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Language tasks used for the presurgical assessment of epileptic patients with MEG

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ABSTRACT – Determining the language dominant hemisphere and the intrahemispheric localization of this function are imperative in the planning of neurosurgical procedures in epileptic patients. New noninvasive diagnostic techniques are being developed to reduce the risks associated with more invasive techniques. The aim of this paper is to review the different protocols for lateralizing and/or localizing language functions using magnetoencephalography (MEG), a noninvasive technique. The reviewed studies include control and patient populations using various protocols which employ different expressive and receptive language tasks. The overall findings reveal high concordance between MEG and the intracarotid amobarbital test (IAT). Moreover, MEG allows intrahemispheric localization of receptive and expressive language functions. However, the different language tasks used with MEG, whether receptive or expressive, appear to activate the left temporal more than frontal areas. The best task to assess language comprehension in both adults and children appears to be a word recognition task. A verbal fluency task could be used to test language production in children and a verb generation task in adults.

Key words: epilepsy surgery, language, magnetoencephalography, localization, lateralization

The most commonly used treatment for epilepsy is pharmacotherapy (Killgore *et al.*, 1999). However, an estimated 35% of patients with epilepsy develop medically intractable epilepsy. In these cases, surgery is widely used to remove the epileptogenic zone (Gates and Dunn, 1999). Resective epilepsy surgery is performed mainly in the temporal and frontal lobes (selective amygdalo-hyppocampectomies, anterior temporal lobectomies, or tailored temporal or frontal corticectomies). However, it must be previously determined that the resection will not have any substantial consequences on cognitive functions, such as language or memory. Determining the language dominant hemisphere and localizing the language function is particularly important in epileptic patients because they present greater variability in language dominance than neurologically healthy individuals (Berl *et al.*, 2005).

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It is estimated that 94% to 96% of healthy right-handers and 74% of left-handers have left-hemisphere language dominance (Pujol *et al.*, 1999; Springer *et al.*, 1999). In contrast, 63% to 96% of right-handed epileptic patients and 48% to 75% of left-handed or ambidextrous epileptic patients show left-hemisphere language dominance (Helmstaedter *et al.*, 1997; Springer *et al.*, 1999).

The medical standard for determining the language dominant hemisphere prior to surgical resection is the intracarotid amobarbital test (IAT), also known as the Wada test (Wada and Rasmussen, 1960), hereinafter referred to as the IAT. It consists of an injection of sodium amobarbital into the left or right internal carotid arteries. This causes a temporary arrest of function in each hemisphere for approximately six to ten minutes, during which the unanaesthetised hemisphere is functionally assessed. Tasks used to assess language dominance include naming common objects, reading single words aloud, counting, and spelling single words. A major drawback of this test is that it determines lateralization only, and does not allow intrahemispheric localization of language functions. Moreover, because it is relatively invasive, this technique cannot be used with normal volunteers and is difficult to use with children. Finally, the IAT is associated with risks of stroke, infection, and haemorrhage (English and Davis, 2010).

When surgery is believed to put language functions at risk, electrical stimulation mapping (ESM) is used to obtain information on the specific location of the language areas. Using an electrical current, specific brain areas are stimulated while the patient is awake and performing a linguistic task. This method is the most reliable and direct way to localize language areas. However, it has several disadvantages: it is very invasive, there are associated risks such as stimulation-induced seizures, it requires that patients be awake, it is costly, and it cannot be revisited if results are ambiguous (McDermott *et al.*, 2005).

Because of the risks and limitations associated with more invasive techniques of language exploration, it is very important to develop alternate, minimally invasive or noninvasive techniques that offer both lateralization and intrahemispheric localization. Recent advances in imaging technology have produced noninvasive and minimally invasive techniques: functional magnetic resonance imaging (fMRI), positron emission tomography, near infra-red spectroscopy, transcranial magnetic stimulation, and MEG to localize language functions. Functional magnetic resonance imaging is the technique that has received the most attention as a possible replacement for the IAT. However, this method presents certain disadvantages: it is very expensive, requires the patient's cooperation, and is less suitable for young or mentally challenged individuals (Pelletier *et al.*, 2007). Of the remaining techniques, MEG is the only completely noninvasive technique offering excellent temporal and spatial resolution that can be used with children.

This paper reviews and examines the efficiency of different language tasks employed in studies that have used MEG to lateralize and localize intrahemispheric language functions in the human brain. The focus is on adaptability to a paediatric population. Following a brief description of the functioning of MEG, a review of studies that have used MEG to lateralize language functions is presented including an overview of the language comprehension and language production tasks used. The second part of the review focuses on studies aimed to determine the intrahemispheric localization of language within the dominant hemisphere. Some of these studies have used language comprehension tasks and others language production tasks. A total of 37 studies from the last decade are reviewed, all of which were conducted either with control subjects or in the context of presurgical assessment of epileptic patients, patients with brain tumours, and other types of patients, including adults and children.

