

## Evidence of cerebral reorganization following perinatal stroke demonstrated with fMRI and DTI tractography

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### Abstract

A 44-year-old man with a left perinatal stroke and recurrent refractory epilepsy underwent functional MRI (fMRI) for motor and language mapping to determine if further epilepsy surgery could be performed without loss of language. Language was activated excessively in the right hemisphere, with only small areas of left hemisphere activation. This suggests bilateral language dominance acquired secondary to the perinatal stroke with the right hemisphere activation resulting from neonatal neuronal reorganization. Functional data were overlaid onto 3D diffusion tensor tractography, providing a unique image of the right hemisphere language recruitment.

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### 1. Introduction

Hemispheric function shifting to the undamaged non-dominant hemisphere after a dominant hemisphere insult has been confirmed with functional imaging, such as positron emission tomography (PET) and transcranial magnetic stimulation (TMS) [1]. Likewise, the phenomenon has been more recently documented with functional MRI (fMRI) showing the nondominant hemisphere acquiring dominance or codominance in motor, visual, auditory and language functions [2–4] following stroke or brain damage in the adult. Perinatal stroke has been less investigated with fMRI, but motor reorganization is well described [3,5,6]. The ability of the nondominant hemisphere to acquire language largely depends on the age at

the time of injury, with early childhood injuries resulting in better language abilities [7]. fMRI verification of language plasticity is rarer and has been described in a 9-year-old child following left hemispherotomy for epilepsy [2]. Bilateral language compensation in an adult with infantile brain damage has been documented with PET [8] but not fMRI.

Diffusion tensor imaging (DTI) is a relatively new MRI technique which diagrams white matter tracts and has rarely been utilized with fMRI [9]. 3D tractography is a further development of DTI, which provides further exquisite anatomic definition of the white matter tracts and has yet to be applied to the study of stroke or epilepsy.

The current authors describe a case in which codominant language activation was documented on fMRI in an adult patient with a history of left perinatal stroke and left anterior temporal lobe resection for epilepsy at the age of 37. The 3D DTI tractography revealed a paucity of left hemisphere fiber tracts, consistent with the old stroke and surgical resection. On the right, normal tracts were seen leading to the eloquent cortex documented with the overlaid fMRI data.

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## 2. Case Report

A 44-year-old ambidextrous man with a history of medically refractory epilepsy and left anterior temporal lobectomy was referred for fMRI motor and language mapping to determine if he was a candidate for further epilepsy surgery. The patient had complex partial seizures with an onset at 12 years of age. No language or motor deficits were identified. He was medically managed with phenobarbital and phenytoin and was seizure-free between the ages of 15 and 23 years. At the age of 23, he began experiencing complex partial seizures. Video electroencephalography at the time revealed a left-sided temporal–parietal focus. The MRI revealed encephalomalacia in the left temporal–parietal area, which was attributed to a stroke sustained in the perinatal period. At age 37, the patient underwent an anterior temporal lobectomy with radical hippocampectomy and multiple subpial transections in the posterior portion of the superior temporal gyrus. Prior to the surgery, an intracarotid amobarbital procedure (IAP) demonstrated bilateral language dominance, with the left hemisphere representation slightly stronger than that of the right hemisphere. Following the operation, the patient experienced a significant decrease in the frequency of seizures until age 39, at which time he began to have frequent simple partial and occasional complex partial seizures. At age 42, he underwent repeat neuropsychological evaluation for possible additional left hemisphere epilepsy surgery. The IAP done at this time found primary language dominance in the left hemisphere, although language functioning in the right hemisphere could not be excluded.

