

A Lateralized Brain Network for Visuo-Spatial Attention

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ABSTRACT

Looking for a friend in the crowd, avoiding a sudden danger or contemplating a work of art are some examples of actions based on the efficiency of our visuo-spatial attention system. The specialization of the right brain hemisphere for visuo-spatial attention is a characteristic of most humans, but its anatomical basis remains largely unknown. Our study is the first to report in humans the existence of a bilateral parieto-frontal network whose hemispheric lateralization predicts the degree of specialization of the right hemisphere for visuo-spatial attention. Our results also suggest that this specialization is associated with an unbalanced speed of visuo-spatial processing between the two hemispheres. This lateralization may be predictive of visuo-spatial recovery in patients with lesions of parieto-frontal networks.

Clinical studies in patients with brain lesions, and decades of neuropsychological testing in split-brain patients, have led to the general assumption that visuo-spatial attention is a function of the right hemisphere¹⁻³. However, bilateral hemispheric activation is frequently observed during neuroimaging studies of visuo-spatial function⁴, and up to 40% of patients with left hemisphere damage show signs of right visuo-spatial neglect⁵. Hence, visuo-spatial attention is probably a bilateral function with right hemisphere dominance in most, but not all, humans⁶⁻⁸. For left dominant functions, such as language, clear leftward brain asymmetries have been described^{9, 10}. In contrast, the anatomical substrate of the right dominance for visuo-spatial attention, and its variability in the general population, remains unknown.

The activity of neurons dedicated to visuo-spatial attention in the monkey brain has been recorded using multiple electrodes simultaneously implanted in the parietal and frontal cortex¹¹. Axonal tracing studies have shown that these neurons are directly connected through a system of long white matter pathways running longitudinally in the dorsal regions of the cerebral hemispheres^{12, 13}. Recent structural¹⁴ and functional imaging studies suggest that a similar system may be present in the human brain⁴. However until recently it has not been possible to directly study the anatomy of the parieto-frontal white matter pathways in the human living brain due to technological constraints.

New developments in diffusion imaging tractography¹⁵⁻¹⁷ offer a unique opportunity to visualize the organization of human brain pathways and to verify the existence of anatomical connections previously described only in the monkey¹⁸⁻²⁰. Diffusion imaging is a modification of conventional magnetic resonance imaging

sequences that permits the quantification of the diffusion characteristics of water molecules¹⁵. Given that cerebral white matter contains connections, and that water molecules diffuse more freely along connections than across them¹⁷, it is possible to obtain in vivo estimates of white matter fiber orientation by measuring the diffusivity of water molecules along different directions¹⁶. Tractography algorithms are used to reconstruct white matter tracts in three dimensions by sequentially piecing together discrete and shortly spaced estimates of fibre orientation to form continuous trajectories¹⁸⁻²⁰. Tractography has previously been used to dissect a large number of white matter connections in the human brain and these in vivo reconstructions are very close to the post-mortem findings derived from classical blunt dissections. However, the existence of a dorsal parieto-frontal system network similar to that described in the monkey^{12, 13} has proven difficult to ascertain in the human brain¹⁴. This is due to inherent limitations of current tractography methods in reconstructing parieto-frontal connections that cross over other populations of fibres within the same voxels²¹.

Spherical Deconvolution (SD) tractography partially overcome these limitations, by identifying and quantifying the orientation of different populations of fibres within a single voxel^{22, 23}.

Therefore we performed virtual in vivo dissections of the parieto-frontal network in the human brain using SD based tractography in 20 right-handed subjects (11 males, 9 females) and confirmed the tractography findings with post-mortem blunt dissections. We carried out quantitative measures of left-right asymmetry in this network and correlated them with behavioural performance on visuo-spatial

processing tasks. We report for the first time in humans the existence of three parieto-frontal white matter pathways whose rightward hemispheric lateralization predicts the degree of leftward bias during tasks assessing visuo-spatial attention. Our findings suggest that hemispheric dominance for visuo-spatial attention in humans depends on a bilateral parieto-frontal network that lateralizes to the right hemisphere in the majority of the population.

RESULTS

Anatomy of the Parieto-Frontal Networks in Human.

Figure 1 shows side by side the dissections from our study and corresponding slices from a monkey atlas¹³ that we have modified for a direct comparison. Overall parieto-frontal connections of the human and the monkey brain are organized similarly in three longitudinal pathways. In humans, the most dorsal pathway originates from the precuneus and the superior parietal lobule (Brodmann areas, BA 5 and 7); and projects to the superior frontal and anterior cingulate gyri (BA 8, 9 and 32). This pathway corresponds to the first branch of the superior longitudinal fasciculus (SLF I) as described in the monkey brain^{12, 13, 24}. In contrast the middle pathway originates in the anterior intermediate parietal sulcus and the angular gyrus (BA 39 and 40) and ends in the posterior regions of the superior and middle frontal gyri (BA 8 and 9). This pathway corresponds to the SLF II in the monkey brain^{12, 13, 24}. Lastly, the most ventral pathway originates in the temporo-parietal junction (BA 40) and terminates in the inferior frontal gyrus (BA 44, 45 and 47); corresponding to the SLF III in the monkey brain^{12, 13, 24}. We were also able to replicate our in vivo

findings using post-mortem blunt dissections in a human brain (see figure 2). Although the post-mortem dissections were limited in identifying the exact cortical projections of the three SLF, a good correspondence was found between post-mortem and in vivo dissections of the central course of the three branches. Overall our results suggest a strong similarity between monkey and human parieto-frontal connections.

Asymmetry of Parieto-Frontal Spatial Networks.

A lateralization index was calculated for the volume of the three branches of the SLF according to the following formula:

$$(\text{Right volume} - \text{Left volume}) / (\text{Right volume} + \text{Left volume}).$$

Negative values indicate a leftward volume asymmetry and positive values a rightward asymmetry. The SLF I showed a symmetrical distribution between left and right hemispheres ($t_{(14)} < 1$); with 60% of subjects showing a leftward trend in the lateralization pattern and 40% a rightward trend. For the SLF II a rightward lateralization was found in 65% of subjects while only 35% were leftward lateralized, although this difference was not statistically significant ($t_{(14)} = 1.141$; $P = 0.268$). In contrast, the SLF III showed a statistically significant rightward lateralization ($t_{(14)} = 6.083$; $P = 0.000$), with 90% of subjects being rightward lateralized and only 10% weakly left lateralized. Our findings show, for the first time, that there is a dorsal to ventral gradient of lateralization in the parieto-frontal connections with the SLF II and particularly the SLF III having the greatest rightward lateralization (Figure 3B).

Patterns of Lateralization and Behavioral Correlates.

To test whether this anatomical lateralization was related to the attentional bias for one visual hemi-field, we asked the participants to perform a line bisection test²⁵ and a modified Posner paradigm²⁶.

In the line bisection test, a small left deviation is observed in the general population²⁵. This is generally referred to as the ‘pseudoneglect effect’ since the left deviation is opposite to that observed in patients with visuo-spatial neglect²⁵. The left deviation in the line bisection is usually regarded as a manifestation of an asymmetrical processing of visuo-spatial information in the normal brain^{25, 27}. The line bisection test consists of asking the examinee to mark the centre of a line with a pen (Figure 3C). For each subject ten trials were acquired, five for each hand, and an average of the ten performances was calculated in millimetres. Negative values indicate a deviation towards the left of the true centre of the line, whereas a positive value indicates a rightward deviation. Our group of participants, consistent with previous studies²⁷, had a significant deviation towards the left ($-1.53 \pm 2.02 \text{mm}$; $t_{(14)} = -3.148$; $P = 0.005$). However almost 30% (7/20) of subjects showed a bilateral or reverse pattern (deviation toward the right). Scores on the line bisection test correlated significantly with the lateralization pattern of the SLF II ($r = -0.698$; $P = 0.001$) (Figure 3D), whereas correlations with the SLF I ($r = 0.332$; $P = 0.153$) or the SLF III ($r = -0.336$; $P = 0.147$) were weaker and not statistically significant. These findings suggest that subjects with a larger right than left SLF II deviate more towards the left in line bisection. A few subjects who showed no deviation or deviated to the right in the line bisection showed a bilateral or reversed pattern of the SLF II asymmetry. Overall, the

correlation between the lateralization of the SLF II and the deviation observed in the line bisection represents the first demonstration that an anatomical asymmetry predicts behavioural performance on a visuo-spatial attention task.

It is not known how differences between the two hemispheres in SLF II volume can lead to asymmetrical processing of visual scenes. Larger tract volumes in the right hemisphere could depend on a number of factors, including greater fibre myelination, higher number of axons and larger axonal diameter. Experimental physiology has shown that the conduction speed of larger diameter axons²⁸, or more myelinated axons²⁹ is faster. Furthermore, cortical recording in monkeys performing attentional tasks has shown that synchrony of neuronal activity within the parieto-frontal network enhances the representation of stimuli, and may resolve competition for attentional selection¹¹. In light of this previous work, we suggest that the left deviation in the line bisection we observed in the majority of subjects may result from unbalanced speed of visuo-spatial processing between the SLF II in the right hemisphere and the left hemisphere. If our suggestion is correct then subjects with a rightward asymmetry of the SLF II should be quicker in detecting targets appearing in the left hemi-field than in the right hemi-field. To test this hypothesis a subgroup of subjects were asked to complete a modified Posner paradigm²⁶. In this task, the subject is asked to detect a target that appears either on their right or left hemi-field as quickly as possible. For each participant a lateralization index of the reaction time was calculated in a similar manner to that calculated for the volume of the SLF. There was a significant correlation between the lateralization index of reaction time and the lateralization index for the volume of the SLF II ($r = -0.494$; $P = 0.027$) (Figure 3F); but weaker and non statistically significant correlation with SLF I ($r = 0.335$; $P = 0.149$) or SLF

III ($r = -0.315$; $P = 0.176$). Moreover, there was a significant correlation between the left deviation on the line bisection and the reaction time index ($r = 0.620$; $P = 0.004$) (Figure 3E).

The findings from both sets of experiments support our hypothesis that during the line bisection task subjects with a left bias are quicker at processing left hemi-field stimuli in relation to a larger SLF II in the right hemisphere. Further studies are needed to clarify whether this correlation is linked to a particular component of the several cognitive processes underlining the detection task.

DISCUSSION

Using SD tractography, we have shown for the first time anatomical similarities between human and monkey parieto-frontal white matter tracts. This suggests a common human-simian architecture of the parieto-frontal networks underlying visuo-spatial attention.

The cortical projections of the three branches of the SLF (Figure 4A) overlap with the functional networks reported engaging during tasks requiring the orientation of attention towards visual targets (see figure 4B adapted from ⁴). In particular, the projections of the SLF I overlap with the dorsal functional network activated during the voluntary orienting of spatial attention and the projections of the SLF III with the cortical functional activation activated during the automatic capture of spatial attention by visual targets (for a review on the dorsal and ventral networks see ⁴). The SLF II overlaps with the parietal component of the inferior network and the prefrontal

component of the superior network. Thus, our findings suggest the SLF II represents a direct communication between the dorsal and the ventral networks during the orienting of attention. This direct connection may mediate the spontaneous synchronous oscillations between the dorsal and ventral networks shown in functional activation studies³⁰. Furthermore, monkey studies suggest that synchronous oscillations of neural activity between the frontal and parietal networks may enhance the representation of visual stimuli^{11,31}. Direct electrical inhibition of the conduction along the SLF II during brain surgery causes transient decrease of the representation of visual stimuli on the contralateral side³². Our findings of a correlation between the strength of the anatomical fronto-parietal connectivity and the bias towards the contralateral side confirm previous monkey and human electrophysiological findings and suggest that the anatomical variability of the SLF II fibres is an important factor for the asymmetrical representation of visual scenes.

Furthermore the asymmetrical representation assessed by the line bisection and the modified Posner paradigm shows a inter-individual variability and a significant correlation with the lateralization index of the volume of the SLF II but not the absolute values in each hemisphere. This suggests that an imbalanced distribution of the SLF II fibres rather than the volume of the tract on the right hemisphere predicts the dominance of visuo-spatial attention. Thus, according to our findings only two thirds of the normal population shows a right hemisphere dominance for visuo-spatial attention whereas the remaining are either symmetrical or left dominant. This could explain why not all subjects with right hemisphere lesions show signs of left neglect and up to 40% of the left damaged brains have right neglect.

Finally, although the SLF III shows the most significant rightward lateralization, this did not correlate with the line bisection performance and the speed of visuo-spatial processing. A possible explanation may be that the function of the SLF III differs between the two hemispheres. In the left hemisphere the SLF III projects to areas involved in verbal fluency³³ and praxis³⁴. In the right hemisphere the SLF III projects to areas involved in visuospatial attention⁴, prosody³⁵ and music processing³⁶. Hence, this suggests that an anatomical asymmetry of the brain should not be taken as direct evidence of hemispheric dominance as the correlation between anatomical lateralization and specialization of functions is not straightforward.

