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Diffuse Cerebral Language Representation in Tuberous Sclerosis Complex

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Abstract

Introduction—Tuberous sclerosis complex (TSC) is a multisystem genetic disorder affecting multiple organs, including the brain, and very often associated with epileptic activity. Language acquisition and development seems to be altered in a significant proportion of patients with TSC. In the present study, we used magnetoencephalography (MEG) to investigate spatiotemporal cerebral language processing in subjects with TSC and epilepsy during a reading semantic decision task, compared to healthy control participants.

Methods—Fifteen patients with TSC and 31 healthy subjects performed a lexico-semantic decision task during MEG recording. Minimum-norm estimates (MNE) were computed allowing identification of cerebral generators of language evoked fields (EF) in each subject.

Results—Source analysis of the language EF demonstrated early bilateral medial occipital activation (125ms) followed by a fusiform gyrus activation around 135ms. At 270ms post stimuli presentation, a strong cerebral activation was recorded in the left basal temporal language area. Finally, cerebral activations were measured in Wernicke's area followed by Broca's area. The healthy control group showed larger and earlier language activations in Broca and Wernicke's areas compared to TSC patients. Moreover, cerebral activation from Broca's area was greater than activation from Wernicke's area in both groups, but this difference between anterior and posterior regions was smaller in the TSC group. Finally, the activation latency difference between Broca and Wernicke's areas was greater in healthy controls than in TSC patients, which shows that activations in these areas are more serial in control subjects compared to TSC patients in whom activations occur more simultaneously.

Conclusions—This is the first study to investigate cerebral language pattern in patients with TSC. Compared to healthy controls, atypical neuromagnetic language responses may reflect cerebral reorganization in these patients in response to early epileptogenic activity or presence at birth of multiple brain lesions.

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Keywords

magnetoencephalography (MEG); source localization; distributed source model; tuberous sclerosis complex (TSC); epilepsy; language

1. INTRODUCTION

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder with an occurrence of 1 of 6,000 live birth (Osborne et al., 1991). Although the phenotype is variable, TSC can affect multiple organs including kidneys, skin, heart and the central nervous system. Several cerebral lesions are characteristic of TSC and include cortical tubers, subependymal nodules and white matter abnormalities (Ridler et al., 2004). Neurologic manifestations of TSC include epileptic seizures in nearly 90% of patients, mental retardation, autism and psychiatric disturbances (Crino et al., 2006). Global intellectual impairment is reported in approximately 50% of patients with TSC (Prather & de Vries, 2004; de Vries & Prather, 2007; Winterkorn et al., 2007) and individuals with a normal intelligence functioning are prone to specific neuropsychological difficulties (Harrison et al., 1999). There are few studies investigating the neuropsychological profile of individuals with TSC, which consistently report long-term memory, working memory, attentional skills and executive functions deficits (Jambaque et al., 1991; Harrison et al., 1999; Prather & de Vries, 2004; Ridler et al., 2007). There have been no specific neuropsychological or neuroimaging studies of language function in TSC. Nevertheless, Prather et al. (2002) investigated neuropsychological profile of 22 children with TSC and no global intellectual impairment. They reported that 24% of these children presented language deficits, which tend to improve with age. Using a parental questionnaire, Prather and de Vries (2004) reported that 66% of 34 children with TSC had abnormal language acquisition or development. These children presented notably difficulties in expressive vocabulary, abstract language skills, and expressive semantic-grammatical abilities. Finally, a survey including 510 children and adults with TSC revealed that only 28% of participants were reported by their family to have had a normal language development (de Vries & Bolton, 2002).

The presence of cerebral lesions or epileptic activity may induce language function abnormalities or reorganization in patients with TSC. Cortical tubers have been shown to contribute to cognitive impairment in TSC, including language abnormalities, by affecting both cortical processing and white matter connections (Zaroff et al., 2006; Jansen et al., 2008; Gallagher et al., 2010). Recently, our group reported decreased language laterality in patients with TSC (Gallagher et al., 2012). In this study, we showed that TSC patients with a bilateral language pattern tend to have more tubers in language-related areas (Broca and Wernicke's areas) than those with a left 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.