Magnetoencephalography

This technique measures the magnetic fields produced by electrical activity in the brain. Channels that record brain activity are placed inside a helmet which is installed on the head, without direct contact. The underlying principle is that synchronized neural currents induce weak magnetic fields that can be measured by MEG. Superconducting quantum interference devices (SQUIDS) allow measuring very low intensity magnetic fields generated by electrical activity in the brain. The device primarily detects neuron clusters located in the sulci of the cortex parallel to the surface of the head. Systematic variations in the strength of the magnetic flux recorded at the scalp in the form of event-related fields (ERF) are observed when regional neural activity exceeds background levels. The early portion of the ERF waveform (150-200 ms) represents activity in the primary sensory cortex, whereas later portions (after 200 ms) reflect activation of association cortex such as areas responsible for language functions. For instance, in a semantic judgment task using visual stimuli (McDonald *et al.*, 2009), activation was observed bilaterally in the visual cortex (80-120 ms), spread to the fusiform cortex (160-200 ms), and was dominated by left hemisphere activity in the frontal and temporal lobe regions (240-450 ms).

Hemispheric language lateralization

In order to find an alternative to the IAT, which, although invasive, is currently the medical standard for lateralization of language functions, many studies have attempted to lateralize language functions using MEG. The term activation, which is derived from the fMRI literature, hereinafter refers to the magnetic field signature of neural activity at a particular point in time, as measured by MEG. Studies that have used language comprehension tasks are reviewed first, followed by studies that have used language production tasks. The methods and results of these studies are summarized in *table 1*.

When patient populations are studied, MEG and IAT findings are often compared. It is important to note that because it is invasive, the IAT cannot be performed on control subjects. Thus, in studies assessing control subjects, handedness is commonly used to determine the accuracy of MEG lateralization findings. However, the discordance between handedness and hemispheric dominance for language in normal populations makes this method problematic (Pujol *et al.*, 1999; Springer *et al.*, 1999).

Language comprehension

The simplest tasks used are passive listening tasks, in which participants listen to vowels, tones, or words (Szymanski *et al.*, 1999; Szymanski *et al.*, 2001; Kim and Chung, 2008). The accuracy of laterality findings using passive listening tasks varies between 71% for patients based on handedness and the IAT and 100% for controls based on handedness (Szymanski *et al.*, 2001; Szymanski *et al.*, 1999). Kim and Chung (2008) compared lateralization findings by looking at two areas of the brain separately: the inferior frontal gyrus (IFG) and the posterior part of the superior temporal gyrus (STG). Based on the IAT, of 17 patients, three were right- and 14 were left-hemisphere language dominant. When comparing IAT lateralization findings to MEG findings for the two structures separately, higher concordance between the IAT and MEG was found in the IFG (94%) than in the posterior STG (71%).

Other tasks are more complex and require participants to pay close attention to the stimuli. In a study using a categorization task, controls were instructed to listen to pairs of words belonging to the same or different semantic categories and silently count the number of different semantic pairs. The same procedure was followed with different tones, where participants had to determine whether pairs of tones were the same or different. It was expected that these two tasks would yield opposite lateralization patterns. As expected, greater left hemisphere activation was seen in 87.5% of subjects with the word-matching task, whereas 62.5% of subjects showed asymmetries favouring the right hemisphere with the tone-matching task (Simos *et al.*, 1998).

Breier *et al.* (1999b) found left hemisphere dominance in 87% of right-handed controls when determining whether a word was repeated, as opposed to 30% when determining whether a low note was repeated. Gootjes *et al.* (1999) asked controls to determine whether the first and last item in a group of vowels, tones, or piano notes were the same. When looking at activations only for groups in which the first and last item differed, they found that left hemisphere responses to vowels were significantly stronger than for tones or piano notes. Kirveskari *et al.* (2006) asked Finish-speaking participants to decide whether pairs of tones and Finish vowels were the same or different. When comparing the laterality index for strengths of the auditory-cortex 100 ms responses to vowels *vs* tones, they found left hemisphere dominance in 80% of right-handed subjects and right hemisphere dominance in 70% of left-handed subjects.

A frequently used word recognition task involves words that are presented either visually or auditorily, with some words being targets and others distractors. Target stimuli are usually presented for study before the test session. Target stimuli are then repeated and mixed with different distractors in each test block. Participants are asked to lift their index finger whenever they detect a repeated word (target). When this task was used with epileptic patients, MEG results showed high concordance with IAT results, varying between 86% and 92% of correct lateralization (Breier *et al.*, 1999a; Breier *et al.*, 2001; Papanicolaou *et al.*, 2004; Maestú *et al.*, 2002; Doss *et al.*, 2009). One group found that, when controlling for IQ and excluding patients with below average scores, the concordance between MEG and the IAT increased from 75% to 90% (Merrifield *et al.*, 2007). It therefore appears that when patients show reduced cognitive capacity, MEG is not 100% specific for language lateralization.