In conclusion our study is the first to report the existence of a bilateral parieto-frontal network, previously described only in monkey, whose hemispheric lateralization predicts the degree of specialization of the right hemisphere for visuo-spatial attention. Our results also suggest that this specialization is associated with an unbalanced speed of visuo-spatial processing between the two hemispheres. This lateralization may be predictive of visuo-spatial recovery in patients with lesions of parieto-frontal networks.

METHODS

For a detailed and fully referenced description of the experimental and analytical techniques, see the Supplementary Methods and Results.

Experimental procedure. The study was approved by the Medical Ethical Committee of the Institute of Psychiatry at Kings College London, and informed consent was obtained from all subjects. Twenty healthy right-handed volunteers (11 males and 9 females) aged between 22-38 years were recruited.

The line bisection paradigm consisted of twenty cm long, 1-mm thick black lines centered on a horizontal A4 sheet (one line per sheet) presented aligned to the subjects' eye-axis, in a central position relative to the patient's sagittal head plane. Subjects were instructed to mark the center of each line with a pencil. Each subject marked 10 lines in total, 5 with the left hand and 5 with the right hand. The deviation from the true centre was recorded and an average of the performance with both hands was used to perform correlation analysis with the tractography lateralization indexes.

The reaction time task consisted of a modification of the Posner paradigm²⁶. The display contained a central fixation point and two boxes (unfilled squares) one on each side of the screen. The participants were asked to fixate on the central point and were instructed to press a button with the right hand each time they saw a star appearing in one of the two boxes. The reaction time (RT) was recorded in milliseconds. Before the appearance of the star, an arrow was briefly presented that pointed either to the left or right. The whole session consisted of 50% of trials with a valid cue (arrow pointing at the direction of the star) and 50% of trials with an invalid

cue (arrow pointing in the opposite direction of the star). The inter-trial interval was randomized between 4760-9440 ms.

Image Acquisition and analysis. For each participant, 60 contiguous near-axial slices were acquired on a 3T GE Signa HDx TwinSpeed system (General Electric, Milwaukee, WI, USA) with the following parameters: voxel size 2.4x2.4x2.4 mm, matrix 128x128, slices 60, NEX 1, TE 93.4 ms, b-value 3000 s/mm², 60 diffusion-weighted directions and 7 non-diffusion-weighted volumes, using a spin-echo EPI sequence with Anterior-Posterior phase encoding. Cardiac gating was applied with effective TR of 20/30 R-R intervals. A sagittal three-dimensional MPRAGE data set covering the whole head was also acquired (166 slices, voxel resolution=1.2x1x1 mm, TE=2.8 ms, TR=7 ms, flip angle= 8°).

Motion and eddy current distortion correction and orientation estimation of the diffusion weighted images were performed as described in ²³. Whole brain tractography was performed following a previously published approach ²⁴.

A multiple region of interests (ROIs) approach was used to isolate different components of the parieto-frontal network. Three ROIs were delineated around the white matter of the superior, middle and inferior/precentral frontal gyri, and another three 'AND' ROIs were delineated posteriorly in the parietal region. Streamlines of the arcuate fasciculus projecting to the temporal lobe were excluded using a 'NOT' ROI in the temporal white matter (The arcuate is not part of the fronto-parietal system as it projects to the temporal lobe.) (Supplementary Figure 2).

Normalization and group statistical mapping of the tracts in the stereotaxic space were performed following a method described in ³⁷. Cortical projections were mapped on the average cortical surface as indicated in ³⁸.

Post-mortem dissections. Human post-mortem Klingler dissections ³⁹ of the three branches of the SLF were performed on the right hemisphere, obtained from the autopsy of a 80 year-old woman's brain. This hemisphere was fixed in formalin for at least one year and then frozen at -15°C for two weeks after removing the pia-arachnoid membrane and vessels. As described in Martino et al. ⁴⁰ the water crystallization induced by the freezing process disrupts the structure of the gray matter and spreads the white matter fibres, facilitating the dissection of the fibre tracts. The SLF III and SLF II were exposed using lateral surface to medial surface dissections. The SLF I was exposed using medial surface to lateral surface dissections (Supplementary figure 4).

Meta-analyses. The monkey maps of the SLF I, II and III presented in figure 1 are modified from the coronal slices provided in an Atlas by Schmahmann & Pandya ¹³. The modification consists of coloring the tract in red (SLF I), yellow (SLF II) and green (SLF III) according to the site of injection for the axonal tracing. Projection and commissural fibres were removed for visualization purposes.

The figure 4B that summarizes the functional activation studies (fMRI and PET) in visuo-spatial attention was adapted from the work of Corbetta et al.⁴. The studies were aimed at detecting cortical activation during two conditions: i) strategic and voluntary orienting of spatial attention towards visual targets; ii) unexpected and automatic orienting of attention towards visual targets. Foci of activation reported in Corbetta et

al.⁴, were projected onto the average 3D rendering of the cortical surface of the 20 participants.

The summary of the brain lesion and electrical stimulation studies presented in figure 4C was created using all previously published studies in the literature. A comprehensive search of group studies with PUBMED identified nine brain lesion studies a⁴¹, b⁴², c⁴³, d⁴⁴, e⁴⁵, f⁴⁶, h⁴⁷ j⁴⁸, k⁴⁹ and 2 intraoperative electrical stimulation studies g³² and I⁵⁰. Foci of maximum overlap of the lesion or electrical stimulation were projected onto the average 3D rendering of the cortical surface of the 20 participants.

Statistical analysis.

Statistical Analysis. Statistical analysis was performed by using SPSS software (SPSS, Chicago, IL). In our analysis, Gaussian distribution was confirmed for all the dependant variables using the Shapiro–Wilk test. This allows the use of standard parametric statistics in our dataset to draw statistical inferences. One-sample t test (test value = 0) was used to assess the lateralization of the volume in voxels of the SLF I, II and III. Pearson correlation analysis was performed between the lateralization index of the three branches of the superior longitudinal fasciculus (volume in voxels) and the behavioural performances.

REFERENCES

1. Gainotti, G., Messerli, P. & Tissot, R. Qualitative analysis of unilateral spatial neglect in relation to laterality of cerebral lesions. *J Neurol Neurosurg Psychiatry* **35**, 545-550 (1972).
2. Sperry, R.W. *Lateral Specialization in the Surgically Separated Hemispheres* (Rockefeller University Press, New York, 1974).
3. Mesulam, M.M. A cortical network for directed attention and unilateral neglect. *Ann Neurol.* **10**, 309-325 (1981).
4. Corbetta, M. & Shulman, G.L. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* **3**, 201-215 (2002).
5. Beis, J.M., *et al.* Right spatial neglect after left hemisphere stroke: qualitative and quantitative study. *Neurology* **63**, 1600-1605 (2004).
6. Heilman, K.M. & Van Den Abell, T. Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology* **30**, 327-330 (1980).
7. Mesulam, M.M. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond, B, Biol Sci* **354**, 1325-1346 (1999).
8. Shulman, G.L., *et al.* Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. *J Neurosci* **30**, 3640-3651 (2010).
9. Geschwind, N. & Levitsky, W. Human brain: left-right asymmetries in temporal speech region. *Science* **161**, 186-187 (1968).

10. Catani, M., *et al.* Symmetries in human brain language pathways correlate with verbal recall. *Proc Natl Acad Sci U S A* **104**, 17163-17168 (2007).
11. Buschman, T.J. & Miller, E.K. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science* **315**, 1860-1862 (2007).
12. Petrides, M. & Pandya, D.N. Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *J. Comp. Neurol.* **228**, 105-116 (1984).
13. Schmahmann, J.D. & Pandya, D.N. *Fiber Pathways of the Brain* (Oxford University Press, Oxford, 2006).
14. Makris, N., *et al.* Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb Cortex* **15**, 854-869 (2005).
15. Le Bihan, D. & Breton, E. Imagerie de diffusion in-vivo par résonance magnétique nucléaire. *Comptes rendus de l'Académie des sciences* **301**, 1109-1112 (1985).
16. Basser, P.J., Mattiello, J. & Le Bihan, D. MR diffusion tensor spectroscopy and imaging. *Biophys J* **66**, 259-267 (1994).
17. Moseley, M.E., *et al.* Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology* **176**, 439-445 (1990).
18. Jones, D.K., Simmons, A., Williams, S.C. & Horsfield, M.A. Non-invasive assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. *Magn Reson Med* **42**, 37-41 (1999).

19. Mori, S., Crain, B.J., Chacko, V.P. & van Zijl, P.C. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol* **45**, 265-269 (1999).
20. Basser, P.J., Pajevic, S., Pierpaoli, C., Duda, J. & Aldroubi, A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med* **44**, 625-632 (2000).
21. Jones, D.K. Studying connections in the living human brain with diffusion MRI. *Cortex* **44**, 936-952 (2008).
22. Tournier, J.D., Calamante, F. & Connelly, A. Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. *Neuroimage* **35**, 1459-1472 (2007).
23. Dell'acqua, F., *et al.* A modified damped Richardson-Lucy algorithm to reduce isotropic background effects in spherical deconvolution. *Neuroimage* **49**, 1446-1458 (2010).
24. Schmahmann, J.D., *et al.* Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain* **130**, 630-653 (2007).
25. Bowers, D. & Heilman, K.M. Pseudoneglect: effects of hemispace on a tactile line bisection task. *Neuropsychologia* **18**, 491-498 (1980).
26. Posner, M.I. Orienting of attention. *Q J Exp Psychol* **32**, 3-25 (1980).
27. Jewell, G. & McCourt, M.E. Pseudoneglect: a review and meta-analysis of performance factors in line bisection tasks. *Neuropsychologia* **38**, 93-110 (2000).
28. Hursh, J.B. Conduction Velocity and diameter of nerve fibers. *American Journal of Physiology* **127**, 131-139 (1939).

29. Waxman, S.G. & Bennett, M.V. Relative conduction velocities of small myelinated and non-myelinated fibres in the central nervous system. *Nat New Biol* **238**, 217-219 (1972).
30. Fox, M.D., Corbetta, M., Snyder, A., Vincent, J.L. & Raichle, M.E. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci USA* **103**, 10046-10051 (2006).
31. Fries, P., Reynolds, J.H., Rorie, A.E. & Desimone, R. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* **291**, 1560-1563 (2001).
32. Thiebaut de Schotten, M., *et al.* Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. *Science* **309**, 2226-2228 (2005).
33. Schiff, H.B., Alexander, M.P., Naeser, M.A. & Galaburda, A.M. Aphemia. Clinical-anatomic correlations. *Arch Neurol* **40**, 720-727 (1983).
34. Heilman, K.M. & Watson, R.T. The disconnection apraxias. *Cortex* **44**, 975-982 (2008).
35. Ross, E.D. The aprosodias. Functional-anatomic organization of the affective components of language in the right hemisphere. *Arch Neurol* **38**, 561-569 (1981).
36. Loui, P., Alsop, D. & Schlaug, G. Tone deafness: a new disconnection syndrome? *J Neurosci* **29**, 10215-10220 (2009).
37. Thiebaut de Schotten, M., *et al.* Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *Neuroimage* **54**, 49-59 (2011).

38. Tsang, J.M., Dougherty, R.F., Deutsch, G.K., Wandell, B.A. & Ben-Shachar, M. Frontoparietal white matter diffusion properties predict mental arithmetic skills in children. *Proc Natl Acad Sci U S A* **106**, 22546-22551 (2009).
39. Klingler, J. Erleichterung der makroskopischen Präparation des Gehirn durch den Gefrierprozess. *Schweiz Arch Neurol Psychiat* **36**, 247-256 (1935).
40. Martino, J., Brogna, C., Robles, S., Vergani, F. & Duffau, H. Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex* (2009).
41. Vallar, G. & Perani, D. The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia* **24**, 609-622 (1986).
42. Husain, M. & Kennard, C. Visual neglect associated with frontal lobe infarction. *J Neurol* **243**, 652-657 (1996).
43. Leibovitch, F.S., *et al.* Brain-behavior correlations in hemispatial neglect using CT and SPECT: the Sunnybrook Stroke Study. *Neurology* **50**, 901-908 (1998).
44. Karnath, H.O., Ferber, S. & Himmelbach, M. Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature* **411**, 950-953 (2001).
45. Mort, D.J., *et al.* The anatomy of visual neglect. *Brain* **126**, 1986-1997 (2003).
46. Karnath, H.O., Fruhmann Berger, M., Küker, W. & Rorden, C. The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. *Cereb Cortex* **14**, 1164-1172 (2004).
47. Corbetta, M., Kincade, M., Lewis, C., Snyder, A. & Sapir, A. Neural basis and recovery of spatial attention deficits in spatial neglect. *Nat Neurosci* **8**, 1603-1610 (2005).

