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Mapping Functional Connectivity in Patients with Brain Lesions

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Abstract

OBJECTIVE—Although electrophysiological measures of functional connectivity between brain areas are widely used, the spatial distribution of functional interactions as well as the disturbance introduced by focal brain lesions remains poorly understood. Based on the rationale that damaged brain tissue can be expected to be disconnected from the physiological interactions among healthy areas, this study aimed to map the functionality of brain areas according to their connectivity with other areas.

METHODS—Magnetoencephalographic (MEG) recordings of spontaneous cortical activity during resting state were obtained from 15 consecutive patients with focal brain lesions and from 14 healthy controls. Neural activity at each volume element (voxel) in the brain was estimated using an adaptive spatial filtering technique. For each brain voxel, the mean imaginary coherence of all its connections with other brain voxels was then calculated as an index of functional connectivity, and the results compared across brain regions and between subjects.

RESULTS—The magnitude of the mean imaginary coherence of all voxels and subjects was greatest in the alpha frequency range corresponding to the human cortical idling rhythm. In healthy subjects, functionally critical brain areas such as the somatosensory and language cortices had the highest alpha coherence. When compared to healthy controls, all lesion patients had diffuse or scattered brain areas with decreased coherence. Patients with lesion-induced neurological deficits displayed decreased connectivity estimates in the corresponding brain area compared to intact contralateral regions. In tumor patients without preoperative neurological deficits, brain areas showing decreased coherence could be surgically resected without the occurrence of post-surgical deficits.

CONCLUSION—Resting state coherence measured with MEG is capable of mapping the functional connectivity of the brain, and can therefore offer valuable information for use in planning resective surgeries in patients with brain lesions, as well as investigations into structural-functional relationships in normal subjects.

Introduction

The ability to map the functions of discrete brain regions has led to unprecedented advances in the understanding of brain physiology and pathology. Besides the enormous utility of cortical maps in cognitive and behavioral research, they are routinely used in the clinical

management of patients. In particular, functional maps of individual patient brains are used during surgical planning, in order to preserve critical brain tissue [Ojemann *et al.* 1996] and avoid disabling post-surgical functional deficits. Intraoperative maps based on direct cortical stimulation mapping [Berger *et al.* 1989] are highly reliable but have the disadvantage of being invasive. Functional maps created with non-invasive techniques such as functional magnetic resonance imaging (fMRI) [Mueller *et al.* 1996; Fandino *et al.* 1999] or magnetic source imaging (MSI) [Roberts *et al.* 1995; Ganslandt *et al.* 1999; Alberstone *et al.* 2000; Schiffbauer *et al.* 2003] generally correlate well with intraoperative findings, but their accuracy can depend on patient cooperation and on study paradigms that are capable of reliably activating the brain area of interest. In particular, paradigms for activating language areas are currently not generally available for clinical functional imaging.

Instead of mapping brain areas using activation or lesion methods, this study aimed to map brain areas by measuring their functional connectivity with other areas. The underlying rationale is that necrotic or structurally disconnected (i.e., non-functional) tissue does not participate in the dynamic interactions occurring between intact brain areas and would therefore be expected to show decreased connectivity. Moreover, it is reasonable to speculate that such decreased connectivity might be observed during the resting state as well as during cognitive tasks. Thus, measurement of functional connectivity of each brain area with sufficiently high spatial resolution, even if done during the resting state, might yield valuable information about their functionality, and such resting state measurements could be made without dependence on patient cooperation or specific activation paradigms. Indeed, a pioneering study assessing functional connectivity in patients with brain lesions using electroencephalographic (EEG) coherence found highly significant decreases in EEG coherence in lesion patients during the resting state, and these decreases were most pronounced in the alpha frequency range corresponding to the human idling rhythm [Harmony *et al.* 1994]. Furthermore, studies using electrocorticographic (ECoG) coherence demonstrated increased short-range coherence between electrodes recording directly from brain lesions, but decreased long-range coherence between tumor and intact tissue [Towle *et al.* 1998].

However, previous non-invasive EEG and magnetoencephalography (MEG) based investigations of the functional connectivity of brain lesions were unable to relate changes measured by extra-cerebral sensors to structural alterations within the brain, and fMRI based connectivity studies were insensitive to focal cerebral lesions [Quigley *et al.* 2001]. Therefore, the spatial distribution of lesion-induced connectivity changes remains poorly understood. Furthermore, the available data appears to be conflicting. Whereas EEG and ECoG studies showed changes restricted to the affected hemisphere [Harmony *et al.* 1994] or to the electrodes overlying tumor [Towle *et al.* 1998], MEG studies found that tumors produce diffuse, not focal, decreases in functional connectivity [Bartolomei *et al.* 2006b; Bartolomei *et al.* 2006a].

