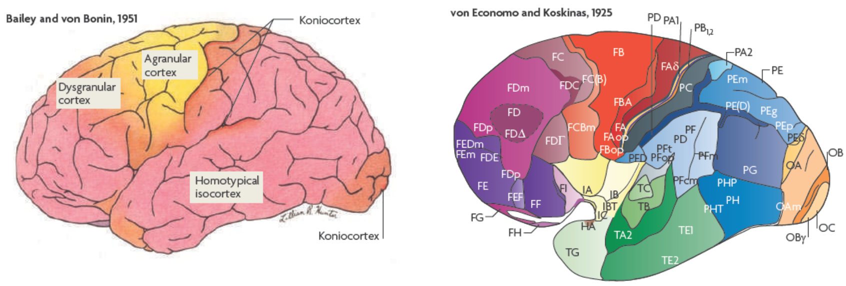

Zilles & Amunts (2010), Nature Reviews Neuroscience

Classic cyto-architectonic maps

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- Obviously it is far from trivial to parcellate the cortex into areas
- Possible reasons for differences
  - Interindividual variability
  - Different techniques (e.g., cell vs. myelin staining)
  - Different skills (staining, pattern recognition)
  - Different criteria (area or subarea?)

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Classic cyto-architectonic maps

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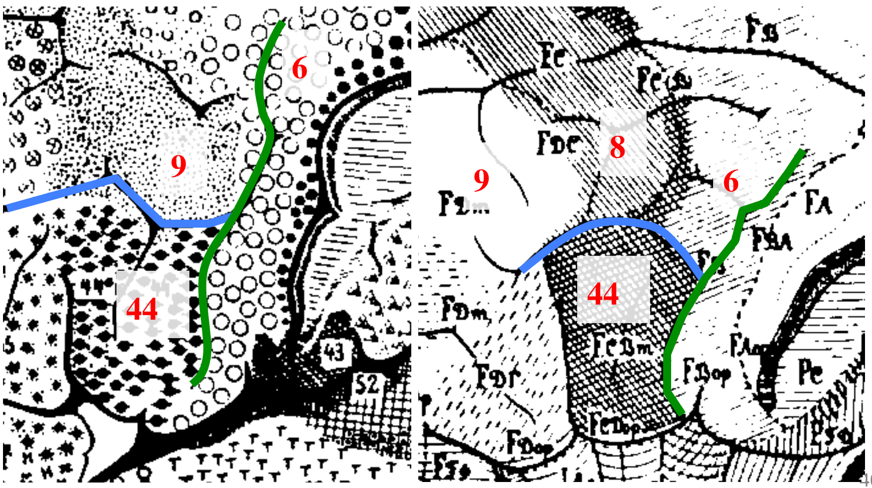
- Result: inconsistencies between maps



Brodmann (1909) von Economo & Koskinas (1925)

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Classic cyto-architectonic maps

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- Other problems with these maps?
  - Oh, yes!:
    - 2-D maps – no information about areas in sulci (2/3 of the cortex!)
    - No standard space
    - Most frequently based on one or very few subjects – with one exception…

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From classic to modern maps

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- So, are we busted?
  - Maybe not completely
  - Starting in the 1980's: development of algorithm-based mapping by Karl Zilles, Axel Schleicher, and others in Düsseldorf and Jülich

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The Jülich approach

- How does the method work?
  - Cytoarchitectonic borders are defined by changes in the number, distribution, and/or size of neurons
  - So, for every piece of cortex, aim to describe these properties quantitatively
  - Then look for significant changes in these properties along the cortex
  - Repeat this procedure for a number of brains, bring them into a standard space, overlay the maps, and create a so-called "cytoarchitectonic probability map"

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The Jülich approach

- Following slides will describe process in more detail
- Appreciate that this might be a lot of new information for some of you
- Try to bear with me; ask questions if things are unclear
- I think it's relevant to understand how these maps are created, given their increasing use in neuroimaging

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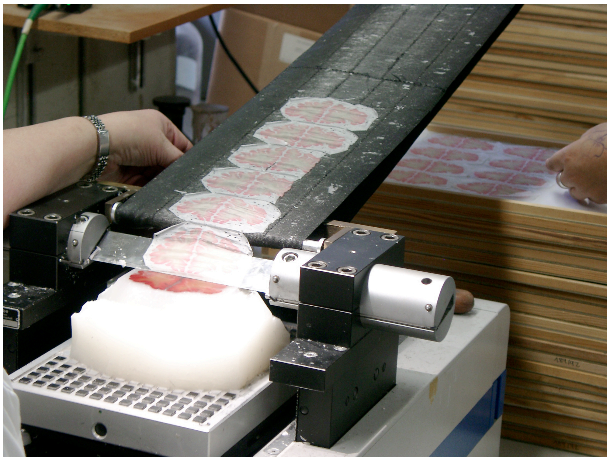
The Jülich approach

