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INVITED REVIEW

Language Mapping With Magnetoencephalography: An Update on the Current State of Clinical Research and Practice With Considerations for Clinical Practice Guidelines

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Summary: Numerous studies have shown that language processing is not limited to a few brain areas. Visual or auditory stimuli activate corresponding cortical areas, then memory identifies the word or image, Wernicke's and Broca's areas support the processing for either reading/listening or speaking and many areas of the brain are recruited. Determining how a normal person processes language helps clinicians and scientist to understand how brain pathologies such as tumor or stroke can affect changes in language processing. Patients with epilepsy may develop atypical language organization. Over time, the chronic nature of epileptic activity, or changes from a tumor or stroke, can result in a shift of language processing area from the left to the right hemisphere, or re-routing of language pathways from traditional to non-traditional areas within the dominant left hemisphere. It is important to determine where these language areas are prior to brain surgery. MEG evoked responses reflecting cerebral activation of receptive and expressive language processing can be localized using several different techniques: Single equivalent current dipole, current distribution techniques or beamformer techniques. Over the past 20 years there have been at least 25 validated MEG studies that indicate MEG can be used to determine the dominant hemisphere for language processing. The use of MEG neuroimaging techniques is needed to reliably predict altered language networks in patients and to provide identification of language eloquent cortices for localization and lateralization necessary for clinical care.

Key Words: Language, Wada, MEG, Brain imaging, Language mapping, ECD.

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INTRODUCTION

Magnetoencephalography (MEG) is a noninvasive clinical and research method for recording patterns of magnetic fields directly related to local neuronal electrical activity of the brain.[1,2] The MEG imaging technique has been validated and is used to identify compact sources of normal and abnormal brain activity.[3] Safe and effective pre-surgical mapping of visual, auditory and somatosensory functions has been accomplished using MEG.[4] Functional language processing is more complex to map than the primary senses. In the clinical environment, MEG language mapping is used primarily for language *lateralization*[5] rather than more specific *localization* of language.[6] The conundrum is that if MEG does not correctly identify (*localize*) the cortical areas that process language it would be hard to believe the MEG language *lateralization* results. It is critical that the language dominant hemisphere be determined prior to surgery in attempts to spare language function when patients undergo interventions such as ablation, resection or radiosurgical procedures for organic or functional brain diseases. Understanding basic language functional brain areas can help identify abnormalities in patients with tumors, stroke and language disorders such as autism and dyslexia. As described below, MEG techniques are replacing the established clinical methods for lateralizing brain function and pathology.

Magnetoencephalography imaging has been used since the early 1990's to investigate the latency and location of cortical activity during language processing.[4] Magnetoencephalography imaging techniques have high spatial resolution and very high temporal resolution. Below we describe select language processes and the brain regions thought to support them, contributions of MEG to illuminating these relationships, comparisons of MEG to other techniques used to image language function, and current clinical considerations in the use of MEG.

Brain Correlates of Language Function

Ever since early brain and language models were developed by Wernicke, Geschwind[7] and others, neurologists and neuropsychologists have been attempting to determine how the brain processes language and which cortical areas underlie specific language functions. Historically, language processing areas were determined by studying patients with lesions, tumors, or head injuries.[8,9] Often postmortem studies were conducted to determine what damage the tumors or lesions had caused that affected speech and language processing. Major breakthroughs in the field of language mapping came with the advent of neuroimaging techniques such as MRI, functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magnetoencephalography (MEG).[10] Vital regions for speech and language processing are generally thought to include Wernicke's and Broca's areas in the language dominant hemisphere.[11] A

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seminal study in 1977 on 371 patients who underwent Wada and testing for hand dominance found that of the 262 patients, without any known clinical or radiologic evidence of an early left hemisphere injury, the left hemisphere is language dominant in 96% of right-handed individuals and 70% of left-handed individuals.[12]

Wernicke's area is in the posterior part of the superior temporal gyrus (Brodmann area [BA] 22) and is generally thought to support comprehension of written and spoken language (Fig. 1). Wernicke's area is activated during receptive language processing. BA 22 is involved in processing auditory input and linking word pronunciations to word meaning (Fig. 1A).[13,14] When written words are presented, the letter strings are perceived in the occipital cortex prior to word recognition and to comprehension. These neuronal pathways flow from the occipital cortex into the angular gyrus [BA 39] then to Wernicke's area [BA22] (Fig. 1B). These areas are important for comprehension but their precise roles are unclear, in part due to differences across methodologies used.[15] Comprehension tasks may involve additional areas such as the supramarginal gyrus [BA40].