The patient's fMRI was performed on a 3T General Electric (Milwaukee, WI, USA) scanner with blood oxygenation level dependent (BOLD) images obtained using an axial single-shot gradient echo planar imaging (EPI) sequence with a resolution of  $64 \times 64$  and a slice thickness of 5 mm to cover a volume of  $220 \times 220 \times 150 \text{ mm}^3$  with a TE/TR=40/3000 ms and a flip angle of  $90^\circ$ . The fMRIs consisted of runs of 30 s of rest followed by 30 s of activity, repeated three times, with an additional rest period at the end. The runs were as follows: (1) motor, bilateral feet tapping (displayed correlation range=.5–.8,  $P < .01$ ); (2) motor, bilateral tapping of the thumb against index, middle and ring fingers sequentially (displayed correlation range=.6–.9,  $P < .01$ ); (3) language, silent word generation to given consonants (displayed correlation range=.5–.8,  $P < .01$ ); and (4) language, silent rhyming to given words (displayed correlation range=.5–.8,  $P < .01$ ). The images were reconstructed and motion corrected, and the correlation coefficient between the ideal activation/rest time course and the measured data was calculated for each voxel in the image. Voxels with correlation coefficients higher than the threshold minimum were colored from red (minimum) to yellow (maximum). Finally, the data were overlaid onto T1 anatomical images and 3D diffusion tensor tractography.

Prior to the performance of the fMRI paradigms, diagnostic imaging was performed with sagittal T1-weighted, axial T1-weighted, axial FLAIR, axial T2-weighted and 3D axial spoiled gradient-echo sequences.

Diffusion tensor data were acquired using a diffusion-weighted single-shot spin-echo EPI sequence with TE/TR=100/1200 ms. Diffusion weighting was applied in 13 unique directions and their inverses, along with six images with no diffusion weighting, to give a total of 32 acquisitions. The  $b$  values varied from 815 to 1152  $\text{s/mm}^2$ , depending on the diffusion weighting direction. Data were acquired at a resolution of  $128 \times 128 \times 60$  to cover a volume of  $220 \times 220 \times 150 \text{ mm}^3$  (voxel size= $1.7 \times 1.7 \times 2.5 \text{ mm}^3$ ), corresponding to the previous anatomical and functional scans. Following image reconstruction, the diffusion tensor was calculated for each voxel in the volume using a least-squares fitting algorithm. Measures of the diffusion trace, relative anisotropy and the direction of maximum diffusion are derived from the tensor on a voxel-by-voxel basis. The tracking algorithm uses a method similar to that published by Mori et al. [10]. From a seed point, a line is generated in the direction of maximum diffusion and continues from one voxel to the next, until the relative anisotropy falls below some threshold value. This is repeated for different seed points.

Diagnostic imaging visualized the hypoplasia of the left hemisphere with encephalomalacia involving the left temporal, frontal and parietal lobes. The left cranial vault was small. There was a prior resection of the left anterior temporal lobe and hippocampus (Fig. 1). There was a metallic susceptibility artifact underlying the craniotomy flap, which distorted the EPI sequence in the region of the adjacent left temporal frontal cortex.

The word generation paradigm is designed to produce and record signal intensity in the area of the brain responsible for expressive language (Broca's area). Marked activation was identified in the right mid to inferior frontal lobe cortex

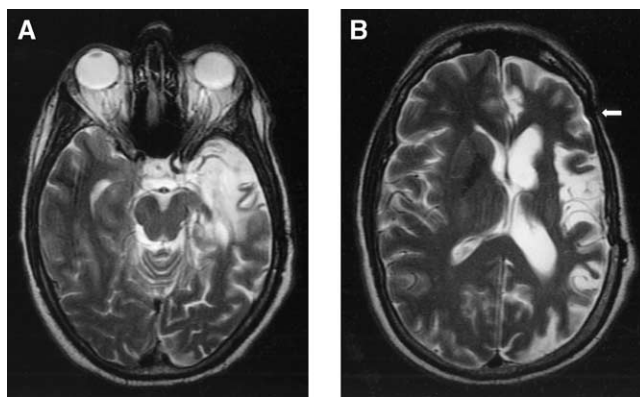


Fig. 1. (A) Axial T2-weighted imaging at the level of the temporal lobe demonstrates a hypoplastic left hemisphere with cortical encephalomalacia. (B) Axial T2-weighted image at the level of the left operculum reveals the left frontal craniotomy with susceptibility artifact at the anterior margin (arrow).