In a semantic judgment task, McDonald *et al.* (2009), found 75% concordance between MEG and the IAT when examining the laterality of temporoparietal sources, *versus* 100% with the IAT when examining the laterality of frontal sources. Hirata *et al.* (2009) used a reading task and found 85% concordance with the IAT in a sample of 60 patients. Finally, when lateralization was determined using both a reading and a picture naming task, it was possible to identify speech-related dominant hemispheric activity in most subjects (Kober *et al.*, 2001).

In summary, although complexity of tasks and stimuli varies greatly, the findings are promising for the use of MEG to lateralize language functions with language comprehension tasks. In the studies that compared frontal and temporal activations to better identify lateralization (Fisher *et al.*, 2008; Kim and Chung, 2008; McDonald *et al.*, 2009), it appears that frontal activations were more accurate. It is important to note that, as indicated in *table 1*, 10 of the 16 studies summarized in this section compared MEG to IAT findings, with concordance varying between 71% and 94%. Studies comparing handedness with MEG findings showed greater variability in concordance (47% to 100%), and results should be interpreted with caution.

Table 1. MEG studies investigating hemispheric language lateralization.

Language comprehension						
Task **Reference**	**Stimuli used**	**# of participants**	**Type of participants**	**Age**	**Concordance with IAT**	**Concordance with handedness**
Passive listening Szymanski *et al.* 1999	Vowels, tones	7	Controls	m = 35	-	100%
Passive listening Szymanski *et al.* 2001	Vowels	15	Patients	14-56	71%	71%
Passive listening Kim and Chung 2008	Words	17	Patients	17-52	71%-94%	-
Categorization Simos *et al.* 1998	Words, tones	16	Controls	28-53	-	87.5%
Auditory recognition Breier *et al.* 1999b	Words, tones	15	Controls	26-44	-	87%
Auditory recognition Gootjes *et al.* 1999	Vowels, tones, notes	11	Controls	23-30	-	91%
Auditory recognition Kirveskari *et al.* 2006	Tones, vowels	27	Controls	21-54	-	70%-80%
Word recognition Breier *et al.* 1999a	Words (visual-auditory)	26	Patients	8-56	92%	-
Word recognition Breier *et al.* 2001	Words (visual-auditory)	19	Patients	8-18	87%	-
Word recognition Papanicolaou *et al.* 2004	Words (auditory)	100	Patients	8-56	87%	-
Word recognition Maestú *et al.* 2002	Words (auditory)	8	Patients	m = 25	87.5%	-
Word recognition Merrifield *et al.* 2007	Words (auditory)	16	Patients	m = 31.5	90%	-
Word recognition Doss *et al.* 2009	Words (auditory)	35	Patients	m = 29.6	86%	-
Semantic judgment McDonald *et al.* 2009	Words (visually)	8	Patients	25-53	75%-100%	-
Reading Hirata *et al.* 2009	Words	60	Patients	-	85%	-
Reading and picture naming Kober *et al.* 2001	Word	15	Controls & Patients	26-67	-	93%
Language production						
Task **Reference**	**Articulation**	**# of participants**	**Type of participants**	**Age**	**Concordance with IAT**	**Concordance with handedness**
Picture naming Bowyer *et al.* 2005b	Covert	27	Patients	10-59	78%	-
Picture naming Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	-	44%
Verb generation Bowyer *et al.* 2005b	Covert	27	Patients	10-59	82%	-
Verb generation Breier and Papanicolaou 2008	Covert	8	Controls	18-75	-	100%
Verb generation Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	-	100%
Letter fluency Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	-	67%
Word generation Yamamoto *et al.* 2006	Covert	11	Controls	21-30	-	91%

Language production

It is also important to assess not only receptive but also expressive language, especially when findings are compared to the IAT, because this test assesses both language production and comprehension. A few language production tasks have been used with MEG to determine language function lateralization: picture naming, verb generation, phonemic fluency, and word generation. In most studies, due to the movement-related artefacts in MEG, tasks involve covert responses (Bowyer *et al.*, 2005b; Breier and Papanicolaou, 2008; Yamamoto *et al.*, 2006). However, in one study participants were asked to first produce answers silently and then vocalize them. This was to ensure that participants completed the task and that the initial data were not contaminated by movement caused by articulating the answers (Fisher *et al.*, 2008). Fisher *et al.* (2008) compared verb generation, letter fluency, and picture naming tasks. They found the highest accuracy with the verb generation task (100%), followed by letter fluency (67%) and picture naming (44%) in controls. Yamamoto *et al.* (2006) obtained 91% accuracy for language lateralization using a word generation task in controls.

