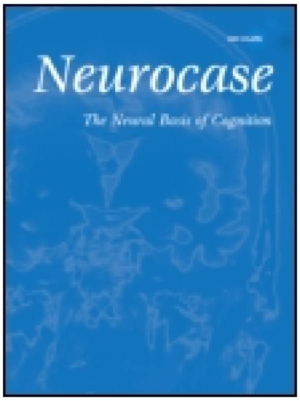

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Is a lone right hemisphere enough? Neurolinguistic architecture in a case with a very early left hemispherectomy

Laura Danelli [a], Giuseppe Cossu [b], Manuela Berlingeri [a], Gabriella Bottini [c d], Maurizio Sberna [e] & Eraldo Paulesu [a f]

[a] Psychology Department, University of Milano-Bicocca, Milan, Italy
[b] Department of Neuroscience, University of Parma, Parma, Italy
[c] Center of Cognitive Neuropsychology, Niguarda Ca' Granda Hospital, Milan, Italy
[d] Psychology Department, University of Pavia, Pavia, Italy
[e] Neuroradiology Department, Niguarda Ca' Granda Hospital, Milan, Italy
[f] IRCCS Galeazzi, Milan, Italy

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Is a lone right hemisphere enough? Neurolinguistic architecture in a case with a very early left hemispherectomy

Laura Danelli[1], Giuseppe Cossu[2], Manuela Berlingeri[1], Gabriella Bottini[3,4], Maurizio Sberna[5], and Eraldo Paulesu[1,6]

[1]Psychology Department, University of Milano-Bicocca, Milan, Italy
[2]Department of Neuroscience, University of Parma, Parma, Italy
[3]Center of Cognitive Neuropsychology, Niguarda Ca' Granda Hospital, Milan, Italy
[4]Psychology Department, University of Pavia, Pavia, Italy
[5]Neuroradiology Department, Niguarda Ca' Granda Hospital, Milan, Italy
[6]IRCCS Galeazzi, Milan, Italy

We studied the linguistic profile and neurolinguistic organization of a 14-year-old adolescent (EB) who underwent a left hemispherectomy at the age of 2.5 years. After initial aphasia, his language skills recovered within 2 years, with the exception of some word finding problems. Over the years, the neuropsychological assessments showed that EB's language was near-to-normal, with the exception of lexical competence, which lagged slightly behind for both auditory and written language. Moreover, EB's accuracy and speed in both reading and writing words and non-words were within the normal range, whereas difficulties emerged in reading loan words and in tasks with homophones. EB's functional magnetic resonance imaging (fMRI) patterns for several linguistic and metalinguistic tasks were similar to those observed in the dominant hemisphere of controls, suggesting that his language network conforms to a left-like linguistic neural blueprint. However, a stronger frontal recruitment suggests that linguistic tasks are more demanding for him. Finally, no specific reading activation was found in EB's occipitotemporal region, a finding consistent with the surface dyslexia-like behavioral pattern of the patient. While a lone right hemisphere may not be sufficient to guarantee full blown linguistic competences after early hemispherectomy, EB's behavioral and fMRI patterns suggest that his lone right hemisphere followed a left-like blueprint of the linguistic network.

Keywords: Left hemispherectomy; fMRI; Language; Reading; Prefrontal cortex; Visual word form area.

Left hemisphere dominance is a hallmark of the neural architecture of language in normal adult subjects (Broca, 1861; Lidzba, Schwilling, Grodd, Krageloh-Mann, & Wilke, 2011; Wada & Rasmussen, 1960). Hence, a severe left hemisphere injury occurring in adulthood (almost) invariably leads to aphasia, notwithstanding inter-individual variability in the degree of hemispheric asymmetry and rare exceptions of right hemisphere aphasias in right-handers (Dewarrat et al., 2009; Trojanowski, Green, & Levine, 1980). The dominance of the left hemisphere is further strengthened by brain

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Address correspondence to Eraldo Paulesu, Psychology Department, University of Milano-Bicocca, Piazza Ateneo Nuovo 1, 20126 Milano, Italy. (E-mail: eraldo.paulesu@unimib.it).

imaging studies indicating that functional asymmetry is present in the brains of typically developing children (Lohmann, Drager, Muller-Ehrenberg, Deppe, & Knecht, 2005; Schapiro et al., 2004; Wood et al., 2004). In keeping with these findings, one would expect extensive left hemisphere damage to have similar consequences on language function in children. However, unlike adults, children suffering from an acquired left hemisphere lesion rarely display long-lasting severe language disorders. Their everyday linguistic skills may be largely preserved (Bates, Devescovi, & Wulfeck, 2001; Woods & Teuber, 1978) even when a lesion of the left hemisphere is acquired at a relatively late stage of development (Cossu, Da Prati, & Marshall, 1995; Vargha-Khadem et al., 1997).

This remarkable recovery of the language function has been known for decades (Basser, 1962), and although it may be debatable whether specific left brain language structures were selectively spared or impaired in some of these cases (Bishop, 1988; Dennis & Kohn, 1975), the occurrence of long-term language recovery after left hemispherectomy in children makes it undisputable that the right hemisphere is able to provide back-up linguistic skills to an extent that is not allowed to adults who have left-hemispheric language dominance (Curtiss & de Bode, 2003; Liegeois, Connelly, Baldeweg, & Vargha-Khadem, 2008; Liegeois et al., 2004; Liegeois, Cross, Polkey, Harkness, & Vargha-Khadem, 2008; Mariotti, Iuvone, Torrioli, & Silveri, 1998).

However, the neural correlates underlying language recovery after hemispherectomy are not yet well understood: indeed, the fine-grained organization of the right-sided language network in hemispherectomized patients remains to be evaluated.

Relatively few studies have investigated the neural correlates of language in left hemispherectomized patients by means of neuroimaging techniques (Hertz-Pannier et al., 2002; Liegeois, Connelly et al., 2008; Voets et al., 2006). A summary of the main findings of these studies is outlined in Table 1 (Hertz-Pannier et al., 2002; Liegeois, Connelly et al., 2008; Voets et al., 2006).

All these studies involved hemispherectomized patients suffering from epilepsy-inducing pathologies with either congenital or postnatal acquired hemiplegia (Liegeois, Connelly et al., 2008) or Rasmussen's syndrome (Hertz-Pannier et al., 2002; Voets et al., 2006). To the best of our knowledge, no study has yet investigated the neural correlates of language in a child with a localized vascular pathology selectively affecting only one hemisphere, while leaving the other hemisphere perfectly spared. Furthermore, a detailed analysis of the neurofunctional architecture of reading is rarely provided in the current literature in children with an early left hemispherectomy.

A point of agreement among the above studies is the recognition of great variability in the functional reorganization of language after hemispherectomy depending on the nature of the lesion, the time of onset, the age of the patient at the time of surgery, the degree of the language impairment, the degree of recovery and the specific language functions being tested. However, there are different opinions as to whether the brain areas involved in the re-organization of the right hemisphere after hemispherectomy are homologues of the dominant hemisphere areas normally observed in controls during linguistic tasks.

In this study, we investigate the functional magnetic resonance imaging (fMRI) linguistic patterns in an early left hemispherectomized patient (patient EB) and we compare them with the left-hemispheric patterns of a sample of young adult control subjects.[1] In particular, we assessed similarities and differences between EB's patterns and those of the normal controls during language production and comprehension tasks using both single words and sentences as stimuli. We explore the following paradigms: (i) language production vs. language perception/comprehension; (ii) automatic language production vs. controlled language production; and (iii) auditory vs. visual linguistic processing.

These data, combined with the behavioral measurements, allowed us to perform an in-depth assessment of EB's neurolinguistic organization and to test whether a lone right hemisphere, being deprived of any input from the left hemisphere from an early age, might nonetheless be able to implement a language organization similar in efficiency and organization to the one assembled within an intact dominant left hemisphere.

[1] Having young adults as normal controls has the advantage of permitting a comparison of EB's language network with its reference normal endpoint, making the similarities between EB and the normal controls even more relevant. However, as EB was studied at age 14 and the age difference with the controls could play a role in causing any fMRI difference, in the paper we emphasise the commonalities with the controls, the differences being commented upon only when they replicated across several tasks.

TABLE 1
Summary of the main fMRI studies investigating language abilities in hemispherectomized patients

Authors	*Sample*	*Pathology*	*Age at onset of symptoms*	*Age of surgery*	*Age at the fMRI assessment*	*Tasks*	*Technique*	*Results*
Herz-Pannier et al. (2002)	1 left hemispherectomized patient	Rasmussen's syndrome	5.9 years	9 years	6.10 years	Semantic verbal fluency	Longitudinal study: fMRI (before and after surgery)	Activations observed in the right hemisphere during word generation in post-operatory session were similar to those observed before surgery in the left hemisphere
					10.6 years	Semantic verbal fluency, sentence generation and story listening		Similar pattern were observed during word and sentence generation
Voets et al. (2006)	1 left hemispherectomized patient	Rasmussen's syndrome	6 years	14 years	12 years 16 years	Phonemic and semantic verbal fluency, picture naming	Longitudinal study: fMRI (before and after surgery)	RIFG activation observed after the surgery was more posterior and more medial than those observed before the surgery
Liegeois, Connelly et al (2008)	3 left and 3 right hemispherectomized patients	Epilepsy	Birth–6 years	4.1–11.11 years	Left hemispherectomized patients = 13.6–14.11 years; Right hemispherectomized patients = 12.5–22.10 years	Semantic word generation	fMRI	Typical activations in right temporal and precentral regions were observed in left and right hemisperectomized patients, while a variable pattern was observed in the inferior frontal region during word generation task
	10 right-handed adults				21–32 years			A correlation between the performance levels and the IFG activation were also observed

fMRI, functional Magnetic Resonance Imaging; RIFG, right inferior frontal gyrus; IFG, inferior frontal gyrus.