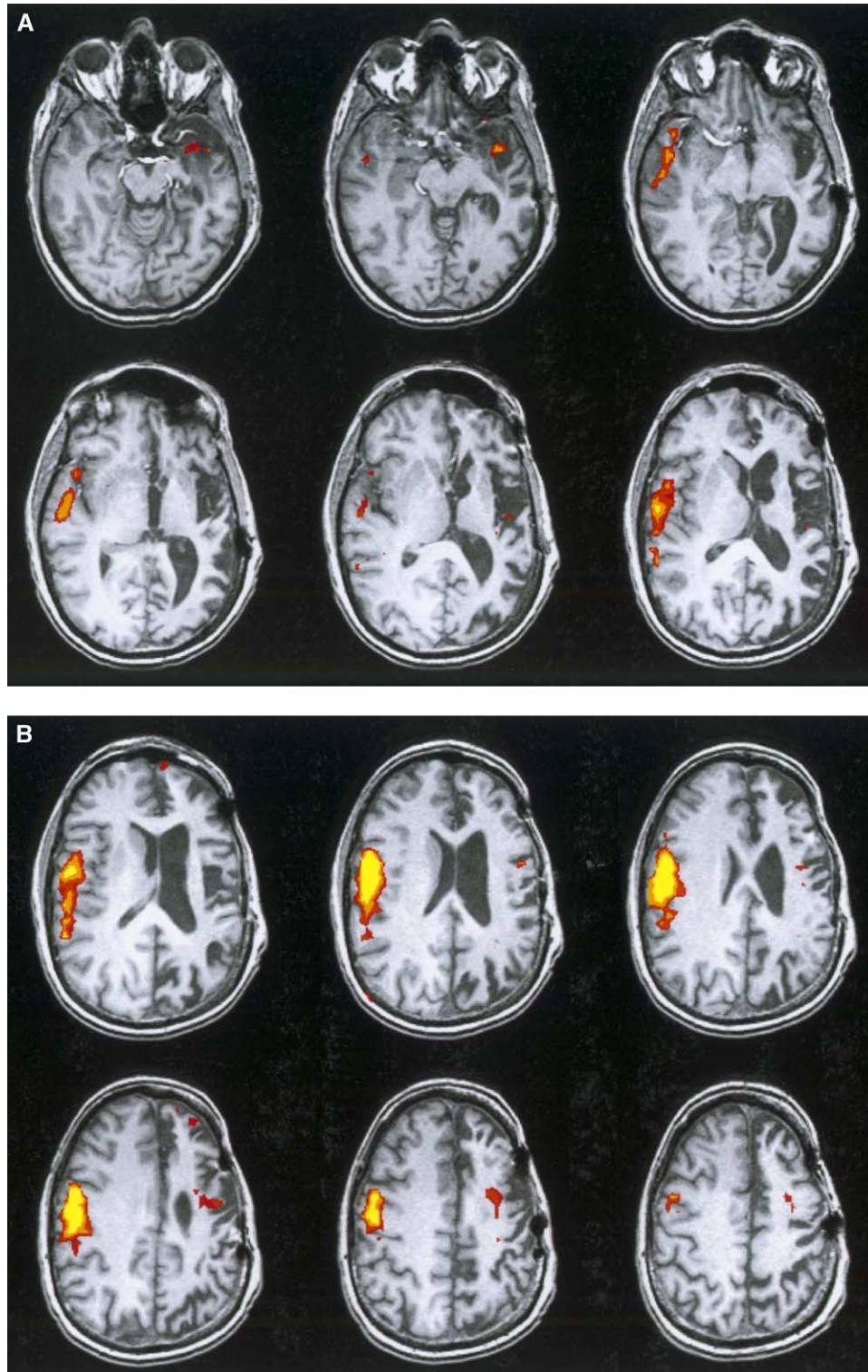


Fig. 2. fMRI data from the language rhyming paradigm overlaid onto T1 images. (A) Axial T1 fMRI images through the middle cranial fossa demonstrate bilateral language activation in the left anterior temporal lobe, right temporal lobe and in the right anterior frontal lobe. (B) Axial T1 fMRI images through the more superior aspect of the hemispheres reveal an unusually large area of right frontal lobe activation. (C) Sagittal T1 fMRI images displaying the large area of right frontal lobe activation with a small area of activation in the superior temporal lobe gyrus below the Sylvian fissure.

