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Decreased language laterality in tuberous sclerosis complex: A relationship between language dominance and tuber location as well as history of epilepsy

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Abstract

Nearly 90% of patients with tuberous sclerosis complex (TSC) have epilepsy. Epilepsy surgery can be considered, which often requires a presurgical assessment of language lateralization. This is the first study to investigate language lateralization in TSC patients using magnetoencephalography. Fifteen patients performed a language task during magnetoencephalography recording. Cerebral generators of language-evoked fields (EF) were identified in each patient. Laterality indices (LI) were computed using magnetoencephalography data extracted from the inferior frontal as well as middle and superior temporal gyri from both hemispheres between 250 and 550 ms. Source analysis demonstrated a fusiform gyrus activation, followed by an activation located in the basal temporal language area and middle and superior temporal gyri responses, ending with an inferior frontal activation. Eleven patients (73.3%) had left-hemisphere language dominance, whereas four patients (26.7%) showed a bilateral language pattern, which was associated with a history of epilepsy and presence of tubers in language-related areas.

Keywords

TSC; Language lateralization; History of epilepsy; Cortical lesions; MEG; Minimum-norm estimate (MNE); Presurgical work-up

1. Introduction

It is now well established that the presence of cerebral abnormalities or pathological activity, such as in epilepsy, in the left hemisphere may lead to language function reorganization, especially when the insult appears at a young age [1]. Considering the presence of multiple cerebral lesions and the high incidence of infantile spasms and early-onset seizures in individuals with tuberous sclerosis complex (TSC) [2], a decrease of left-hemisphere language dominance would be likely to occur in this population. Recently, we found that TSC patients present a diffuse language representation compared to healthy controls, which probably reflects cerebral reorganization of language function. The high occurrence of refractory epilepsy often leads to language investigation as part of a presurgical work-up in

these patients. Due to the presence of multiple cortical tubers, the presurgical evaluation of patients with TSC poses several unique challenges and often requires lateralizing language function.

Magnetoencephalography (MEG) has been used as a noninvasive tool to successfully lateralize language functions in patients with epilepsy (for a review of neuroimaging techniques, see [3]). Magnetoencephalography is effective in localizing both receptive and expressive language regions [4,5], can be recorded in patients who have conditions incompatible with MRI (e.g., claustrophobia, a vagus nerve stimulator) [6], and has an excellent temporal resolution (less than 1 ms) [7]. Magnetoencephalography has been shown to be effective in localizing the epileptogenic zone in patients with TSC [8], but has never been used as a language lateralization tool in a significant number of TSC patients.

The present study aims to evaluate language lateralization in patients with TSC using MEG and to investigate relationships between language lateralization patterns and tuber cerebral location as well as history of epilepsy.

2. Methods

2.1. Participants

The clinical sample was composed of fifteen patients (11 females (73%), mean age=38.5±9.1 years, 12 right-handed) who met clinical diagnostic criteria for TSC [9] and who were seen at the Carol and James Herscot Center for Tuberous Sclerosis Complex at Massachusetts General Hospital. Selection criteria for inclusion in the TSC group were those aged 12 years old or older, no daily seizures, no mental retardation (based on professional and occupational level or on previous neuropsychological assessment), no history of acquired cerebral lesion, traumatic brain injury or intracranial surgery, no claustrophobia or condition incompatible with MRI, and no actual pregnancy. All female participants had to undergo a pregnancy test before the MRI recording. Demographical and clinical data of all participants with TSC are presented in Table 1.

The handedness of all participants was assessed using the Edinburgh Inventory [10]. The MGH institutional review board approved this study and written informed consent was obtained from all patients prior to their inclusion in the study.

2.2. Language paradigm

All patients performed a lexico-semantic decision task during MEG recording. The testing took place in a dimly lit, three-layer magnetically shielded room (Imedco, Hägendorf, Switzerland). A camera, microphones, and speakers were placed into the room to allow the participants and the experimenter to communicate while the participant was seated in the shielded room.

The lexico-semantic decision task consisted of a sequential visual presentation of 160 English words. Patients were instructed to indicate, using a button press response, if the presented word was abstract (ex: freedom) or concrete (ex: apple). Each word was presented for 1000 ms on a screen placed 150 cm from the participant's eyes. The interstimulus interval (ISI) was 2000 ms. Each trial had a duration of 3000 ms. Two blocks of 80 stimuli were presented to the participants. The first block was preceded by a practice session of 10 words. The practice session was repeated if needed. The total duration of the task was about 10 min including the practice session and an interblock resting period. During the ISI and the interblock resting period, participants were instructed to relax and to fix a cross located in the middle of the screen. The same testing protocol was administered to all patients.