- Fixate, MR scan, embed in paraffin, cut in 20 µm slices (0.02 mm)



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The Jülich approach

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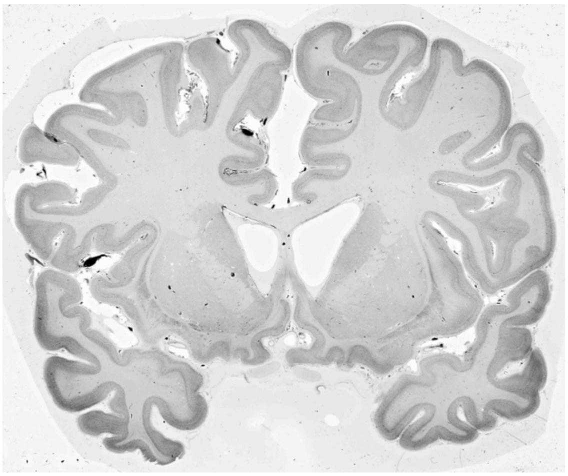
- Mount on glass slides, stain for cell bodies



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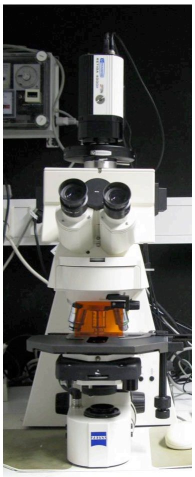
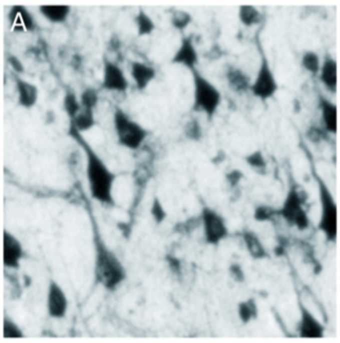
The Jülich approach

- Digitize, spatial filtering, threshold, binarize





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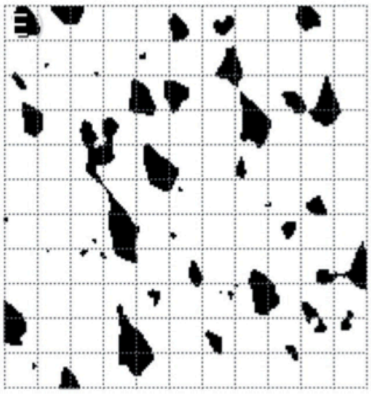
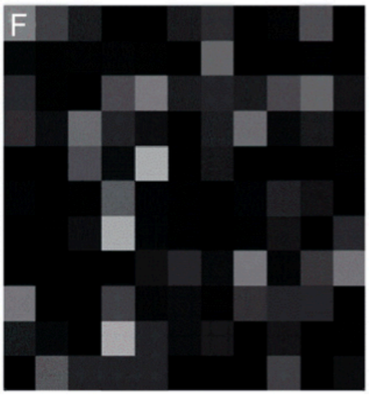
The Jülich approach

- Compute **gray level index**
  - Volume fraction of cell bodies in a 16 μm pixel
  - The more cell bodies, the higher the grey level index





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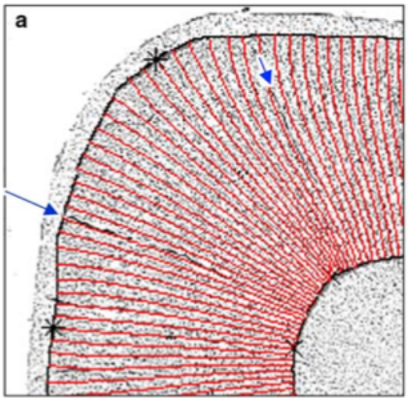
The Jülich approach

- Identify inner and outer cortical boundary, compute cross-cortical traverses



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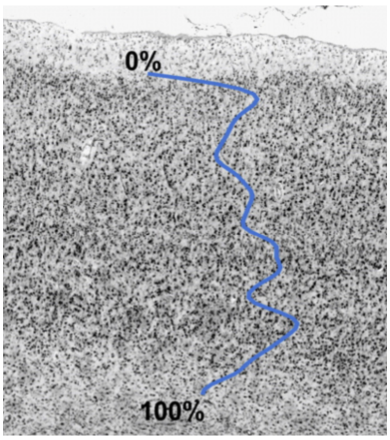
The Jülich approach