Broca's area is described as the motor speech center of the brain and is located in the inferior frontal cortex, specifically the pars triangularis [BA45] and pars opercularis [BA44] (Fig. 1). Broca's is activated during expressive language processing. Wernicke's area and Broca's area are thought to be connected via direct and indirect segments of the arcuate fasciculus, the indirect portion made up of anterior and posterior segments.[16] Verbal naming of heard or viewed stimuli involves Wernicke's area (i.e., supporting linguistic processing of the meaning of the abstract word form) and transmission of this information to Broca's area to support speech production.[17] Speech motor programs are subsequently communicated to the motor cortex and to the speech musculature.

In addition to the location of language relevant brain regions, there is evidence of complex connections of these areas constituting language networks. For example, the Dual Language model[18–20] describes the dorsal and ventral pathways connecting prefrontal and temporal language-relevant regions. The dorsal pathway connects the temporal cortex and premotor cortex (supporting speech repetition) as well as the temporal cortex and posterior Broca's area (supporting complex syntactic processes). In this model, ventral pathways are described as connecting temporal and inferior fronto-occipital regions to support semantic and syntactic processing (speech comprehension).[21]

Patients with left lateralized stroke, tumor or epilepsy may develop atypical language organization. Developmental language disorders (autism[22] and dyslexia[23]) also have atypical language organization (Kleinhans, 2008 #866). Over time, the nature of these impairments can result in a shift of language processing from the left to the right hemisphere, or re-routing of language pathways from traditional to non-traditional areas within the dominant left hemisphere.[24] Clinical features such as location of seizure onset, age of seizure onset, and extent of interictal epileptiform activity might contribute to the reorganization of language.

A **Hearing a word**

B **Reading a word**

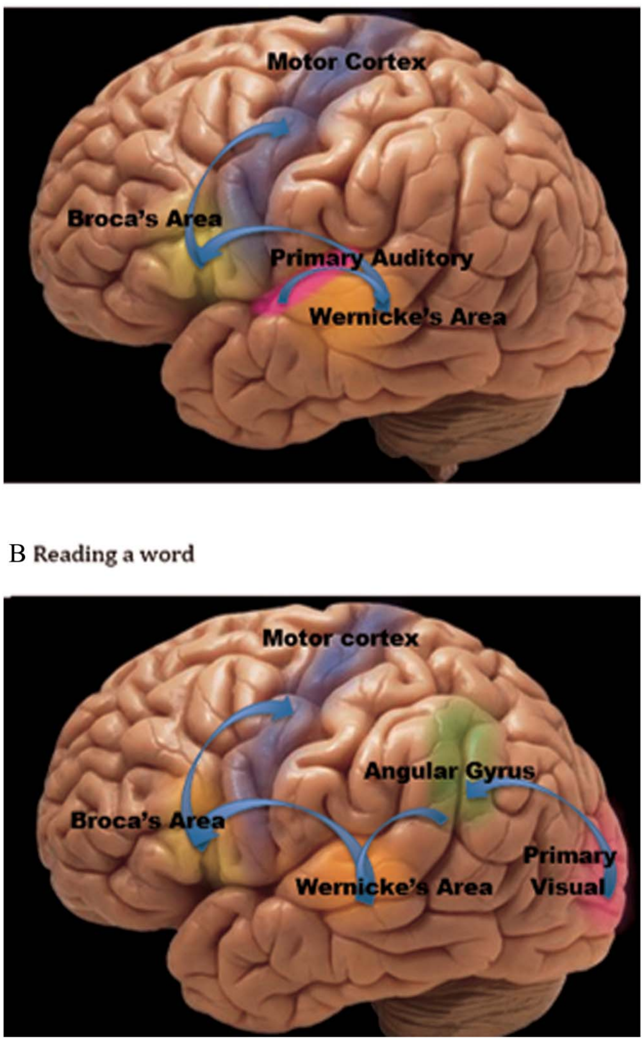

FIG. 1. Cortical brain areas, that are active during language processing and pathways of information flow (blue arrows), identified in two different stimulus routes: (**A**) after Hearing a word (**B**) after reading a word.

