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Treatment-related changes in functional connectivity in brain tumor patients: A magnetoencephalography study

Linda Douw [a,*], Hans Baayen [b], Ingeborg Bosma [a], Martin Klein [c], Peter Vandertop [b], Jan Heimans [a], Kees Stam [d], Jan de Munck [e], Jaap Reijneveld [a,f]

[a] Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands
[b] Department of Neurosurgery, VU University Medical Center, Amsterdam, The Netherlands
[c] Department of Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands
[d] Department of Clinical Neurophysiology, VU University Medical Center, Amsterdam, The Netherlands
[e] Deparment of Physics and Medical Technology, VU University Medical Center, Amsterdam, The Netherlands
[f] Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands

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ABSTRACT

Widespread disturbances in resting state functional connectivity between remote brain areas have been demonstrated in patients with brain tumors. Functional connectivity has been associated with neurocognitive deficits in these patients. Thus far, it is unknown how (surgical) treatment affects functional connectivity. Functional connectivity before and after tumor resection was compared in primary brain tumor patients. Data from 15 newly diagnosed brain tumor patients were analyzed. Patients underwent tumor resection, and both preoperative (up to five months prior to surgery) and postoperative (up to ten months following surgery) resting state magnetoencephalography (MEG) recordings. Seven of the patients (47%) underwent radiotherapy after neurosurgery. Functional connectivity was assessed by the phase lag index (PLI), a measure of the correlation between MEG sensors that is not sensitive to volume conduction. PLIs were averaged to one short-distance and two long-distance (interhemispheric and intrahemispheric) scores in seven frequency bands. We found that functional connectivity changed in a complex manner after tumor resection, depending on frequency band and functional connectivity type. Post-hoc analyses yielded a significant decrease of interhemispheric PLI in the theta band after tumor resection. This result proved to be robust and was not influenced by radiotherapy or a variety of tumor- and patient-related factors.

Introduction

It is increasingly acknowledged that the brain is a complex network of dynamical systems with abundant functional interactions between local and more remote brain areas (Varela et al., 2001). Particularly higher brain functions (such as planning, attention, and memory) are thought to require the integrated action of many, sometimes widely distributed specialized brain areas (Reijneveld et al., 2007; Stam and Reijneveld, 2007). These networks are based on anatomical connections, but also rely on functional interactions between brain areas (Tononi and Edelman, 1998; Singer, 1999; Bressler, 2002). The concept of functional connectivity refers to the study of statistical interdependencies between physiological time series recorded in various brain areas (Aertsen et al., 1989).

Electroencephalography (EEG) and magnetoencephalography (MEG) are methods used to assess functional connectivity within the brain. In MEG registration, interference of signals by skull and scalp characteristics occurs less than in EEG measurement. Also, MEG does not require the use of a reference electrode, hereby making it superior to EEG in assessment of functional connectivity (Parra et al., 2004; Guevara et al., 2005). The phase lag index (PLI) is a novel method that can be used to detect synchronous neural activity of the brain in EEG and MEG recordings (Stam et al., 2007). The PLI assesses statistical interdependencies between time series, and reflects the strength of the coupling between these time series. In contrast to other methods of analysis, the PLI is scarcely influenced by volume conduction, hereby making it a highly suitable method of computing functional connectivity based on neurophysiological data.

Patients with brain tumors often suffer from neurocognitive deficits, and changes in EEG coherence in these patients have previously been reported (Harmony et al., 1994). Recently, abnormalities in functional connectivity during resting state were observed in primary brain tumor patients compared to healthy controls (Bartolomei et al., 2006b,a). Remarkably, these differences were found throughout the brain, were not confined to regions close to the tumor, and involved pathological decreases as well as increases in functional connectivity. More importantly, cognition was found to be

* Corresponding author. VU University Medical Center, Department of Neurology, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail address: l.douw@vumc.nl (L. Douw).

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significantly associated with functional connectivity in low-grade glioma patients (Bosma et al., in press). However, the effects of tumor treatment (resection, radiotherapy, chemotherapy) on functional connectivity and cognition are unknown.

The effects of brain tumor resection on cognition and functional outcome have previously been studied. Most studies do not report a change in neurocognitive functioning of glioma patients after tumor resection (Scheibel et al., 1996; Klein et al., 2001, 2002; Reijneveld et al., 2001; Duffau, 2006). However, beneficial effects of surgery on cognitive functioning in low-grade glioma patients have been reported recently (Teixidor et al., 2007). Tumor resection generally does not induce permanent loss of function (Desmurget et al., 2007), and functional rehabilitation as well as neuronal plasticity in some areas is quite common in operated brain tumor patients (Duffau, 2006; Shinoura et al., 2006). Recently, functional connectivity has proven to be related to the functionality of brain areas in patients with brain tumors, indicating the clinical relevance of functional connectivity when considering tumor resection (Guggisberg et al., 2008). However, changes in functional connectivity after tumor resection have not been studied before.

In the present study, it is hypothesized that treatment and specifically tumor resection affects and possibly even restores normal functional connectivity patterns in brain tumor patients. In order to study this, fifteen brain tumor patients underwent resting state MEG recording before and after tumor resection. Subsequently, we calculated the phase lag index (PLI) in seven frequency bands in order to determine changes in functional connectivity.