- Extract grey-level index profiles along traverses



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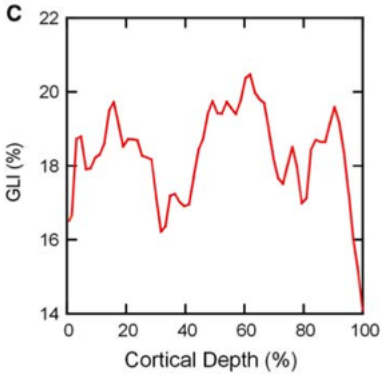
➤ Resample profiles to same length (0 to 100% of cortical depth)



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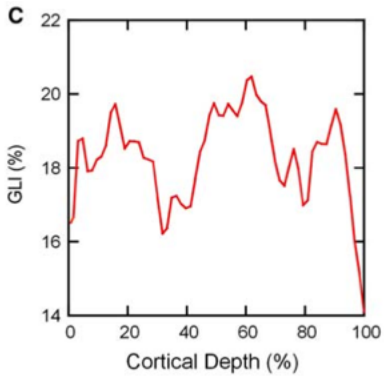
➤ Extract feature vectors for original profiles and for the absolute of their derivatives
- Mean y (orig. profile: mean GLI)
- Mean x
- Standard deviation
- Skewness
- Kurtosis



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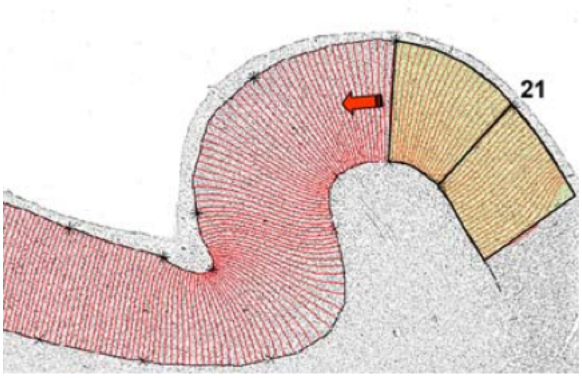
- Calculate feature distances for neighbouring blocks of profiles (using Mahalanobis distance and a sliding-window procedure)



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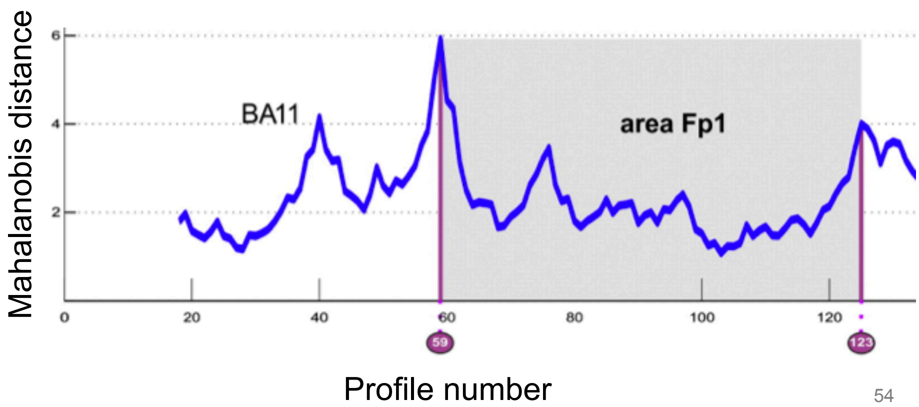
- Plot distances as a function of profile position
- Conduct statistical tests for maxima in the distance function (Hotelling's T^2 with Bonferroni correction)



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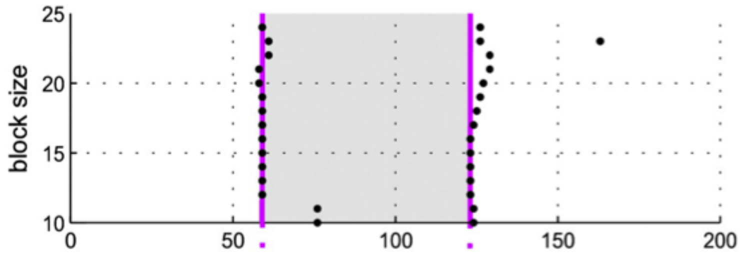
➢ Repeat for different block sizes