It is worth noting that we also studied EB's behavioral and fMRI patterns during reading, this being the first such study in a patient with an early left hemispherectomy and ensuing the removal of the left occipitotemporal cortex (Cohen et al., 2002; Gaillard et al., 2006), a brain region committed to the processing of printed words, a skill that normally develops much later in life with respect to the age of the hemispherectomy in our patient (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011).

MATERIALS AND METHODS

Subjects

Case report: patient EB

Medical history. EB was born in November 1992 following an uneventful pregnancy and delivery. Developmental milestones were likewise acquired within the normal age range, with a clear-cut evidence of right-handedness in EB's daily activity. At the beginning of April 1995, however, when EB was approximately 2.5 years old, he began complaining of a headache. In the following days, the headache increased with occasional episodes of vomiting.

An acute episode of loss of consciousness provoked referral to an emergency care unit. On admittance to the hospital, a neurological examination indicated that EB was able to understand verbal commands and showed no behavioral signs of abnormality. An MRI was performed, showing 'a massive expanding process, partly cystic and hemorrhagic, expanding through the left frontal-insular area, involving the nucleus caudatus, the nucleus lenticularis and the internal capsule'.

Owing to the diagnostic suspicion of a large 'cavernous angioma' (Chad et al., 2010; Kim et al., 2011), to the chronic bleeding thereof and to the risk of further massive brain hemorrhage, EB underwent a left hemispherectomy by the end of April 1995, despite the absence of epileptic seizures. His left hemisphere was completely removed with the exception of a small portion of the orbital-basal-frontal area, of the medial parietal cortex and of the left calcarine fissure.

The histopathological examination of the left hemisphere revealed widespread signs of recent as well as past hemorrhages in cortical and sub-cortical areas. The leptomeninges were also involved. At the periphery of these areas, histopathology also documented a diffuse proliferation of small arterial vessels characterized by a 'cavernous' shape and very thin walls. The histopathological diagnosis was: 'haemorrhagic angio-cavernoma of the left hemisphere'.

The left posterior and lateral ventricle was likewise enlarged. Atrophy of the left cerebral peduncle was also evident, extending to the bulbar pyramid. The residual trunk and splenium of the corpus callosum were atrophic. The right hemisphere was unimpaired, as evident from the morphological MRI documenting the left hemispherectomy (see Figure 1). To prevent the occurrence of epileptic seizures, an antiepileptic drug therapy (phenobarbital 100 mg/day) was prescribed. None of the several EEGs that were performed over the years ever revealed any sign of epileptic activity; hence, the antiepileptic drug-therapy was discontinued at the age of 4.

According to the parents' report, like his older brother, EB was clearly right-handed until neurosurgery. Likewise, both parents are right

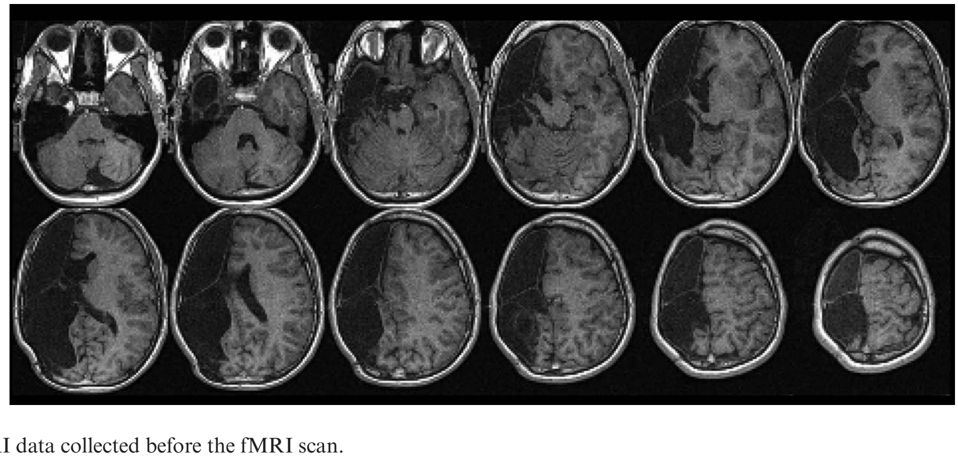

Figure 1. MRI data collected before the fMRI scan.

handed, and no case of left-handedness has been reported for any of their relatives.

After neurosurgery, EB presented with a marked right hemiparesis and complete anarthria, which, according to the parents' report, lasted for approximately 3 weeks and then began to attenuate, though at a slow pace. In the subsequent years, the recovery of language was effortful and very slow, notwithstanding an intensive speech and language rehabilitation program. In particular, EB achieved a full mastery of the phonetic inventory of the Italian language about 2 years after neurosurgery, but even then, his conversational language was hampered by morphological and syntactic mistakes, indicating clear signs of agrammatism. Furthermore, word-finding problems were detected until he was approximately 5 years of age, misnaming, for example, *sheep* for goat, *tin* for vase, or *pot* for glass. By contrast, EB was very bright at many visual games and his spontaneous drawings were quite remarkable. Indeed, in a routine clinical assessment at age 5, he earned a non-verbal IQ of 95 on the Leiter scale, and a year later, he achieved a score in the 95th percentile on the Raven Coloured Matrices. According to the parents' reports, in the subsequent few years EB's language fluency improved remarkably, with almost no sign of impairment at either the lexical or syntactic level. Language comprehension problems of clinical relevance were never detected in the family or school environment.

When EB entered primary school, at the age of 6, as requested by the standard Italian school program, notwithstanding having acquired basic orthographic and mathematical skills at approximately the expected time, both parents and teachers noticed that he was 'a bit slow (and inaccurate) in completing many school activities as he got tired very easily'. Because of these enduring problems, at the age of 8.3 years, EB was referred to one of the authors (GC) to undergo a systematic neuropsychological assessment (see Table 2 for details).

An ophthalmological investigation showed that extrinsic ocular motility was normal. Regarding binocular vision, stereopsis was absent and homonymous right hemianopia was detected on visual field examination. Visual evoked responses had normal morphology in the right eye, whereas latency was increased for the left eye.

Recently, at the age of 17, a further neuropsychological re-assessment was undertaken (see Table 2 for details).

Neuropsychological assessment at 8.3 years. Intelligence quotient (I.Q.): EB was a cooperative and talkative boy, well-oriented in time and place. His full scale IQ on the WISC-R was 78, with a verbal IQ of 73 and a performance IQ of 87 (Wechsler, 1986). Verbal Similarity and Story Pictures tasks were performed poorly.

On a further non-verbal intelligence test (Raven Matrices, PM 47) EB obtained 22/36 correct, which corresponds to the 75th percentile (Basso, Capitani, & Laiacona, 1987).

Visual and visuo-spatial skills: EB's performance was at ceiling in visual discrimination tasks using strings of either Roman or Cyrillic letters (Cossu & Marshall, 1990). Moreover, EB showed performance within the normal range in a number of tasks from the Birmingham Object Recognition Battery (BORB) test (Riddoch & Humpreys, 1993), excluding the results from two particularly complex tasks: the 'Foreshortened match' (Test 8) and the 'Association match' (Test 12).

In the Facial Recognition Task (Benton, VanAllen, Hamsher, & Levin, 1978) and in the Line Orientation test (Benton, Varney, & Hamsher, 1978), EB's performance fell within the range of the normal control group.

Praxic skills: EB earned a score within the normal range for his age in two tasks, the Bender Visual Gestalt test (Bender, 1938) and the Rey Complex Figure test (Ardila, Rosselli, & Rosas, 1989).

Language skills: An investigation of EB's language skills using a phoneme discrimination test (Miceli, Laudanna, Burani, & Capasso, 1994) and a non-word repetition test (Gathercole, Willis, Baddeley, & Emslie, 1994) revealed no impairment at the phonological level.

Comprehension of the morphosyntactic relations was assessed by means of the Test for the Reception of Grammar (TROG Test; Bishop, 1982) and the Token Test (De Renzi & Faglioni, 1978); in both tests EB's responses were fully within the normal range (Table 2). On the phonemic, semantic and unconstrained fluency test (Riva, Nichelli, & Devoti, 2000) EB performed within the normal range with the exception of the 'food' category in the semantic fluency task.

