

Can small lesions induce language reorganization as large lesions do?

Fernando Maestú,^{a,b,c} Cristobal Saldaña,^d Carlos Amo,^a Mercedes González-Hidalgo,^e
Alberto Fernandez,^{a,f} Santiago Fernandez,^{a,c} Pedro Mata,^d Andrew Papanicolaou,^g
and Tomas Ortiz^{a,f,*}

^a Centro de Magnetoencefalografía Dr Pérez Modrego, Pabellón 8, Facultad de Medicina, Universidad Complutense de Madrid, Madrid 28040, Spain

^b Departamento de Psicología Básica II (procesos cognitivos), facultad de Psicología UCM, Madrid 28223, Spain

^c Departamento de Psicología, Universidad Camilo José Cela, Madrid 28692, Spain

^d Departamento de neurocirugía, Hospital Universitario San Carlos, Madrid 28040, Spain

^e Departamento de neurofisiología, Hospital Universitario San Carlos, Madrid 28040, Spain

^f Departamento de Psiquiatría, Facultad de Medicina, Universidad Complutense Madrid, Madrid 28040, Spain

^g Vivian L. Smith Center for Neurologic Research, Department of Neurosurgery, University of Texas-Houston Medical School, Houston, TX 77030, USA

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Abstract

Shift of the cortical mechanisms of language from the usually dominant left to the non-dominant right hemisphere has been demonstrated in the presence of large brain lesions. Here, we report a similar phenomenon in a patient with a cavernoma over the anterolateral superior temporal gyrus associated with epilepsy. Language mapping was performed by two complementary procedures, magnetoencephalography, and electrocorticography. The maps, indicated right temporal lobe dominance for receptive language and left frontal lobe dominance for expressive language. These results indicate that a small lesion, associated with epilepsy, may produce selective shifting of receptive language mechanisms as large lesions have been known to produce.

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1. Introduction

Language reorganization in the course of recovery from brain damage has been traditionally studied in various clinical situations (Vicari et al., 2000). Functional neuroimaging, such as positron emission tomography (PET) (Stowe et al., 2000) and functional magnetic resonance imaging (fMRI) (Billingsley, McAndrews, Crawley, & Mikulis, 2001), have demonstrated reorganization of language functions. However, there seem to be differences between reorganization of language involving regions adjacent to the lesion and that involving homotopic regions in the contralateral (pre-morbidly dominant) hemisphere. Specifically, it appears that shift of the language mechanism to the

right hemisphere, after left temporal lobe damage, occurs in infants with early brain injury (Muller et al., 1999), but peri-lesional reorganization (Stowe et al., 2000) or incompletely crossed lateralization (Muller et al., 1999) occurs after language acquisition has been completed, in older children and adults. However, several studies have also shown greater activity over the temporal areas homotopic to those of the dominant (usually left) but damaged hemisphere (Billingsley et al., 2001; Hertz-Pannier et al., 2002; Papanicolaou, Levin, & Eisenberg, 1984, 1987, 1988; Weiller et al., 1995) suggestive of radical reorganization involving hemispheric dominance shift even in adults.

Traditionally, assessment of hemispheric dominance for language, is made using the Wada test (Wada & Rasmussen, 1960) or intraoperative electrocortical stimulation mapping (Ojeman, Ojeman, Lettich, & Berger, 1989). Recently, however in a series of normative

* Correspondence author. Fax: +34-91-394-22-94.

E-mail address: cmeg@rect.ucm.es (T. Ortiz).

(Breier, Simos, Zouridakis, Constantinou, & Papanicolaou, 1998; Simos, Breier, Zouridakis, & Papanicolaou, 1998) and patient studies (Breier et al., 1999; Papanicolaou et al., 1999; Simos et al., 1999) it has been repeatedly demonstrated that magnetic source imaging (MSI), a completely non invasive neuroimaging method (Papanicolaou, 1998) can provide as valid language lateralization and intra-hemispheric localization data as the Wada test (Breier et al., 1999) and the intraoperative (Simos et al., 1999) or extraoperative (Papanicolaou et al., 1999) electrocortical stimulation mapping.