48. Committeri, G., *et al.* Neural bases of personal and extrapersonal neglect in humans. *Brain* **130**, 431-441 (2007).
49. Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A. & Vuilleumier, P. Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. *Brain* **133**, 880-894 (2010).
50. Gharabaghi, A., Fruhmann Berger, M., Tatagiba, M. & Karnath, H.O. The role of the right superior temporal gyrus in visual search-insights from intraoperative electrical stimulation. *Neuropsychologia* **44**, 2578-2581 (2006).

CAPTIONS

Figure 1: Reconstruction of the three branches of the SLF: comparison between post-mortem axonal tracing in monkey (A)^{12, 13} and in vivo SD tractography in humans (B).

Figure 2: Side-by-side comparison of the SLF I (in red), II (in yellow) and III (in green) obtained after a virtual dissection of a human living brain (A) and a real dissection of a post-mortem brain (B).

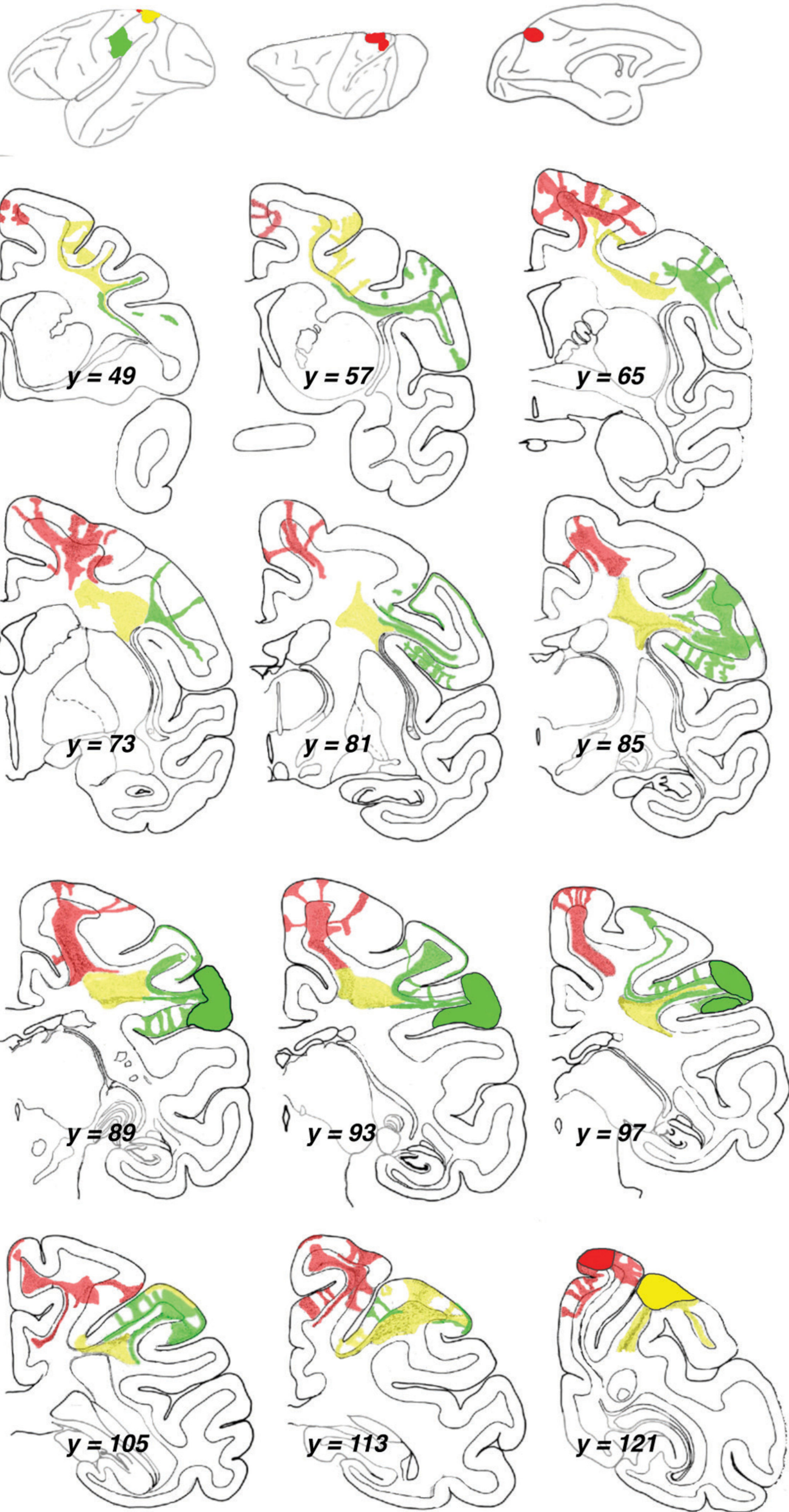
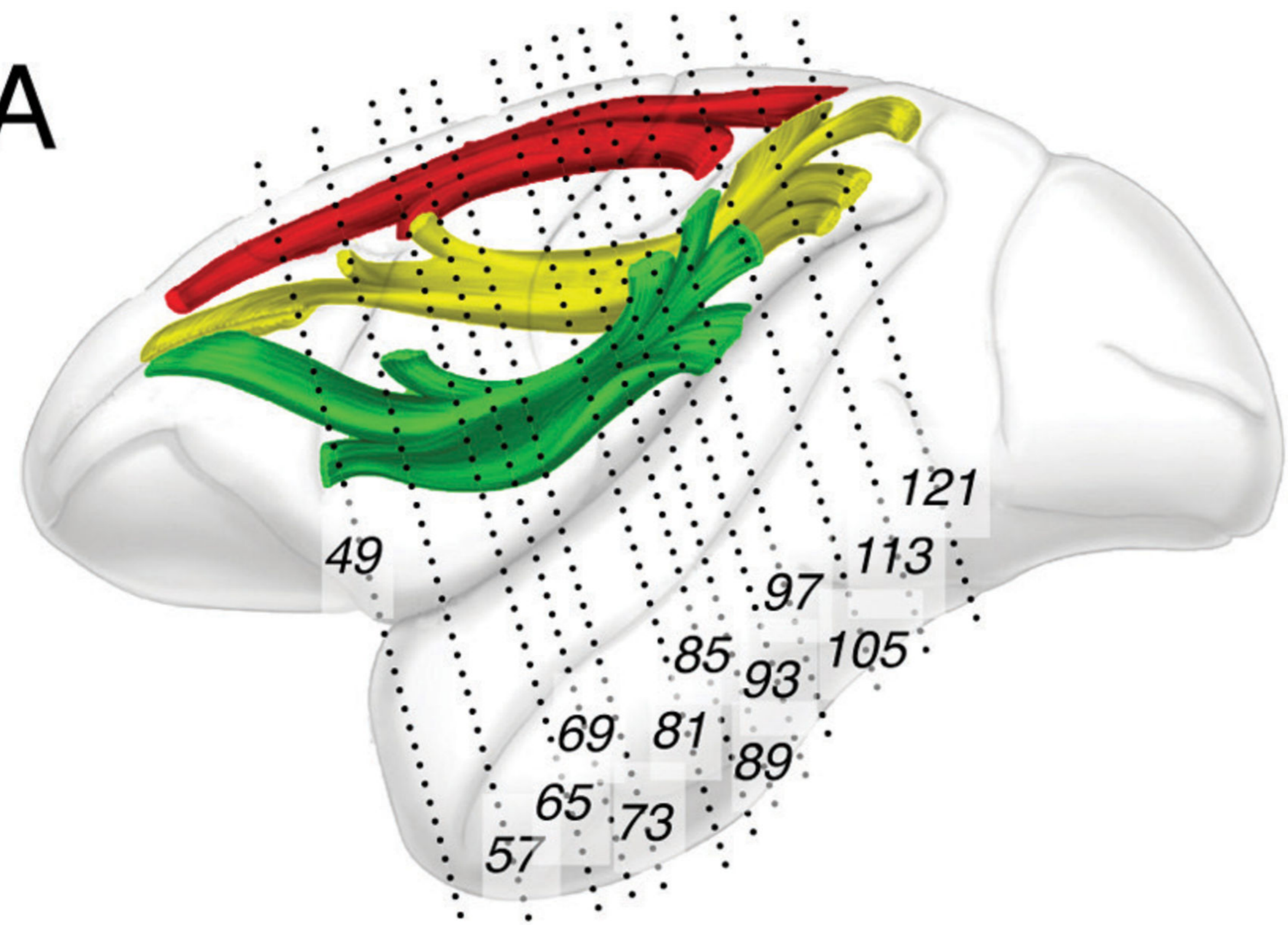
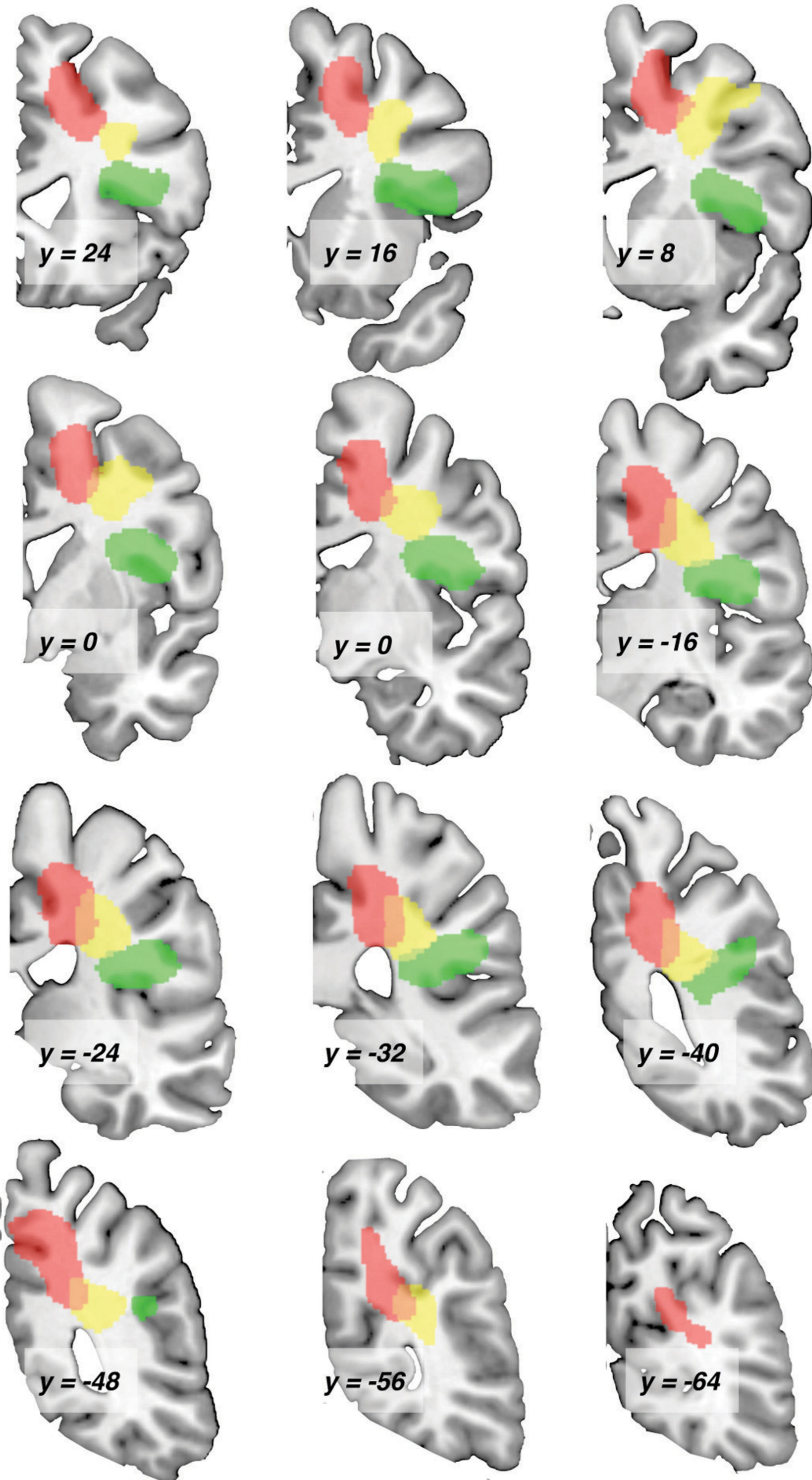
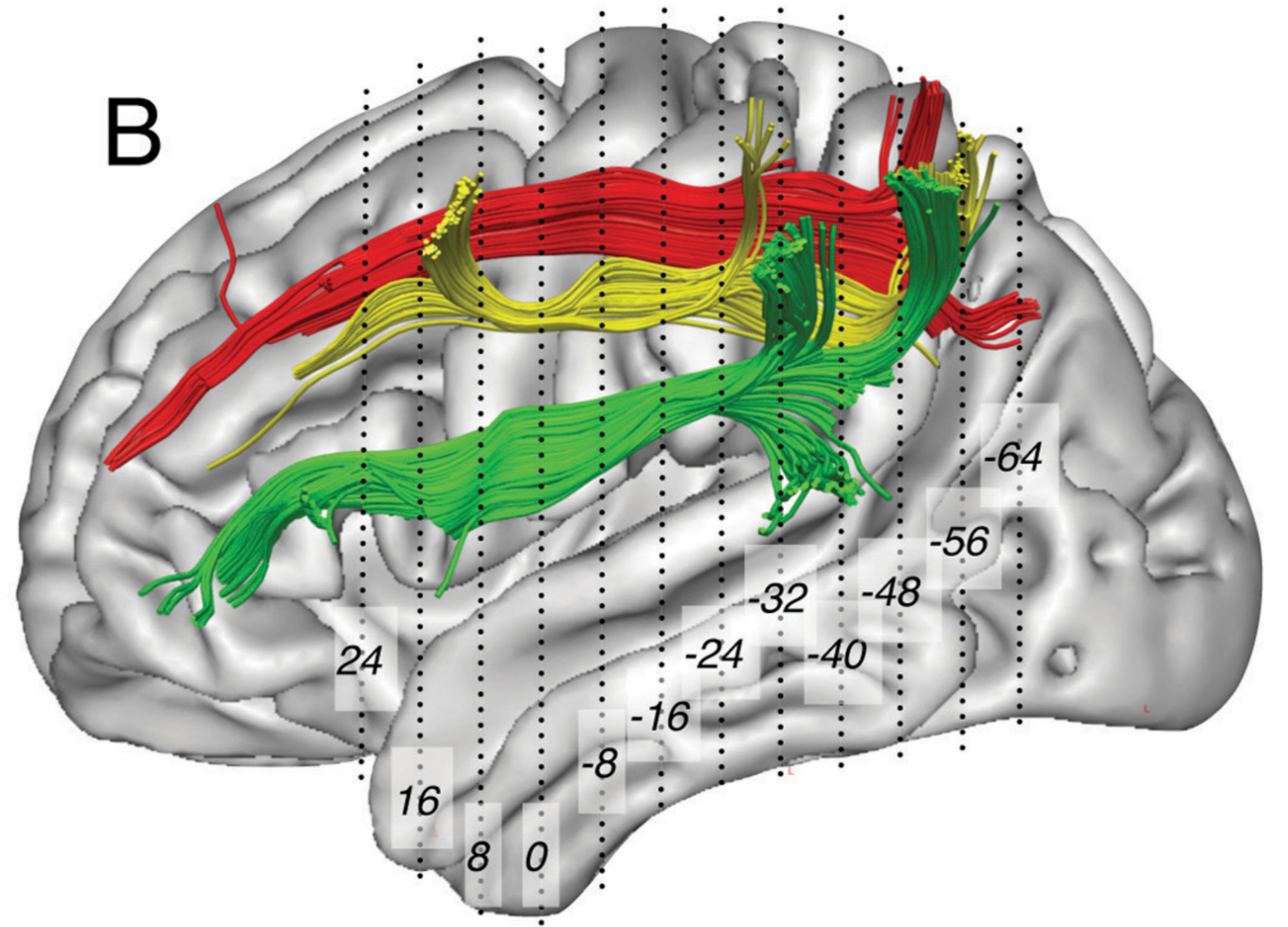
Figure 3: Volume lateralization of parieto-frontal pathways and behavioural correlates. (A) Top view of the three branches in an average brain. (B) Hemispheric lateralization of the three branches with 95% confidence intervals. (C) Diagrams of the two paradigms used. (D, F) Significant correlations between the lateralization of the SLF II and both, the deviation on the line bisection task (D) and the lateralization of the reaction time (F). (E) Performance on the line bisection task was positively correlated with the lateralization of the reaction time in the modified Posner's paradigm. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