However, difficulties surfaced at the lexical level in a number of tasks tackling either word retrieval (e.g., the Boston Naming Test, Riva et al., 2000) or word comprehension (e.g., the Peabody Picture Vocabulary Test, PPVT; Dunn, 1981; Stella, Pizzoli, & Tressoldi, 2000). In the Boston Naming Test, for instance, EB made 4 visual errors

TABLE 2
Neuropsychological assessment at the age of 8.3 and at the age of 17

	EB (8.3 years)	*Controls (8 years) Mean (SD)*	*EB (17 years)*	*Controls (17 years) Mean (SD)*
Visual and visuo-spatial skills				
Roman alphabetic letter ($n = 20$)	20	19.9 (0.43)	–	–
Cyrillic Trygrams ($n = 20$)	20	19.4 (1.54)	–	–
BORB[a]				
Length Match ($n = 30$)	26	26.9 (1.6)	–	–
Size Match ($n = 30$)	24	27.3 (2.4)	–	–
Overlapping 2 letters ($n = 36$)	36	–	–	–
Overlapping 3 letters ($n = 36$)	36	–	–	–
6 shapes paired ($n = 36$)	36	–	–	–
6 shapes triplets ($n = 36$)	36	–	–	–
6 drawings ($n = 20$)	18	18.2 (1.4)	–	–
7 minimal feature view ($n = 25$)	23	23.3 (2.1)	–	–
8 foreshortened view ($n = 25$)	$19^{*-7.4}$	24.2 (0.7)	$22^{*4.68}$	24.5 (0.53)
12 associative match ($n = 30$)	25^{*-9}	29.5 (0.5)	29	29.7 (0.46)
Face recognition ($n = 22$)	20		–	–
Line orienting (Benton) ($n = 18$)	8	8.8 (4.19)	–	–
Praxic skills				
Bender Visual Gestalt Test ($n = 9$)	3	3.7 (3.6)	–	–
Complex Rey Figure ($n = 36$)	26.5	50° percentile	–	–
Language skills				
Phonemic discrimination task ($n = 60$)	59	–	–	–
Non-word repetition ($n = 15$)	14	–	–	–
Boston Naming Test ($n = 60$)	$27^{*-1.6}$	36.7 (6.2)	$44^{*4.59}$	53.5 (2.07)
Peabody Picture Vocabulary Test ($n = 175$)	67*	95 (age equivalent)	$150^{*3.76}$	163.7 (3.65)
TROG ($n = 20$)	15	50° percentile	–	–
Auditory lexical decision ($n = 24$)	–		24	24 (0)
Token Test ($n = 36$)	34	31.8 (2.59)	–	–
Verbal Fluency:				
Phonemic: ‘A’	–	–	11	12.1 (4.26)
Phonemic: ‘B’	5	6.9 (2)	12	12.0 (3.42)
Phonemic: ‘S’	6	6.7 (3)	12	13.63 (2.92)
Semantic: ‘clothes’	–	–	14	16.2 (3.73)
Semantic: ‘animals’	11	14.8 (3)	17	17.0 (5.71)
Semantic: ‘food’	$9^{*-1.6}$	15.4 (4)	17	21.7 (5.26)
Semantic: ‘any words’	19	22.4 (10)	24	26.6 (11.24)
Reading skills				
Word time (Cossu, 1999)	32 sec.	44.7 (15.1)	–	–
Word time (Sartori, Job, & Tressoldi, 1995)	–	–	53 sec.	50.1 (10.56)
Non-Word time (Cossu, 1999)	46 sec.	73.3 (29.4)	–	–
Non-Word time (Sartori, Job, & Tressoldi, 1995)	–	–	40 sec.	38.7 (6.36)
Word accuracy	20/20	–	–	–
Word accuracy	–	–	112/112	111.6 (0.74)
Non-Word accuracy	20/20	–	–	–
Non-Word accuracy	–	–	48/48	46.4 (1.41)
Irregular Word time[b]	–	–	36 sec.	30.0 (5.68)
Irregular Word accuracy	–	–	$58/60^{*3.78}$	59.7 (0.46)
Loan word time ($n = 30$)	–	–	21 sec.	24.1 (6.45)
Loan word accuracy ($n = 30$)	–	–	$18^{*9.82}$	28.5 (1.07)
Loan word repetition ($n = 30$)	–	–	30	30 (0)
Loan word comprehension ($n = 30$)	–	–	22^{*-10}	29.4 (0.74)
(3) Lexical Decision ($n = 48$)	31*		$44^{*7.00}$	47.6 (0.52)

(*Continued*)

TABLE 2
(Continued)

	EB (8.3 years)	*Controls (8 years) Mean (SD)*	*EB (17 years)*	*Controls (17 years) Mean (SD)*
(7) Orthographic/semantic ($n = 24$)	13*	< 10° percentile	16*[4.05]	22.5 (1.6)
(8) Orthographic fusion task ($n = 20$)	19	> 25° percentile	–	–
(9) Misspelling Judgement ($n = 20$)	20	> 25* percentile	–	–
Writing skills				
Word ($n = 20$)	19	19.5 (2.3)	–	–
Non-Word ($n = 20$)	18	18.1 (1.96)	–	–

[a]BORB, The Birmingham Object Recognition Battery. The tests assess low- and high-level aspects of visual perception (using same-different matching test of basic perceptual features, such as orientation, length, position and object size, or matching test of objects in different viewpoint), access to stored perceptual knowledge about objects (object decision), access to semantic knowledge (function and associative matches) and access to lexicon from object (picture naming).
[b]As a consequence of the high degree of orthographic transparency of the Italian language, the reading of words with unpredictable stress can be considered as an instrument to identify "surface-dyslexia like symptoms" in Italian subjects (Miceli & Caramazza, 1993). In particular, in this study we used the standardized test (task 6) proposed by Sartori, Job, and Tressoldi (1995) and included in the neuropsychological battery for the evaluation of developmental dyslexia. Some examples of 'irregular' words in Italian, taken from the Sartori, Job, and Tressoldi's test, are 'passero', 'cellula', 'rompere', 'camera', words in which the stress is on the third last syllable. As in standard Italian print the stress is omitted unless it is on the final syllable, a sublexical procedure cannot be used to extract the stress pattern from print.
*Pathological scores (Z-scores are reported in superscript).

(misnaming *sword-fish* for arrow, *funnel* for trumpet, or *roof* for pyramid), but 30 semantic errors out of a total of 34 errors (misnaming *carriage* for wheelchair, *trumpet* for harp, *pencil-sharpener* for compass, etc.).

Orthographic skills and reading: Reading was assessed by means of the Sartori, Job, and Tressoldi (1995) battery. As shown in Table 2, EB was at ceiling in reading accuracy. There were no significant differences between EB and chronological age-matched controls in reading speed with either words or non-words. Similar results emerged in writing tasks with both words and non-words and in two homophone identification tasks. In Test 8, which requires checking 20 written sentences to find 'fusion' mistakes (e.g., 'mistero divino' [divine mistery] and 'un bicchiere di acqua e di vino' [a glass of water and wine]), EB made only one mistake, and in Test 9, comprising 20 words, half of which are misspelled, he gave 100% correct responses.

In the 'Lexical decision test', the subject was required to read silently a scrambled list of words and non words and, for each printed string, to say 'yes' or 'no' whether it corresponded to a word or to a non-word, respectively. EB earned a low score placing him below the 25th percentile; likewise, in the 'Homophone discrimination test', EB achieved a low score in the 25th percentile. This last test consists of 24 beginnings of sentences that have to be read silently and completed by pointing to one out of four printed words. For example: *L'ago* è *fatto di* [The needle is made of] is presented with four alternatives *acqua,* [water] *legna* [wood], *terra* [soil], *ferro* [iron]. By contrast, the correct word completing the similarly sounding sequence: *Lago* è *fatto di* [Lake is made of] is *acqua* [water].

Neuropsychological assessment at 17 years. Recently, we presented EB with some of the same tasks in which he showed pathological performance in the previous assessment (at the age of 8). His performance was compared with the average performance of a group of eight males with the same age and schooling.

No significant variations were detected in the overall clinical profile: the performance of EB was within the normal range in both phonological and semantic fluency tasks (Riva et al., 2000), but difficulties emerged at the visuo-spatial level in the 'Foreshortened view task' and the 'Associative match task' (Riddoch & Humpreys, 1993) as well as at the lexical level in the Boston Naming Test (Riva et al., 2000) and in the PPVT (Dunn, 1981; Stella et al., 2000).

Orthographic skills and reading. EB was within the normal range in word and non-word reading tests (Sartori et al., 1995), with the exception of the irregular word reading task, in which he showed pathological performance in terms of accuracy.

Moreover, he was below the normal level in a visual lexical decision task and in a visual homophone discrimination task (Sartori et al., 1995). Finally, the accuracy of EB's performance was below the normal level when reading loan words (e.g., privacy, leader, shuttle, download) and in the loan word comprehension test.

However, EB was in the normal range in the auditory version of the lexical decision task mentioned above, and in a loan word repetition test.

fMRI experiments

Control subjects for fMRI experiment

To compare EB's fMRI patterns with those from a control sample, a database of 24 right-handed healthy normal volunteers was used. The group was composed of 12 males and 12 females (age range: 20–30 years; college education for all subjects). Handedness was determined according to the Edinburgh Handedness Inventory (Oldfield, 1971). No subjects had any medical history of a neurological disorder of any kind and all gave informed written consent for the study. Although these subjects were not matched with EB with respect to IQ or age, we took their fMRI data as a representative indication of the neural correlates of mature brains of young right-handers for a comparison of EB's activation patterns.