In the present study we present MSI-derived evidence for a shift of the receptive language mechanisms to the right temporal lobe in the presence of a small left temporal lesion. In addition, we present evidence derived from electrocortical stimulation in the same patient that although radical reorganization of the receptive language mechanisms appeared to have taken place, the expressive language mechanism appears to have remained in the left frontal lobe.

2. Case description

AA, a 42-year-old right-handed male with refractory epilepsy, was referred to the Department of Neurosurgery, Hospital Universitario San Carlos, to be considered as a candidate for epilepsy surgery.

During the patient's childhood his parents noticed nocturnal terror episodes, random mood changes, language problems and scholastic difficulties. The patient reported that his language problems had begun with stuttering, followed by more serious ones including difficulties in the production of palatal phonemes such as "Q" and "R." The severity of those language problems was progressively and spontaneously minimized without speech therapy. At the age of 13 years, although occasional stuttering problems would reappear in the context of stressful situations, the patient still reported a "more or less permanent difficulty with fluent speech production."

At the age of sixteen, the patient suffered his first partial complex seizure, with a left temporal focus (as evidenced

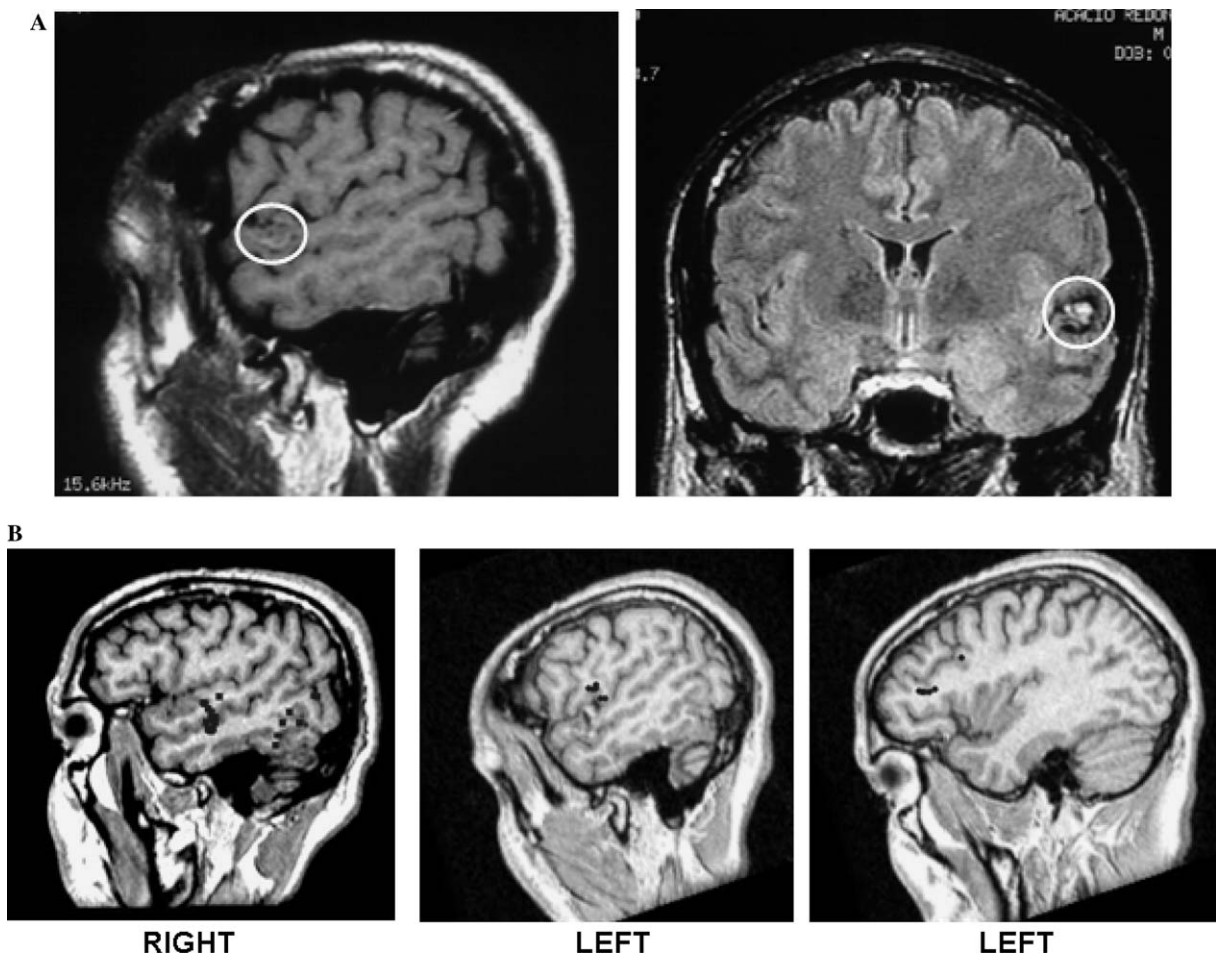


Fig. 1. (A) The location of the cavernoma on the sagittal and the coronal plane over the superior temporal gyrus. (B) The activity sources for the right temporal and left frontal regions.

by routine EEG testing). At that time he was diagnosed as epileptic. From the time of this diagnosis, the patient has been treated with different drugs (carbamazepine, topiramate, and lamotrigine), but the treatment has not resulted in adequate control of his seizures.