Magnetoencephalography (MEG) data acquired during a language task can be combined with structural MRI to produce a spatiotemporal map of cortical activity (e.g. Dale et al. 2000; Breier & Papanicolaou, 2008). MEG can thus quantify specific changes in neural currents including magnitude of response and latency in language processing in the human cortex and specific cortical areas (Salmelin, 2007). These changes can be used as sensitive markers of disease, such as in multiple sclerosis, autism, and brain tumors (Douw et al., 2008; Dell'Acqua et al., 2010; Roberts et al. 2011). In the present study, we used MEG to investigate spatiotemporal cerebral language processing in subjects with TSC during a reading semantic decision task, compared to healthy control participants. Figure 1 illustrates the sequence of cerebral language processing in healthy adults during a reading semantic

decision task (Cohen et al., 2000; Dale et al., 2000; Kamada et al., 2006; Salmelin, 2007). In the present study, these regions of interest were used for analysis.

2. METHODS

2.1. Participants

The clinical sample was composed of fifteen patients (11 females (73%), mean age = 38.5 ± 9.1 years, mean education duration = 15.4 ± 2.8 , 12 right-handed) who met clinical diagnostic criteria for TSC (Roach et al., 1998) and who were seen at the Herscot Center for Tuberous Sclerosis Complex at Massachusetts General Hospital. Seven patients had a history of epilepsy, and five of the seven were seizure free at the time of testing. All patients showed structural lesions on MRI such as cortical tubers or white matter abnormalities. Selection criteria for inclusion were: age of 12 years and 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.

A control group was also formed and included thirty-four healthy control participants. The data from three healthy control participants had to be rejected because either the lack of MRI data (one participant) or the presence of significant artifacts on MEG data (two participants). Among the 31 remaining participants, 19 were females (61%), the mean age was 22.2 ± 3.0 years, the mean education duration was 15.5 ± 2.06 years, and all participants were right-handed. Demographical data from both groups are presented in Table 1 and clinical data from TSC patients are presented in Table 2.

The handedness of all participants of TSC and healthy control groups was assessed using the Edinburgh Inventory (Oldfield, 1971). The MGH institutional review board approved this study and written informed consent was obtained from all participants.

2.2. Language paradigm

All participants performed a semantic decision task during MEG recording. 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 into MEG dewar within the shielded room.

The semantic decision task consisted on a sequential visual presentation of 160 English words. Participants 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 1000ms on a screen placed at 150cm from the participant's eyes. The inter stimuli interval (ISI) was 2000ms. Each trial had a duration of 3000ms. 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 minutes including the practice session and an inter block resting period. During the ISI and the inter block 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 participants.

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, the nasion, preauricular points (tragus bilaterally), the 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 (Hämäläinen et al., 1993). MEG data were collected in two epochs lasting around 4 minutes 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. MEG 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 600Hz) and were stored digitally for off-line data analysis.

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

2.4. Data analyses

MEG data were visually reviewed and trials with eyeblinks and other artifacts were rejected from analysis. A temporally extended Signal-Space Separation method (tSSS) was used in order to remove magnetic interference signals from MEG measurements (for methods see Taulu & Hari, 2009). 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 0.1–30Hz was applied off-line. Data were averaged across all 160 trials without distinction between concrete and abstract words. MEG data was 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 minimum-norm estimates (MNE), using MNE software (version 2.5, Hamalainen, 2006), allowing identification of cerebral generators of language evoked fields (EF) in each subject (Dale et al., 2000). Using the cortex derived from a FreeSurfer reconstruction (Dale et al., 1999; Fischl et al., 1999), an anatomically constrained linear estimation approach was applied, assuming the sources are distributed in the cerebral cortex (Dale & Sereno, 1993). 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 (Hämäläinen & Sarvas, 1989; Oostendorp & Van Oosterom, 1989), derived from the MRI FLASH scan. The surface was tessellated with 5120 triangles, providing adequate numerical accuracy (Crouzeix et al., 1999; Fuchs et al., 2001; Tarkiainen et al., 2003; de Jongh et al., 2005). We used 5000 sources in each hemisphere. Each source corresponded to a dipolar source, with an average distance of 5mm. The activation at each cortical location was estimated by using the noise covariance calculated from individual subject's data. For locating the sources of activation, a noise-normalized MNE was calculated, i.e., a 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 activation of brain activity during a language task (Dale et al., 2000).