2.3. Data acquisition

A 306-channel whole-head MEG (VectorView, Elekta Neuromag, Helsinki, Finland) was recorded in all participants. The MEG system consisted of 204 gradiometers and 102 magnetometers distributed over 102 locations in a helmet-shaped array inside the liquid helium Dewar. Prior to recording, a 3D digitizer (Polhemus, Colchester, VT, USA) was used to determine the position of fiducial landmarks, nasion, preauricular points (tragus bilaterally), individual head shape, and the position of four head position indicators (HPI) coils, used to determine the position of the head in relation to the MEG sensors before each run. Magnetoencephalography data were collected in two epochs lasting around 4 min each and corresponding to each block of the language task. Before each epoch, a measurement of the head position (using the HPI coils) was taken. Magnetoencephalography signal was amplified, filtered (low-pass filter of 200 Hz and high-pass filter of 0.03 Hz), analog-to-digital converted (sampling rate of 600 Hz), and was stored digitally for off-line data analysis.

Structural MRI scans obtained with a 1.5 T Avanto system (Siemens, Erlangen, Germany) in all participants included a magnetization-prepared rapid acquisition gradient-echo sequence (MPRAGE; TR 3.36 ms, TE 2730 ms, slice thickness 1 mm), a multi-echo fast low-angle shot pulse sequence (FLASH5; TR 20 ms, TE 1.85 ms, flip angle 5, slice thickness 1 mm), a fast spin-echo (FSE) T2 sequence (TR 3200 ms, TE 368 ms, flip angle 120, slice thickness 1 mm), and a fluid attenuation inversion recovery (FLAIR; TR 6000 ms, TE 390 ms, flip angle 120, slice thickness 1 mm).

2.4. Data analyses

Magnetoencephalography data were visually reviewed, and trials with eyeblinks and other artifacts were rejected from the analysis. A temporally extended Signal-Space Separation method (tSSS) was used in order to remove magnetic interference signals from the MEG measurements (for methods see [11]). A correlation limit of 0.800 or 0.980 was used, based on the level of noise found in each data set. A digital band pass filter of 0.1–30 Hz was applied off-line. Data were averaged across all 160 trials without distinction between concrete and abstract words. Magnetoencephalography data were co-registered with structural MRI using fiducial points and individual participant's head shape from the 3D digitizer using MRILab software (version 1.7.25, Elekta Neuromag, Helsinki, Finland).

Source analysis was performed using the minimum-norm estimate (MNE) software, version 2.5 (Matti Hämäläinen, Charlestown, MA, USA) allowing identification of cerebral generators of language evoked fields (EF) in each subject [12]. Using the cortex derived from a FreeSurfer reconstruction [13,14], an anatomically constrained linear estimation approach was applied, assuming that the sources are distributed in the cerebral cortex [15]. The forward solution, which models the signal pattern generated by a unit dipole at each location on the cortical surface, was calculated by using a linear collocation single-layer boundary element method (BEM) with the inner skull boundary approach, for each participant [16,17], derived from the MRI FLASH scan. The surface was tessellated with 5120 triangles, providing adequate numerical accuracy [18–21]. We used 5000 sources in each hemisphere. Each source corresponded to a dipolar source, with an average distance of 5 mm. The activation at each cortical location was estimated by using the noise covariance calculated from the individual subject's data. For locating the sources of activation, a noise-normalized MNE was calculated, i.e., dynamic statistical parametric maps (dSPM) were displayed on the inflated cortical surfaces. The activity displayed on a dSPM provides an F-statistic of the neural currents on the cortical surface. It also conveniently provides depth weighting of activity that more accurately localized the activation of brain activity during a language task [12].

Laterality indices (LI) were computed in all patients based on a source amplitude method using the dSPM results. The strength of each source was extracted between 250 and 550 ms from four regions of interest (ROIs) using the MNE software. Regions of interest were language-related areas, which included the anterior language area or Broca's area (pars opercularis and triangularis of the left inferior frontal gyrus, or respectively Brodmann's areas 44 and 45), the posterior language area or Wernicke's area (posterior section of the left superior temporal gyrus as well as the infero-posterior part of the left parietal lobe, or Brodmann's areas 22, 39 and 40) as well as their homologous regions in the right hemisphere. Regions of interest were manually defined on individual MRIs relying on anatomical landmarks. A source amplitude threshold was set in each subject at half of the maximal source amplitude extracted from all ROIs. Thus, all sources with an amplitude equivalent or higher to the half of the maximal amplitude source value were included in the LI calculation. This provided an objective method for setting the detection threshold. Laterality indices were then calculated using this formula:

$$LI = (L - R) / (L + R)$$

where L is the number of sources that exceeded the amplitude threshold in the left-hemisphere ROIs, and R is the number of sources, which exceeded the amplitude threshold in the right-hemisphere ROIs. $LI > +0.20$ was interpreted as a left-hemisphere language dominance, $LI < -0.20$ as a right-hemisphere language dominance, and LI between -0.20 and $+0.20$ as bilateral language pattern [22].