Activation tasks

Each subject silently performed 5 tasks: (i) automatic word generation; (ii) phonemic and semantic word fluency; (iii) word listening; (iv) plausibility decision task on sentences; and (v) word and non-word reading. In the visual domain, we also tested shape-similarity judgments of line drawings.

These tasks allowed us to test a number of effects in language processing at the single word level such as automatic/voluntary dissociation by comparison of two tasks (automatic series recall vs. verbal fluency or word listening vs. verbal fluency) and input channel effects by comparison of listening and reading. Furthermore, given that EB's reading performance fell in the dyslexic range, at least for lexical knowledge, and because we needed to ascertain the functioning of the visual reading areas for more elementary aspects of visual processing, we added a shape similarity judgment task for false fonts known to depend also on the ventral extrastriate visual cortex (Dolan, Paulesu, & Fletcher, 1997).

Automatic series recall: Subjects were required: (i) to silently count recursively from 1 to 20 (number production); (ii) to silently recite, in order, the days of the week (day production); and (iii) the months of the year (month production) at approximately one word per second for 30 seconds. The baselines used for these tasks were resting state epochs. The task was composed of a series of 12 blocks (6 blocks of recall condition and 6 blocks of rest) and each series was required twice.

Verbal fluency: In the first part of the task, subjects were asked to silently generate as many words as possible belonging to a semantic category (animals, fruits and tools). In the second part of the task, subjects were asked to silently generate as many words as possible belonging to a phonemic category (words beginning with the letter ‘B’, ‘L’, ‘S’). The baselines for these tasks were resting state epochs (Paulesu et al., 1997).

Phonemic and semantic verbal fluency tasks were presented in one 6-minute long fMRI session. Subjects performed the phonemic fluency firstly and the semantic fluency secondly. In particular, every 30 seconds a recorded voice indicated the semantic or phonemic category (animals, fruits and tools or words beginning with the letter ‘B’, ‘L’, ‘S’) to the subjects, that were instructed to silently generate as many words as possible for each category. Each category was presented once for a total of 6 blocks of verbal production and 6 blocks of baseline. A recorded voice indicated to the subjects also when the 30 seconds of baseline were beginning saying ‘stop, rest’. For all the duration of the task, subjects were instructed to close their eyes.

Out of the scan, the verbal fluency task was reassessed in order to provide a measure of the word generation ability in response to a given phonemic or semantic constraint.

Word listening: Subjects heard a list of words and no action was required. In the control task, subjects heard pure tones matched for length with the words and for pitch with the human voice. The stimuli lasted 1 second each and were presented at 2-second intervals.

Stimuli presented were matched across blocks for frequency, and included bi, tri-, and quadrisyllabic words. No particular semantic constraints were considered. We tried to avoid words that could have been produced by the subjects during the fluency in order not to induce spurious recognition memory/priming processes.

Word and non-word reading: Subjects were asked to silently read single words and non-words presented in 30” blocks over a 6-minute long session and alternated with 30” blocks of a control task that involved watching strings of differently oriented lines. The subjects were also asked to press the response button at each stimulus presentation. The words delivered in these tasks were different from those used in the auditory comprehension task. As in the word listening task, words were bi-, tri-, and quadri-syllabic Italian words. The task included high and low-frequency words. Only six items on 45 had irregular spelling, as far as the stress was concerned.

Non-words were generated by changing the internal consonants of Italian words, while keeping the whole word shape (full lists of the item are report in the Appendix).

The presentation rate was as for the word listening task. This was well within the reading latencies of our subjects.

Sentence plausibility decision: Subjects were asked to decide whether a heard sentence was semantically plausible or not. The control task involved listening to pure tones. The subjects were instructed to press the response button both for sentences judged as ‘plausible’ and for tones ending with a rising pitch. Flat tones and sentences judged ‘implausible’ required no response. Tone length was matched with sentences so that each sentence was linked with a twin (in length) tone. There were 36 stimuli for the experimental condition and 36 for the baseline. Targets comprised 50% of the stimuli. The stimuli lasted 3 seconds each and were presented at 5-second intervals,

Shape similarity judgment: Subjects were asked to judge which item from a list of Korean letters (or a similarly looking line-drawing) was similar to a target Korean letter always available on the screen (Paulesu et al., 1995). In the baseline condition, the subjects were presented with a series of Latin letters displayed one at a time and were required to decide whether the name of the presented letter rhymed with the letter name ‘B’, which was constantly present on the screen. Responses to the target were given by pressing a response key with the left index finger. There were 90 stimuli for each task with a 1-in-3 target rate. Stimuli were presented every 2 seconds lasting 1 second each. For this task only, in which the activations are normally right lateralized, commonalities and differences between EB and the controls were tested using the right hemisphere of the normal controls.

fMRI scanning

All tasks were performed over 12 blocks of alternating baselines or experimental tasks. Each block consisted of 10 scans. The MRI scans were acquired using a 1.5-T Marconi-Philips *Infinion* scanner equipped with an echo-speed gradient coil and amplifier hardware using a standard quadrature head-coil. Activation images were acquired using an Echo Planar Imaging (EPI) gradient echo sequence (Flip angle $= 90°$, TE $= 60$ ms, TR $= 3050$ ms, FOV $= 240 \times 240$, matrix $= 64 \times 64$). The selected volume consisted of 26 contiguous transverse slice images. The voxel size of the raw fMRI data was $3.75 \times 3.75 \times 4.00$ mm.

fMRI data analysis

After image reconstruction, raw-data visualization and conversion from DICOM to ANALYZE format were performed with MRIcro (Rorden & Brett, 2000) to generate neurologically oriented images where the anatomical right is visualized on the right of images.

All subsequent data analyses were performed in MATLAB 6.5 (MathWorks, Natick, MA, USA) using SPM2 (Statistical Parametric Mapping software, Wellcome Department of Cognitive Neurology, London, UK). fMRI scans were first realigned to account for any movement during the experiment and then stereotactically normalized to a symmetrical template space to permit comparisons across tasks and across subjects. The stereotactically normalized scans (voxel size $2 \times 2 \times 2$ mm) were smoothed through a Gaussian filter of $10 \times 10 \times 10$ mm to improve the signal-to-noise ratio. High-pass filtering was used to remove confounding contributions to the fMRI signal, for example, physiological noise from cardiac and respiratory cycles. Stereotactic normalization of EB’s data were performed by explicitly masking the anatomical space once corresponding to the left hemisphere.

EBs’ images, before entering fixed effect analysis, were masked with a region of interest (ROI). This mask excluded from fixed effect analysis the stereotactic space of the left cranial fossae filled by cerebrospinal fluid (CSF) rather than by the brain tissue of the left hemisphere. This was done to exclude a massive contribution of CSF in the calculation of global blood oxygen level dependent (BOLD) signal fluctuations.

At the first level, the data were analyzed in a subject-specific manner. Condition effects were estimated according to the general linear model (Friston, Frith, Turner, & Frackowiak, 1995). The contrasts of interest were estimated by comparing each experimental activation condition relative to its specific baseline condition (e.g., word listening vs. pure tone listening).

Comparison between EB's fMRI patterns and normal controls

As expected, the left hemisphere was clearly dominant in our control subjects for all language tasks. In order to compare EB's '*dominant and lone*' hemisphere with the dominant hemisphere of the controls, the contrast images of the controls were flipped along the *x*-axis and saved in radiological convention. We flipped the normal controls data rather than EB's data to make the visualization of the results more obvious in relationship with the lone-right hemisphere of our patient. The resulting flipped contrast images in radiological convention and the EB's contrast images in neurological convention were then entered into second level ANOVAs conforming to a random effect analysis (Holmes & Friston, 1998; Penny, Holmes, & Friston, 2004).

The statistical analyses were thresholded at $p < .001$ uncorrected. In the tables, we indicate the regional effects that survived one of the corrections for multiple comparison offered by SPM2.

Differences between a single subject and control sample may not exclusively represent the effect of a distinct neurofunctional organization in that subject, but instead could be a random deviation from the usual cerebral functioning in a given experimental session.

To protect ourselves from unjustified claims due to idiosyncratic effects, the commonalities between EB and the normal controls were assessed as conjunction effects of the independent activation patterns. These will be the main focus of our discussion, a substantial amount of shared effects being taken as an indication of a similar neuronal architecture for EB and the controls.

In the case of fMRI differences, we will adopt the more conservative approach of commenting only on those that replicated across tasks while bearing in mind that the age difference between EB and the controls could have played a role. In any event, neural differences between the patient and the controls were assessed only in terms of interaction effects, i.e., after a formal statistical comparison of EB's and the normal controls' fMRI patterns.

In particular, we assessed the following effects:

(i) voluntary vs. automatic dissociation by comparing the verbal fluency task vs. the automatic series task or the word listening task;
(ii) auditory vs. visual language dissociation by comparing word listening vs. word reading and vice versa; and
(iii) sentence comprehension.