Overall, it appears that verb and word generation tasks are more accurate in determining language function lateralization with MEG. Nevertheless, most of these studies were conducted in controls, such that the findings could not be compared with the IAT. However, Bowyer *et al.* (2005b) compared MEG findings with the IAT and found 82% concordance with the verb generation task.

Intrahemispheric language localization

Because the IAT allows hemispheric language lateralization only, IAT and MEG findings for intrahemispheric localization of language functions cannot be compared. MEG findings are compared to those obtained from other imaging techniques (fMRI). In many studies, researchers determined regions of interest, brain areas that are typically involved in language tasks, such as Broca's area in language production tasks and Wernicke's area in language comprehension tasks. First, the protocols used for language comprehension are presented followed by the language production protocols *(table 2)*.

Language comprehension

Passive listening tasks, which require participants to simply listen to stimuli without responding, were used to localize intrahemispheric sources of activation (Szymanski *et al.*, 1999; Szymanski *et al.*, 2001; Kim and Chung, 2008). Activation was found in the primary auditory cortical regions of the supratemporal plane (Szymanski *et al.*, 1999), the superior temporal gyrus and posterior inferior frontal lobe (Szymanski *et al.*, 2001) and the left inferior frontal gyrus and superior temporal gyrus (Kim and Chung, 2008). Shtyrov and Pulvermüller (2007) investigated the early dynamics of semantic context integration in neurologically healthy, Finnish-speaking participants. They used Finnish word pairs, with the second word being semantically congruent with the first (*e.g.* "jam-eat") or incongruent (*e.g.* "jam"-kick"). Surprisingly, they found that semantically incongruent stimuli elicited a brain response as early as 115 ms after the critical word onset, but not with semantically congruent words. Responses were maximal at the left temporal and inferior frontal cortical sites. This is the only study that reports such early activation, which is commonly associated with sensory treatment of information. In contrast to these listening tasks, Cornelissen *et al.* (2009) used a passive viewing task to determine when the contribution of the left IFG begins, as IFG is known to play an important role in reading and visual recognition. Left-lateralized IFG response to words was found at 100-250 ms (peak at 130 ms), which was significantly stronger than the response to consonant strings or faces.

Other more complex linguistic tasks have been studied using MEG. Martin *et al.* (1993) used a listening task in a case study using preoperative MEG to map the speech-receptive cortex in response to auditorily presented phonemes. The consonant-vowel syllables "da" and "ga" were presented. Patients had to covertly count all stimuli. Peak activation was observed anterior to Wernicke's area. Härle *et al.* (2002) used a decision-making task in which drawings of objects were presented to German-speaking subjects. In two separate tasks, subjects had to indicate whether the name of the object was masculine or feminine or whether the object was man-made or natural by pressing a button. The grammatical gender decision task was expected to trigger brain activity around 200 ms during the retrieval of morphological information, and the activity was expected to be found predominantly in the left hemisphere. In contrast, the control task, which focused on semantic processes only, was expected to show bilateral activation. Results showed a left-temporal focus of activity 150-275 ms after stimulus onset in the gender decision compared to the semantic classification task, which showed right fronto-central activation as well as more extensive left hemispheric activity in the gender decision task 300-625 ms after stimulus onset.

Three studies (Breier *et al.*, 1999b; Papanicolaou *et al.*, 1999; Sun *et al.*, 2003) used auditory recognition or decision tasks using words, tones, and pictures. Activation was found in the temporal lobe in the dominant hemisphere for all three tasks.

McDonald *et al.* (2009) used a semantic judgment task to investigate language comprehension. They hypothesized that language-related activity would spread along a posterior to anterior gradient, becoming increasingly left-lateralized in the temporoparietal and frontal lobe regions

Table 2. MEG studies investigating intrahemispheric localization of language.