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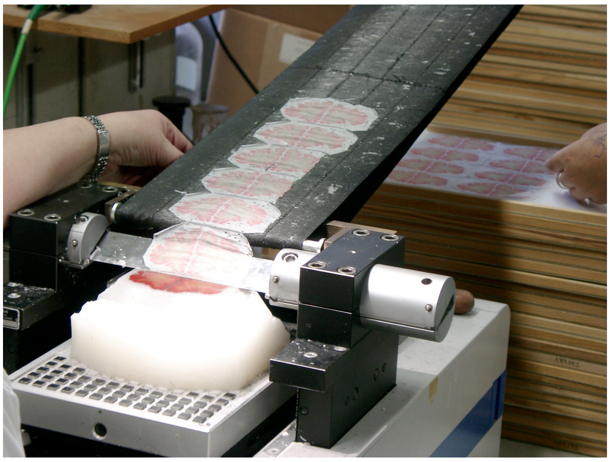
➢ Compare across neighbouring sections



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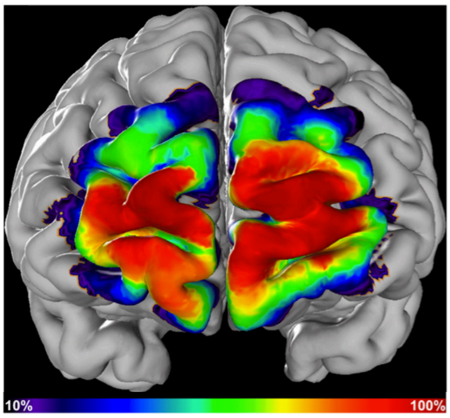
The Jülich approach

- Repeat process for 10 brains
- Label areas (find correspondences across brains!)
- Register maps to stereotaxic space, overlay maps



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The Jülich approach

- Further reading/figures
  - Bludau et al. (2014), Neuroimage
    - Mapping of frontopolar cortex
  - Schleicher et al. (2009), J Autism Dev Disord; Schleicher et al. (2005), Anat Embryol
    - Recent summaries of the method
  - Schleicher et al. (2000), J Chem Neuroanat; Schleicher et al. (1999), Neuroimage
    - More technical treatments

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Limitations of the Jülich approach

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- Does this method solve all problems?
  - Still based on only a small number of brains
  - And, obviously, not the brains of your participants
  - Not truly 3-D, ability to identify borders depends on how brain is cut
  - Interindividual variability much higher than intraindividual variability
  - Method tends to identify only borders that are sharp, but not gradual transitions; however, such borders very likely exist (false negatives)
  - False positives?: check neighbouring slices, but can be difficult due to folding

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Limitations of the Jülich approach

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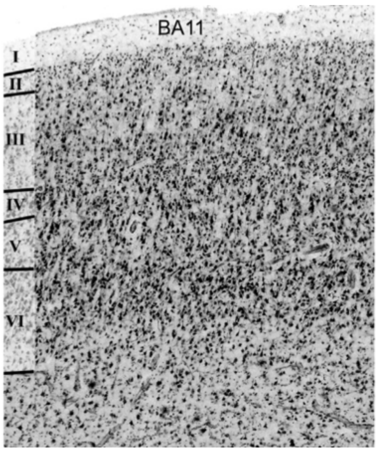
- Observer influence
  - Drawing of inner and outer contours (inner contour, i.e. grey matter-white matter border can be difficult to identify)



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Limitations of the Jülich approach

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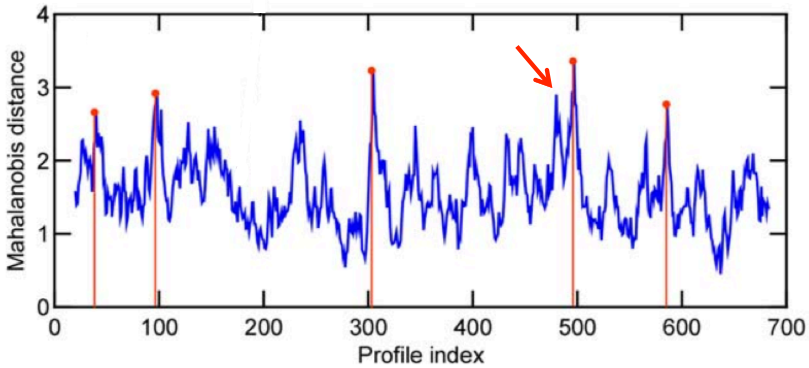
- Observer influence
  - Statistical decisions: distance metric, significance threshold, correction for multiple comparisons
  - Decide on minimum size of area