Finally, we also assessed the commonalities and differences for single word and non-word reading and for more elementary aspects of visual processing as depicted by the shape matching task.

RESULTS

Behavioral results collected during fMRI scans

Performance on tasks with an explicit output, such as shape similarity judgment of line drawings and plausibility assessment of sentences, was at ceiling in all control subjects and in EB.

No differences emerged from the sentence judgment task notwithstanding EB's difficulties at the lexical-semantic level, although the task might have been facilitated by the simple syntactic structure (subject-verb-object).

The verbal fluency tasks after the fMRI scans revealed that both the control subjects and EB were able to recall several items for each verbal fluency epoch (i.e., words beginning with 'B', 'L', or 'S' and for the semantic categories animals, fruits, tools).

For all reading tasks we inferred normal performance as all subjects were in the normal range for reading both regular words and non-words.

fMRI results

We reported the activation map of each task for EB and the control group separately in the Figure 2.

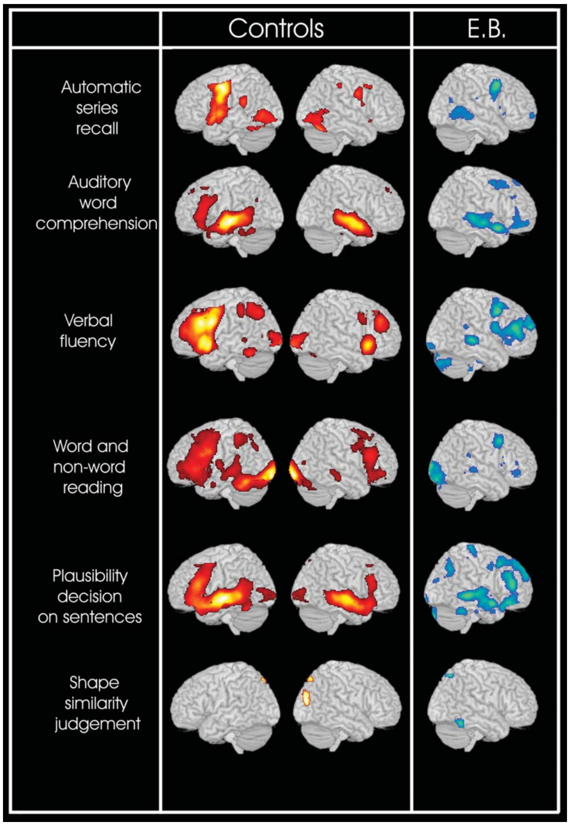

Figure 2. Brain activation data. We reported the activation maps of each task for both EB and controls. The effects were thresholded at $p<.001$ (uncorrected). [To view this figure in color, please see the online version of this Journal].

Single word processing: voluntary/automatic dissociation

Verbal fluency vs. word listening (see Figure 3 and Table 3a). In both the controls and EB the superior, middle and inferior frontal gyri, the rolandic opercular region, the anterior cingulum and the thalamus were more activated during verbal fluency than during word listening. No areas were more activated in the controls than in EB, whereas the mesial part of the superior frontal gyrus and the anterior cingulum were more activated in EB than in the controls. The plot in Figure 3 suggests that the neurofunctional differences in the frontal cortex reflect a stronger activation of this area in EB during controlled lexical retrieval tasks.

Verbal fluency vs. automatic series recall (see Figure 3 and Table 3b). Both the controls and EB showed greater activation of the mesial part of the superior frontal gyrus, of the middle and inferior frontal gyri, of the anterior and middle cingulated cortex during verbal fluency than during automatic series recall. The lingual gyrus and the calcarine cortex were more activated in the controls than in EB, whereas EB activated the mesial part of the superior frontal gyrus and the postcentral gyrus more than the controls. The plot in Figure 3 suggests that the neurofunctional differences in the frontal cortex reflect a stronger activation of this area in EB during controlled lexical retrieval tasks.

Single word processing: auditory/visual dissociation

Word listening vs. word reading (see Figure 3 and Table 4a). In both the controls and EB, the middle temporal gyrus was more activated during word listening than during word reading. This differential activation was of a larger magnitude in EB than in the normal controls. The plot in Figure 3 suggests that the neurofunctional differences in the temporal cortex reflect a hypoactivation of this area in EB during the word reading task.

Word reading vs. word listening (see Figure 3 and Table 4b). In both the controls and EB, the inferior occipital gyrus and the calcarine cortex were more activated during word reading than during word listening. The inferior parietal lobule was more activated by the controls than EB, whereas no areas were more activated in EB than in the controls when comparing the reading and listening tasks. The plot in Figure 3 suggests that the neurofunctional differences in the parietal cortex reflect a stronger activation of this area in EB during the word listening task.

Visual-orthographic processing

The frontal cortex, the middle temporal gyrus and the occipital lobe were activated in both the controls and EB during both word and non-word reading.

There were also some important differences: the controls displayed more extensive activation in frontal cortices and in the part of the occipitotemporal cortex that contains the so-called Visual Word-Form Area (Cohen et al., 2002) and in the angular gyrus. On the other hand, EB displayed more extensive activation in occipital cortices devoted to early visual analyses of the orthographic input (see Figure 3 and Table 5a). The plot in Figure 3 suggests that the neurofunctional differences in the ventral occipitotemporal cortex reflect

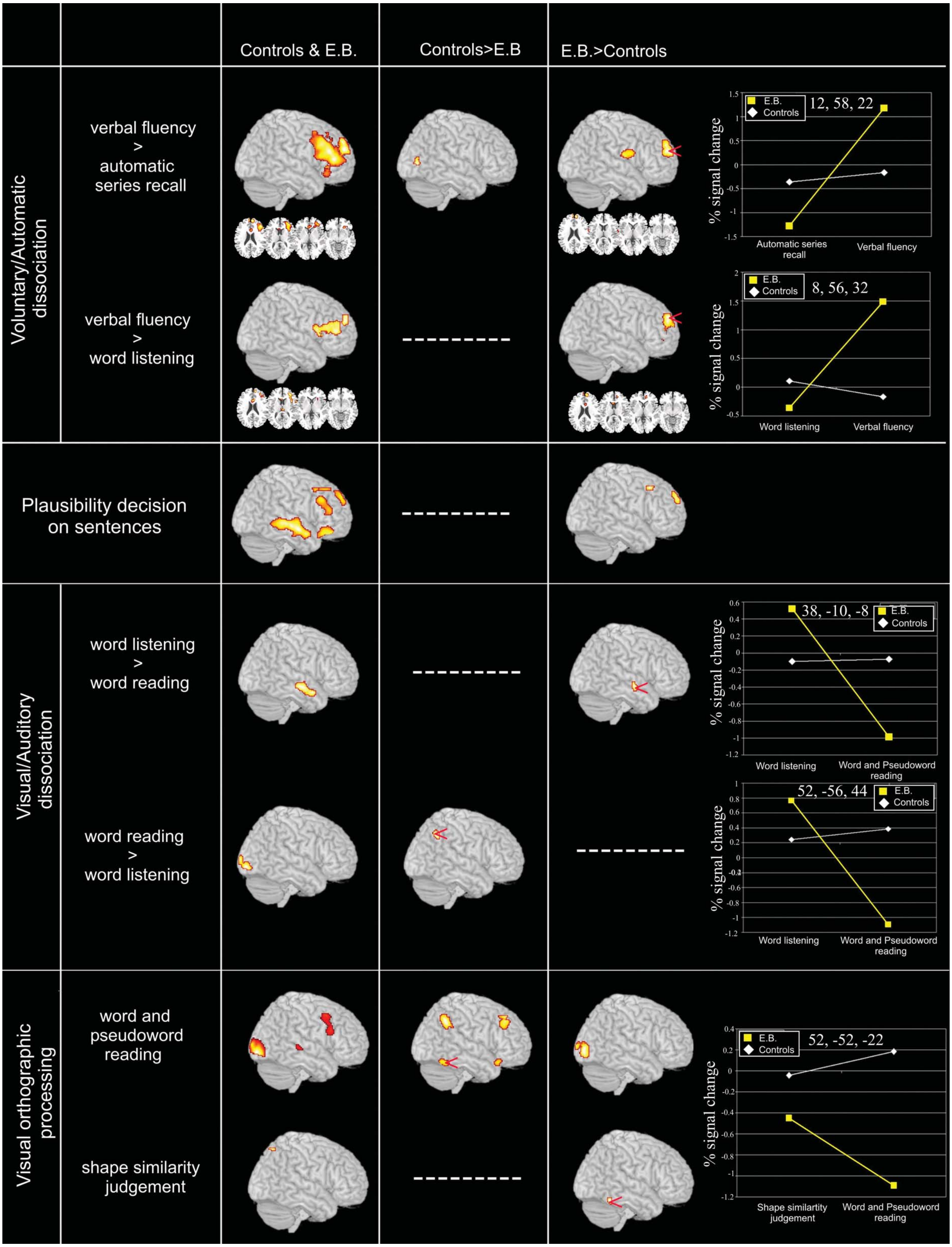

Figure 3. Brain activation data. From left to right, we report neurofunctional commonalities between EB and volunteers, neurofunctional differences between controls and EB (controls > EB and EB > controls) and the BOLD-signal plot of the pointing regions. [To view this figure in color, please see the online version of this Journal].