Structural MRI sequences of all patients with TSC were reviewed by a neuroradiologist (SMS) to identify the number of tubers in ROIs. Tubers were defined as areas of cortical gray matter distortion with decreased or isointense subcortical signal intensity on MPRAGE images and increased signal intensity on FSE T2 and FLAIR sequences, which are the diagnostic criteria established in prior reports [23].

For all patients, clinical records, including EEG reports and neuropsychological assessment results, were available and reviewed.

2.5. Statistical analyses

Statistical analyses were performed on MNE data using Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). Independent Student's *t*-tests were performed to investigate the relationship between the language pattern found in each patient and the number of tubers in ROIs. A Pearson Chi-square test was also performed to evaluate for an association between the language pattern and a history of epilepsy in TSC patients. All reported *p* values used two-tailed tests of significance with α set at 0.05.

3. Results

3.1. Magnetoencephalography language-evoked field during lexico-semantic decision task

The lexico-semantic task evokes a strong MEG language response in all patients. Cerebral activation starts with a bilateral occipital activation measured around 115 ms after the words' appearance (Fig. 1A). This visual activation is followed by a fusiform gyrus activation around 130 ms, reflecting basic visual feature analysis. At 175 ms post-stimuli presentation, a strong cerebral activation is measured in the basal temporal language area (Fig. 1B). Finally, cerebral activations are consistently measured in Wernicke's area (between 220 and 620 ms in Fig. 1C) and then in Broca's area (between 250 and 620 ms in Fig. 1D). As shown in Fig. 1, no significant activations, except the primary visual activity recorded in bilateral median occipital areas, are measured in the right hemisphere of this

patient who presents a clear left-hemisphere language dominance. All of these activations were expected from prior studies [24,25].

3.2. Hemispheric lateralization of language function

Laterality index in each patient is shown in Table 2. A left-hemisphere language dominance ($LI > 0.2$) is found in eleven patients (73.3%) with TSC, and a bilateral language pattern ($-0.2 < LI < 0.2$) is obtained in four patients (26.7%; patients 2, 6, 12, 13). No patient presents a right-hemisphere language dominance. Fig. 2A shows an example of a patient (patient #7 in Tables 1 and 2) with a clear left-hemisphere language dominance (as shown in Table 2, $LI = 0.95$) in both regions. This patient has no history of epilepsy and does not have tubers in ROIs seen on MRI. Fig. 2B shows an example of a patient (patient #2 in Tables 1 and 2) with a bilateral language representation (as shown in Table 2, $LI = 0.17$). This patient has no tubers in ROIs, but has a history of epilepsy and was not seizure free at the time of testing.

3.3. Relationship between hemispheric lateralization of language function and symptomatology

In each patient, individual MRI scans were revised to evaluate the presence of tubers in ROIs. Locations of each tuber in ROI are presented in Table 2. History of epilepsy is also reported. Statistical analysis investigating the relationship between cerebral language pattern and clinical as well as anatomical TSC characteristics shows that patients with a bilateral language pattern tend to have more tubers in ROIs than those with a left-hemisphere language dominance ($t = 2.05$, $p = 0.061$). Fig. 3 illustrates this relationship showing that TSC patients with multiple tubers in language ROI tend to have a lower LI than those with a lower number of tubers. Pearson Chi-square analyses also reveal that TSC patients with a history of epilepsy are significantly more prone to present a bilateral language pattern than TSC patients with no history of epilepsy (Pearson $\chi^2 = 6.23$, $p = 0.013$).