(Broca's area), as well as the right anterior–superior temporal lobe gyrus. A significant but small focus of activation was also seen in the left posterior temporal area corresponding to

Wernicke's area. While no significant left frontal activation was identified with this paradigm, the susceptibility artifact obscured the pertinent areas of the left cortex.

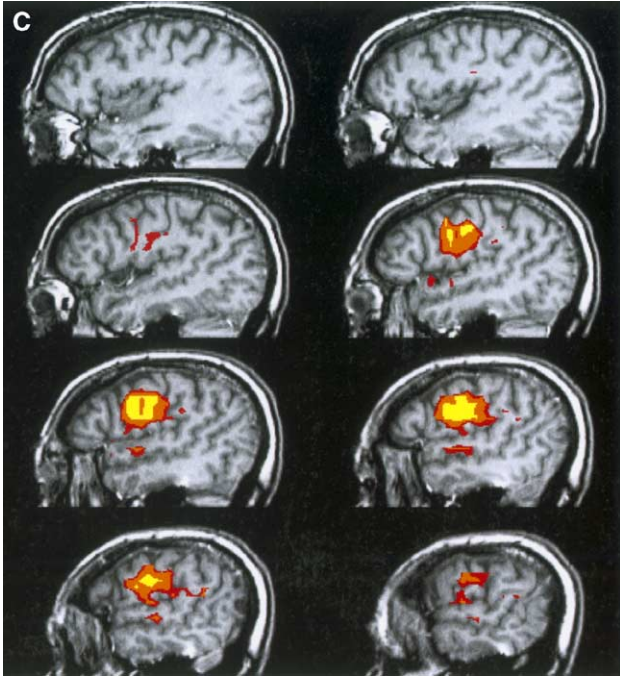


Fig. 2 (continued).

The rhyming paradigm helps assess the phonologic component of language and will normally activate both Broca's and Wernicke's areas. A very large area of the right frontal cortex was activated with this paradigm, including the entire right insular lobe, mid and inferior right frontal lobe cortex (Broca's area), as well as the right anterior–superior temporal lobe gyrus and left posterior temporal lobe cortex (Wernicke's area). Small but statistically significant foci of activation were seen involving the left frontal lobe in the anterior and superior margins of the

encephalomalacic insular cortex, as well as a focus in the medial aspect of the left anterior temporal lobe at the medial margin of the previous resection (Fig. 2). It is assumed that some left hemisphere activation may have been unrecorded due to the susceptibility artifact obscuring the left frontal and temporal cortices.

Tractography revealed a paucity of fibers going to the left hemisphere consistent with the cortical encephalomalacia typical of a perinatal stroke. The white matter fibers tracking into the right hemisphere were more numerous and extended closer to the corticomedullary junction than in the damaged left hemisphere but were not qualitatively more than the current authors have seen in normal hemispheres (Fig. 3).

### 3. Discussion

Cortical reorganization following brain damage is well documented clinically, with the greatest plasticity and recovery seen in the perinatal period [11]. This structural rerouting is now being investigated with various functional imaging techniques [1]. The current authors report fMRI documenting the presence of bilateral language activation in a man with a left hemisphere perinatal stroke plus left temporal epilepsy surgery (Fig. 1). The amount of language activation in the right hemisphere was greater than that seen in a normal right or left language hemisphere dominant individual (Fig. 2). It appears that cortical reorganization requires more extensive cortical recruitment [2,12]. The size of the right hemisphere activation suggests that the patient was not originally right hemisphere dominant or even codominant. It is further believed that the patient was originally left language dominant, and subsequently, compensatory sprouting to the right hemisphere occurred