CURRENT CLINICAL ROLE OF MEG IN LANGUAGE MAPPING

Since language mapping is complex, the ability of MEG to image activity with millisecond temporal resolution can provide an inclusive overview of all aspects of language processing from reception to expression, with millimeter spatial resolution,. The American Clinical MEG Society outlined the best clinical practice guidelines for imaging language processes in 2011. These guidelines are still current and provide detailed information on how to collect MEG activity related to language processing. This update provides more information on specific strengths and weakness of the different analytical techniques that could be used to provide language results, as well as a detailed list of the previous studies that validated the use of MEG to replace the language portion of the Wada test.

Methods for data analysis differ across MEG laboratories, but overall signal processing methods are becoming increasingly sophisticated for enhancing signal-to-noise which improves the specificity of source *localization* and therefore *lateralization*. Advanced MEG data analysis techniques can be used to address the magnetic inverse problem, as there may be several cortical areas active simultaneously during language processing. Several mathematical modeling approaches have been developed, beyond the single equivalent current dipole (ECD), for MEG mapping. These include current distribution techniques (such as MR-FOCUSS or minimum norm estimate (MNE)) and the beamformer (such as synthetic aperture magnetometry (SAM)). The ability of clinical MEG Labs to use these more advanced analysis techniques has advanced the universal use of language mapping at most MEG centers.

UPDATE ON THE CLINICALLY PERTINENT RESEARCH PROGRESS

LEF Latency Examples

Language-evoked magnetic fields (LEFs) appear after the primary sensory components (early responses) and are generated in language-related areas of the brain (late responses) regardless of whether the modality of stimulus presentation is auditory or visual.

In general, the LEF waveform will have several peaks (Figs. 3 and 4). The initial peaks (<150 ms) are generally associated with basic sensory processing in the modality of stimulation (auditory or visual). Occasionally peaks of activity may be seen between 150 and 250 ms; these are believed to be associated with feature processing, memory and integration. If there is a peak of activity in this latency range, it is typically localized in the basal temporal language areas (fusiform gyri).[25] Peaks of activity between 250 and 750 ms, or later, evoked by language stimulation are associated with higher-order cognitive processing, and contain several peaks of activity arising from multiple language areas such as supramarginal gyrus, angular gyrus, inferior frontal gyri.[6] Language-evoked magnetic field studies of receptive language (comprehension) localize sources to the posterior aspects of the superior and middle temporal lobe (including Wernicke's area) and the temporoparietal junction whereas LEF studies of expressive language (speech production) localize activity in frontal (including Broca's area) and basal temporal areas. Such responses are enhanced when attention to the task is displayed.[26] The latency and location of the peak activity should be included in the clinical MEG report, including the primary response followed by peaks observed in Wernicke's area and then in Broca's area, followed by the laterality index (LI).

Laterality Index

A laterality index is calculated based on summing the number of valid dipole fits or by summing current in each hemisphere depending on the source estimation method used. Here LI is defined by $100 \times (R - L)/(R + L)$ where L and R are the number of accepted dipoles fit in the left and right hemispheres, respectively. Laterality index values from -100 to -20 indicate strong left hemisphere language dominance. Laterality index values from -19 to $+19$ indicate bilateral language activation. Laterality index values from $+20$ to $+100$ indicate right hemisphere language dominance. Laterality index for the patient in Fig. 2 is $+100$, indicating Right hemisphere language processing during the latency 150 to 300 ms. A similar LI can be calculated for current density by summing the current flowing in each hemisphere (Fig. 5) and inserting these values in the LI above.[5] Laterality index for the Control subject in Fig. 3 is -50, indicating Left hemisphere language processing during the latency 150 to 300 ms. Laterality index for the Control subject in Fig. 4 is -23, indicating Left hemisphere language processing during the latency 300 to 500 ms.

Clinical reports should include the LI when calculated along with a clear statement of which hemisphere is language dominant (left dominant, right dominant, bilateral or inconclusive) and what the value represents (dipoles or current density techniques). Alternative analyses including beamforming strategies and multiple dipole strategies may also be viable.