Figure 4: The parieto-frontal networks for visuo-spatial attention as identified by tractography (A), functional neuroimaging (B) and brain lesion/electrical stimulation (C) studies. The SLF I projects to areas activated in tasks requiring controlled goal directed attention, whereas the SLF III projects towards areas activated during tasks requiring automatic reorienting of spatial attention to unexpected stimuli. The cortical projections of the SLF II overlap with both dorsal and ventral functional networks (B

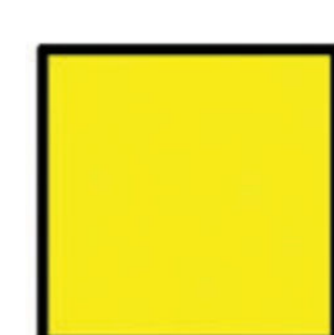
adapted from⁴). Disorders of spatial attention are frequently associated with either cortical or subcortical lesions of the ventral parieto-frontal network (C) a⁴¹, b⁴², c⁴³, d⁴⁴, e⁴⁵, f⁴⁶, g³², h⁴⁷, i⁵⁰, j⁴⁸, k⁴⁹. IPs: intraparietal sulcus; SPL: superior parietal lobule, FEF: frontal eye field, TPJ: temporo-parietal junction, IPL: inferior parietal lobule, STg: superior temporal gyrus, VCF: ventral frontal cortex, IFg: inferior frontal gyrus, MFg: middle frontal gyrus.

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A**B**

SLF I

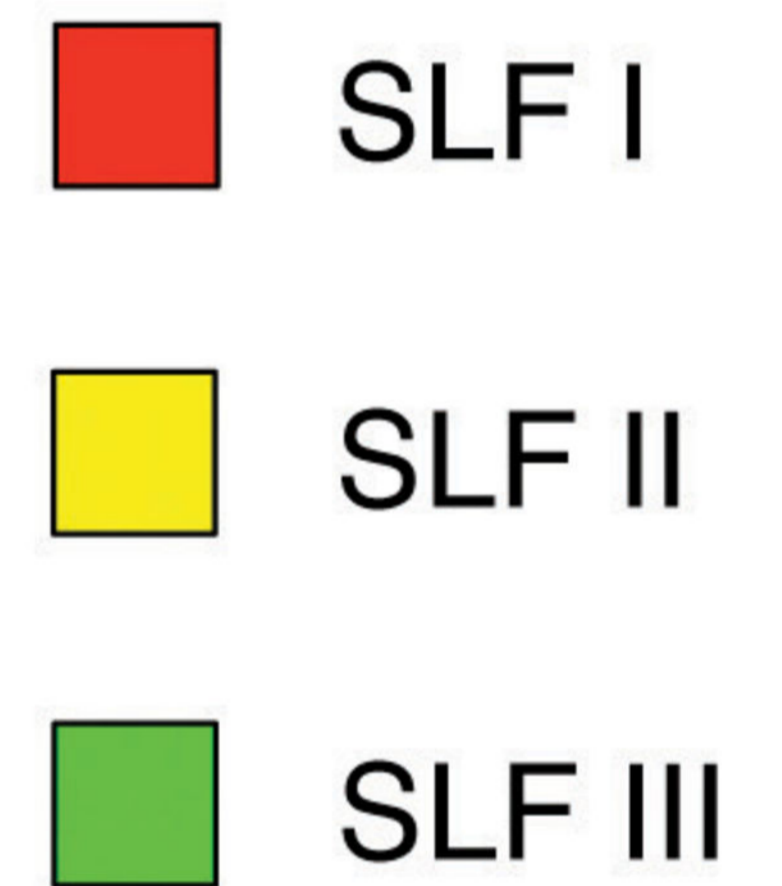
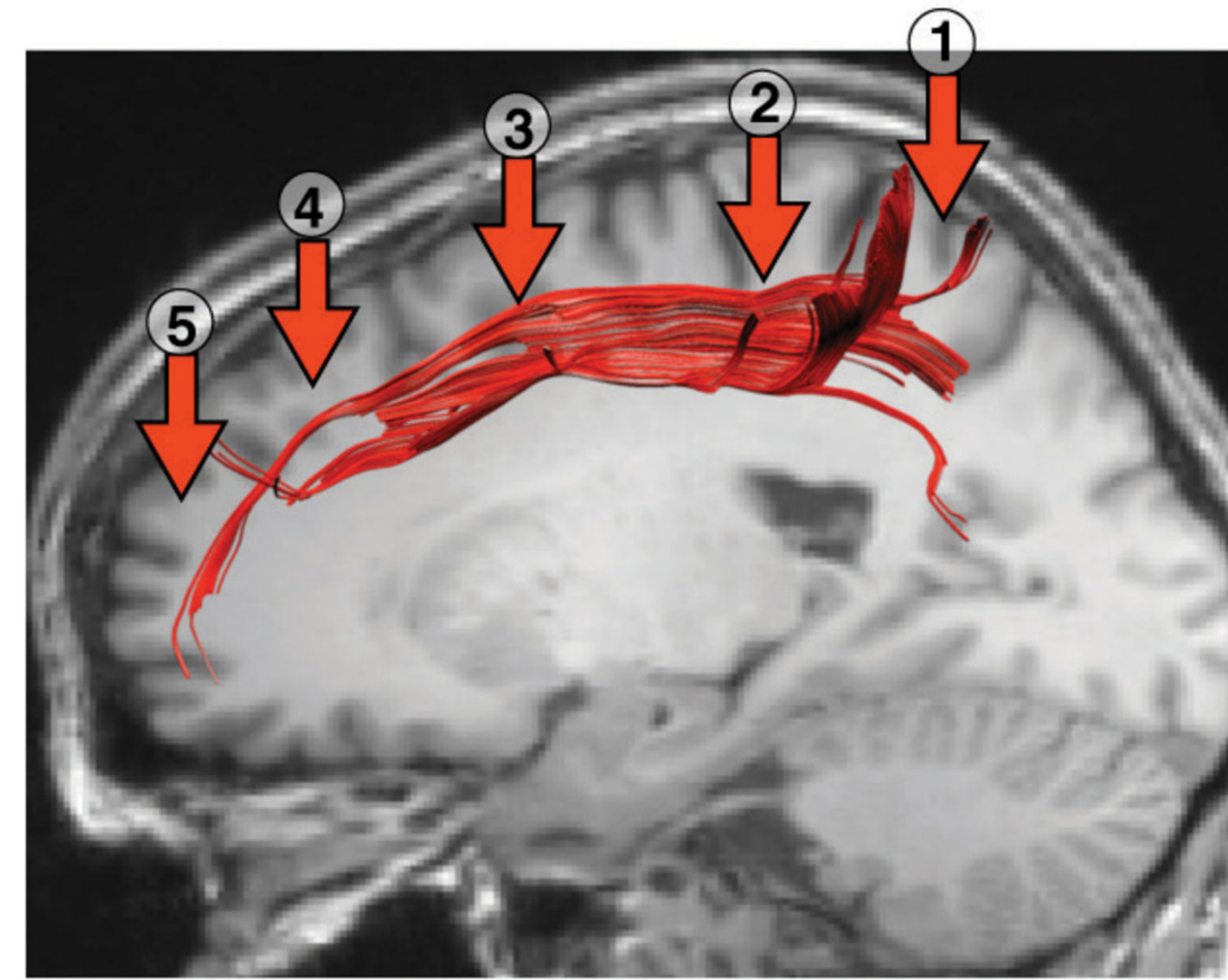
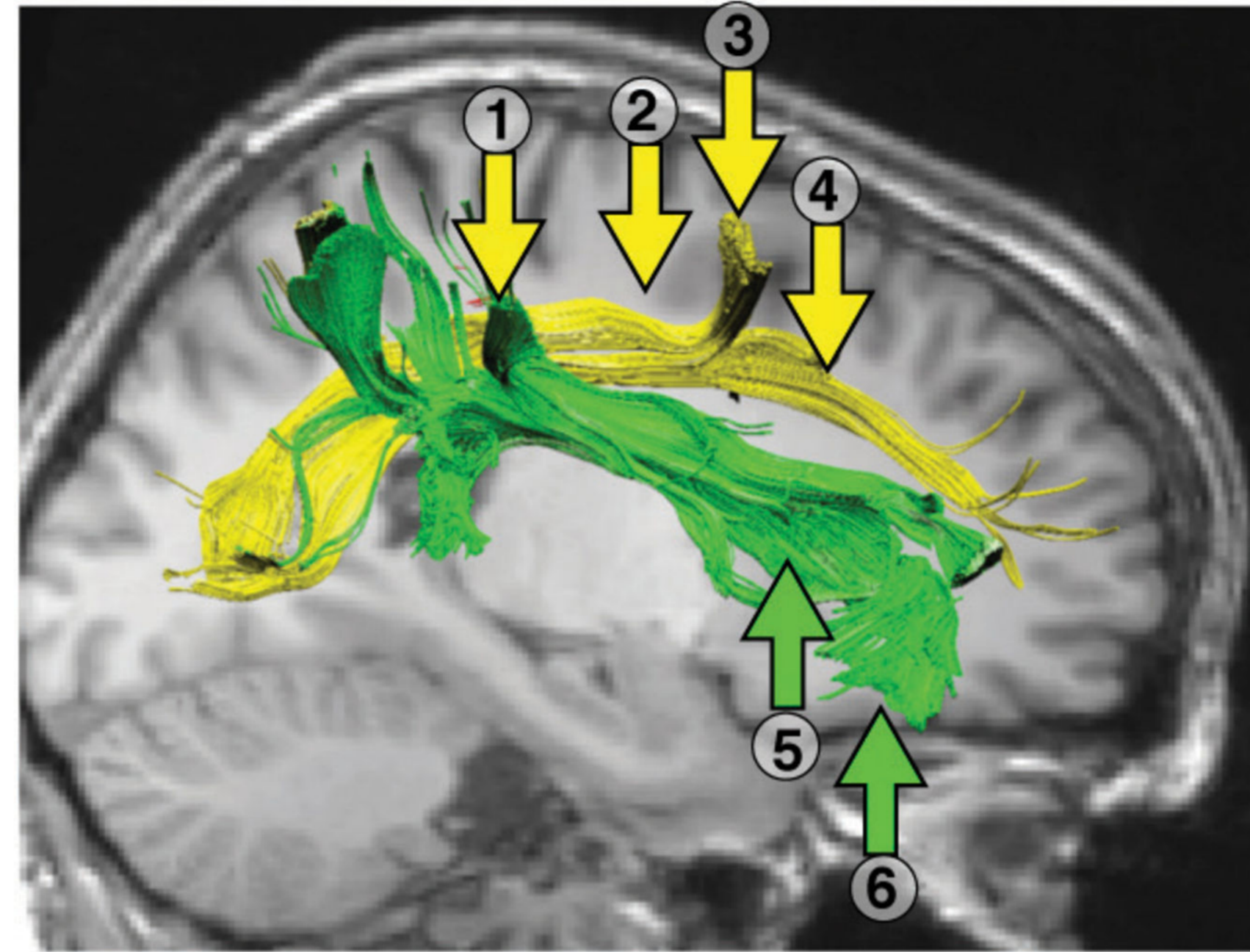
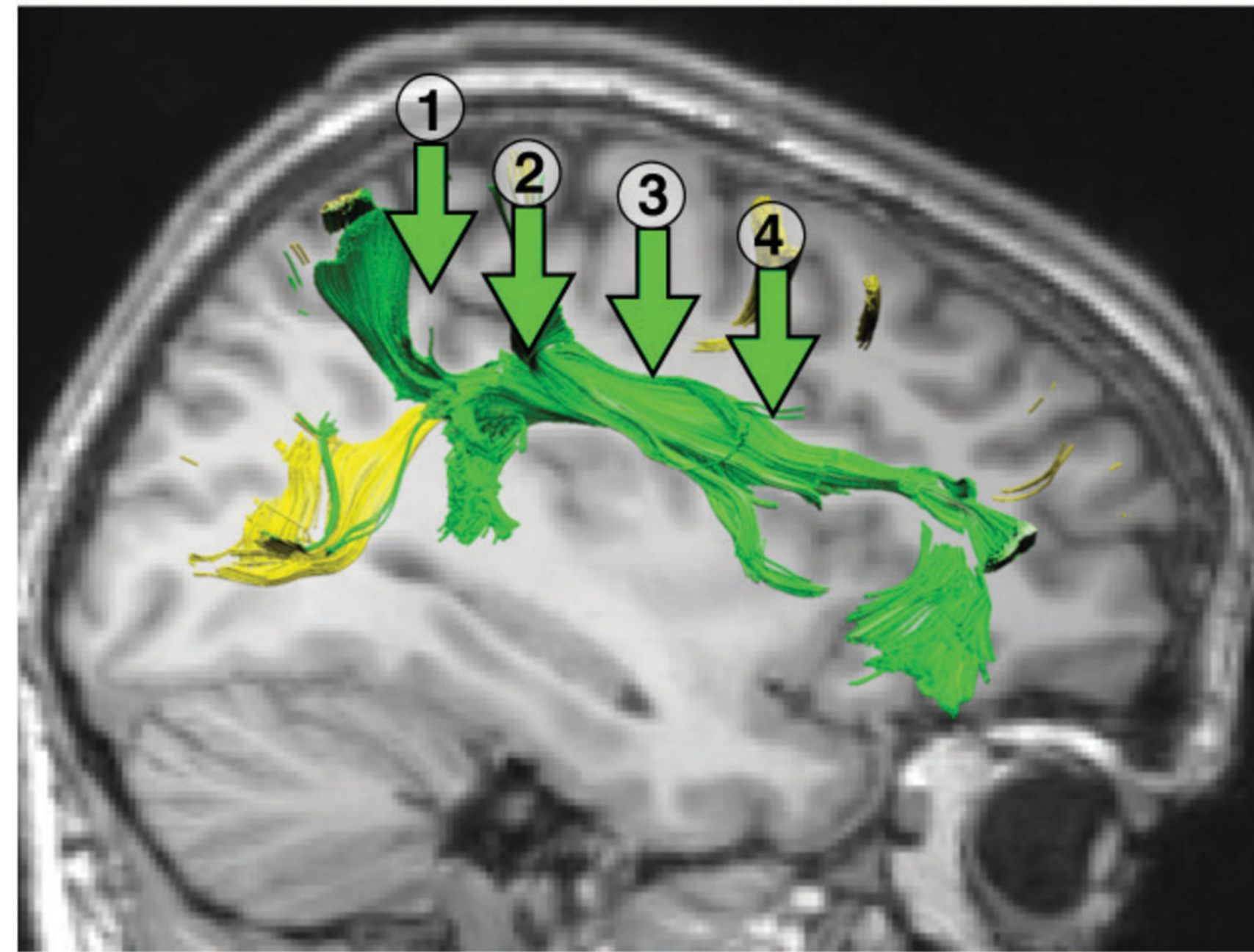