4. Discussion

This work constitutes the first study to investigate language lateralization in patients with TSC. We used a lexico-semantic decision task during MEG recording that allowed measurement of strong language cerebral activation in language-related areas that was expected from prior studies [24,25]. Cerebral activation starts with an occipital activation measured around 115 ms, which is followed by a fusiform gyrus activation around 130 ms reflecting basic visual feature analysis. At this stage, written words are clearly distinguished from geometrical forms, faces or other objects, but there is no discrimination between words/nonwords and random consonant strings [26]. At 175 ms post-stimuli presentation, a strong cerebral activation is measured in the basal temporal language area that would reflect the letter-string analysis. Some authors suggest that this region may support the transformation of written words into sounds, possibly involving phonological working memory [27]. Finally, cerebral activations are consistently measured in Wernicke's area (between 220 and 620 ms) and then in Broca's area (between 250 and 620 ms). Wernicke's area activation is associated with reading comprehension, including lexico-semantic aspects as well as phonological processing [28]. Broca's area activation is associated with semantic processing as well as graphophonological conversion of words that might reflect subvocal articulatory processes of the written word [29].

Interestingly, we found decreased language laterality in our TSC patient sample. Data show that, among the 15 patients involved in this study, 11 patients (73.3%) with TSC have a left-hemisphere language dominance whereas the remaining four patients (26.7%) have a bilateral language representation. In the healthy adult population, 94–96% of individuals present left-hemisphere language dominance [30]. However, when the left hemisphere has

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been injured or exposed to chronic deleterious episodes such as seizures, language function reorganization is likely to occur, especially when these events occur at a young age. Language functions can then be taken over by the right hemisphere or both hemispheres. There is an increase of aberrant brain circuits that support language functions in patients with cortical pathology [31,32]. Consistent with this view, individuals with epilepsy show greater language dominance variety than healthy individuals characterized by higher percentages of non left-hemisphere language dominance in epileptic than non-epileptic populations [33,34]. Atypical language patterns in lesional patients (for instance, brain tumor, vascular lesions) have also been reported [24,32]. In the present study, atypical language representations are associated with the clinical presentation of TSC. Investigation of the relationships between language lateralization patterns in patients with TSC and tuber cerebral location as well as a history of epilepsy showed that patients with a bilateral language pattern tend to have more tubers in language-related areas than those with a left-hemisphere language dominance, and that TSC patients with history of epilepsy are significantly more prone to present a bilateral language pattern than TSC patients with no history of epilepsy. These results show that multiple factors, including cerebral abnormalities and history of epilepsy, may contribute to the inter-hemispheric cerebral language reorganization predisposing to a decrease of left-hemispheric language dominance in patients with TSC. In the present study, the sample size is small; a research project including more patients would confirm these findings. In future studies, a comparison with control groups including patients without epilepsy with other developmental lesions (e.g., tumors, vascular lesions) or non-lesional patients with epilepsy would help to better specify respective influence of cortical tubers and epileptogenic activity on functional language dominance in patients with TSC.

Previous studies showed that right-handed patients with epilepsy present left-hemisphere language dominance in 63 to 96% of cases, whereas only 48 to 75% of left-handed or ambidextrous patients with epilepsy present a left-hemisphere language dominance [35,36]. In the present study, three out of fifteen participants (patients # 7, 11 and 13 in Table 1) present a left-or bilateral-handedness, presuming a presence of abnormal language dominance in our sample. However, there is no clear correlation between atypical manual dominance and abnormal language pattern in our group. Anomalous manual and language dominances may have been induced by multiple causes, including cortical tubers and epileptogenic activity, which may have affected independently both functional representations. White matter abnormalities are often found in patients with TSC and may have also influenced anatomo-functional networks. A study including fiber tractography may help to explain the relationship between manual and language dominances in patients with TSC. For instance, tractography would allow for investigation of the intra-hemispheric language representation in patients presenting left-hemisphere language dominance and an atypical manual dominance. Our research group is currently analyzing diffusion tensor imaging data acquired in these patients in order to investigate the relationship between fiber track anomalies and tuber location, epilepsy history as well as language and manual dominances. We hope to publish these data in the near future.

Language laterality index calculation is threshold-dependent; therefore some would consider this a limitation [34]. There is no consensus of procedures for determining the threshold. Here, we propose an objective method to obtain an appropriate threshold. A source amplitude threshold was set in each subject at half of the maximal source amplitude extracted from all ROIs. Thus, all sources with an amplitude equivalent or higher to the half of the maximal amplitude source value were included in the LI calculation. This provided an objective method for setting the detection threshold, which renders the laterality index calculation statistically robust.