Analytical Methods

The equivalent current dipole is a mathematical model that has been widely used with MEG to determine the location of compact magnetic fields measured at the scalp surface during language processing.[27,28] An example of typical single ECD results are shown in Fig. 2 during a visual object naming task. The single ECD technique poorly *localizes* cortical language processing areas because numerous cortical areas are simultaneously active and the single ECD technique can *only* detect one

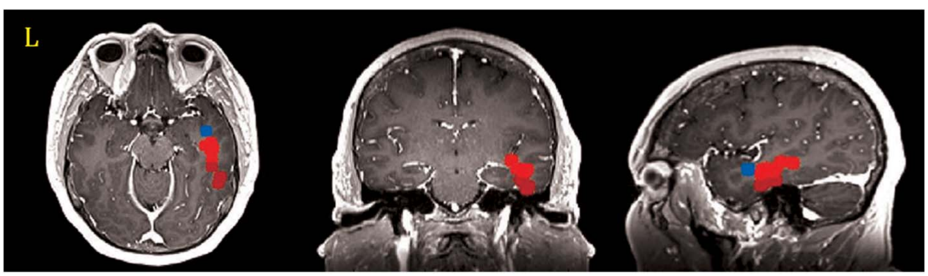

FIG. 2. MEG ECD source localization of the right hemispheric homologue of Wernicke's activation during visual object naming in a patient with epilepsy in the left temporal lobe. Dipoles are constrained to the right temporal region, indicating right language hemispheric dominance for this patient. $LI = R - L/R + L = 8–0/8 = 1 \times 100 = +100$, Right dominant for the time interval 150 to 300 ms. NOTE the single ECD technique may not correctly *localize*, but it can still be used for *lateralization*.

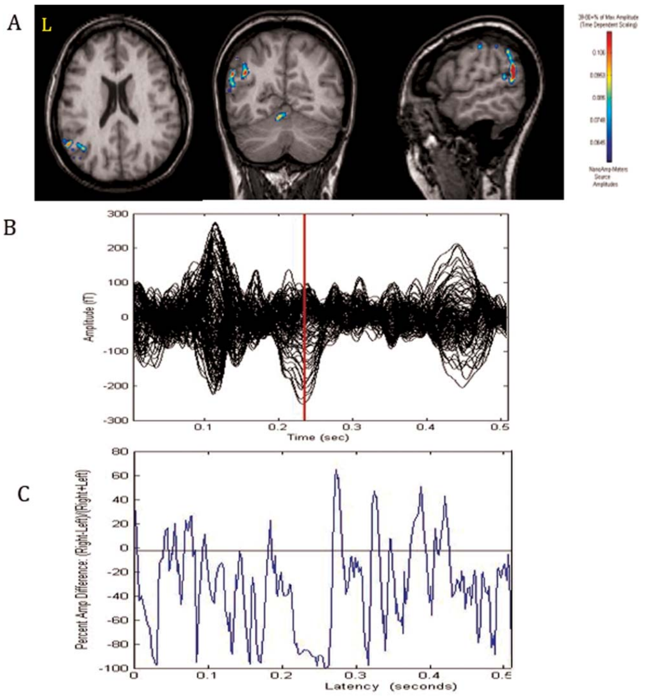

FIG. 3. **A**, MEG current distribution source localization of Wernicke's area. Red is most intense area of activation. Scale is in nano Amp meters. **B**, The butterfly plot of the evoked wave form shows the peaks of activity within the latency window for Wernicke activity. Peak latency is at 235 ms after onset of visual word. **C**, In this control subject Wernicke's area is lateralized to the Left angular and supramarginal gyri with a LI of −50 for the latency window 150–300 ms. MEG, magnetoencephalography; LI, laterality index.