TABLE 3
Brain regions showing a significant effect in voluntary versus automatic tasks[a]

	MNI Coordinates of local maxima			
Brain regions	*x*	*y*	*z*	*Z-score*
(a) Verbal fluency versus word listening				
Brain activations shared by EB and controls				
Sup. frontal gyrus	30	46	12	3.7
Sup. frontal med. gyrus	12	54	24	4.1
	8	56	32	4.0
	−4	52	30	4.0[b]
	−4	42	34	3.9[b]
Mid. frontal gyrus	34	44	18	3.7
Inf. frontal tri. gyrus	40	38	14	3.8
	44	36	18	3.7
Inf. frontal op. gyrus	40	12	14	3.9
	60	18	6	3.9
Rolandic opercular gyrus	58	10	14	3.6
Ant. cingulum	6	14	26	4.0
Thalamus	6	−22	14	3.6
	−4	−20	14	3.3[b]
Controls > EB	–	–	–	–
EB > controls				
Sup. frontal med. gyrus	8	56	32	5.1*
	12	54	24	5.1*
	−4	52	30	4.7[b]***
	−4	62	20	3.8[b]
Ant. cingulum	14	48	14	3.6
	−2	8	26	3.2[b]
(b) Verbal fluency versus automatic series recall				
Brain activations shared by EB and controls				
Sup. frontal med. gyrus	10	58	24	6.1*
	8	28	42	3.7
	−4	54	32	6.1[b]*
	−4	60	22	5.0[b]*
Mid. frontal gyrus	44	32	22	6.1*
	36	42	10	6.1*
Inf. frontal orb. gyrus	38	30	−12	3.7
	34	30	−10	3.6
Inf. frontal tri. gyrus	42	38	16	5.7*
Inf. frontal op. gyrus	32	8	34	3.7
Olfactory cortex	−4	28	0	4.5[b]***
Ant. cingulum	4	32	2	4.3
	6	16	26	4.3
Mid. cingulum	8	36	36	4.7***
Controls > EB				
Calcarine fissure	18	−76	12	3.3
Lingual gyrus	20	−76	2	3.9
EB >controls				
Sup. frontal med. gyrus	12	58	22	5.0*
	−4	62	20	5.0[b]*
	−4	54	32	4.8[b]**
Postcentral gyrus	64	−8	18	4.4*
	62	2	20	3.9

[a]In order to compare the EB's "dominant and lone" hemisphere with the dominant hemisphere of controls, the contrast images of the controls were flipped along the *x*-axis and saved in radiological convention. We flipped the normal controls data rather than EB's data to make the visualization of the results more obvious in relationship with the lone-right hemisphere of our patient.
[b]The apparent left-sided location of this peak simply refers to its spatial position in stereotactic space most likely due to a smearing effect of the in plane Gaussian filter; indeed there was no residual left hemisphere in our patient in these stereotactic locations.
*$p <$ FWE 0.005; **FWE 0.005 $< p <$ FWE 0.01; ***FWE 0.01 $< p <$ FWE 0.05.

TABLE 4
Brain regions showing a significant effect of input modality presentation

	MNI Coordinates of local maxima			
Brain regions	*x*	*y*	*z*	*Z-score*
(a) Word listening versus word reading				
Brain activations shared by EB and controls				
Mid. temporal gyrus	60	−10	−12	4.2
	62	−14	−10	4.2
Controls > EB	–	–	–	–
EB >controls				
Mid. temporal gyrus	38	−10	−8	4.1
(b) Word reading versus word listening				
Brain activations shared by EB and controls				
Inf. occipital gyrus	32	−92	−8	4.5***
Calcarine fissure	16	−102	4	4.2
Controls > EB				
Inf. parietal gyrus	52	−56	44	3.8
EB > controls	–	–	–	–

***FWE 0.01 $< p <$ FWE 0.05.

a stronger activation of this area in EB during shape-similarity task and a hypoactivation of the same area in EB during the reading task.

Sentence plausibility decision task

Finally, we observed that both EB and the controls activated the mesial part of the superior frontal gyrus, the middle and inferior frontal gyri and the middle temporal gyrus during a sentence judgment task. No areas were more activated by the controls than EB during this semantic task, whereas the mesial part of the frontal gyrus and the middle frontal gyrus were more activated in EB than in the controls (see Figure 3 and Table 6).

Shape similarity judgment

Both the controls and EB activated the occipitoparietal, occipital and occipitotemporal cortices. In particular, the stereotactic coordinates of the occipitotemporal cortex in EB were compatible with where a right Visual Word-Form Area would be located. There were no differences between EB and the controls (see Figure 3 and Table 5b).

DISCUSSION

Previous studies exploring the neural correlates of language in hemispherectomized patients have mostly concentrated on language production tasks such as verbal fluency and picture naming (Hertz-Pannier et al., 2002; Liegeois, Connelly et al., 2008; Voets et al., 2006). The single-case study we describe here represents an attempt towards a more systematic assessment of the brain activation patterns associated with a range of linguistic tasks; both language production, as verbal fluency and automatic series recall, and comprehension of words and sentences were assessed in the same hemispherectomized patient.

In the following paragraphs, we will discuss the behavioral and functional anatomical patterns of patient EB with particular emphasis on the issue of whether the fMRI patterns in EB's lone right hemisphere mirror those observed in the left dominant hemisphere of normal people. We believe these observations may have relevance for theories about the neural segregation/lateralization of cognitive functions and the neural reorganization following massive brain injury in childhood.

Convergence between neuropsychological theories and neuropsychological results

From a behavioral point of view, EB did not show clinically relevant signs of language impairment in his everyday life. Indeed, in the linguistic domain, EB's phonology, basic lexicon, morphology and syntax appeared to be plainly efficient in his daily life interactions, hardly revealing minor signs of limitation. It should be noticed, though, that in the TROG test EB failed to pass five blocks out of

TABLE 5
Visual tasks: comparison between EB and controls

	MNI Coordinates of local maxima			
Brain regions	*x*	*y*	*z*	*Z score*
(a) Word and non-word reading[a]				
Brain activations shared by EB and controls				
Mid. frontal gyrus	42	10	50	4.2
	40	10	38	3.2
Inf. frontal tri. gyrus	38	16	26	4.1
Inf. frontal op. gyrus	42	14	38	3.3
Precentral gyrus	46	10	48	4.2
Mid. temporal gyrus	60	−30	2	3.7
Inf. occipital gyrus	32	−94	−6	Inf*
Calcarine fissure	20	−100	4	6.6*
	16	−102	4	6.3*
Controls > EB				
Sup. frontal med. gyrus	12	34	48	5.2*
Mid. frontal gyrus	38	34	40	4.7°
Inf. frontal orb. gyrus	34	22	−20	3.9
Angular gyrus	50	−56	40	5.2*
Inf. temporal gyrus	52	−56	−20	4.0
EB > controls				
Sup. occipital gyrus	16	−102	6	4.2
	20	−100	8	4.0
Mid. occipital gyrus	36	−90	2	4.8**
Inf. occipital gyrus	36	−90	−2	4.8**
(b) Shape similarity judgement on line drawings[b]				
Brain activations shared by EB and controls				
Sup. parietal gyrus	18	−76	58	4.5***
Mid. temporal gyrus	50	−52	−18	4.0
	48	−56	−16	4.0
Mid. occipital gyrus	32	−78	26	3.6
	30	−82	28	3.6
Sup. parietal gyrus	18	−70	58	4.3
Mid. temporal gyrus	48	−52	−20	3.8
controls > EB	–	–	–	–
EB > controls	–	–	–	–

[a]Word reading and non-word reading were presented in a one long session in alternated blocks and we analyzed these tasks as a main effect comparing the reading tasks (words and non-words together) with the baseline conditions (strings of lines with different orientation).
[b]The analysis on controls' activations showed that this task was right-lateralized. Thus, in this case we compared the right dominant hemisphere of controls with the right hemisphere of EB.
$^{*}p <$ FWE 0.005; **FWE 0.005 $< p <$ FWE 0.01; ***FWE 0.01 $< p <$ FWE 0.05.