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Jülich maps in FSL

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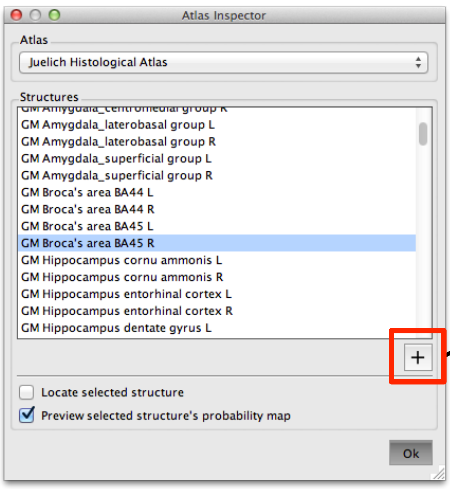
➢ FSLview → Tools → Toolbars → Atlas tools → Juelich Histological Atlas



view multiple maps at the same time

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Jülich maps in FSL

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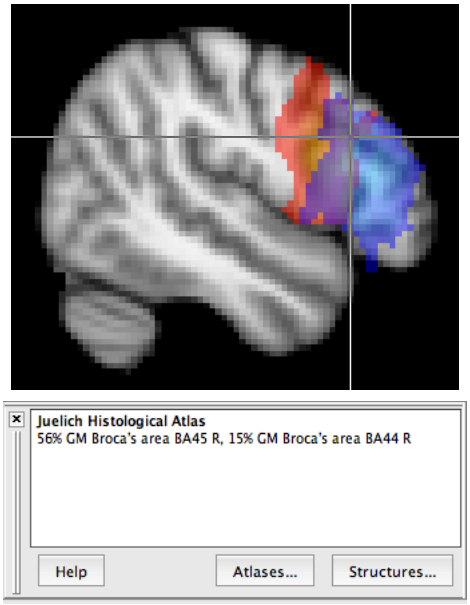

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Relationship of micro-anatomy and macro-anatomy

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- Question: Are sulci or gyri indicators of areal borders?
  - Campbell: "(…) we cannot be blind to the fact that each one of the vast majority of the furrows on the surface of the hemisphere presents a definite causal relationship to some given cortical area (or areas)"
  - Brodmann: "The borders do not match, with a few exceptions, sulci and gyri of the cortical surface, or any other external morphological features."

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Relationship of micro-anatomy and macro-anatomy

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- The answer very likely is 'yes' and 'no':
  - E.g., Brodmann area 44 does not extend beyond the inferior precentral sulcus or the inferior frontal sulcus (Amunts et al., 1999, J. Comp. Neurol.)
  - But it does extend beyond the diagonal sulcus
  - Thus, inferior precentral sulcus and inferior frontal sulcus are limiting sulci, whereas the diagonal sulcus is not
  - Note, however, that the exact position of the border is very variable within the sulcus!

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Relationship of micro-anatomy and macro-anatomy

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- Possible explanation why some sulci are limiting and others are not: ontogenesis
  - Sulci develop at different time points (Chi et al., 1977, Ann Neurol)
  - Inferior frontal and inferior precentral: around week 24
  - Diagonal: around week 35

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Relationship of micro-anatomy and macro-anatomy

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- Tension-based models of morphogenesis (Van Essen, 1997, Nature): development of connections is a critical factor in determining cortical folding
- Connections determine function (Passingham et al., 2002, Nature Rev Neurosci)
- Thus, macro-anatomy and connections (and, therefore, possibly functions) are not independent
- The earlier a sulcus develops, the stronger this association might be

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Recommendations

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- If Jülich maps for your fMRI activations are available, use these
  - Consider reporting multiple areas with associated percentages (84% BA 44, 24% BA 45)
  - Check Jülich publications; new maps might be available, but not yet included in FSL
- If not, use Talairach labels
  - Note below your table that these are approximate
  - Consider using knowledge about limiting sulci to check whether these labels make sense for your single-subject activations
- Report how cyto-architectonic labels were determined

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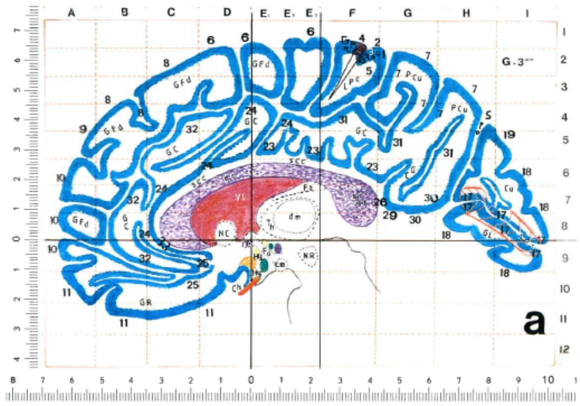
Standard space(s)