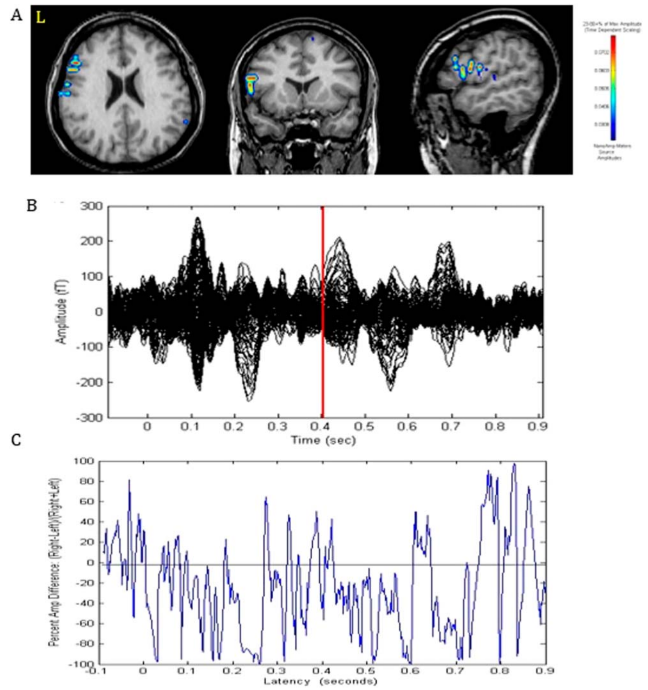

FIG. 4. **A**, MEG current distribution source localization of Broca's area. Red is most intense area of activation. Scale is in nano Amp meters. **B**, The butterfly plot of the evoked wave form shows the peaks of activity within the latency window for Broca activity. Peak latency is at 405 ms after onset of visual word. **C**, In this control subject Broca's area is lateralized to the Left inferior frontal gyrus with a LI of—23 for the latency window 300 to 500 ms. MEG, magnetoencephalography; LI, laterality index.

location at any given time point. This one location may be just the center of mass of all the cortical activity at each instant in time during language processing. This technique has been used more to *lateralize* language by calculating the LI.

Lee[25] investigated test-retest and inter-rater reliability for MEG/ECD localization of language and found their MEG brain mapping protocols to be adequate for receptive language localization in epilepsy surgery candidates. Simos et al[27] used MEG to localize cortical areas associated with language comprehension. Using their single ECD technique, they found activity in the left temporo-parietal cortex. Recognizing the limitations of the ECD technique, they concluded that the dipolar MEG patterns which were imaged may have represented the summation of multiple and spatially distinct sources. Thus, while their MEG/ECD imaging results may be useful, they should be viewed with caution. Kamada et al[29] demonstrated that MEG/ECD alone was not sufficient to accurately locate expressive and receptive language, but when combined with fMRI they obtained high reliability for localizing these language areas as there are overlapping areas to provide confirmation.

Current density distribution techniques[30] are another approach for addressing the inverse problem and for revealing a more complex map of cortical activity than can be revealed using the single ECD model. Current density imaging techniques are able to accommodate all variations of brain activity including those that characterize cortical language processing.[5,6,31,32] One drawback is some current density imaging techniques have poor resolution of compact source structures.[33] As a result, weighted minimum norm techniques have been developed that enforce focal imaging constraints by statistical control of source amplitudes and allow integration of prior knowledge of source activity. MR-FOCUSS[34] minimizes sensitivity to noise and controls the focal imaging by incorporating a multi-resolution cortical model designed to generate a solution with a specific statistical distribution of cortical source amplitudes. This allows the norm of the solution to be adjusted to suit the imaging task. Examples of this current distribution technique for language mapping are shown in Figs. 3 and 4.

A different approach to language mapping is beamforming. Beamformer techniques[35] are spatiotemporal covariance-based techniques for estimating compact source activity. For each location of a brain model grid, a filter is applied to the MEG data, scanning for dipoles in the brain.[30,35–38] A beamformer performs spatial filtering on data from a sensor array to discriminate between signals arriving from a location of interest and those originating elsewhere.[33] Beamformer imaging techniques do not