Here, we introduce an MEG based approach that allows a precise relation of changes in functional connectivity to structural lesions. It first uses a well established adaptive spatial filtering technique [Vrba and Robinson 2001; Sekihara *et al.* 2001] to estimate the neural oscillations at each volume element (voxel) in the brain from the signal recorded by all MEG sensors. Then, imaginary coherence (IC) is calculated and used as a non-biased index of the functional connectivity between voxels [Nolte *et al.* 2004].

Methods

Patients and healthy controls

All 15 patients with unilateral brain lesions who underwent MEG scanning and magnetic source imaging (MSI) at the UCSF Biomagnetic Imaging Lab between February 2006 and February 2007 and who had a subsequent craniotomy with biopsy and/or resection at UCSF were included in the study. The mean age of the patients was 39.6 years (range 20–74) and 9 were female. In addition, 14 healthy controls (mean age 42 years, range 25–75, 5 females) were studied. All participants gave their written informed consent to participate in the experiments, all procedures were approved by the UCSF Committee on Human Research, and all experiments were conducted according to the Declaration of Helsinki.

Structural images

Magnetic resonance imaging (MRI) was performed at 1.5 Tesla. The protocol typically included the following sequences: 1) a T1-weighted, 3D spoiled gradient-recalled echo in a steady state sequence with TR 34 ms, TE 3 to 8 ms, flip angle 30°; 2) a T2-weighted 3D fast-spin echo sequence with TR 3000 ms, TE 105 ms. Both sequences had a slice thickness of 1.5 mm, matrix 256×256×(108–140), and a field view of 260×260 mm with skin-to-skin coverage to include the nasion and preauricular points. Tumor volumes were estimated by transforming the MRI images into a 1×1×1 mm voxel space, delineating the lesions (without edema) in 3 planes, and calculating the number of voxels included. In addition, voxels that were located within 2 cm of a tumor or of related edema were manually delimited in the 3D structural MRI images and defined as “*tumor voxels*”.

MEG Recordings

The participants were lying awake and with their eyes closed in a magnetically shielded room. One minute of artifact-free, continuous, resting state MEG was recorded with a 275 channel whole-head CTF Omega 2000 system (VSM MedTech, Coquitlam, BC, Canada), using a sampling rate of 600 Hz.

General Algorithms

An adaptive spatial filtering technique was used to reconstruct the electromagnetic neural activity at each brain voxel from the signal recorded by the entire MEG sensor array. The detailed algorithms for this algorithm are described elsewhere [Vrba and Robinson 2001; Sekihara *et al.* 2001]. In short, the raw MEG data was band pass filtered with a 4th order butterworth filter, and the spatial covariance matrix was calculated for the entire recording of 1 minute duration. We also computed the forward field matrix, corresponding to the forward solution for a unit dipole at a particular voxel, for each voxel of interest in the brain. From the spatial covariance and the forward field matrix, a spatial weight matrix was then obtained for optimal estimation of the signal power in each voxel. The activity at each time in each voxel was calculated as the linear combination of the spatial weighting matrix with the sensor data matrix. Thus, all sensors contribute to some degree to all voxel time series estimates from which we analyze functional connectivity. Most of the commonly used measures of functional connectivity such as coherence [Lopes da Silva *et al.* 1973], phase locking value [Lachaux *et al.* 1999; Le Van *et al.* 2001], and synchronization likelihood [Stam *et al.* 2003] overestimate the magnitude of true connectivity in this setting due to common references with crosstalk between voxel time series, a problem that is also well known in connectivity estimation from EEG time-series [Fein *et al.* 1988]. In addition, traditional approaches to functional connectivity are sensitive to volume conduction [Nunez *et al.* 1997] and spatial blur in reconstruction.