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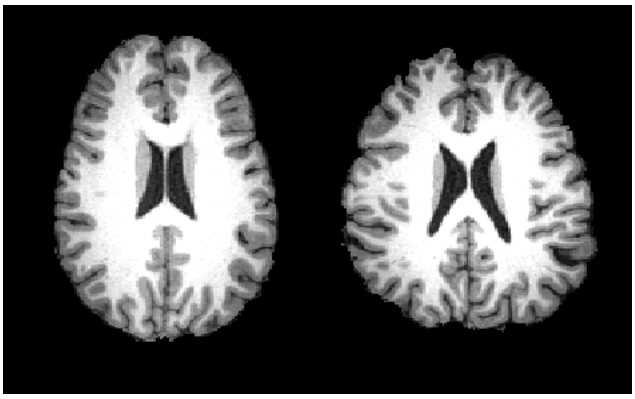
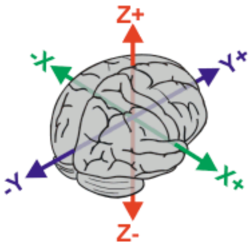
Why standard space?

- To compensate for interindividual differences in anatomy and thus allow for group statistics



The Talairach system

- The human brain in a standard space
  - Origin: anterior commissure
  - x-axis: left to right
  - y-axis: posterior to anterior
  - z-axis: inferior to superior
  - Size of Talairach space determined by the brain studied (60-year-old right-handed woman)
- Published in 1988, 122 pages, $230
- Software version: Talairach Daemon (http://www.talairach.org)



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The Talairach system

- Horizontal plane: **superior** edge of anterior commis-sure (AC) and **inferior** edge of posterior commissure (PC)
- Origin: plane vertical to horizontal plane at **posterior** edge of anterior commissure (VAC) + midline

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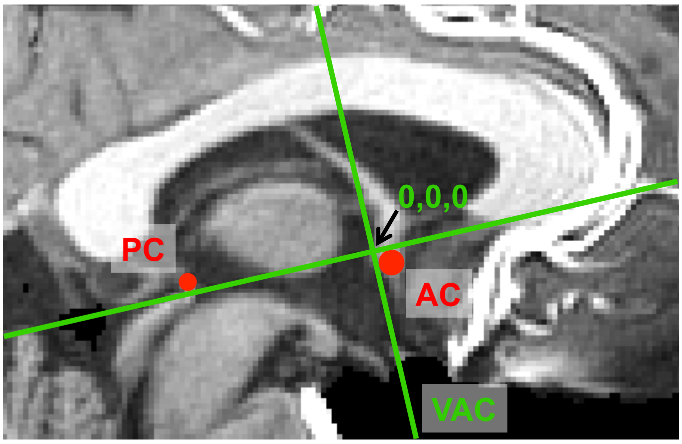
The Talairach system



Limitations of the Talairach system

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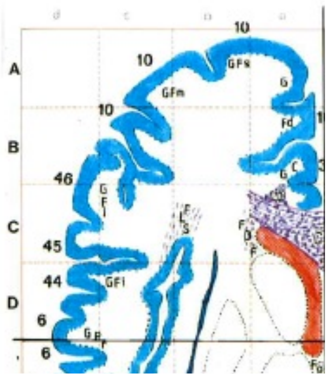
- Only one brain
- No cytoarchitectonics



The cytoarchitectonic areas are a guess based on the Brodmann map (which had no information about areas in sulci…)

Limitations of the Talairach system

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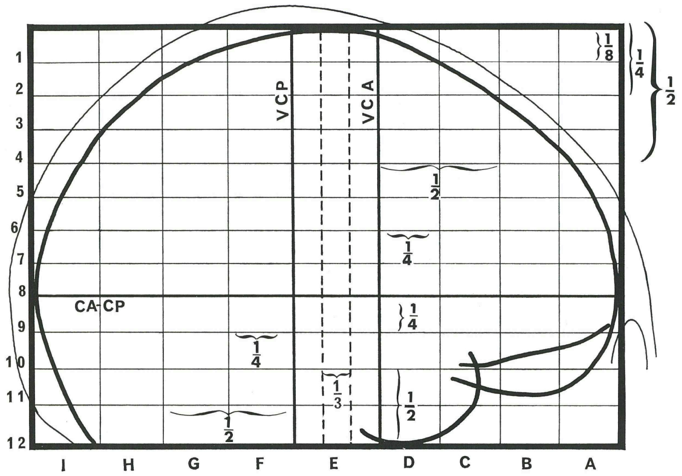
- Complicated way to normalise brains following Talairach's atlas (6 linear transformations per hemisphere)