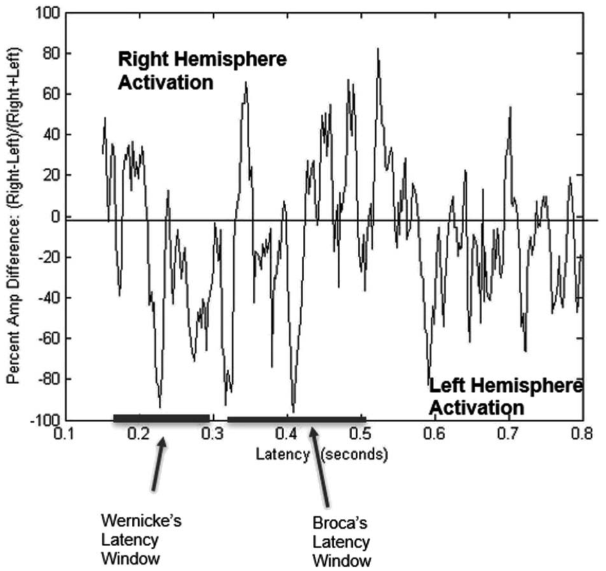

FIG. 5. Laterality graph indicating the sum of the current density in the brain at each time point. The lower half is when average activity is higher in the left hemisphere than the right. When activity is in the top half of the graph the activity is more in the right hemisphere than the left. The overall index can be calculated over the time interval 0.15 to 0.8 seconds. Laterality for this subject was −11, indicating more left dominant language processing.

require an estimate of the number of sources and, compared to multiple dipole techniques, provide superior source localization when the data contain significant noise.[38]

These varied approaches to analyzing MEG data should be considered when performing language mapping. The current density techniques as well as beamforming both reveal a more complex map of cortical activity than can be acquired using the ECD model alone. The most commonly employed methods are based on dipoles and minimum norm estimates[5,27,39–42]. The studies most often cited are those performed by Papanicolaou and colleagues for which they calculated a LI by counting the number of ECD fits for language localizations in each hemisphere.[27,39–41,43,44] See Table 1 for a list of pros and cons for each technique.

Validation of MEG by Wada

Magnetoencephalography is noninvasive and thus provides an advantage over the invasive intracarotid amobarbital procedure for language lateralization. The intracarotid amobarbital procedure, also known as the Wada test after its inventor, Juhn Wada,[45] is a gold standard of epilepsy surgery evaluations because it can provide lateralizing information about language and memory.[46] Wada uses an anesthetic (sodium amobarbital, methohexital, pentobarbital, propofol and etomidate)[47] injected into the internal carotid artery using a catheter via the femoral artery. Its flow through the brain includes the hippocampal structure, which is normally involved in memory function. During the injection, the patient holds up both arms and counts aloud; when one arm drops, the contralateral hemisphere has been anesthetized. The language portion of this test determines in which hemisphere motor speech is located, by noting if speech is arrested during the injection. The Wada is conducted prior to implantation of intracranial electrodes. One drawback for using the results from the Wada to determine the language dominant hemisphere is that in some individuals Broca's area activity is in the left hemisphere, but Wernicke's area activity is in the right hemisphere. This type of language displacement is often seen in patients with left temporal lobe epilepsy.[24]

Because of the very brief interval of hemispheric anesthesia during the Wada test, a variety of noninvasive methods have been advocated as potential replacements. The two most often cited are fMRI[48] and MEG.[44] However, while both are very good clinical tests for language, neither has been found to be a valid replacement for the memory portion of the Wada test. Working memory or short-term memory can be tested to determine the dominant hemisphere, but it is much more difficult to identify the dominant hemisphere for long-term memory (i.e., life-time memory).

Many studies have been performed that validate the MEG technique by comparing its *localization* of language specific cortex to electrical stimulation mapping with invasive intracranial mapping of language.[49] Several MEG studies have successfully investigated the *laterality* of the language dominant hemisphere (Table 2) and found very high correlations with the Wada test. Breier et al.[39] found MEG ECD language laterality correlated well (87%) with Wada results in 19 children. Maestu et al. studied the same MEG ECD technique (magnetic source imaging) to validate MEG language paradigms in Spanish

TABLE 1. MEG Source Analysis Strengthens and Weaknesses

Analytical Technique	Pros	Cons
Single ECD	Easy to use	Only one location in the entire brain can be mapped at each millisecond in time.
Current distribution (MR-FOCUSS, MNE)	Multiple brain locations can be mapped at each millisecond in time.	More difficult to perform the analysis. Poor resolution of compact source.
Beamforming (SAM, vector)	Work well in MEG labs that have large magnetic disturbances in the environment (i.e., Trains).	More difficult to perform the analysis. Correlated sources in the brain may cancel each other out.

ECD, equivalent current dipole.