SLF II

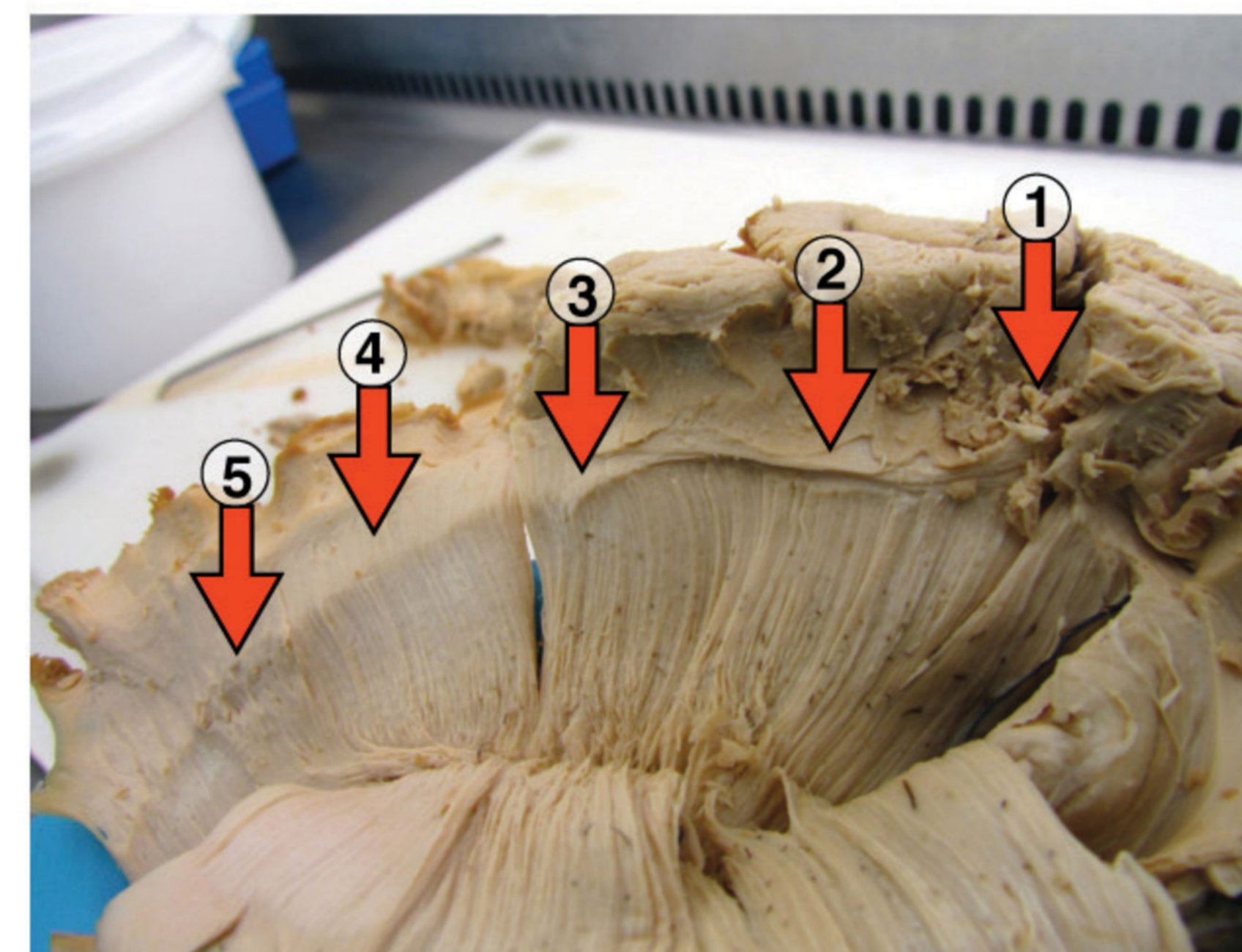
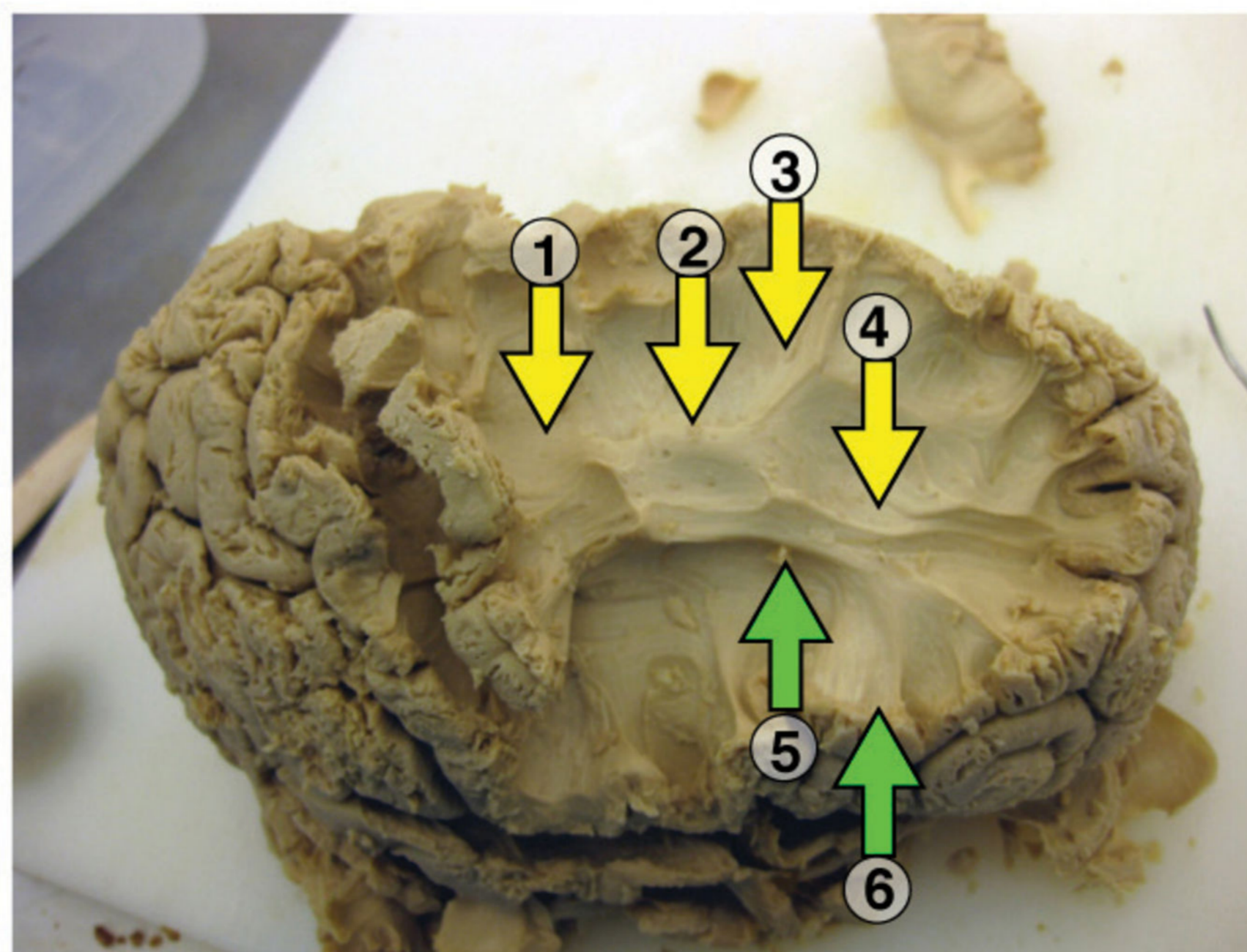
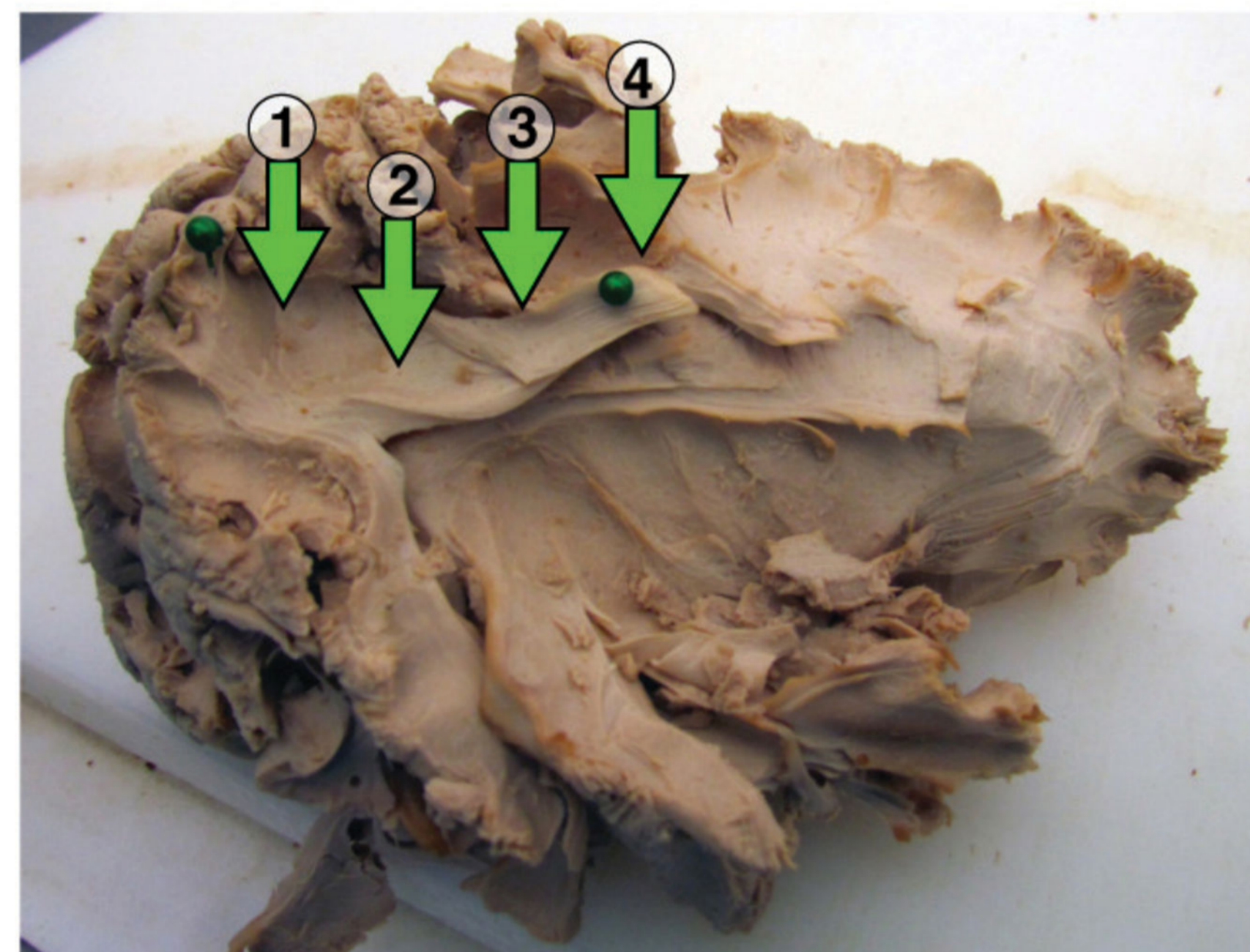