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Montreal Neurological Institute (MNI) approach

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- Aim: overcome (some) limitations of the Talairach system
  - Create standard brain that is based on many brains
  - Simplify registration
  - Automatise registration

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Montreal Neurological Institute (MNI) approach

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- Stage 1: MNI250
  - AC-PC line not identified directly, but estimated based on manual identification of
    - Inferior margin of genu of corpus callosum
    - Inferior margin of splenium of corpus callosum
    - Inferior margin of thalamus
    - Superior margin of cerebellum
    - Occipital pole
  - This method was slightly biased: AC at 0,0,-2

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Montreal Neurological Institute (MNI) approach

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- Extents in lateral and vertical directions were assumed to lie on the perpendicular bisectors of the AC-PC line (diverts from Talairach's bounding box approach)
- Also, MNI group used a single scaling factor in each direction of space (9 parameters overall)
- As a result, MNI250 was larger than Talairach brain in some areas

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Montreal Neurological Institute (MNI) approach

- Stage 2: MNI305
  - Automatic registration procedure: 9-parameter linear transformation to maximise cross-correlation with MNI250
  - No further constraints
  - As a result: AC at 0,-1,-3.5

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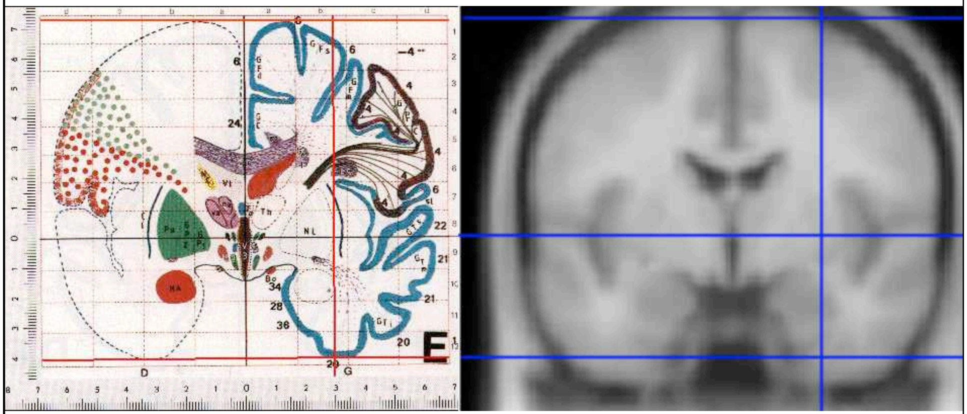
Montreal Neurological Institute (MNI) approach



http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach

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Montreal Neurological Institute (MNI) approach

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- Stage 3: MNI152 = ICBM152
  - Higher resolution (1 mm isotropic)
  - More contrasts: T1, T2, proton density
  - Includes cerebellum
  - Non-linear registration
  - AC at 0,1,-3

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Montreal Neurological Institute (MNI) approach

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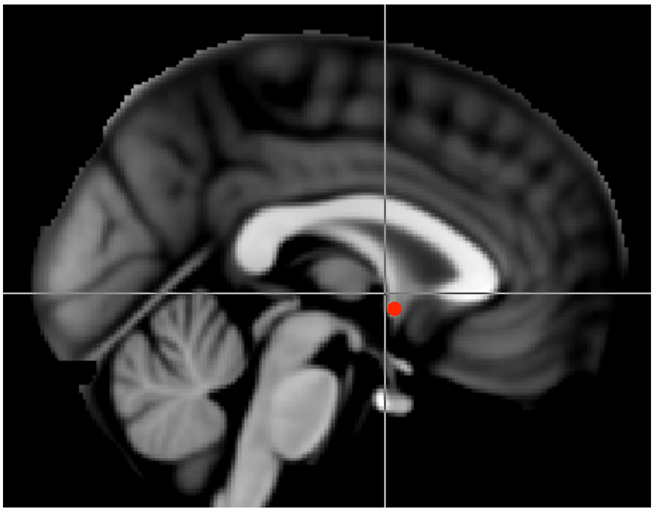

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Montreal Neurological Institute (MNI) approach

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- More info
  - Collins (2011). In Petrides, The human cerebral cortex.
  - Collins (1994, J Comp Assist Tomogr)
  - Collins (1994, PhD thesis)
- Converting Talairach to MNI coordinates (and vice versa)
  - Lancaster et al. (2007, Human Brain Mapp), http://www.brainmap.org/icbm2tal/