TABLE 2. MEG Studies That Were Validated by WADA or IAP

Group	Sample Size	Method	Task/Stimuli Expressive/Receptive	Visual/Auditory	Validated Wada or Intracarotid Amobarbital Procedure
Papanicolaou 1999	12	MSI	Word identification	Auditory (3) Visual (9)	100%
Breier 2000	26	MSI	Words/reception	Visual and auditory	92%
Breier 2001	19	MSI	Words/reception	Visual and auditory	87%
Szymanski 2001	15	MSI	Vowels/reception	Auditory	71%
Maestu 2002	8	MSI	Words/reception	Auditory	87.5%
Papanicolaou 2004	100	MSI	Words/reception	Auditory	87%
Hirata 2004	20	SAM	Words (silent reading)	Visual	95%
Bowyer 2005	27	MR-FOCUSS	Words Receptive and expressive	Visual	63% frontal later latencies 56% temporal early latencies
Bowyer 2005	27	MR-FOCUSS	Picture naming Receptive and expressive	Visual	96% frontal later latencies 48% temporal early latencies
Pataraia 2005	12	MSI	Words (listening)	Auditory	92%
Merrifield 2007	12	MSI	Words/reception Memory recall	Auditory	75%
Kamada 2007	117	MSI combined with FMRI	Words (read)	Visual	100%
	99 MEG	MSI			82.4%
Kamada 2007	22	MSI	Word reading	Visual	100%
Kim Chung 2008	17	MNE/spatial filter	Words/reception	Auditory	94% frontal later latencies 71% temporal early latencies
McDonald 2009	8	Dynamic statistical parametric mapping	Words/reception	Visual	100% frontal later latencies 75% temporal early latencies
Doss 2009	35	MSI	Word recognition receptive	Auditory	86%
Hirata 2010	60	SAM	Words (silent reading	Visual	85%
Ota 2011	28	MSI	Word reception (read)	Visual	85.7%
Findlay 2012	14	SAM– beamforming	Verb generation overt Receptive and expressive	Auditory	93%
Tanaka 2013	35	Dynamic statistical parametric mapping	Word decide if abstract or concrete (semantic task)	Visual	91.4%

fMRI, functional magnetic resonance imaging.

speaking patients and also found ∼87% correlated with Wada testing.[50] Kober et al.[42] used the current source strength in each hemisphere to determine the dominant hemisphere, which was found to be left dominant in all 15 of their right-handed normal subjects. Bowyer and colleagues[5] studied the results of Wada testing and MEG current distribution lateralization indices, and found MEG correlated highly (89%) with Wada results of language dominance (Fig. 5). Findley and colleagues used the SAM beamforming technique and found 93% match between language laterality and Wada.[51] Dynamic statistical parametric mapping has been used by McDonald and colleagues, who found 100% match for later latencies that correlated with Broca's activation.[52] Tanaka et al.[53] also used dynamic statistical parametric mapping and found a 91.4% match rate between MEG language laterality and Wada.

At present, some factors may require the use of both MEG and electrocorticography (ECoG) testing to study brain-language correlates, such as differences in brain reorganization across patients with brain disorders, differences in paradigms (activation in MEG and fMRI vs. disruption during ECoG), and the effects of noise. However, the results of the currently available studies are often interpreted as indicating that MEG is a valid method for determining the language dominant hemisphere; laterality of the language areas, as measured by MEG, has been found to correlate between 80% to 95% with results from the Wada procedure and intracranial recordings. From this view, the results from these studies illustrate that MEG LEF studies are able to replace the language portion of the invasive Wada procedure.

Comparisons of MEG With EEG, fMRI and PET for Language Mapping

Magnetoencephalography also has been compared to other techniques for imaging brain-language relationships, including EEG, structural MRI, PET, and functional MRI. The temporal resolution of EEG recordings is equal to that of MEG; however, complex realistic models of volume currents and boundary potentials must be calculated in order to obtain accurate mathematical models for EEG source localization imaging.[54] On the other hand, with MEG imaging, good mathematical model accuracy can often be achieved using calculations based on a spherical volume conductor that has been matched to the local skull curvature.[55] MEG mathematical model calculations are less sensitive to pathology or anatomical defects that alter tissue conductivity.[56] These aspects of MEG indicate the superiority of MEG localization, with errors less than 5 mm compared to ∼20 mm in EEG. The signal to noise ratio of MEG for mostly neocortical areas is also better than that of EEG[57] such that EEG would need a higher number of trials to obtain the same signal.