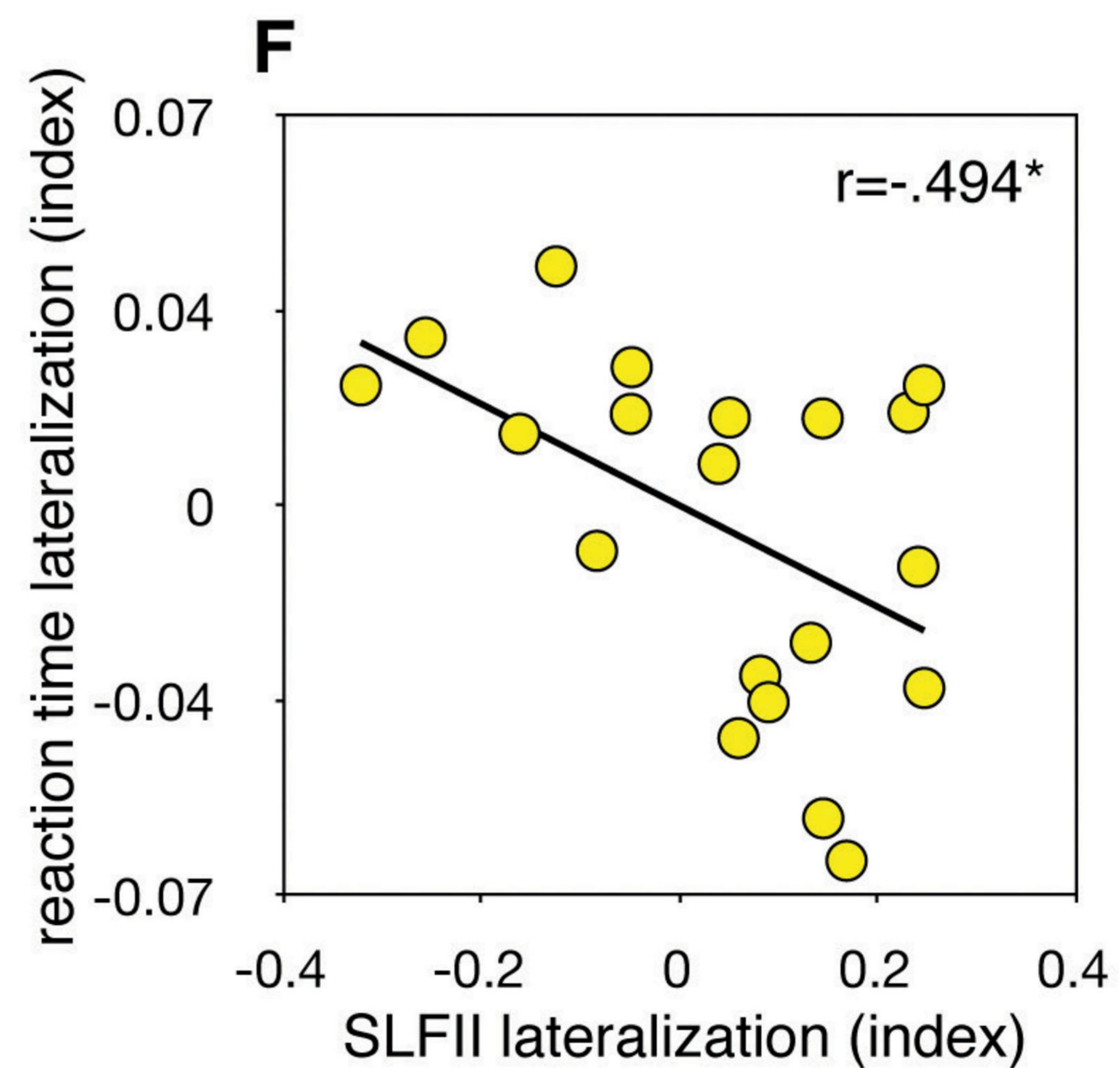
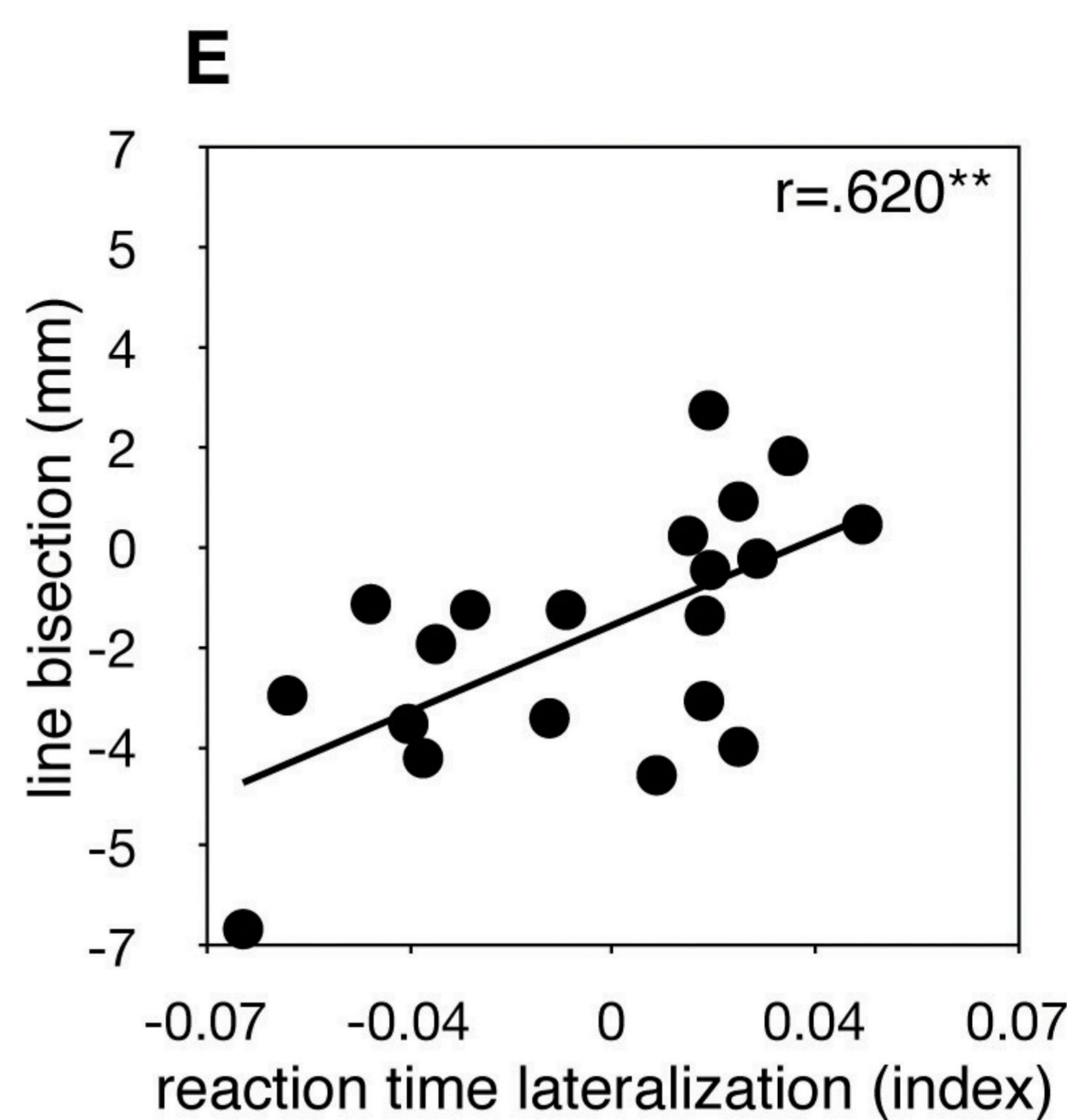
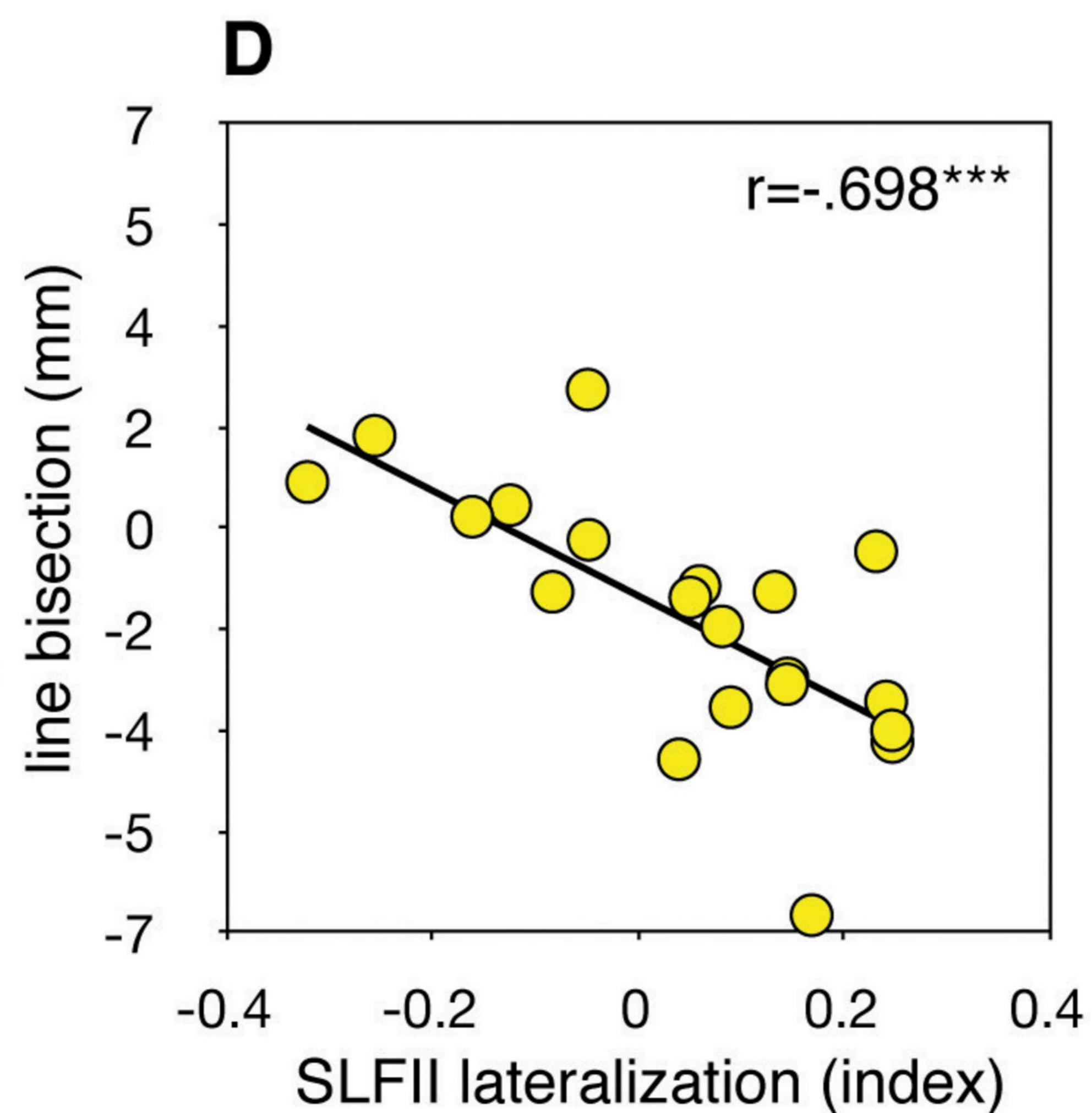