A few words about Colin27…

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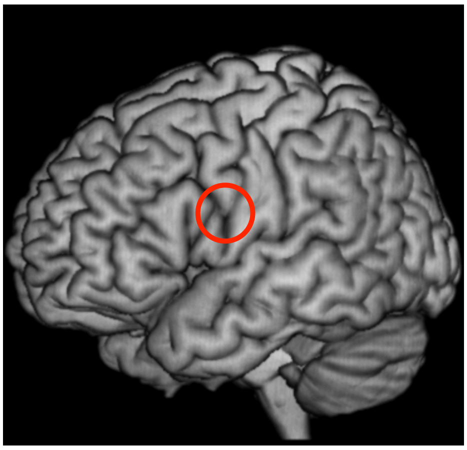
- Rather strange anatomy in some places
- Better avoid as normalisation target



Avoid SPM surface projection

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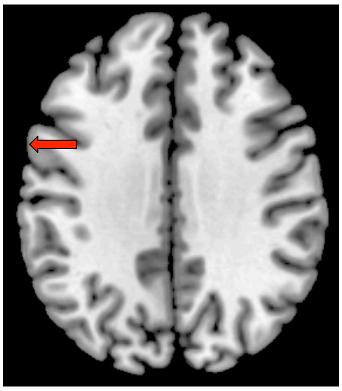

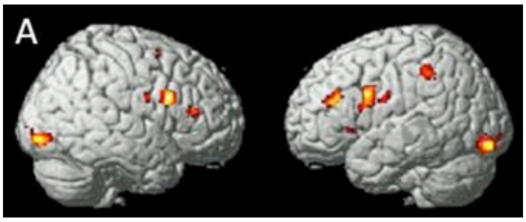

Normalisation

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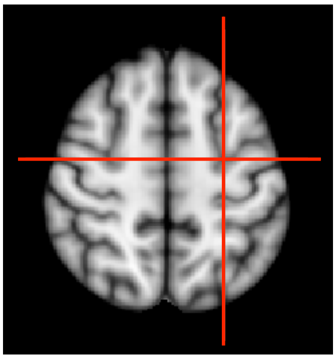
- MNI152, cross-hair at junction of superior frontal sulcus and superior precentral sulcus (-27,-8,53)



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Normalisation

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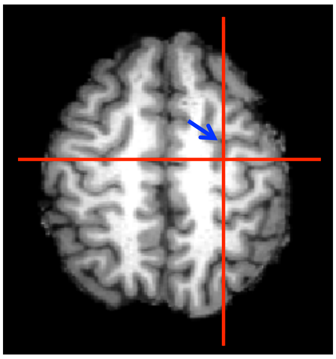
- Individual after 12-parameter affine registration to MNI152



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Normalisation

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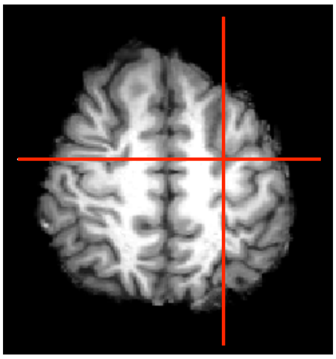
- Individual after non-linear registration to MNI152 using **FNIRT** (~16 min)



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Normalisation

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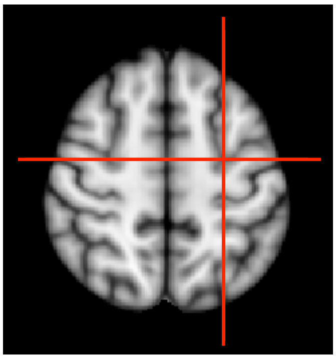
- MNI152



Normalisation

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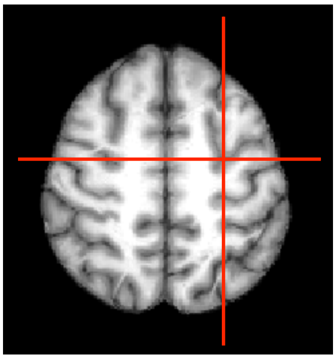
- Individual after non-linear registration to MNI152 using **ANTS** (~1 h)



Normalisation

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- Comparison of non-linear registration tools: Klein et al. (2009, Neuroimage)
  - Best performance overall
    - ANTS/SyN: http://picsl.upenn.edu/software/ants/
    - ART: http://www.nitrc.org/projects/art/
- But note that anatomical alignment does not necessarily imply functional alignment
  - Remember limiting vs. non-limiting sulci

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Recommendations

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- Keep the differences between Talairach and MNI space in mind
- Use Lancaster transform to convert between the two
- Register non-linearly to ICBM152, preferably with ANTS or ART

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