Recently, an alternative method for estimating functional connectivity was introduced that overcomes the overestimation biases arising from cross-talk or volume conduction [Nolte *et al.* 2004]. Imaginary coherence exploits the fact that all true interactions in the brain occur with a certain time lag due to neural transmission whereas biased similarities due to a common reference or due to volume conduction occur with 0 time delay. The imaginary component of coherence represents true similarities having a certain time lag, whereas the omitted real component mostly contains (biased) similarities with 0 time delay. Thus, this approach yields a conservative and unbiased measure of true interactions between brain areas. Imaginary coherence I between a given voxel pair for each frequency bin f was calculated according to the formula [Nolte *et al.* 2004]:

$$I_{XY}(f) = \left| \operatorname{Im} \frac{\sum_{k=1}^K X_k(f) Y_k^*(f)}{\sqrt{\sum_{k=1}^K |X_k(f)|^2 \sum_{k=1}^K |Y_k(f)|^2}} \right| \quad (1)$$

where X_k and Y_k are Hanning windowed, Fourier transformed, segments of 2 virtual time series, and * indicates the complex conjugate. Each segment k was 2 s long and overlapped adjacent segments by 1 s. The absolute value of imaginary coherence was used rather than coherency, since we were interested in the magnitude of connectivity at each voxel rather than in the directionality of the information flow [Nolte *et al.* 2004]. IC values for frequency bands were calculated from the sum of auto- and cross-spectra of the corresponding frequency bins.

Estimates of functional connectivity can also be obtained with the previously introduced “dynamic imaging of coherent sources (DICS)” algorithm [Gross *et al.* 2001] by examining the imaginary part of the cross-spectrum in voxel coordinates. Unlike the proposed method, DICS uses correlations in the frequency domain for source estimation instead of temporal correlations. It first calculates a cross-spectrum density matrix of all physical MEG sensors, and then applies an adaptive spatial filter to reconstruct source power and coherence for a given frequency bin or band. It can be shown that the resulting estimates are computationally equivalent.

Functional images

A 3-dimensional grid of voxels covering the entire brain was created for each subject and recording, based on a multi-sphere head model of co-registered structural MRIs. Alignment of structural and functional images was ensured by marking 3 prominent anatomical points (nasion and preauricular points) of the subject’s head in the MRI images, and localizing 3 fiducials attached to the same points before and after each MEG scan.

The selection of the band pass filter settings, i.e., of the frequency band used for adaptive spatial filtering, is a compromise between increasing the information for the spatial filter and optimizing the obtained weighting matrix for the actual band of interest. At first, a broad 1–55 Hz band was used for calculation of the spectral distribution of IC magnitude. A narrower band of 1–20 Hz was chosen for calculation of IC in the alpha band.

After calculating the time series at each voxel, pairs of voxels were subjected to analysis of IC as described above. For the creation of IC spectra, frequency bins between 1 and 55 Hz were analyzed, using a resolution of 0.59 Hz (1024 frequency bins). For analysis of idling rhythms, alpha frequency bins that showed greatest power density during resting state were

chosen individually for each subject and averaged. A frequency resolution of 1.17 Hz (512 frequency bins) was used.

The connectivity at each voxel of interest was estimated by averaging across all its Fisher's Z-transformed connections C [Nolte *et al.* 2004].

$$\bar{I} = \tanh \left(\frac{1}{C} \sum_C \tanh^{-1}(I) \right) \quad (2)$$

In order to obtain maps of *lesion specific connectivity changes (L-images)*, all connections between “tumor voxels” (see definition above) of 8×8×8 mm extension and a centered, equally spaced, whole brain grid of each 4th voxel within the entire set of 8×8×8 mm voxels were analyzed. As a control, the connectivity was also calculated for connections between voxels contralateral to tumor voxels and the same whole brain voxel grid:

$$\bar{I}(\text{Patient}_{\text{Tumor}}, \text{Patient}_{\text{WholeBrain}}) \iff \bar{I}(\text{Patient}_{\text{Contralateral}}, \text{Patient}_{\text{WholeBrain}}) \quad (3)$$

In order to obtain maps of *patient specific connectivity changes (P-images)*, all possible connections between 2 voxels of 20×20×20 mm extension were analyzed for each tumor patient and, as a control, for each healthy subject:

$$\bar{I}(\text{Patient}_{\text{WholeBrain}}) \iff \bar{I}(\text{HealthyControls}_{\text{WholeBrain}}) \quad (4)$$