For purpose of intersubject group averaging (TSC and healthy control groups), the reconstructed surface for each participant was also morphed into the FreeSurfer standard averaged brain (Dale et al., 1999, 2000; Fischl et al., 1999, 2001). Two regions of interest (ROIs) were manually defined on each hemisphere of the averaged brain, relying on anatomical landmarks. ROIs included anterior and posterior areas. Anterior ROI included

pars opercularis and triangularis of the inferior frontal gyrus, which corresponded to Broca's area in the left hemisphere and its right counterpart or respectively Brodmann's areas 44 and 45, whereas posterior ROI included posterior section of the superior temporal gyrus as well as the infero-posterior part of the parietal lobe, which corresponded to Wernicke's area in the left hemisphere and its right homologous regions, or Brodmann's areas 22, 39 and 40. For each participant, mean source amplitude values were extracted from 150ms time windows from 300ms and 750ms (300–450ms, 450–600ms, and 600–750ms) from source distribution for each ROIs. Peak latencies were extracted from the averaged signal during a 500ms time window recorded between 250 and 750ms after stimulus onset. This time window was established based on visual inspection of all individual data and included peak language activation for all participants. A baseline correction was applied on individual averaged waveform to ensure that all brain responses had an amplitude of 0nAm at stimulus onset.

2.5. Statistical analyses

Statistical analyses were performed on MNE data using Statistic Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). Repeated measures analyses of variance (ANOVA) were used to compare mean amplitude value as well as peak latency of the language evoked field between groups (TSC *vs* healthy control), hemispheres (left *vs* right), and ROIs (anterior *vs* posterior). A Bonferroni correction was used for multiplicity of tests. Independent Student's *t*-tests were performed to compare the task performance between both groups. All reported *p*-values used two-tailed tests of significance with α set at 0.05.

3. RESULTS

3.1. Behavioral data

Performance of the semantic decision task was measured in each group to ensure that the participants' attention level was acceptable, that they were performing the task adequately, and that there was no significant differences between both groups. On average, healthy controls obtained similar performance (mean success rate = $80.47\% \pm 5.41\%$) to the language task than the patients with TSC (mean success rate = $82.11\% \pm 4.60\%$). No significant difference was obtained between both performances ($p > 0.05$).

3.2. MEG

The semantic decision task evoked a strong MEG signal in all participants. Figure 2 shows scalp waveforms from four MEG channels, each located over a region of interest (occipital cortex, basal temporal language area (BTLA), Wernicke's Area and Broca's Area), in a healthy control participant. Figure 3 presents the dSPM of typical cerebral activations and scalp topographies through time in the same control subject. As shown on these figures, a bilateral medial occipital activation was first measured around 125ms after words appearance (Figs 2a and 3a). This visual activation was followed by a fusiform gyrus activation around 135ms reflecting basic visual feature analysis (not shown on Figures). At 270ms post stimuli onset, a strong cerebral activation was recorded in the left basal temporal language area (BTLA, Figs 2b and 3b). Finally, cerebral activations were consistently measured in Wernicke's area (between 310 and 430ms on Figs 2c and 3c) followed by Broca's area (between 330 and 440ms on Figs 2d and 3d). As shown on Figure 1, all of these cerebral activations were expected from prior studies involving similar task (i.e. Cohen et al., 2000; Dale et al., 2000; Kamada et al., 2006; Salmelin, 2007). No significant activations were measured in the right hemisphere of this control participant.

Figure 4 shows averaged MNE cerebral source waveforms measured in left (related to Broca's area, red line) and right (blue line) anterior ROIs (Figure 4a for TSC group and 4c for control group) as well as left (related to Wernicke's area, red line) and right (blue line) posterior ROIs (Figure 4b for TSC group and 4d for control group) in both groups. Both groups showed a strong language response to presented words (represented by the green line labeled "Stimulus ON" on all graphs) in both ROIs and hemispheres. Healthy control group showed larger and more sustained language activation in both ROIs and hemispheres compared to TSC group. For both groups, activations returned to baseline at around 2900ms after stimulus onset or 100ms before the next stimulus onset (not shown here on Figure 4).