At the time of the MSI evaluation the patient's symptoms included nocturnal episodes (two per month) consisting of involuntary movements of all four extremities, along with guttural sound emissions and head torsion to the left. Episodes occurring during the day (two or three per month) consist of simple partial seizures involving speech arrest and speech onset difficulties followed by dysnomia and paraphasic language, but without receptive language difficulties. In fact, evaluation during such episodes, showed that the patient could maintain his capacity to respond to verbal instructions, documented with Video-EEG monitoring. The Video-EEG during sleep showed interictal spike and wave patterns in the left temporal region. The MRI showed a 9 mm diameter intra-parenchymal lesion in the left superior temporal gyrus, with a T1 heterogeneous intensity signal (high intensity nucleus and low intensity surrounding region), suggestive of a cavernoma (Fig. 1A).

3. Neuropsychological assessment before and after surgery

A standard assessment of cognitive function for epilepsy patients (see Martin, Maestú, & Sola, 2002) including handedness, language, memory, attention, executive function, arithmetic, praxis, and gnosis was carried out before and after the surgery.

The patient's language was assessed using the Boston aphasia and the Boston Naming Test (Goodglass & Kaplan, 1986). His spontaneous speech revealed hesitations related to palatal phoneme production. In the formal test, only the "non-words repetition test" revealed problems of expressive language. No writing, reading, naming, or receptive language problems were found, with the patient's performance scores falling in the middle range. The Edinburgh Handedness Inventory (Oldfield, 1971) showed a clear right hand dominance. In the visuo-spatial skills test, the patient's scores were lower than his verbal skill scores, although they fell close to the normal range (see Table 1). Six months after surgery neuropsychological evaluation revealed no significant changes in the patient's cognitive status, although there was complete remission of seizures. However, the patient continued to report some residual language problems (i.e., stuttering in stressful situations).

4. MSI language mapping procedure

This procedure has been explained in detail elsewhere (Breier et al., 1999; Maestú et al., 2002; Papanicolaou,

Table 1
Pre- and 6 months post-surgery neuropsychological performance in different cognitive functions