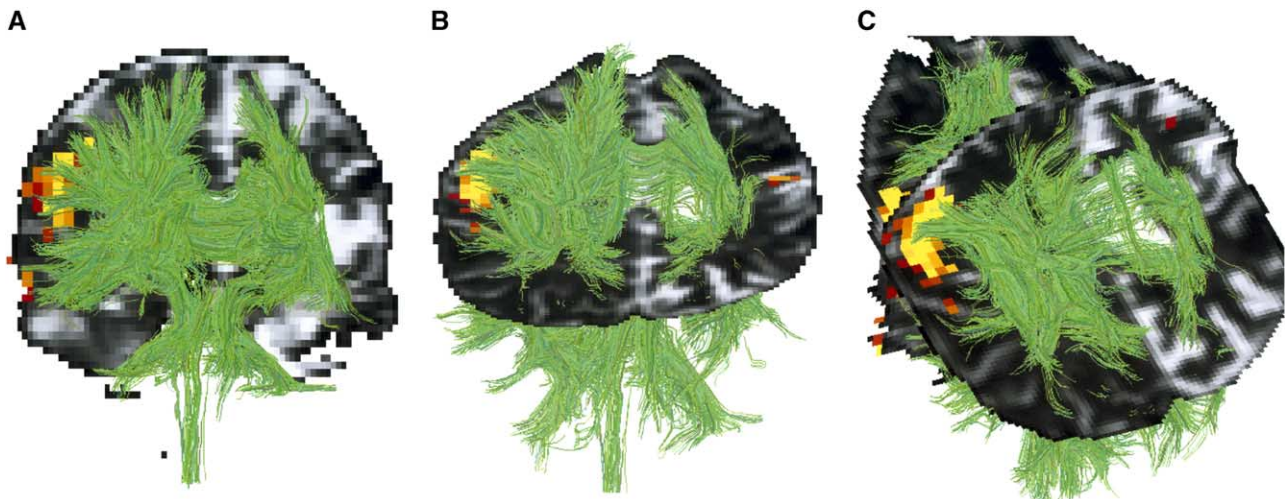


Fig. 3. Three-dimensional DTI tractography overlaid onto both a fitted T2-weighted EPI image and the fMRI data from the language rhyming paradigm. (A) Coronal view. (B) Axial view. (C) Single axial and coronal combined images (frontal lobes in the upper left hand corner).

following the perinatal stroke. Significant left temporal activation also was seen (Fig. 2), despite the left temporal lobe craniotomy creating susceptibility artifact in the region. These fMRI results concur with the patient's initial IAP results of codominant language. The postoperative IAP suggested that the patient was left dominant, but right-sided language could not be excluded, and the fMRI still supports the presence of significant left hemisphere activation. The patient had no detectable language abnormality in childhood or following his surgery.

fMRI is being used with increasing frequency to document language dominance. While it has not replaced the preoperative gold standard of IAP, its noninvasiveness is particularly appealing, especially in children. Equivocal IAP results may be an indication for fMRI language mapping. In addition, IAP cannot localize the cortical location for language within a hemisphere, and here, fMRI has the advantage. fMRI results of language location are beginning to be compared with the results of intraoperative mapping using direct cortical stimulation [13]. Published comparisons reveal conflicting results, with excellent concordance found by some [14] and more equivocal results by others [15]. Our results found more left-sided activation with the rhyming paradigm than with word generation alone. Currently, fMRI language mapping certainly cannot replace direct cortical stimulation, but the potential exists. fMRI can also be used to study longitudinal language development.

Experimental work in multiple neonatal animal species has shown that, following unilateral cortical ablation, axonal sprouting occurs from the opposite spared hemispheric cortex [16]. However, even adult rats with an induced ischemic lesion of the sensorimotor cortex had marked axonal sprouting from the contralateral homotypic cortex into the denervated striatum [17]. This suggests that our patient may have been able to further reorganize his language cortex following the left temporal lobe resection. However, the lack of a language deficit following his resection makes this unlikely and implies that all language reorganization occurred earlier.