Clinical analyses

MSI of the somatosensory and auditory cortices was performed for all tumor patients according to standard procedures [Nakasato *et al.* 1997; Schiffbauer *et al.* 2003]. After the MEG scans, all patients underwent craniotomy. In 10 patients, intraoperative cortical mapping of the motor cortex, language areas, or both, was performed, depending on the tumor location. Subcortical stimulation was sometimes used to identify the corona radiata and the internal capsule at the border of the resection [Keles *et al.* 2004]. Biopsy samples were obtained in all cases. In 14 patients, neoplasms were histologically confirmed and resected while avoiding critical tissue. Neurological deficits before and after surgery were assessed by qualified physicians. [[Tumor classifications moved further down]]

Statistical analyses and classifications

The mean Z-transformed IC values of all alpha frequency bins between 8 and 12 Hz were tested for across-subject differences between tumor voxels and non-tumor voxels of patients with brain tumors using two-tailed paired t-tests, and between tumor voxels and voxels of healthy control subjects using two-tailed unpaired t-tests. In accordance with the hypothesis that damaged brain tissue is associated with lower values of functional connectivity, only patients without resection-related post-surgical functional deficits, i.e., without relevant functional tissue in vicinity of the tumor, were included for this analysis step ($N=10$).

L-images were used to assess tumor voxels of all patients for within-subject differences with contralateral voxels using two-tailed t-tests for one sample, which tested the null-hypothesis that the Z-transformed connectivity between a given tumor voxel and reference voxels is equal to the mean of the Z-transformed connectivities between all contralateral voxels and the same reference voxels. The resulting probabilities can easily be corrected for multiple testing by using a false discovery rate. However, since the uncorrected maps proved to be

conservative even in the absence of corrections (i.e., no brain area was erroneously mapped as non-functional while containing critical tissue), we report here the uncorrected images.

L-images of all patients were classified into 3 grades of tumor tissue disconnection according to the percentage of tumor voxels that showed significant increases or decreases in connectivity as compared to the contralateral tissue:

- Grade 2: >50% of the tumor voxels show significant decrease and 0% show significant increase;
- Grade 1: 20–50% show decrease and 0% show increase;
- Grade 0: <20% show decrease or >0% show increase.

The tumors were classified as invading or being located close to eloquent tissue if at least one of the following criteria was fulfilled: MSI equivalent current dipoles (ECD) located within 5 mm of the tumor, neurological deficits induced by electrical stimulation over the tumor during intraoperative cortical mapping, or increased neurological deficits* after surgery. Disconnection grades were then tested for significant associations with the presence or absence of eloquent tissue in vicinity of the tumor, and with the risk of post-surgical deficits using Pearson's Chi-Square tests.

In order to test *P-image* voxels of all 15 tumor patients for differences with healthy controls, they were spatially normalized to the canonical Montreal Neurological Institute (MNI) space according to the co-registered structural MRI, using the toolbox SPM2 for MATLAB (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>). All normalized *P-image* voxels of tumor patients with Z-transformed connectivity estimates above or below the 95% confidence interval of the values of healthy controls were considered significant. The proportion of “disconnected voxels” in each patient was defined as the ratio between the number of voxels with significantly decreased connectivity compared to healthy controls and the total number of voxels. The percentage of disconnected voxels was tested for associations with age of patient and tumor volume using Spearman correlations, and with tumor histology using a nonparametric Kruskal Wallis test.

Results

Figure 1A shows the frequency spectrum of IC magnitude averaged over all connections between all 20×20×20 mm voxels, and over all subjects (mean ± standard error of mean). A single and distinctive peak can be observed in the alpha frequency range between 8 and 12 Hz, corresponding to the human idling rhythm (arrow). IC magnitude in this band was significantly lower in tumor voxels than in non-tumor voxels of brain tumor patients ($t(9)=-3.2$, $p=0.011$) and than in healthy controls ($t(22)=-2.3$, $p=0.029$).

In healthy subjects, brain areas that are responsible for critical neurological functions showed greatest idling rhythm IC values (see Figure 1B). Thus, voxels in the somatosensory and visual cortex as well as in language areas had greatest estimates of functional connectivity even during resting state.

Table 1 summarizes, for each patient included in the study, clinical features (demographic, clinical, and pathological data) as well as measures of tumor-related functional connectivity.

*Some of these neurological deficits were transient only and probably due to swelling, but were also considered as a sign of eloquent tissue in vicinity of the tumor.