	Presurgery	Postsurgery
Rey Complex Figure (copy) (Osterrieth, 1944)	39	41
Rey Complex Figure (recall) (Osterrieth, 1944)	40	38
Logic Memory (WMS-R) (Wechsler & Strong, 1987)	87	83
Forward Digits (WMS-R) (Wechsler & Strong, 1987)	76	79
Backward Digits (WMS-R) (Wechsler & Strong, 1987)	68	65
Stroop Test (interference) (Stroop, 1935)	89	92
Boston Naming Test* (Goodglass & Kaplan, 1986)	53/60	54/60
Wisconsin Card Sorting Test (categories)* (Heaton, Talley, Kay, & Curtis, 1993)	10	11
Phonemic Fluency* (Benton & Hamsher, 1983)	19	21
Semantic Fluency* (Benton & Hamsher, 1983)	48	43
Block design** (Wechsler, 1990)	7	7

Scores refer to percentiles in comparison with standardized measures, except for the BNT (score/maximum score), Fluency, WCST, and Block design tests.

* Direct scores.

** Standard scores.

1998; Papanicolaou et al., 1999; Simos et al., 1999) and will be briefly summarized here. Language-specific brain activity was elicited using an auditory word recognition task. A list of 63 abstract Spanish nouns were recorded by a native speaker of Spanish with a flat intonation and was stored on a Neuroscan STIM stimulation system (Neurosoft, Inc., El Paso, TX). The stimuli were arranged in three lists of 43 words: 33 "target" words that were the same in all three lists, and 10 distractors that were unique in each list, for a total 129 auditory events. A second sequence of 129 events was also created, using the same targets, in different random ordering in each block, and a different set of distractors, permitting replication of the task in the same patient when necessary. The recorded words were presented binaurally via two 5 meter-long plastic tubes terminating in ear inserts. The intensity was set at 80 dB Sound Pressure Level measured at the patient's outer ear. The patients were then asked to lift their right index finger whenever they recognize a target word (i.e., a word repeated in all three lists). The Spanish words employed in the study were rated with a score of four or lower on Nácher's concreteness scale (Nácher, Gotor, & Algarabel, 1998). The language mapping task was applied twice to the patient in order to know the replicability of the results.

5. MSI recordings and data analysis

MEG recordings were made with a whole-head neuromagnetometer (Magnes 2500, 4-D Neuroimaging, Inc., San Diego, CA) consisting of 148 magnetometers coils. The instrument is housed in a magnetically shielded room designed to reduce environmental magnetic noise that might interfere with biological signals. The typical recording session requires the participant to lie motionless on a bed with their head inside the helmet-like magnetometer for approximately 10 min. The signal was filtered online with a band pass between 0.1 and 50 Hz, digitized for 1000 ms (254 Hz sampling rate) including a 150 ms prestimulus period, and subjected to an adaptive filtering procedure that is part of the 4-D Neuroimaging signal analysis package. The single trial event-related fields (ERFs) elicited by target stimuli were then averaged together after removing those during which an eye movement or blink had occurred (as indicated by a peak to peak amplitude in the electrooculogram channel in excess of $50 \mu\text{V}$). A minimum of 80 ERF epochs were collected to calculate each averaged waveform. Finally, the averaged epochs were digitally filtered with a low pass 20 Hz filter.

The intracranial generators of the observed ERFs (henceforth referred to as “activity sources”) were modeled as single equivalent current dipoles (ECDs) and fitted at successive 4 ms intervals by using the nonlinear Levenberg–Marquardt algorithm. For a given point in time, the ECD fitting algorithm was applied to the magnetic flux measurements obtained from a group of 34–38 magnetometers, always including both magnetic flux extremes. The ECD computation was restricted to latency periods during which a single pair of magnetic flux extremes dominated the left and/or the right half of the head surface. The algorithm used in this study searched for the ECD that was most likely to have produced the observed magnetic field distribution at a given point in time. The ECD solutions were considered satisfactory after meeting two criteria: (1) a correlation coefficient of at least 0.9 between the observed and the “best” predicted magnetic field distribution, and (2) a goodness-of-fit of at least 0.9 or higher. The procedure for precise co-registration of the ECD coordinates on structural, T1-weight, magnetic resonance (MR) images (TR 13.6 ms; TE 4.8 ms; recording matrix 256×256 pixels, 1 excitation, 240 mm field of view, and 1.4 mm slice thickness) is described in detail elsewhere (Maestú et al., 2001).