Language comprehension					
Task **Reference**	**Stimuli used**	**# of participants**	**Type of participants**	**Age**	**Activation**
Passive listening Szymanski *et al.* 1999	Vowels, tones	7	Controls	m = 35	Left auditory cortex[a]
Passive listening Szymanski *et al.* 2001	Vowels	15	Patients	14-56	Left STG and post. inf. frontal lobe[a]
Passive listening Shtyrov and Pulvermüller 2007	Words	11	Controls	17-28	Left temporal and inferior frontal[b]
Passive listening Kim and Chung 2008	Words	17	Patients	17-52	Left IFG and posterior STG[c]
Passive viewing	Words, consonants	10	Controls	Left IFG[c]	Cornelissen *et al.* 2009
Active listening Martin *et al.* 1993	Syllables	1	Patients	25	Anterior to Wernicke's (LH)[a]
Decision making Härle *et al.* 2002	Drawings	14	Controls	18-37	Left temporal[b]
Auditory recognition Breier *et al.* 1999b	Words, tones	15	Controls	26-44	Left superior and middle temporal gyri[a]
Auditory recognition Papanicolaou *et al.* 1999	Words, tones, pictures	4-15	Controls & patients	21-68	Wernicke (LH)[a]
Auditory decision Sun *et al.* 2003	Words, tones	9	Controls	14-32	Wernicke (dominant hemisphere)[a]
Semantic judgment McDonald *et al.* 2009	Words (visually)	18	Controls & patients	21-54	Left temporal and frontal[d]
Word recognition Breier *et al.* 1999a	Words (visual-auditory)	26	Patients	8-56	Left temporal and frontal[a]
Word recognition Simos *et al.* 1999	Words (visual-auditory)	13	Patients	16-68	Left and bilateral temporal[a]
Word recognition Breier *et al.* 2001	Words (visual-auditory)	19	Patients	8-18	Left and bilateral temporal and frontal[a]
Word recognition Papanicolaou *et al.* 2004	Words (auditory)	100	Patients	8-56	Left and bilateral temporal and frontal[a]
Word recognition Breier *et al.* 2005	Words (auditory)	83	Patients	9-54	Temporal (dominant hemisphere)[a]
Word recognition Papanicolaou *et al.* 2006	Words (visual-auditory)	97	Controls	7-84	Bilateral STG and left MTG[a]
Word recognition Maestú *et al.* 2002	Words (auditory)	21	Patients	m = 25	Left temporoparietal and frontal[a]
Word recognition Lee *et al.* 2006	Words (auditory)	21	Patients	m = 31.1 ±16	Wernicke (dominant hemisphere)[a]
Word recognition Mohamed *et al.* 2008	Words (auditory)	8	Controls	6-12	Left temporal[e]

(continued)

Table 2 MEG studies investigating intrahemispheric localization of language *(continued)*.

Language comprehension					
Task **Reference**	**Stimuli used**	**# of participants**	**Type of participants**	**Age**	**Activation**
Reading Levelt *et al.* 1998	Sentences	10	Controls	20-37	Left auditory cortex[a]
Reading Kober *et al.* 2001	Words	8/7	Controls & patients	26-67	Wernicke and Broca (LH)[a]
Reading Hirata *et al.* 2009	Words	137	Controls & patients	m = 25.4/ 36.3	Left frontal and parietotemporal[e]
Categorization Kamada *et al.* 2007	Words (visually)	87	Patients	m = 4 3.6 ±14.1	Left temporal[a]
Categorization Kamada *et al.* 2006	Words (visually)	20	Patients	-	Left STG, MTG, supramarginal[a]
Language production					
Task **Reference**	**Vocalization**	**# of participants**	**Type of participants**	**Age**	**Activation**
Picture naming Salmelin *et al.* 1994	Overt and covert	6	Controls	25-34	Left temporal[a]
Picture naming Levelt *et al.* 1998	Overt	8	Controls	21-30	Left posterior temporal[a]
Picture naming Kober *et al.* 2001	Covert	8/7	Controls & patients	26-67	Wernicke and Broca (LH)[a]
Picture naming Bowyer *et al.* 2004	Covert	18/24	Controls & patients	-	Broca (LH)[f]
Picture naming Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	Left frontal[e]
Verb generation Bowyer *et al.* 2005a	Covert	25	Patients	10-59	Left BTLA[f]
Verb generation Kamada *et al.* 2006	Covert	20	Patients	-	Left inferior and middle frontal gyri[a]
Verb generation Breier and Papanicolaou 2008	Covert	8	Controls	18-75	Left frontal areas[b]
Verb generation Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	Left IFG[e]
Word generation Yamamoto *et al.* 2006	Covert	11	Controls	21-30	Left frontal and temporal[e]
Letter fluency Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	Left frontal[e]

[a] Equivalent current dipoles (ECD).
[b] Minimum norm estimate (MNE).
[c] Time-frequency analyses.
[d] Spatiotemporal analysis.
[e] Synthetic aperture magnetometry (SAM).
[f] MR-FOCUSS.
STG: superior temporal gyrus; IFG: inferior frontal gyrus; LH: left hemisphere; MTG: middle temporal gyrus; BTLA: basal temporal language area.

of interest. Activity was observed in the visual cortex bilaterally from 80-120 ms in response to novel words. Thereafter, activity spread to the fusiform cortex (160-200 ms) and was dominated by left hemisphere activity in response to novel words. From 240-450 ms, novel words produced activity which was left-lateralized in frontal and temporal lobe regions, including the anterior and inferior temporal, temporal pole and pars opercularis, as well as bilaterally in the posterior superior temporal cortex.