Both patients who had tumor-induced, pre-surgical functional deficits (patients 8 and 12) had decreased connectivity estimates in the brain area invaded by the tumor and responsible for the corresponding function as compared to the functional contralateral side. Figure 2A shows the example of a female patient (number 8) with monoparesis of right foot and toe levator/flexor muscles due to an astrocytoma WHO grade III in the left medial sensorimotor cortex. The *L-image* (indicating lesion specific connectivity changes) shows decreased connectivity estimates in the sensorimotor cortex of the foot, which is also localized by an MSI equivalent current dipole (ECD) evoked by tactile stimulation of the right toe, thus matching the clinically observed deficits. In patient 12 with anomia and aphasia, decreased connectivity estimates were found in the superior temporal gyrus and the angular gyrus that were damaged by lesion for which the pathology showed unspecific gliosis without signs of malignancy, and which was most probably caused by a chronic demyelinating disease.

L-images also predicted the presence or absence of critical tissue in the tumor area and the risk for post-surgical functional deficits. Figure 2B illustrates this in 3 typical patients. Voxels showing a significant connectivity decrease (in blue) marked brain areas that could be surgically resected without ensuing deficits, whereas voxels with non-decreased (no color) or even increased connectivity (red) potentially contained eloquent brain tissue. In patient 1, decreased functional connectivity estimates were calculated in almost the entire right temporal lobe invaded by a large glioblastoma multiforme WHO grade IV, thus indicating a functional disconnection of the entire tumor area. In accordance with these findings, the patient had no neurological deficits after radical (>95%) resection of the tumor (Table 1). In contrast, patient 6 had increased connectivity values in the antero-lateral part of a right medial centro-parietal astrocytoma WHO grade III, corresponding to the sensorimotor cortex, and co-localizing with MSI ECD evoked by tactile stimulation of the fingers and lips. Accordingly, transient sensory deficits in the left arm and leg (Table 1) were observed after a >85% resection of the tumor, probably due to swelling. In patient 9, the ventral and dorsal parts of an astrocytoma WHO grade II in the fronto-temporal junction showed decreased connectivity values, which was not the case for a region in the frontal operculum. Intraoperative language mapping indeed demonstrated that electrical stimulation in this region elicited speech arrest and anomia, thus indicating that it corresponded to a functionally critical expressive language area. Moreover, as predicted by the *L-image*, resection of the remaining areas did not produce any functional deficits (Table 1).

In order to quantify the validity of *L-images* across all patients, they were classified into 3 grades of tumor tissue disconnection. The close relationship between the degree of lesion specific connectivity reduction and the functionality of the tissue can be seen in Table 1 and Figure 3. Note that none of the patients with tumor disconnection grade 2 had eloquent tissue in vicinity of the tumor, and none had post-surgical functional deficits. In contrast, this was only the case in 29% of the patients with grade 0 ($\chi^2(13)=7.8$, $p=0.021$ for post-surgical outcome; $\chi^2(14)=5.2$, $p=0.073$ for presence of critical tissue).

P-images were created to assess patient specific connectivity changes as compared to healthy controls. Voxels with significant functional connectivity deficits were found in all patients (Table 1), whereas none of the patients had any voxels with significantly greater functional connectivity than healthy controls. As shown in Figure 2, the spatial pattern of *P-image* voxels with decreased connectivity was unrelated to tumor location and clinical deficits. Furthermore, no relationship could be found between the percentage of disconnected voxels and age of patient, tumor volume, or tumor histology ($p>0.16$).

Discussion

This is the first study to demonstrate that non-invasive measures of connectivity are capable of predicting the functionality of brain tissue in healthy subjects as well as in patients with focal lesions. This has implications for the understanding of brain physiology as well as important potential clinical applications.

Functionally critical brain areas show greatest connectivity estimates during resting state

As expected, we found a single spectral peak of imaginary coherence magnitude in the alpha frequency range when analyzing resting state recordings (Figure 1A). The human alpha rhythm is thought to be generated by thalamo-cortical as well as cortico-cortical interactions, with the magnitude of alpha coherence between different areas depending on the similarity of the inputs they receive as well as on the frequency selectivity of the underlying neural networks [Lopes da Silva *et al.* 1973]. In this study, we estimated the overall connectivity of a given voxel by averaging IC values of all its connections. The observation in Figure 1B that functionally critical brain areas were associated with the greatest connectivity estimates suggests that these important regions interact with numerous other regions not only during their intrinsic task but even during the awake resting state. This opens a new and accessible window for the study of various brain functions. Furthermore, the physiological spatial distribution of alpha coherence seems to be optimal for imaging critical tissue before surgery, since (1) intact eloquent tissue can be contrasted with non-critical regions, and (2) dysfunctional eloquent areas can be contrasted with intact eloquent regions.