Statistical analysis on the mean amplitude of the MEG activations showed that the healthy control group had significantly greater activations compared to the TSC group ($F_{1,44}=11.29$, $p=0.002$). Due to this group amplitude difference, the amplitude scale (y-axis) on Figure 4 is unequal in order to preserve dynamic range in each group. A ROI main effect was also obtained ($F_{1,44}=32.26$, $p<0.0001$) revealing that cerebral activation from anterior ROI (Broca's area and its right counterpart) was greater than activation from posterior ROI (Wernicke's area and its right homologous region). Finally, an interaction between Groups and ROIs was obtained ($F_{1,44}=5.08$, $p=0.029$), showing that the difference of activation between anterior and posterior ROIs was significantly larger in the control group compared to the TSC group. In other words, the latter showed a smaller difference in amplitude of activation between ROIs, which may reflect a more diffuse cerebral activation in the TSC group. Although the hemisphere main effect was not significant, both groups showed larger amplitude in the activation over the left compared to the right hemisphere, and this difference was slightly larger in the control group compared to the TSC group.

Statistical analysis on the latency of the MEG activations revealed that peak latencies are greater in healthy control participants compared to TSC patients, because the control group has significantly greater and more sustained language activations in both ROIs and hemispheres than the TSC group (Figure 4). In order to compare equivalent latencies without this amplitude bias, latency values were corrected. First, a peak amplitude ratio between both groups for each ROI has been calculated. For instance, the averaged peak amplitude between 250 and 750ms in Broca's area is equal to 1.15nAm in the TSC group whereas it is equal to 4.18nAm in the control group. For this ROI, the peak amplitude ratio was $(1.15/4.18) = 0.275$. For each participant, the latency value at $[0.275 \times \text{peak amplitude value}]$ in Broca's area was recorded. The same approach was applied in Wernicke's area and in right homologous regions. A repeated measures ANOVA revealed that shorter latencies were measured in the healthy control group compared to the TSC group ($F_{1,44}=84.03$, $p=0.00001$). A ROI main effect and a ROI x Group simple interaction showed that language activations occurred significantly earlier in posterior areas than in anterior areas ($F_{1,44}=27.78$, $p=0.00001$), and that this difference is greater in healthy controls than in TSC patients ($F_{1,44}=4.12$, $p=0.048$). In fact, the latency difference between anterior and posterior ROIs is significant in healthy control group ($F_{1,44}=40.86$, $p=0.00001$), whereas it tend to be significant in the TSC group ($F_{1,44}=3.89$, $p=0.055$). A Hemisphere main effect was also obtained showing that cerebral activations occurred earlier in the left hemisphere compared to the right hemisphere ($F_{1,44}=4.39$, $p=0.042$). A Hemisphere x Group simple interaction ($F_{1,44}=3.77$, $p=0.059$) showed that this difference tend to be greater in TSC patients ($F_{1,44}=6.05$, $p=0.018$) than in healthy controls ($F_{1,44}=0.018$, $p=0.893$).

4. DISCUSSION

This study presents the first neuroimaging investigation of language functions in individuals with TSC.

4.1. Spatiotemporal neuromagnetic response during the semantic decision task

Strong language activations were recorded in TSC patients as well as in healthy controls, and averaged MEG activations from both groups correspond to brain responses reported in prior MEG studies involving similar task (i.e. Kamada et al., 2006, Salmelin, 2007). Early bilateral medial occipital activation reflects visual processing of the visually presented word starting around 100ms after stimulation. Medial occipital activation is followed by a fusiform gyrus activation that shows basic visual feature analysis around 135ms. 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 (Pammer et al., 2004). At 270ms post stimuli presentation, a strong cerebral activation is recorded in the left basal temporal language area probably reflecting the letter-string analysis. This is the first stage of language-specific analysis, which corresponds to pre-lexical processing (Salmelin, 2007; Tarkiainen et al., 1999). At this stage, words are now distinguished from nonwords (Pammer et al., 2004). Finally, cerebral activations are measured in Wernicke's area followed by Broca's area and reflect language processing. Wernicke's area is associated with reading comprehension, including lexico-semantic aspects as well as phonological processing (Wydell et al., 2003). Broca's area activation is associated with semantic processing as well as grapho-phonological conversion of words that might reflect subvocal articulatory processes of the written word (Mainly et al., 2008). As expected, cerebral activations occur earlier in the left than in the right hemisphere, reflecting left hemisphere language dominance, and in Wernicke's area compared to Broca's area.