The word recognition task, described above in the first section, is probably the most extensively used task with MEG for the intrahemispheric localization of language functions. It has been used with both visual and auditory stimuli and has yielded promising results for localizing activity sources in both the frontal and temporal lobe (Breier *et al.*, 1999a; Simos *et al.*, 1999; Breier *et al.*, 2001; Papanicolaou *et al.*, 2004; Breier *et al.*, 2005). This task has been performed using visual and auditory modalities. Overall, sources of late activity have been observed in the following areas with this task: the posterior part of the superior and middle temporal gyri, the angular and supramarginal gyri, the mesial aspects of the temporal lobe, the inferior frontal areas of the left hemisphere, and the basal temporal areas, although using the visual mode only. Moreover, it is important to note that bilateral activity is often observed in these areas. In three of the studies that used this task, very large samples of control participants (n = 97; Papanicolaou *et al.*, 2006) and large patient populations (n = 100; Papanicolaou *et al.*, 2004; Breier *et al.*, 2005) were studied. Moreover, children were included in some samples. In the large control group study, significant bilateral activity was centred in the superior temporal gyrus (STG) and activity was lateralized to the left middle temporal gyrus (MTG) after 150 ms. These findings were consistent across age, gender, and variation in task characteristics, such as presentation mode or number of stimuli used (Papanicolaou *et al.*, 2006). One group examined the cross-language generalizability of this task with Spanish-speaking patients with epilepsy, and found activation in the left temporoparietal areas and the inferior frontal and insular regions (Maestú *et al.*, 2002). Other groups that attempted to validate this task (Lee *et al.*, 2006; Mohamed *et al.*, 2008) confirmed activation in Wernicke's area.

One group (Levelt *et al.*, 1998) used a reading comprehension task to localize language functions by visually presenting four categories of sentence endings:

– probable final words;
– semantically appropriate but unexpected endings;
– anomalous endings;
– semantically inappropriate endings that started with the same phonemes as the most probable word.

Words were presented one at a time, and participants were instructed to concentrate on the meaning of the sentences. The cortical structures most consistently involved with comprehension were located near the left auditory cortex. The inappropriate final words evoked longer activation (250-600 ms). This activation could be related to the analysis of the meaning of the word and its role in the sentence. Kober *et al.* (2001) conducted a silent reading task with words presented visually to German-speaking participants. Wernicke's area was localized in the posterior part of the superior temporal gyrus and Broca's area was localized in the left frontal gyrus in all subjects. Hirata *et al.* (2009) also used a silent reading task with healthy subjects and patients to examine local oscillatory changes in the brain. Activation profiles differed between the two groups. In healthy volunteers, the left frontal and parietotemporal areas showed oscillatory changes. In the patient group, left frontal language areas were detected in 95.9% of cases, although activity in the posterior language areas was not as lateralized.

Finally, Kamada *et al.* (2006 and 2007) used a word categorization task to localize language functions intrahemispherically. Activation was found in the superior temporal, middle temporal, and supramarginal gyri of the dominant hemisphere. Moreover, Kamada *et al.* (2007), in a study of 177 patients, found that combined MEG and fMRI data yielded a 100% match with IAT results, including data on two patients who showed dissociation of expressive and receptive language areas. Grummich *et al.* (2006) used different language tasks with patients who had tumours to compare MEG and fMRI findings. Congruence was found between fMRI and MEG in 77% of patients for intrahemispheric language localization, results differed in 4% of cases, and in 19% of cases one modality showed activation but not the other. They concluded that more information about language centres is obtained by combining measurements and using multiple paradigms.

In summary, the different language comprehension tasks used to localize intrahemispheric sources of activity showed activation in the left temporal lobe in most cases, in both control and patient populations.

Language production

Different language production tasks have also been used with MEG to localize intrahemispheric language functions. The picture naming and verb generation tasks are the two most often used tasks with MEG to localize language production functions. As mentioned above, the verb generation task was found to be much more accurate than the picture naming task in lateralizing language functions. When looking at the source of these activations, the frontal lobe, responsible for expressive language, is expected to be activated. Most of the studies using picture naming tasks reported activation localized in the left temporal lobe (Salmelin *et al.*, 1994; Levelt *et al.*, 1998; Kober *et al.*, 2001). However, in two studies activation was also observed in Broca's area (Kober *et al.*, 2001; Bowyer *et al.*, 2004). Using the verb generation task, more studies found activation in the frontal lobe (Kamada *et al.*, 2006; Breier and Papanicolaou, 2008; Fisher *et al.*, 2008) than in the temporal lobe (Bowyer *et al.*, 2005a). Fisher *et al.* (2008) found that the verb generation task elicited decreased spectral power in regions of the left frontal lobe in all participants. The localization of this decrease varied across individuals, but was present in the IFG for all participants and typically extended to include areas of the precentral gyrus and premotor cortex. Moreover, in a Japanese noun generation task, subjects had to successively generate a noun which started with the last kana letter (a syllable) of the noun generated immediately previously. Activation was found in the left frontal and temporal areas (Yamamoto *et al.*, 2006). In addition, in a letter fluency task, participants had to generate a single word beginning with a given letter. Left-lateralized patterns of spectral power decrease in the frontal cortex were found in 67% of participants (Fisher *et al.*, 2008).