In the present study, the sample of patients was small, and no comparison with standard invasive techniques such as intracarotid amobarbital injection (the Wada Test) or cortical electrostimulation mapping was made for validation of language dominance pattern. In further studies, using a protocol including multiple tasks would be helpful in order to assess multiple aspects of language functions, such as receptive and expressive language. Magnetoencephalography may also be used to better understand functional reorganization in patients with different cerebral pathologies such as epilepsy and TSC. Factors influencing atypical language representation have theoretical importance in understanding the organization and reorganization of higher cognitive functions and the underlying pathology as well as practical implications in some patients such as cognitive and language rehabilitation in individuals with acquired lesions (e.g., traumatic brain injury, tumors or strokes) as well as presurgical assessment of language function in candidates for epilepsy surgery. Functional connectivity measures using MEG and fMRI, both at rest and during activation, also are a new way to characterize the integrity of cortex. Combining functional connectivity and structural connectivity, or the human connectome, will in future studies lead to a better understanding of how tubers affect functional networks [37]. In addition to language mapping, MEG has also been shown to be helpful for the localization of epileptic activity in patients with TSC who are candidates for epilepsy surgery [8,38]. Inclusion of a MEG recording for localization and lateralization of epileptogenic zone as well as language functions in the presurgical assessment protocol of patients with TSC who are epilepsy surgery candidates may diminish the need for invasive procedures or at least help in choosing stimulation sites and reduce the number of intracranial electrodes used during invasive mapping.

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Fig. 1. dSPM statistic maps of language cerebral response. dSPM statistic maps of cerebral activations through time in response to a language task in a patient with TSC (patient #7 in Tables 1 and 2). Cerebral response starts with (A) a bilateral median occipital response, followed by (B) a left basal temporal language area activation. Subsequent activation appears in (C) Wernicke's area and is later accompanied by (D) a Broca's area activation.

Fig. 2.

MNE waveforms of language cerebral response. MNE waveforms between -100 and 3000 ms measured in the left (red line) and right (blue line) (I) anterior ROIs (Broca's area and its right counterpart), as well as in the left (red line) and right (blue line) (II) posterior ROIs (Wernicke's area and its right counterpart) of two patients with TSC: (A) Patient #7 and (B) Patient #2. Green horizontal lines show the stimulus duration. The amplitude scale is not equal between both participants, in order to preserve dynamic range in each patient.

Fig. 3. Relationship between number of tubers in language-related ROIs and language laterality index. Only patients with tubers in ROIs are shown on this graph. Larger number of tubers in ROIs is associated with decreased laterality indices.

Table 1

Demographical and clinical data of participants with TSC diagnosis.

TSC patients	Age (yrs)	Sex	Handedness	Education (yrs)	History of epilepsy (age at onset)	EEG	Sz frequency
1	35	F	R	16	Yes (18 yrs)	Partial complex Sz	2 Sz/month
2	47	F	R	12	Yes (unclear ^a)	Some clinical Sz did not have definite EEG correlates and others showed generalized high frequencies. Interictal activity showed left>right fronto-temporal epileptiform spikes	Unclear ^a
3	42	F	R	16	Yes (6 months)	N/A	Sz free
4	40	F	R	16	No	–	–
5	44	F	R	16	No	–	–
6	31	M	R	16	Yes (4.5 yrs)	Generalized, simple partial Sz	Sz free
7	16	F	B	11	No	–	–
8	32	M	R	11	No	–	–
9	51	M	R	18	Yes (16 yrs)	N/A	Sz free
10	44	F	R	18	No	–	–
11	43	M	L	21	No	–	–
12	40	F	R	16	Yes (0 month)	N/A	Sz free
13	41	F	B	12	Yes (1 yr)	Complex partial and generalized tonic-clonic Sz	Sz free
14	46	F	R	15	No	–	–
15	26	F	R	17	No	–	–

Abbreviations: N/A = not available; yrs = years; Sz = seizures.

^aSome of the reported seizures might be syncopal episodes, which makes it hard to define the seizure frequency in this patient who is actually under cardiologic evaluation.

Table 2

Language lateralization and clinical characteristics in TSC patients.

TSC patients	Language LI	Language pattern	History of epilepsy	Tuber location (in ROIs)
1	0.42	L	Yes	–
2	0.17	B	Yes	–
3	0.62	L	Yes	–
4	0.30	L	No	–
5	0.33	L	No	–
6	0.10	B	Yes	–
7	0.95	L	No	–
8	0.53	L	No	L inferoparietal
9	0.40	L	Yes	R STG, L inferoparietal
10	0.48	L	No	–
11	0.32	L	No	–
12	–0.06	B	Yes	Multiple lesions in anterior and posterior ROIs
13	0.13	B	Yes	Multiple lesions in anterior and posterior ROIs
14	0.31	L	No	L and R pars opercularis, L STG
15	0.31	L	No	L pars opercularis, L pars triangularis, L and R inferoparietal

Abbreviations: L = left; R = right; B = bilateral; STG = superior temporal gyrus. Patients with bilateral language dominance are emphasized in bold.