4.2. Comparison of spatiotemporal neuromagnetic response between both groups

Although TSC patients show numerous similarities with healthy controls in their cerebral responses to the language task (such as in Figure 1), two major spatial and temporal discrepancies are measured between activations from both groups, which reflect aberrant cerebral language circuits and possible functional cerebral reorganization in TSC patients.

First, the healthy control group shows larger and earlier language activations in Broca and Wernicke's areas compared to TSC patients. This difference has been reported in the literature between healthy controls and epileptic patients (Bowyer et al., 2005) and might be related to the underlying pathology caused by epilepsy or TSC, anticonvulsant drugs, frequency of interictal epileptiform discharges, or a combination of these factors. In TSC, there are both cortical and white matter abnormalities that could affect the timing and magnitude of the cortical neuromagnetic response. White matter abnormalities, as observed on MRI, are varied and include radial bands and other non-specific changes often proximal to cortical tubers. Some of the abnormalities are related to changes in myelination, presence of abnormal cells such as balloon cells, and abnormal connections. Cortical tubers themselves may also be hypomyelinated. Both the cortical and white matter abnormalities TSC may affect the timing of neural events, as well as the presence of epileptiform discharges. Magnetoencephalography (MEG) has a temporal resolution of milliseconds, making it exquisitely sensitive to neural timing and has been used extensively for non-invasively studying language processing in health and disease. Healthy subjects have more homogeneous myelination of white matter that may result in more rapid conduction and thus a reduced latency.

Secondly, cerebral activations from anterior ROI (Broca's area and its right counterpart) were greater than activations from posterior ROI (Wernicke's area and its right homologous region) in both groups, but this difference between anterior and posterior regions was smaller in the TSC group. Moreover, the activation latency difference between Broca and Wernicke's areas was greater in healthy controls than in TSC patients, which shows that

activations in these areas are more serial in control subjects compared to TSC patients in whom activations occur more simultaneously. These findings are of great interest because they show a more diffuse cerebral language activation in the TSC group compared to healthy controls, which may reflect cerebral reorganization of language function in TSC patients. Inter- and intra-hemispheric cerebral language reorganization has been previously reported in epileptic patients as well as in patients with left hemisphere lesion (Pataria et al., 2004; Cousin et al., 2008; Tanriverdi et al., 2009). In a recent study (Gallagher et al., 2012), we investigated language dominance in this group of patients with TSC. All patients present multiple cerebral lesions, such as cortical tubers, and nearly half of them have a history of epilepsy. We found that patients with history of epilepsy are significantly more prone to present a bilateral language pattern than patients with no history of epilepsy. Furthermore, TSC patients with multiple tubers located in language-related areas (Broca and Wernicke's areas) tend to have more bilateral language pattern than those with a lower number of tubers in language-related areas, who present more frequently typical left-language cerebral pattern. History of epilepsy and the presence of cerebral lesions in language-related areas may explain the possible functional cerebral reorganization seen in the present study and characterized by more diffuse language activations in TSC patients compared to healthy controls.

5. CONCLUSIONS

We found profound differences in the timing and the magnitude of language-related neuromagnetic activity between TSC subjects and healthy controls. The current findings are consistent with previous studies showing an increased incidence of aberrant brain circuits that support language functions in patients with cortical pathologies (Satz et al., 1988; Thulborn et al., 1999). Atypical neuromagnetic language responses may reflect cerebral reorganization in these TSC patients in response to early epileptogenic activity or presence at birth of multiple brain lesions. As shown in the present study, MEG is a powerful imaging technique that can be especially helpful to potentially quantify cerebral reorganization and language functions in patients with 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 presurgical assessment of language function in candidates for epilepsy surgery. Future studies using other language tasks as well as correlating with clinically identified language deficits from neuropsychological testing may reveal other abnormalities in language processing in patients with TSC. This study demonstrates, nevertheless, that MEG safely localizes language in TSC patients, which could be useful as part of a presurgical assessment.

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Figure 1.