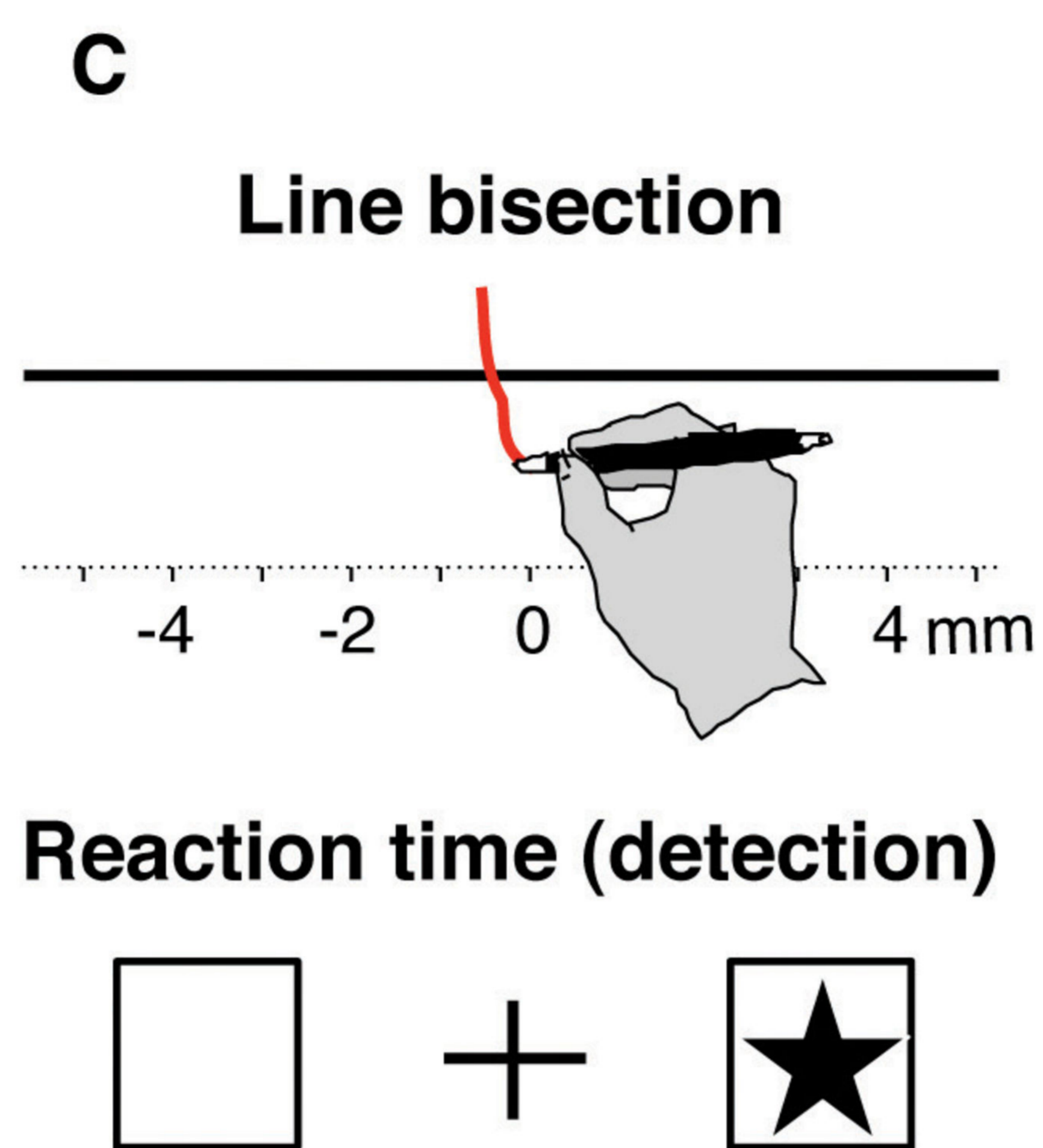
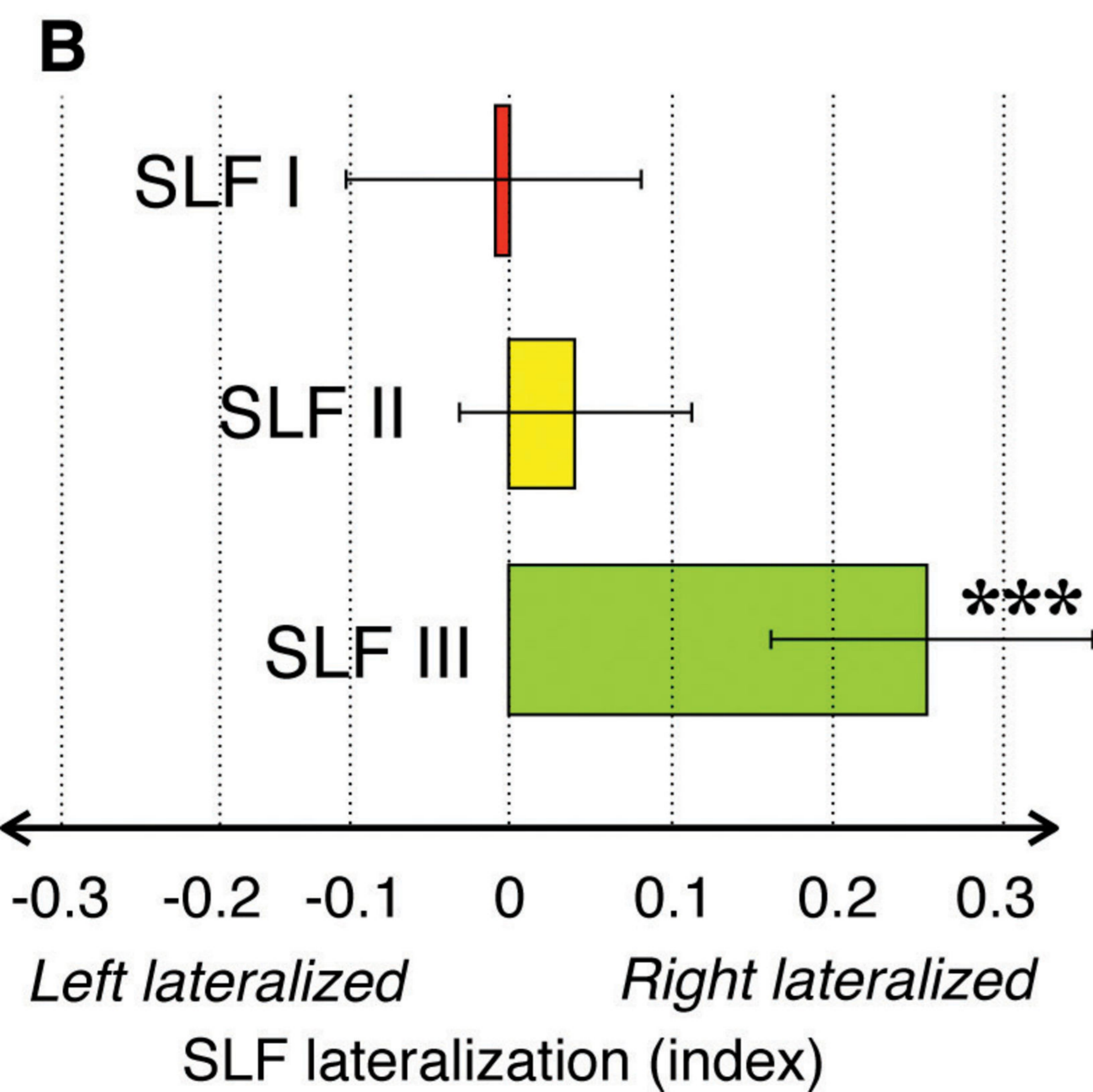
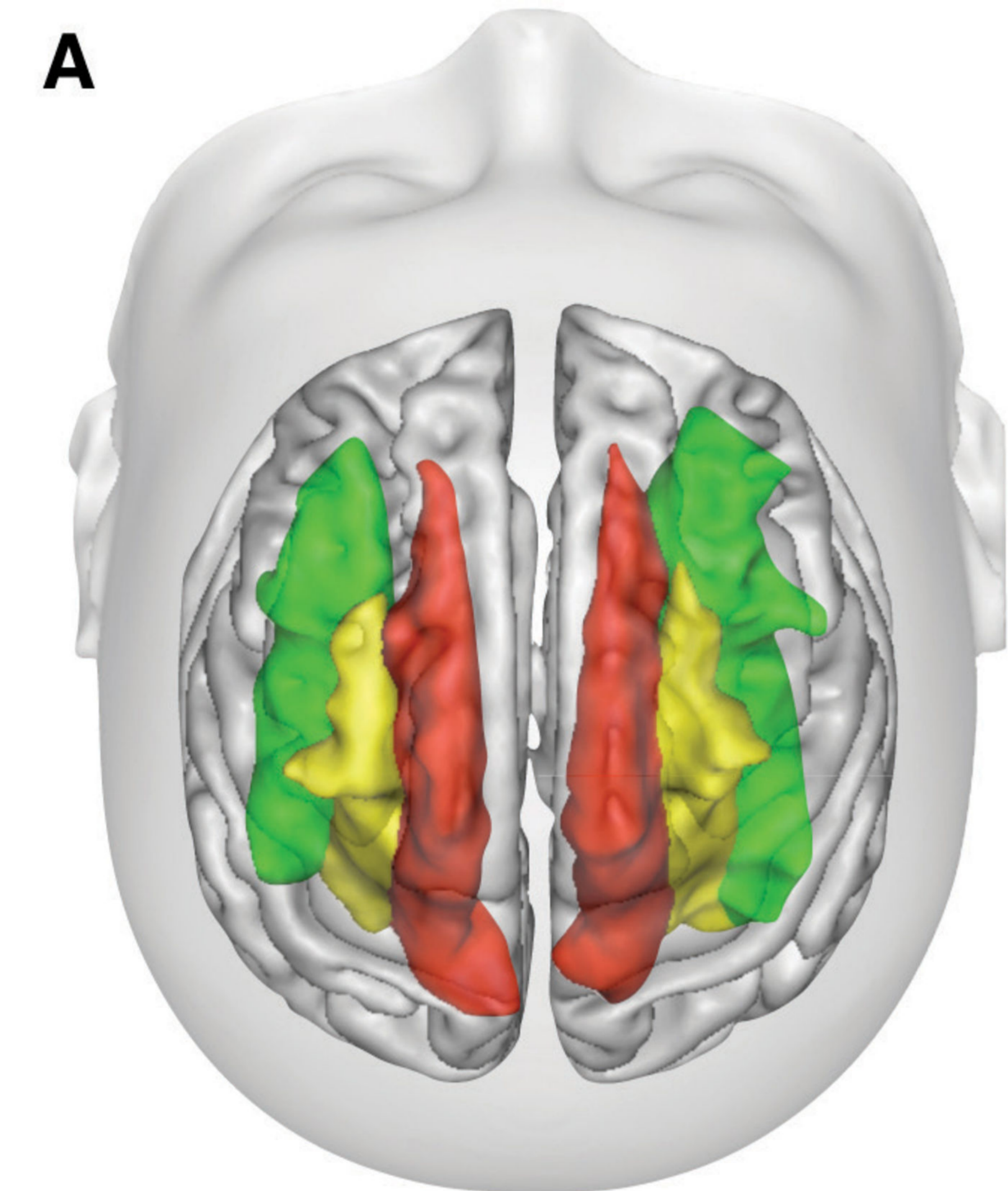
SLF III