20 and most of his errors were provoked by relative sentences in block 14 ('*The boy who is chasing the horse is fat'*) or in the block 20 ('*The cat that the cow is chasing is brown'*). Other syntactic error included locatives (*on, in*) and a determiner, in block 16 and 18, respectively. The 15 blocks passed with the TROG test placed EB's syntactic comprehension level between the 25th and the 50th percentile. These findings were further corroborated by the Token test, where EB made only two mistakes out of 36 items and both in the section F ('*Touch the black circle with the red square*' and '*Touch the squares slowly and the circles quickly*'): his 34 correct responses placed EB's language comprehension within the normal range. Yet, the persistence over time of subtle syntactic deficiencies is likely to lead to a lowering of EB's linguistic proficiency, as a mastery of more complex syntactic structures is required at higher chronological age. Furthermore, the above caveats on EB's current syntax are enhanced by a set of specific linguistic tasks assessing lexical retrieval and word comprehension for pictorial stimuli: limitations surface from the low scores in the Boston Naming task and the lexical

TABLE 6
Plausibility decision on sentences: comparison between EB and controls

	MNI Coordinates of local maxima			
Brain regions	*x*	*y*	*z*	*Z score*
Brain activations shared by EB and controls				
Sup. frontal med. gyrus	2	52	42	3.3
	8	32	48	4.1
	−4	56	36	4.2[a]
	−4	58	32	4.2[a]
Mid. frontal gyrus	50	36	22	3.6
	26	18	48	4.1
Inf. frontal orb. gyrus	48	40	−18	4.8**
Inf. frontal tri. gyrus	50	28	32	4.6***
	48	38	16	3.9
Mid. temporal gyrus	58	−6	−12	5.6*
Mid. temporal gyrus	62	−18	−6	5.5*
Controls > EB	–	–	–	–
EB > controls				
Sup. frontal med. gyrus	−4	58	30	3.9[a]
	−4	56	36	3.9[a]
Mid. frontal gyrus	26	18	48	4.5***

[a]The apparent left-sided location of this peak simply refers to its spatial position in stereotactic space most likely due to a smearing effect of the in plane Gaussian filter; indeed there was no residual left hemisphere in our patient in these stereotactic locations.
*$p <$ FWE 0.005; **FWE 0.005 $< p <$ FWE 0.01; ***FWE 0.01 $< p <$ FWE 0.05.

comprehension task (PPVT). These language deficiencies are also in agreement with the findings from the verbal section of the IQ test: the Similarities and the Vocabulary tasks from the WISC-R scale are below the normal level.

In a similar vein, EB's orthographic skills, qua reading and spelling, display an outstanding degree of accuracy, besides revealing that speed is fully within the normal range in both kinds of tasks. However, the lexical deficiencies are somehow reflected in EB's orthographic lexicon, as detected by the low scores in reading loan words, in the visual lexical decision and in the visual homophone tasks. Our suggestion is that his lone right hemisphere and, perhaps more in general *the lone* right hemisphere, cannot provide, by itself, a perfect mastery of each component of language and language-related functions.

Despite the subtle syntactic and lexical limitations we have discussed thus far, a detailed neuropsychological assessment of EB's main cognitive functions (such as language, executive functions, and praxis) revealed a near-normal cognitive profile in most of the neuropsychological tests. These findings are in agreement with previous studies showing that language abilities may be largely (though far from completely) preserved after left hemispherectomy (Bates et al., 2001; Woods & Teuber, 1978), even with late-onset lesions of the left hemisphere (Cossu et al., 1995; Vargha-Khadem et al., 1997).

Indeed, the majority of patients with early left hemispherectomy show normal language skills with the exception of some specific linguistic aspects such as comprehension (Vanlancker-Sidtis, 2004), word retrieval (Boatman et al., 1999) and syntactic skills (Stark, Bleile, Brandt, Freeman, & Vining, 1995). These data confirm that the lone right hemisphere is capable, at least partially, of compensating for the loss of the left hemisphere, maintaining near-normal behavioral performance in most linguistic tests (Vanlancker-Sidtis, 2004) and an adequate level of performance in other cognitive functions such as visuo-spatial skills. The largely spared behavioral profile of EB enabled a systematic investigation of the neurofunctional networks recruited during the execution of different linguistic tasks, as discussed below.

Neurofunctional results

Our fMRI study showed that EB's right hemispheric language system is organized around brain regions largely corresponding to homologues of the left brain regions activated in our sample of healthy controls. This was true across a number of latitudes tested by our tasks, including the primary patterns associated with each task the patient was presented with and the more specific comparisons such as the dissociation between stereotyped vs. controlled word retrieval and the comparison between auditory vs. visual word processing.

Thus, we suggest that the overall neurofunctional architecture of EB's right hemispheric language system mirrors a left-like linguistic neural blueprint. This finding is in agreement with the results reported by Liegeois, Connelly et al. (2008) and Hertz-Pannier et al. (2002) on controlled word retrieval, and the data of the present paper extended these previous findings to a number of linguistic behaviors such as single word and sentence comprehension.

However, in our experiment we also found a number of task-specific differences in the magnitude of the activations when EB was formally compared with the normal controls. In particular, EB showed a stronger recruitment of the prefrontal cortex in most of the controlled linguistic processes investigated (e.g., controlled word retrieval vs. automatic production or word listening, but also tasks like sentence judgment; see the plots in Figure 3).

In principle, any topographical difference between EB and the normal controls could be due to the fact that we compared EB's right hemisphere with the controls' left hemispheres. However, if this were the case then one would expect a completely random neurofunctional distribution of the hyperactivations and of the hypoactivations in EB's right hemisphere. Indeed this was not the case, as for example EB's hyperactivations in cognitively more demanding tasks are always located in the dorsal prefrontal cortex. Moreover, the conjunction analyses of EB's and the controls' patterns clearly showed a large degree of overlap between EB and the controls.

Accordingly, we are inclined to attribute a biological significance to the differences between EB and the controls, particularly to those findings that were replicated across tasks, like the hyperactivation of the dorsolateral prefrontal cortex (DLPFC). This last finding may suggest that controlled language processes are generally more demanding from a neurofunctional point of view.[2] Indeed, although EB's level of activation in the DLPFC, either during automatic serial recall or during word listening, was similar to that of the healthy controls, a significant difference emerged in the verbal fluency condition (see the BOLD signal plots for the DLPFC reported in Figure 3). This interpretation of the stronger DLPFC activations in EB during controlled language processes is in line with several studies investigating the role of the prefrontal cortex in attentional processes and working memory, and with the experiments on the effect of cognitive load on this brain region (Gilbert, Spengler, Simons, Frith, & Burgess, 2006; Owen, McMillan, Laird, & Bullmore, 2005; Pochon et al., 2002). It is worth noting that, notwithstanding these hyperactivations, EB showed an adequate level of behavioral performance in controlled linguistic tasks, such as phonemic and semantic verbal fluency. Taken together, this evidence suggests that the over-recruitment of the prefrontal cortex (PFC) may represent a neurofunctional manifestation of compensatory processes[3] required to produce adequate behavioral output.

Finally, we notice that some other neurofunctional differences emerged in other brain regions beyond the DLPFC (see the BOLD signal plots for the middle temporal cortex reported in Figure 3). In particular, EB showed a significant hyperactivation in the middle temporal gyrus when processing auditory verbal input (word listening task), but not when he was presented with a visual verbal input. This hyperactivation was coupled with a significant decrement of EB's BOLD signal in the angular gyrus and in the occipitotemporal cortex during the word reading task. This result, together with

[2] It could be the case that some activations in EB's DLPFC still reflected functions typical of the right hemisphere as well. In order to investigate this hypothesis we compared EB's pattern with the right hemispheric activations of the normal controls. As in the previous analyses, we observed that EB had stronger activations than controls in the DLPC (data not formally presented in the paper). This evidence supports the hypothesis that EB's right frontal stronger activations may represent compensatory processes rather than the fMRI equivalents of functions typical of the right hemisphere.

[3] In the literature about aging, the over-activation of new brain regions (e.g., prefrontal cortex and posterior parietal cortex), in association with the maintenance of a good level of performance, is defined as 'compensation' (Berlingeri et al., 2010; Cabeza, Anderson, Locantore, & McIntosh, 2002; Grady, 2008).

the behavioral dissociation between auditory and visual lexical decision, suggests that EB's lexical access may be susceptible to the input modality (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Graves, Desai, Humphries, Seidenberg, & Binder, 2010).

Reading

The study of reading in a patient like EB is of particular interest for a number of reasons. First, EB's left hemisphere was removed several years before any formal teaching of reading was started; furthermore, his left hemisphere was clearly the dominant linguistic hemisphere, as attested by his slow recovery from aphasia and the persistence of morphosyntactic problems for some years following neurosurgery. Second, the reading system is perhaps one of the most left-hemisphere lateralized, particularly in Broca's area, in the ventral occipitotemporal cortices containing the so-called visual word form area (VWFA) and in the neighboring cortices implicated in the conversion from print to sound. Yet, our findings show that, in developmental age, a highly efficient orthographic system (although far from functional perfection) can be successfully assembled by a previously non-dominant hemisphere.

A neurofunctional reorganization of such magnitude may have implications for both the clinical and the scientific domains, although we are aware that the findings from a single case-study, suggestive as they can be, deserve great interpretative caution and any attempt toward general conclusions must be tempered with prudence. However, EB's unexpected mixture of great accuracy and subtle difficulties in reading, deserve some brief considerations. On a behavioral assessment, EB's high proficiency in reading both words and non-words (conforming to Italian orthography) stands in contrast with his difficulties in reading loan words and in the homophone test. We maintain that such discrepancy is most likely fostered by two components: (a) the structure of Italian orthography and (b) the neurofunctional limitations arising from the early left hemisperectomy.