Source localization methods

Linear inverse source estimates of cortical current density are used to locate sources of MEG activity. Results depend on the underlying assumptions of the particular source model used. The methods of analysis used in the reviewed studies are summarized in *table 2*, right column.

Inverse solutions or source localization methods can be divided into two big groups: the equivalent current dipoles (ECD) and the distributed solutions. In most of these studies, the neuromagnetic fields elicited by the stimuli were recorded and the sources modelled as single ECD fitted at different successive time intervals (*e.g.* 1 ms, 4 ms). A current dipole consists of a point source, with a given position, orientation and dipolar moment (strength). The ECD is the best-fitting current dipole, in terms of maximum field variance. In some cases the estimated activity sources associated with the late components of the ERFs (200 ms after stimulus onset) were examined (Simos *et al.*, 1998). Others limited ECD computation to latency periods during which a single pair of magnetic flux extremes dominated the left and/or right half of the head surface (*e.g.* Maestú *et al.*, 2002). According to the article by Simos *et al.* (1998), the single ECD model was part of the standard analysis protocol in essentially all clinical MEG applications. A single ECD has been found sufficient to account for 90–95% of the variance in ERF data. Levelt *et al.* (1998) integrated the ECDs in a multidipole source model, derived by fitting dipoles to the entire spatiotemporal field pattern. They obtained source models which explained 80-90% of the data variance. However, such findings should be interpreted with caution due to the ill-posed nature of the inverse problem, given that the possible sources are far more than the number of sensors used to measure the source activities. Boundary effects, multiple dipolar activity, and cancellation effects can influence the brain's neuromagnetic fields and the resultant ECD modelling.

Other studies used distributed solutions such as the minimum norm estimate (MNE) and multi resolution FOCUSS (MR-FOCUSS). For example, Härle *et al.* (2002) used the MNE, an inverse method for reconstructing the primary current underlying extra-cranially recorded responses. Unlike ECD modelling, MNE requires no *a priori* knowledge of the possible source configuration or restriction of the MEG channels included in the model (Breier and Papanicolaou, 2008). McDonald *et al.* (2009) applied a spatiotemporal analysis to estimate the time courses of cortical activity using a distributed source solution.

Bowyer *et al.* (2004, 2005a, 2005b) used multi resolution FOCUSS (MR-FOCUSS), a current density imaging technique that detects focal concentrations of cortical activity. MR-FOCUSS enables a time sequence of whole brain images of focal and extended source structures to be constructed. They also used ECD source localization in their analysis and compared the two methods. Results showed that MR-FOCUSS analysis can provide the anatomical location of the multiple cortical areas involved in the language process. Moreover, because MR-FOCUSS produced reasonable localizations in a large number of patients, with similar temporal and spatial evolution in the several patients with whom it was not possible to fit dipoles even when using less rigid criteria, it would appear that MR-FOCUSS is more sensitive and useful than ECD. The authors argue that ECD works well for stationary, non-distributed sources such as early cortical latencies in evoked response data. However, for spontaneous transients such as language comprehension, the model would not be robust, in part, because multiple cortical sites originating from non-stationary distributed sources are active for only a short period. Because language processing involves numerous cortical areas that may be simultaneously active, current density imaging techniques such as MR-FOCUSS are well suited for mapping MEG data onto corresponding cortical structures. This approach provides a temporal display of all the concurrent activity involved during language processing.

Supplementary analyses

Synthetic aperture magnetometry (SAM) is a beamforming technique used to locate frequency-specific spectral power changes associated with a task (Mohamed *et al.*, 2008; Fisher *et al.*, 2008) in a given time range. It is not a proper inverse solution but is used to estimate spectral changes in the space of sources. For instance, Fisher *et al.* (2008) found decreases in beta-band power associated with sources in the left hemisphere. Similarly, other groups used time frequency analyses and found differences in beta band oscillation activity (Kim and Chung, 2008; Cornelissen *et al.*, 2009).