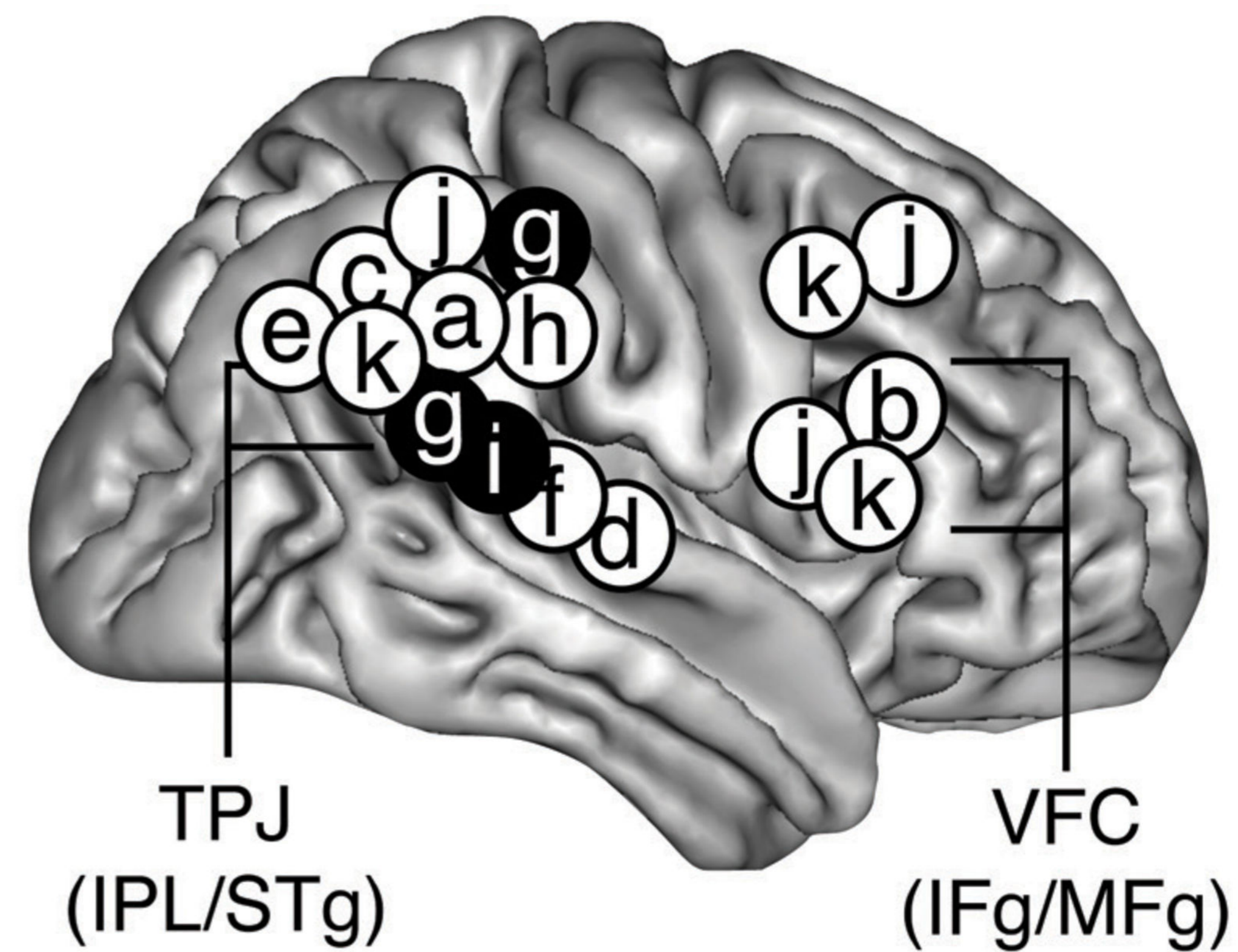
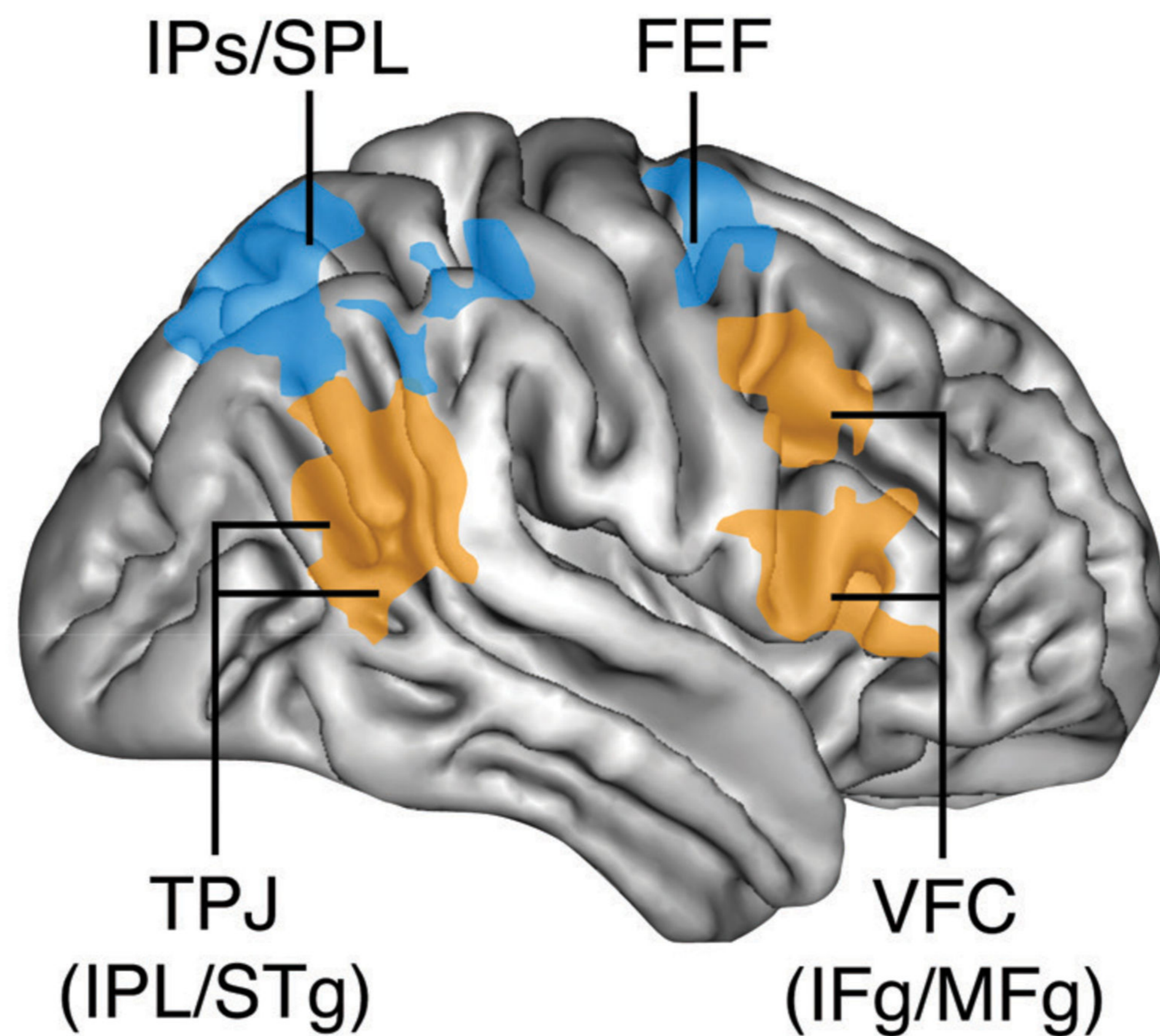
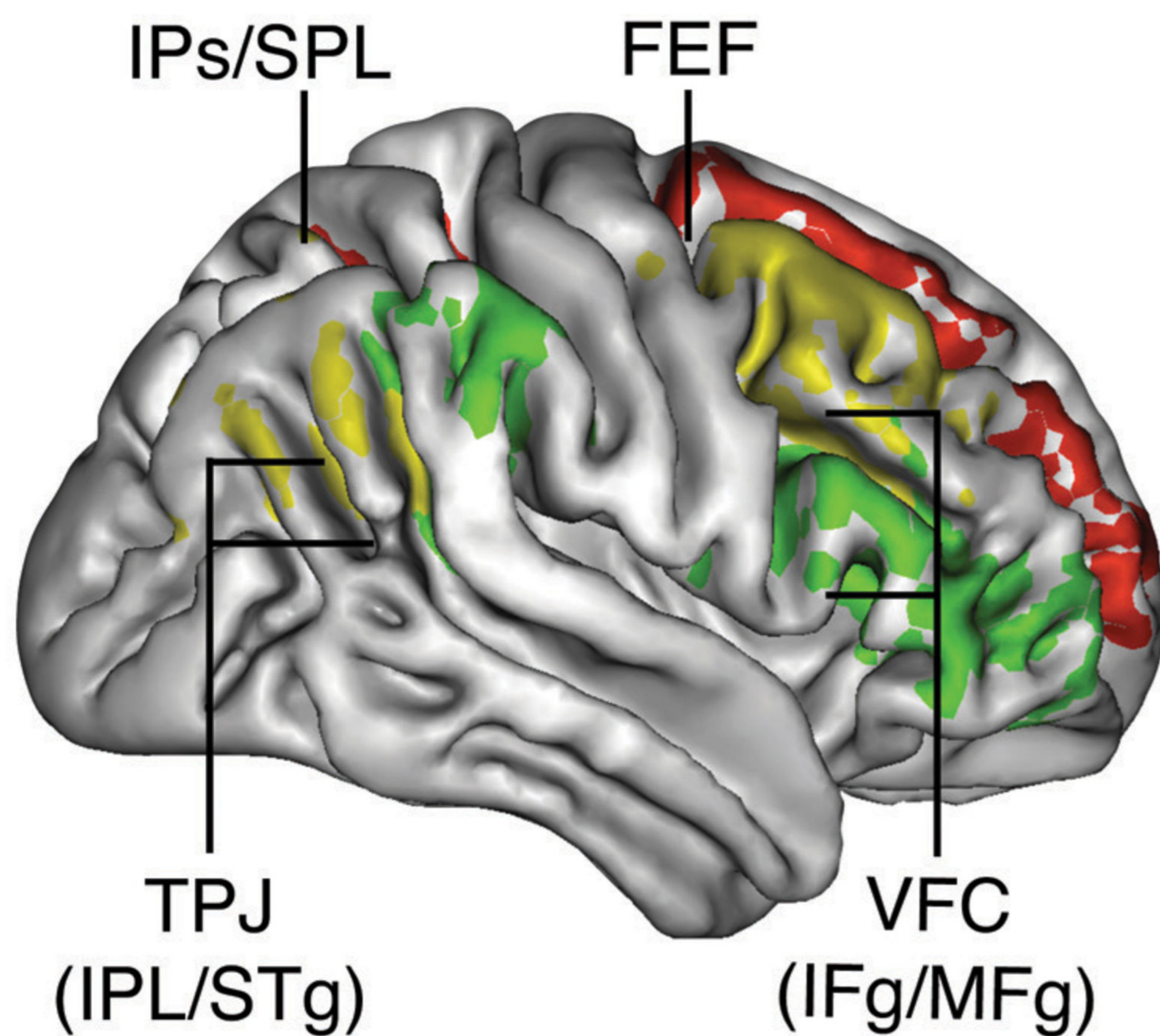
A: In Vivo tractography



B: Post-mortem histology







A CORTICAL AREAS CONNECTED BY THE SLF I,II and III

- Projections of the SLF I
- Projections of the SLF II
- Projections of the SLF III

B CORTICAL AREAS INVOLVED IN SPATIAL ATTENTION

- **Controlled goal directed attention:**
strategic and voluntary orienting of attention towards visual targets
- **Grabbed stimulus driven attention:**
Unexpected and automatic orienting of attention towards visual targets

C CORTICAL AREAS DAMAGED IN SPATIAL NEGLECT

- electrical stimulation studies
- lesion overlapping studies