Correlations between functionally related areas during resting state have also recently been demonstrated in fMRI studies, in particular, when very low frequency signal oscillations are considered [Fox *et al.* 2005]. Future work is needed to assess whether and how resting state connectivity in the alpha frequency range, as demonstrated here, is related to previously reported correlations of low-frequency oscillations of the fMRI hemodynamic signal.

Dysfunctional brain areas show decreased resting state connectivity

In accordance with our hypothesis, we found significantly lower connectivity values in brain areas that were damaged by a lesion (Figure 2A) than in the intact contralateral tissue (*L-image*), thus confirming that dysfunctional tissue is disconnected from the interactions among healthy areas. Importantly, connectivity estimates were found to be significantly decreased only in the regions corresponding to the clinically observed functional deficit rather than in the entire area invaded by the tumor. Thus, the measure seems to be capable of distinguishing between functional and dysfunctional tissue within a tumor [Ojemann *et al.* 1996], at least within the limits of the spatial resolution of the applied spatial filter.

Brain areas with low resting state connectivity can be surgically resected with low risk of ensuing functional deficits

In order to further test the reliability of our MEG based measure of functional connectivity, we analyzed the obtained connectivity maps in relation to intraoperative cortical stimulation results and post-surgical outcome. As shown in Table 1, Figure 2B, and Figure 3, a local decrease in functional connectivity as compared to the contralateral region (*L-image*) reliably indicated the resectability of the underlying tissue in all our patients. Moreover, 71% of the patients with no connectivity deficit or with increased connectivity estimates in the brain area invaded by the tumor suffered from transient or permanent functional deficits after its surgical resection ($p=0.021$). The reliability of the method was better in patients with tumors in the vicinity of (or contralateral to) eloquent tissue (central sulcus, language areas, e.g., patients 1, 3, 6–9) than in patients with tumors outside of critical areas (dorsomedial prefrontal cortex, e.g., patients 4 and 11). This fits with the finding that critical

tissue has the greatest intrinsic connectivity and thus allows a better contrast with dysfunctional areas. Future studies might be able to further improve the reliability of connectivity maps by segmenting grey and white matter of the individual brains and limiting the calculation of connectivity measures to gray matter voxel pairs, and by using novel non-linear and unbiased measures of connectivity [Stam *et al.* 2007].

Comparison with healthy controls

When performing a voxel-wise comparison of connectivity estimates between lesion patients and healthy controls (*P-images*), we found scattered or diffuse areas with decreased connectivity in all patients, which, however, were unrelated to tumor location, clinical deficits, tumor histology, tumor volume, and age of the patient. This confirms the findings of a previous study using MEG based measures of functional connectivity in patients with brain tumors [Bartolomei *et al.* 2006b]. In agreement with these authors, we conclude that focal lesions produce a diffuse decrease in brain connectivity, when tumor patients are compared to a healthy population. However, we demonstrate here that when performing statistical analyses on the individual patient level, significant focal changes can be observed corresponding to the location of the tumor and to the patient's functional state, which agrees with previous ECoG studies [Towle *et al.* 1998].

Conclusions

We may thus conclude that, unlike conventional imaging techniques that localize a limited brain area activated by a given paradigm, the proposed approach is capable of mapping the connectivity and functionality of the entire cortex while requiring merely one minute of recording time and no active participation from the subjects. This reduces the patient effort to a minimum and makes the method also suitable for patients that are unable to cooperate.

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Figure 1.

Frequency spectrum and spatial distribution of imaginary coherence (IC). **A.** The mean ($\pm$ standard error of mean) imaginary coherence across all connections between $20 \times 20 \times 20$ mm voxel pairs is plotted for all healthy subjects ($N=14$) and for all patients with brain tumors that did not contain functional tissue ($N=10$). Note the peak in the alpha frequency range. Tumor tissue was associated with significantly lower functional connectivity estimates in the alpha frequency range than non-tumor tissue of lesion patients ($p=0.011$) and than brain tissue of healthy controls ($p=0.029$). **B.** The average functional connectivity map of all 14 healthy subjects is superimposed on a 3-dimensional individual brain. An arbitrary threshold of $>90\%$ of the maximum IC value was used to visualize the regions with largest connectivity estimates. The Broca area and the right visual cortex are opened to demonstrate the high functional connectivity of these critical areas.