Laterality, indices were computed for each recording based on the following formula (Breier et al., 1999): $(LH - RH)/(LH + RH)$ where LH represents the number of activity sources in the left hemisphere and RH the number of activity sources in the right hemisphere. According to the above formula, but considering only the temporal lobe activity sources the lateralization in-

indices for the first and second mapping sessions were -0.83 and -0.79 , respectively indicating a right temporal lobe dominance for receptive language. When only the frontal sources were introduced into the formula, a reverse pattern appeared for the first and second sessions, respectively (0.93 and 0.90). The Presence of frontal lobe sources are usually interpreted as covert articulation during speech perception. Therefore, preponderance of left over right frontal lobe sources may be indicating of left dominance for expressive language. In fact, this possibility was supported by the findings of intraoperative cortical stimulation mapping detailed below. Fig. 1B represents the MSI activity sources showed for both replications in temporal and frontal areas.

6. Stimulation mapping procedure and surgical outcome

A left anterior frontotemporal craniotomy (Fig. 2A) was carried out under local anesthesia with the patient awake and alert, although sedated. The structural as-

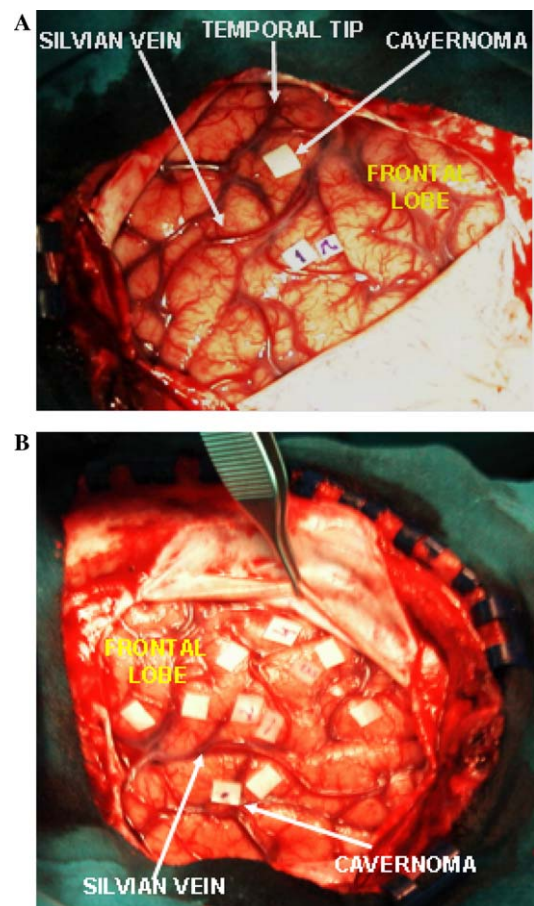


Fig. 2. (A) The locations for the mild language disruption (matching with MSI activation) produced by the intraoperative stimulation. (B) The total stimulated area, indicating, by numbers, the places where the electrical stimulation was positive and, by the white marks, locations where stimulation had no effect.

pects of the lesion as revealed by the MRI and the language related activity sources derived from MSI were entered into a navigator system (Brain-Lab).

During surgery, electrical cortical stimulation was carried out with a bipolar pulse of 2 mA intensity, 0.1 ms width and 50 Hz frequency, and a total duration of 4 s (Ojeman et al., 1989). The patient was tested for expressive language, by asking him to count from 1 to 20 while the stimulation was administered at different specific locations including those active during MSI mapping. The stimulation was begun over the superior anterior-lateral temporal areas surrounding the lesion. Following stimulation of the temporal lobe areas, the inferior frontal regions were stimulated. Given that counting is an expressive task not mediated by temporal mechanism, as expected, left temporal lobe stimulation did not interfere with the task. Figs. 2A and B shows the total cortical extent stimulated during expressive language testing. In regions 1, 2 (corresponding with two MSI activity sources), the electrical stimulation produced mild expressive deficits and in regions 3 and 4 complete speech arrest. The stimulation over the remaining cortical regions, represented by unlabeled white squares in Fig. 2B, did not produce any speech problems. No other MSI-language related areas were tested with the stimulation method, due to the limited extent of the craniotomy.