Methods

Patients

This study made use of an existing dataset of MEG recordings at the VU University Medical Center. From this dataset, which has been used for previous studies (Baayen et al., 2003; de Jongh et al., 2003), we selected all patients with primary brain tumors who underwent (sub) total tumor resection [J.C.B.] between March 1999 and February 2001 and had preoperative and postoperative magnetoencephalography (MEG) recordings (within five months prior to and ten months following surgery). No further inclusion criteria regarding post-operative treatment (i.e. radiotherapy and/or chemotherapy) were used. Preoperative tumor volume was measured by contouring T1-weighted MPRAGE MRI images, slice by slice (2 mm slices), using a navigation system (BrainLAB AG, Heimstetten, Germany). Epilepsy frequency and burden were used as an indication of clinical outcome of the tumor resection, and were assessed by case-note review. We reviewed all case-notes from diagnosis to postoperative MEG measurement, and based our classifications on this time period. The modified Engel scale (Engel et al., 1993) was used to score surgical outcome in terms of seizure frequency on a 4-point scale, with scores indicating the following: (class I) free of seizures or residual auras; (class II) intermittent, infrequent seizures or relapse after a significant seizure-free period; (class III) worthwhile improvement, i.e. more than 75% reduction in seizure frequency; and (class IV) less than 75% reduction in seizure frequency. Furthermore, we indexed both preoperative and postoperative epilepsy burdens, as described by Klein et al. (2003). This 6-point scale has the following levels: (level 1) epilepsy-free; (level 2) epilepsy, seizure-free in the year before testing without AEDs; (level 3) epilepsy, seizure-free in the previous year with AED monotherapy; (level 4) epilepsy, seizure-free in the previous year with AED polytherapy; (level 5) epilepsy, less than six seizures in the previous year and on AED monotherapy or polytherapy; and (level 6) epilepsy, more than six seizures in the previous year and on AED monotherapy or polytherapy. Patients all signed written informed consent forms. Approval was obtained from the medical ethical committee of the VU University Medical Center.

Magnetoencephalography

Magnetic fields were recorded while subjects were seated inside a magnetically shielded room (Vacuumschmelze GmbH, Hanau, Germany) using a 151-channel whole-head MEG system (CTF Systems Inc., Port Coquitlam, BC, Canada). A third-order software gradient (Vrba et al., 1999) was used with a recording pass band of 0.25–125 Hz. Fields were measured during a no-task eyes-closed condition, with a sample frequency of 625 Hz. At the beginning and end of each recording, the head position relative to the coordinate system of the helmet was recorded by leading small alternating currents through three head position coils attached to the left and right preauricular points and the nasion on the subject's head. Head position changes during a recording condition up to approximately 1.5 cm were accepted. During the MEG recordings, the patients were instructed to close their eyes to reduce artefact signals due to eye movements. For this study, 150 of the 151 channels could be used.

Functional connectivity

Functional connectivity was assessed with the phase lag index (PLI). The PLI calculates the asymmetry of the distribution of (instantaneous) phase differences between two MEG signals. It assumes that the presence of a consistent, nonzero phase lag between two time series cannot be explained by volume conduction alone. Thus, finding true interactions instead of volume conduction effects is more likely when using this method. See Stam et al. (2007) for a complete description of PLI calculation.

Four artefact free epochs of 4096 samples (6.5 s) were carefully selected by visual analysis from both the preoperative and postoperative registrations in each patient [L.D.]. PLIs between each pair of MEG sensors were computed after filtering the MEG signals in seven frequency bands (respectively delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz), lower gamma (30–45 Hz), and upper gamma (55–80 Hz)) (Stam et al., 2006). Computation of the PLI was done offline with DIGEEGXP software, developed at our department [C.S.]. These PLI scores were averaged over each set of the selected four epochs. Further averaging was performed to obtain long-distance intra- and interhemispheric and short-distance local measures. For this, MEG channels were grouped into (left and right) central, frontal, occipital, parietal, and temporal regions (based upon the naming of the sensors (Stam et al., 2006)). Long-distance PLI scores involved (1) interhemispheric PLI (between the two hemispheres), and (2) intrahemispheric PLI (between all regions within the hemispheres),

Table 1
Patient characteristics

Patient	Gender	Age	Lateralization	Localization	Histology	Epilepsy	Engel class
1	M	29	L	F	AIII	GS	I
2	F	66	R	T	Me	GS	I
3	F	39	L	F	AIII	GS	I
4	M	33	R	P	AIII	GS	I
5	F	30	R	FP	AII	FS	II
6	M	32	L	F	AII	GS	II
7	F	27	R	FP	OB	GS	I
8	M	31	L	F	AIV	GS	I
9	M	38	L	F	AIII	GS	II
10	F	41	L	P	OC	GS	I
11	F	35	L	FT	AII	FS	III
12	M	63	L	P	AIV	FS	I
13	F	48	R	T	AII	GS	I
14	F	26	L	F	OB	GS	I
15	M	43	R	F	Me	GS	I

Note. T = temporal; F = frontal; P = parietal; FP = fronto-parietal; FT = fronto-parietal; Me = meningioma, AI–IV = astrocytoma grade I–IV; OB = oligodendroglioma grade B; OC = oligodendroglioma grade C, OD = oligodendroglioma grade D, GS = generalized seizures, FS = focal seizures.