Conclusion

In summary, based on the reviewed studies, the word recognition task is the only language comprehension task used in both children and adults that yields high concordance between MEG and the IAT for language lateralization. This task also allows intrahemispheric localization of language functions in the areas of interest (Wernicke's and Broca's areas). For language production, the verb generation task yielded high concordance between MEG and the IAT and enabled location of activation in the frontal lobe. However, this task is difficult to use with young children. A simpler version, such as a verbal fluency task, would be more appropriate for children, and this has been used in studies where participants hear a letter name and have to produce words beginning with that letter. A similar task could involve producing words from a particular category.

MEG directly measures neurophysiological processes with a high temporal resolution and therefore has the potential to localize neurophysiological processes within the whole brain. It has been useful in determining hemispheric language dominance in presurgical patients and mapping language function areas. MEG has been used to identify both frontal and temporal areas of activation and to identify language dominance in agreement with other methods, such as fMRI and the IAT. The reliability and validity of this technique have also been confirmed.

When drawing from the literature to develop a language protocol, certain factors need to be taken into account, especially if the protocol must be adapted for children. For example, tests should be relatively short because MEG requires immobility. The presentation mode can also influence results. Some argue that the auditory mode elicits asymmetric cerebral activation in favour of the left hemisphere, while others prefer visual presentation because visual stimuli activate areas located further from Broca's and Wernicke's areas. Of the studies reviewed here, many more used auditory than visual mode. Moreover, it is easier to use auditory stimuli with children who cannot read or who have reading disabilities. It is imperative that the tasks are accomplished by a paediatric population. In addition, the complexity of stimuli may influence results. For example, vowels are acoustically and linguistically simpler than words. Therefore, a word-related task would more likely evoke a greater portion of the linguistic neural pathways involved in lexical and semantic processing. It is also very important to note that because MEG has high temporal resolution, when long stimuli are used and analyzed (sentences), more variability will be found between participants due to inter-subject differences in processing. Consequently, averaged signals will be blurred and imprecise. Ideally, the analysis should be limited to a portion of the signal equal to or smaller than the word length. Moreover, in any language protocol, it is important to assess language comprehension and language production, especially if the findings are to be compared with IAT results. Based on the studies reviewed here, covertly produced responses allow investigating language production and yield activation in the areas of interest (Wernicke's and Broca's areas).

For the reviewed studies, different methods of analysis were used to determine the location of cortical sources involved in language processing and these locations were subsequently mapped using brain MRIs. These methods need to be taken into account when addressing the limitations of MEG, as they restrict the potential for interpretation. They may also contribute to differences in findings. The inverse solution is often used to estimate the source of language activation. However, this method presents drawbacks, and it allows only indirect estimates of the activity source based on MEG findings. Most of the studies reviewed here used ECD to model the data. Other analysis methods (MNE, MR-FOCUSS, SAM, etc.) were also used, and in all cases, activation in regions of interest was obtained. However, when different methods are compared for similar tasks, the findings are inconsistent. Across studies, the timing of lateralization and localization also varied. In most cases, late fields were analyzed (after 150 ms), but in some cases early fields (before 150 ms) yielded interesting findings. The paradigm used can influence these findings (Shtyrov and Pulvermüller, 2007; Gootjes *et al.*, 1999). Overall, there is a clear need for standardized protocols and methods of analysis to enable comparisons of findings from different research centres.

A significant advantage of MEG is that it allows examining both hemispheres simultaneously, which is especially useful in epileptic populations, in which language lateralization is more variable. Similarly, in neurologically intact individuals, language often involves bilateral cortical networks. This was observed in the studies reviewed here, which showed bilateral activity in many cases, although left hemisphere activations were generally stronger. Furthermore, there is rarely a single source of activation during language comprehension, but rather multiple areas of activation. From the results of these studies, one might conclude that no task is purely linguistic: they all involve to a greater or lesser degree other cognitive operations such as attention or memory. Thus, the results of language studies also showed cortical activity that depended on other cognitive functions.

To conclude, MEG offers many important advantages: it is completely noninvasive, can be used with children, has excellent temporal resolution, and allows intrahemispheric localization of sources of activity. In short, it is an excellent presurgical assessment tool for localizing language functions. Nonetheless, MEG has some limitations. For example, it cannot be used with patients who have metal implants, very young children or non-cooperative patients, and it is relatively expensive. It has also been argued that it is difficult to assess language production with MEG. In the studies reviewed here it was possible to examine language production using MEG. However, it should be noted that the language production tasks did not systematically activate frontal regions, which should have been the case. This may be due to the fact that most tasks used covert production of answers. MEG is less sensitive than other techniques to detect deep and very small sources. Ultimately, it appears that using more than one technique could yield a more complete picture of activation profiles. It is important to include more than one task when assessing language functions in patient populations prior to surgery, and to include both language comprehension and production tasks, which have been shown to yield activation in the regions of interest. Thus, the best task to assess language comprehension in both adults and children appears to be a word recognition task. A verbal fluency task could be used to assess language production in children and a verb generation task in adults. □

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