The utility of mapping white matter fibers with DTI tractography is just beginning to be appreciated. It has been used to investigate such anatomic abnormalities as neuronal migrational abnormalities, cerebral neoplasm and traumatic white matter injury [18].

Overlaying the functional (i.e., cortical) MRI data over the 3D white matter tractography creates a unique map of the cerebral hemisphere incorporating both functional and anatomic data ideal for preoperative localization (Fig. 3). This case illustrates that many powerful anatomic applications have yet to be made in the preoperative analysis of brain tumors and epilepsy.

## References

- [1] Rijntjes M, Weiller C. Recovery of motor and language abilities after stroke: the contribution of functional imaging. *Prog Neurobiol* 2002;66:109–22.
- [2] Hertz-Pannier L, Chiron C, Jambaque I, Renaux-Kieffer V, Van de Moortele P, Delalande O, Fohlen M, Brunelle F, Le Bihan D. Late plasticity for language in a child's non-dominant hemisphere: a pre- and post-surgery fMRI study. *Brain* 2002;125(2):361–72.
- [3] Rutten G, Ramsey N, van Rijen P, Franssen H, van Veelen C. Interhemispheric reorganization of motor hand function to the primary motor cortex predicted with functional magnetic resonance imaging and transcranial magnetic stimulation. *J Child Neurol* 2002;17(4):292–7.
- [4] Santhouse A, Ffytche D, Howard R, Williams S, Stewart A, Rooney M, Wyatt J, Rifkin L, Murray R. The functional significance of perinatal corpus callosum damage: an MRI study in young adults. *Brain* 2002;125(8):1782–92.
- [5] Staudt M, Grodd W, Gerloff C, Erb M, Stitz J, Krageloh-Mann I. Two types of ipsilateral reorganization in congenital hemiparesis: a TMS and fMRI study. *Brain* 2000;125:2222–37.
- [6] Cao Y, Vikingstad E, George K, Johnson A, Welch K. Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke* 1999;30:2331–40.
- [7] Neville H, Bavelier D. Neural organization and plasticity of language. *Curr Opin Neurobiol* 1998;8:254–8.
- [8] Tierney M, Varga M, Hosey L, Grafman J, Braun A. PET evaluation of bilingual language compensation following early childhood brain damage. *Neuropsychologia* 2001;39:114–21.
- [9] Werring D, Clark C, Parker G, Miller D, Thompson A, Braker G. A direct demonstration of both structure and function in the visual system combining diffusion tensor imaging with functional magnetic resonance imaging. *NeuroImage (United States)* 1999;9(3):352–61.
- [10] Mori S, Crain B, Chacko V, van Zijl P. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol* 1999;45:265–9.
- [11] Bower A. Plasticity in the adult and neonatal central nervous system. *Br J Neurosurg* 1990;4:253–64.
- [12] Gaillard W, Hertz-Pannier L, Mott S, Barnett A, Le Bihan D, Theodore W. Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology* 2000;54:180–5.
- [13] Lurito J, Dzemidzic M. Determination of cerebral hemisphere language dominance with functional magnetic resonance imaging. *Neuroimaging Clin N Am* 2001;11(2):355–63.
- [14] Hirsch J, Ruge M, Kim K, Correa D, Victor J, Relkin N, Labar D, Krol G, Bilsky M, Souweidane M, DeAngelis L, Gutin P. An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. *Neurosurgery* 2000;47:711–22.
- [15] Roux F-E, Boulanaouar K, Lotterie J-A, Mejdoubi M, LeSage J, Berry I. Language functional magnetic resonance in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery* 2003;52:1335–47.
- [16] Z'Graggen W, Fouad K, Raineteau O, Metz G, Schwab M, Kartje G. Compensatory sprouting and impulse rerouting after unilateral pyramidal tract lesion in neonatal rats. *J Neurosci* 2000;20(17):6561–9.
- [17] Carnicheal S, Chesselet M-F. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. *J Neurosci* 2002;22(14):6062–70.
- [18] Ito R, Mori S, Melham E. Diffusion tensor brain imaging and tractography. *Neuroimaging Clin N Am* 2002;12(1):1–19.