Figure 2.

Functional maps obtained with magnetic source imaging or intraoperative cortical mapping as well as L-images and P-images of 4 patients with brain tumors are superimposed over their 3D-rendered individual brain. **A.** Twenty-five year old woman *with* a central paresis of the right foot due to an astrocytoma WHO grade III that infiltrated the left medial sensorimotor cortex. Note that the L-image displays a corresponding decrease in functional connectivity in the sensorimotor cortex of the right foot. **B.** The L-images of these 3 tumor patients *without* pre-surgical functional deficits indicate functional disconnection (in blue) of different proportions of the corresponding tumor tissue (graded 0–2, with 0 indicating

smallest proportion with disconnection). In agreement with the L-images and the clinical status, functional cortex was mapped outside of disconnected (blue) areas by MSI and cortical mapping in all patients. In addition, L-images predicted the functional status after radical surgery: whereas patient 6 suffered from post-surgical sensible deficits in the left arm and leg, no deficits were observed in patient 1 and 9. P-images show diffuse or scattered areas with significantly lower connectivity estimates than a healthy control population, but these areas are unrelated to tumor location and brain regions with functional deficits.

Figure 3.

Bar plots illustrating the percentage of patients without critical tissue in vicinity of the tumor and without functional deficits after tumor resection, in relation with the functional disconnection score derived from L-images.

Demographic and clinical profile of the patients included in the study, and quantification of functional connectivity measures.

Table 1

Nr	Sex	Age	Location	Histology	Volume [cm ³]	Neurological Deficits		MSI	Intraoperative Mapping	Imaginary Coherence	
						Pre-surgical	Post-surgical	ECD in Tumor Area	Stimulation Induced Deficits	Disconnection Grade (L-image)	Disconnected Voxels [%] (P-image)
1	M	74	R-T	GBM IV	84	none	none	none	--	2	7.3
2	M	33	L-F-d	re GBM IV	12	none	none	none	Language: none	2	7.2
3	F	53	L-F-dl	GBM IV	7	none	transient expressive aphasia and anomia	none	Language: speech arrest	0	7.2
4	F	60	R-F-dm	GBM IV	40	none	none	none	Motor: none	1	12.2
5	M	49	L-T-a	re A III	91	none	transient anomia and paraphasias	AEF noise bursts	Language: none	0	3.0
6	M	34	R-CP-m	re A III	219	none	transient hemihypesthesia, dysproprioception arm and leg L	SEF fingers and lip L	Motor: foot	0	0.8
7	F	34	R-C	A III	7	none	paresis, hemihypesthesia, dysproprioception hand L	SEF fingers and lip L	Motor: hand, face	0	18.5
8	F	25	L-C-m	A III	10	paresis foot R	paresis foot and distal leg R	SEF toe R	Motor: leg, arm, hand	0	4.1
9	F	34	L-FT	A II	36	none	none	AEF 1kHz	Language: speech arrest, anomia Motor: none	1	8.0
10	M	35	L-T-a	A II	81	none	none	none	Language: none	0	11.5
11	F	45	L-F-dm	OA II	53	none	none	none	Motor: none	0	25.8
12	M	39	L-TP	Gliosis	41	expressive aphasia, anomia, left-right confusion	no resection	AEF 1kHz and noise bursts	--	1	24.3
13	F	25	L-T-m	DNET	1	none	none	none	Language: none	2	3.6
14	F	20	L-T-pi	DNET	2	none	none	none	--	2	10.7
15	F	29	L-F-dm	AVM	1	none	none	none	--	1	4.1

Abbreviations. Sex F refers to female; M, male. **Location** is reported as side-lobe-sublobe: L, left; R, right; F, frontal w/o pre-central gyrus; T, temporal; C, pre- and post-central gyrus; P, parietal; a, anterior; p, posterior; d, dorsal; m, medial; l, lateral. **Histology** GBM, glioblastoma multiforme; A, astrocytoma; OA, oligoastrocytoma; DNET, dyssembryoblastic neuro-epithelial tumor; AVM, arterio-venous malformation; II-IV, WHO grading. **MSI**, magnetic source imaging; ECD, equivalent current dipole; SEF, somatosensory evoked field; AEF, auditory evoked field.