The lesion as well as the adjacent area which seemed compatible with previous glycolysis/bleeding, was completely resected. As mentioned previously, the resection did not result in additional language deficits. Nine months after surgery, the patient is seizure free with no post-surgical neurological deficits, while he continues treatment with topiramato (400 mg/day) and lamotrigin (200 mg/day).

7. Discussion

Early brain insult can produce drastic changes in the cortical language mechanism, including hemisphere dominant shift to a right hemisphere representation (Muller et al., 1999; Papanicolaou et al., 1987, 1988). Although it was previously believed that only early damage, over the dominant temporal lobe, can produce hemispheric dominance shift (Stowe et al., 2000), plasticity in response to lesions later in life has also been demonstrated (Hertz-Pannier et al., 2002; Papanicolaou et al., 1984, 1987, 1998, 2001). Moreover, the Wada test results (Strauss, Staz, & Wada, 1990) have indicated that early epilepsy onset may be implicated in hemispheric dominance shift.

The presence of an early brain malformation such as a cavernoma and epilepsy in the left temporal lobe may have resulted in a shift of the receptive language mechanisms to the homotopic right temporal lobe region, as

indicated by MSI mapping. The relation between the number of activity sources and the presence of receptive language has been repeatedly validated in a series of studies involving comparisons with the results of the Wada test and the results of the intraoperative and extraoperative cortical stimulation mapping (see e.g., Breier et al., 1999; Castillo et al., 2001; Papanicolaou et al., 1999; Simos et al., 1998). In our patient, the fact that simple partial seizures with left temporal area onset, produces expressive language difficulties but non receptive language disruption, offers additional support for the notion of a hemispheric dominance shift for only the receptive language mechanism. Finally, the patient's neuropsychological profile indicates that he performs significantly worse on neuropsychological measures of visuo-spatial function suggestive of the presence of "crowding" (Loring et al., 1999; Strauss et al., 1990).

The concurrence of the number of MSI-derived activity sources over the areas surrounding the third frontal convolution with the disarthria and speech arrest phenomena induced by the electrocortical stimulation, strongly suggest left hemisphere dominance for expressive language in this patient. These findings are also supported by the difficulties the patient experiences in speech production (i.e., disfluencies and stuttering), which have been related with lesions in the supplementary motor and Broca's area (Forster & Webster, 2001), indicating a language disruption induced by interictal discharges in the left hemisphere (Duggal, Jagadheesan, & Nizamie, 2002). While, the paradigm used in this study essentially tested receptive language, it has been previously reported that frontal activity appears secondary to a subvocal covert articulation (e.g., Simos et al., 1999).

Similar patterns of right temporal but left frontal dominance for receptive and expressive language respectively have been reported previously in fMRI studies with epilepsy patients (Billingsley et al., 2001; Weiller et al., 1995). While some studies suggest that only large insults that compromise Wernicke's area are related to the shift of the language mechanisms to the contralateral hemisphere (Weiller et al., 1995), others have demonstrated that focal left hemisphere damage not restricted to Wernicke's area could produce shift of language to the right hemisphere (e.g. Papanicolaou et al., 1984). In the present single case study, an anterolateral superior temporal gyrus cavernoma with an associated partial complex epilepsy lasting for 26 years appears to have mediated a similar shift in the language mechanism, to those associated with large lesions.

In summary, this rare case of partial reorganization of language involving a shift to the non-dominant hemisphere of only the receptive language mechanism constitutes evidence that even small lesions may be sufficient to induce drastic functional reorganization of the brain. This leads us to believe in the necessity of mapping language before surgery, with high spatial

resolution complementary methods such as MSI and electrocorticography, even in patients with small lesions over the, presumably, dominant temporal lobe.

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