The Italian orthography has a high degree of transparency (Cossu, 1999), thus minimizing the processing discrepancies between regular vs. irregular words, as well as between words vs. non-words. Indeed, EB's orthographic skills were exceptionally well preserved *qua* reading words and non-words in terms of both accuracy and speed. No significant difference emerged by comparison with age-matched controls across different ages at 8, 3, or 17 years of age. Furthermore, equally unimpeachable was EB's efficiency at writing to dictation both words and non-words. However, in our case, the ontogeny of a dedicated neural system for reading seems to have suffered from significant limitations, since EB made significantly more errors than controls do in a visual lexical decision task, in discriminating written homophones and in reading irregular and loan words (that is, common words from English or French present in the Italian vocabulary). In sum, EB's neuropsychological pattern was akin to that of a surface dyslexia patient (Patterson, Marshall, & Coltheart, 1985).

How these observations compare with previous similar case reports as far as reading? A direct comparison is made difficult by a number of factors. For example, there is evidence showing that deep and transparent orthographies place different burdens on similar brain areas (Paulesu et al., 2000) and that the differences in reading performance among dyslexics of different countries are most likely due to the different complexity of the orthographies (Paulesu et al., 2001) rather than to the underlying brain dysfunction. For these reasons, it may be difficult to compare the reading performances of patients from cultures with orthographies of different complexity, particularly when discussing single cases like EB. Perhaps the most similar case is the one described by Cossu et al. (1995), a right-handed Italian boy (SG) who sustained extensive left hemisphere damage after a massive subarachnoid hemorrhage at the age of 12 years; his right hemisphere was fully intact. Unlike EB, SG's reading skills showed all the characteristics of deep dyslexia: recognition of printed words in a lexical decision paradigm showed 87.5% correct for words vs. chance performance for non-words (50% correct). In reading aloud SG achieved a 55% correct for words, but only 10% correct for non-words. Likewise, in writing to dictation, SG spelled 32.5% of words and 10% of the non-words correctly. The behavioral discrepancies between EB and SG clearly reveal how much the time of the lesion onset may matter and how vastly different can be the ensuing compensatory resources of the lone right hemisphere in previously right-handed children.

From a neurophysiological point of view, EB's reading-activations included a subset of the typical reading-network homologous areas such as the inferior frontal gyrus, the precentral gyrus, and the inferior occipital gyrus; however, he also showed a significantly reduced neural activity – as measured during word and non-word reading – in the inferior temporal and occipitotemporal cortices, in the angular gyrus and in the frontal cortex. Portions of these cortices have been associated with whole word visual recognition (Binder et al., 2003; Cohen, Dehaene, Vinckier, Jobert, & Montavont, 2008; Cohen et al., 2002; Herbster, Mintun, Nebes, & Becker, 1997; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Pugh et al., 2010): precisely the level of processing that is selectively defective in EB[4], as attested by his poor performance in a visual lexical decision task, while being at the ceiling in an auditory lexical decision task. Indeed, his right ventral occipitotemporal cortex (spatially congruent with a right-sided VWFA) was activated by the more elementary shape-matching task, as was the same right-sided area of the controls, but seemed to be uncommitted for the reading task. Taken together, these results suggest that EB's impairment in specific aspects of reading behavior may be due to the fact that he was unable to develop specific neural representations within the ventral occipitotemporal cortices, as normally observed in the left hemisphere of controls. It is important to note that the ventral occipitotemporal cortices seem to be an important bridge between different systems (such as the orthographic and phonological/semantic systems), as suggested by some authors (Devlin, Jamison, Gonnerman, & Matthews, 2006; Hillis et al., 2005; van der Mark et al., 2011). Moreover, EB's functional results in reading and shape-similarity judgment showed how the occipitotemporal area was not completely deprived of its functional role as this brain region was still able to process simple shapes as in normal controls, but at the same time the occipitotemporal region was not able to develop any kind of reading-specificity.

Even though reading has never been investigated with fMRI in early left hemispherectomized patients and therefore we cannot compare EB with previous cases, the behavioral patterns of EB were in line with previous behavioral studies in hemispherectomized patients (Cummine, Borowsky, Winder, & Crossley, 2009; Ogden, 1988; Patterson, Vargha-Khadem, & Polkey, 1989), suggesting that a lone right hemisphere is not fully equipped to completely master reading, and it provides only a partial control of the reading processes. However, the magnitude of the functional recovery in reading after an early left hemispherectomy may be substantially determined by the nature of the orthographic system to be acquired (being easier with regular orthographies), besides the side of the hemispheric lesion. Overall, our suggestion is that the lone right hemisphere cannot provide, by itself, a perfect mastery of each component of language and language-related functions (such as orthography), the magnitude and quality of compensatory resources being strictly biased by the degree of brain plasticity, namely by the time of lesion (Chalupa, Berardi, Caleo, Galli-Resta, & Pizzorusso, 2011; Lomber & Eggermont, 2006).

CONCLUSIONS

The single case described here allowed us to investigate the neuropsychological and neurofunctional outcomes of an early left-hemispherectomy with a number of interesting features in comparison with previous studies: (a) the left hemispherectomy had occurred in a pre-literate child and (b) the patient's right hemisphere was intact, being unaffected by the vascular pathology that led to the left hemispherectomy; furthermore, the child had never suffered from a single epileptic seizure (not even during the post-operative phase).

Overall, our findings show that EB's right hemisphere may implement a number of basic linguistic skills by largely replicating a left-like neural blueprint: nonetheless, some differences were observed in comparison with normal controls, in particular that more extensive prefrontal cortex activation was seen for linguistic tasks not characterized by an overwhelming cognitive load.

The vision-to-lexicon difficulties observed in the patient were associated, at least for reading, with abnormal activation of the right-sided inferior temporo-occipital cortex whose defective activation, in the left hemisphere, is typically observed in dyslexia (Paulesu et al., 2001; Shaywitz et al., 2002). We conclude that, even in this respect, EB's right hemisphere is reminiscent of the organization of a left-sided linguistic network. However, we are aware

[4] A further analysis, showed that no differences emerged when we compared word reading and non-word reading in controls, while the same comparisons in EB showed a stronger activations in the word reading rather than non-word reading in the frontal areas; on the other hand, no brain differences emerged in the opposite comparison (non-word reading more than word reading). These data may suggest that regular word reading could be more demanding for EB than non-word reading, while performance remained within the normal level.

that a deeper understanding of the compensatory role of the right hemisphere and of EB's forthcoming linguistic trajectories require a more thorough and systematic inspection of both syntax and lexicon in future years. Likewise, more studies using fMRI are needed to establish whether a right-side VWFA can develop in patients like EB.

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APPENDIX

TABLE 1
We report here all the stimuli used in the word listening task

Items	*Word frequency*[5]	*Items*	*Word frequency*
cioccolato	46	sfida	244
ricatto	54	carne	232
calcio	479	accordo	514
bagaglio	50	notizia	550
microfono	53	biblioteca	102
entusiasmo	175	ghiaccio	87
alba	144	affetto	176
cervello	178	tulipano	3
prodotto	490	fessura	26
anello	90	rumore	188
scena	627	denaro	337
freno	68	benzina	108
tempesta	77	altalena	17
ortica	6	liquore	17
viaggio	526	regina	190
riso	104	vasca	68
accento	60	bomba	210
frittata	27	magia	92
colla	12	occhio	1297
marciapiede	62	cassiere	17
battuta	267	aiuto	371
campagna	527	sapone	19
scommessa	64	disegno	319
faccia	409	asfalto	53
torcia	21	acqua	1113
allarme	248	piazza	347
pubblicità	163	filosofia	184
pace	401	sorella	332
lago	131	idea	1058
affanno	33	pesce	318
acciuga	23	brivido	91
danza	110	pollice	36
negozio	328	avversario	287
candidato	358	foresta	121
qualità	409	opinione	297
lenzuolo	61	indirizzo	125
fatica	265	lana	50
agenzia	188	moda	416
gancio	12	albero	305
ragione	785	scaffale	35
roccia	102	elemento	427
serbatoio	37	tegola	19
allegria	64	ricetta	152
paese	1857	addio	93
umore	114	vernice	29

TABLE 2
We report here all the stimuli used in the word and non-word reading task

Items (words)	*Word frequency*	*Items (non-words)*
farina	52	adurio
lavoro	2114	dinte
pugno	168	manipo
benessere	87	viba
scuola	856	restapo
oggetto	513	ortuso
vetrina	70	forsecca
calore	128	grapo
mare	630	fime
rifugio	108	crespino
debito	182	infomio
sedia	122	firna
gara	468	elintioso
affitto	77	arba
accendino	9	damisio
casa	2954	bansa
ricerca	652	eschiota
caffè	14	intiano
abuso	71	mirite
mamma	491	amiroso
numero	1196	nisota
afa	19	cipiere
poeta	161	faronte
fabbrica	168	olsa
data	227	nebro
impegno	477	risatta
banca	387	vadio
affermazione	103	pomite
vagone	21	sporella
cifra	282	toritio
elezione	524	cebi
cucina	271	frada
aereo	206	dimido
lotta	285	oresto
formaggio	79	lugno
alluvione	23	povente
bottega	57	udistà
sindaco	710	remuta
musica	568	borta
capriccio	56	encipio
sale	206	meso
anima	341	nuso
pelliccia	38	parico
guerra	954	tepola
radice	148	straco

[5] Word frequency was entracted from the vocabulary of frequency of the institute of Computational Linguistics (Genova; http://www.ge.ilc.cnr.it/).