Diagram of the expected brain sequence of language processing during a reading semantic decision task in healthy adults. A primary visual activity is recorded over bilateral median occipital regions (between 100 and 125ms) followed by a fusiform gyrus activation (around 200ms). A basal temporal language area response is then recorded around 270ms) likely reflecting letter-string analysis and pre-lexical processing. Finally, Wernicke's and Broca's Areas activations appears (from 300ms until 450–500ms), showing specific language processing. The rendering of the brain shows the regions of interest of the anterior (Broca's area) and posterior (Wernicke's area) language areas involved in language processing. We used these regions of interest in our analysis described in this paper.

Figure 2.

Waveforms recorded through time from a gradiometer, each located over a region of interest (occipital cortex, basal temporal language area (BTLA), Wernicke's and Broca's areas), in a healthy control participant. Subject's left hemisphere, scalp (in gray) and MEG helmet (in blue) 3D reconstructions are shown. Cerebral response starts with (a) an occipital activation measured around 125ms after words onset, followed by (b) a left BTLA activation occurring around 270ms post stimulus onset. Subsequent activation appears in (c) Wernicke's Area around 325ms, and is later accompanied by (d) a Broca's Area activation (around 365ms). These time points were selected in order to correspond to the dSPM statistic maps shown on Figure 3.

Figure 3.

dSPM statistic maps of typical cerebral activations through time in a healthy control participant (same subject than shown on Figure 2) in response to a visual semantic decision task. Cerebral response starts with (a) a bilateral median occipital activation measured around 125ms after words onset, followed by (b) a strong left basal temporal language area activation occurring around 270ms post stimulus onset. Subsequent activation appears in (c) Wernicke's Area between 310 and 430ms, and is later accompanied by (d) a Broca's Area activation (between 330 and 440ms). Two regions of interest (ROIs) were manually defined on each hemisphere, including posterior (Wernicke's) and anterior (Broca's) areas, and are shown in green under these areas' labels (top left). Scalp topographies corresponding to the four cerebral activation time points are also shown below cerebral maps.

Figure 4.

Grand averaged MNE waveforms measured in left (red line) and right (blue line) anterior ROIs of (a) TSC and (b) control groups as well as in left (red line) and right (blue line) posterior ROIs of (c) TSC and (d) control groups between 0 and 2000ms. On each graph, the green horizontal line labeled "Stimulus ON" shows stimulus duration. The amplitude scale is not equal between both groups, in order to preserve dynamic range in each group. For both groups, a strong cerebral response to words is recorded in both ROIs and hemispheres. Healthy control group showed larger and more sustained language activation in both ROIs and hemispheres compared to TSC group.

Table 1

Demographical data from TSC and control groups

	TSC Patients	Healthy Controls
N	15	31
Sex (female)	11 (73%)	19 (61%)
Age (years)	38.5 ± 9.1	22.2 ± 3.0
Education (years)	15.4 ± 2.8	15.5 ± 2.06
Handedness(right)	12	31

Table 2

Demographical and clinical data of participants with TSC diagnosis

TSC Patients	Age (yrs)	Sex	History of Epilepsy (age at onset)	History of Treatment	Current AEDs	Sz Frequency (age at Sz arrest)
1	35	F	Yes (18 yrs)	Multiple AEDs	Lamotrigine	2 Sz/month
2	47	F	Yes (unclear ^d)	Multiple AEDs	none	Unclear ^d
3	42	F	Yes (6 months)	Phenobarbital	none	Sz free (18 yrs)
4	40	F	No	No	-	-
5	44	F	No	No	-	-
6	31	M	Yes (4.5 yrs)	Phenytoin sodium	none	Sz free (10 yrs)
7	16	F	No	-	-	-
8	32	M	No	-	-	-
9	51	M	Yes (16 yrs)	Phenytoin sodium	none	Sz free (N/A)
10	44	F	No	-	-	-
11	43	M	No	-	-	-
12	40	F	Yes (0 month)	Lamotrigine, valproic acid, phenobarbital, carbamazepine	Lamotrigine	Sz free (35 yrs)
13	41	F	Yes (1 yr)	Multiple AEDs	none	Sz free (14 yrs)
14	46	F	No	-	-	-
15	26	F	No	-	-	-

Abbreviations: N/A = not available; yrs = years; AED = antiepileptic drug; Sz = seizures

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