Conventional structural MRI provides an image of the anatomical structure or morphology of the sulci and gyri of the cerebral convexity.[58] Although MRI cannot provide any functional information, tumors and lesions can be clearly visualized. In 1988, PET was used for initial investigations of the cortical areas involved in language processing of a single word.[59] Since radiation dosage limits the number of times a task can be administered, repetition of the task with the patient was not possible. Two noninvasive imaging techniques, fMRI[60] and MEG,[61] were since developed. Functional magnetic resonance imaging identifies local changes in the blood oxygen level dependent MRI signal (BOLD response) associated with changes in neuronal metabolic activity.[62,63] Thus, fMRI provides neurosurgeons with functional maps of cortical regions of interest. The actual mechanism by which the BOLD response varies with neuronal activity is not well understood. Anomalous blood vessel development (e.g., deep venous anomaly, arteriovenous malformations, tumor angiogenesis) tends to distort fMRI features and may create false impressions of cerebrocortical excitability. MEG, on the other hand, records the pattern of magnetic fields directly related to local neuronal electric activity. As noted above, MEG imaging techniques have high spatial resolution and very high temporal resolution. In a review of published fMRI, MEG (using ECD), and PET language mapping studies, MEG was found to be superior to the other two techniques.[64] This review study found that though PET had good concordance for language mapping it has poor temporal resolution and is highly invasive.[64] fMRI was found to be generally quite favorable for language mapping but significant variability was found across studies with respect to methodology, preventing assessment of the reliability.[64] The authors found MEG had strong reliability and validity for language mapping.[64]

RAMIFICATIONS AND RECOMMENDATIONS FOR CLINICAL PRACTICE

The following are the best practices for obtaining reliable language mapping results. Magnetoencephalography language paradigms should be ordered when the removal of temporal cortices in the language dominant hemisphere is being considered. In patients with epilepsy, tumors and lesions, the language processing pathways may have been modified based on the extent of their disease. Language mapping should be ordered if language difficulties are noted during seizure activity or if the epilepsy involves the left temporal cortex. To help determine when MEG language mapping is appropriate to order we have included a decision tree in Fig. 6.

Language Tasks and Stimuli

A variety of language tests have been used to *localize* or *lateralize* language function with MEG. Verb generation and object naming evoke cortical activation sufficiently robust to allow neuroimaging techniques such as fMRI, PET, and MEG to detect and localize where the brain responses are occurring.[65] In the verb generation task, the patient is presented with a noun (either in picture or auditory form) and is asked to think of a verb that goes with the noun (e.g., Ball: KICK). In the object naming task, the patient is presented with a picture of an object and is asked to think of its name. Intracranial mapping of these two

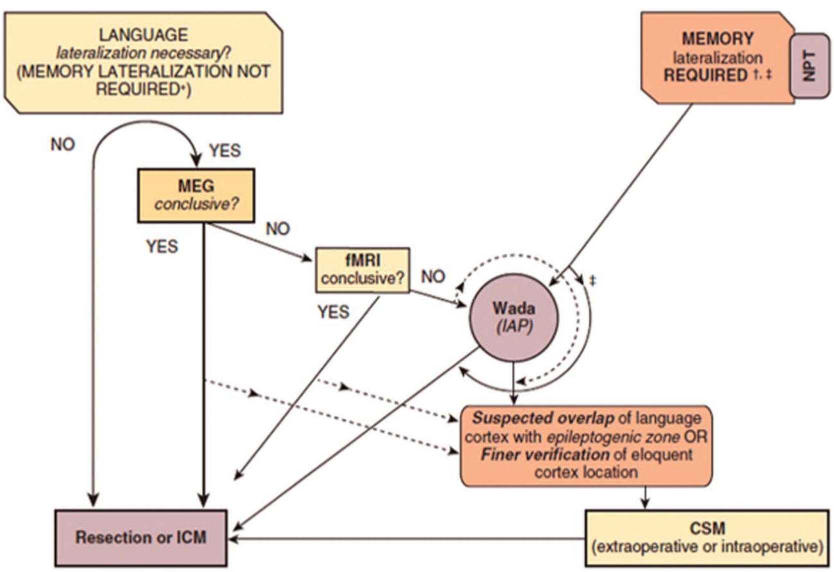

FIG. 6. Graph of a MEG based algorithm for presurgical lateralization of language function. Reprinted with permission from Elsevier Book: Winn, Chapter:66, Page:11. CSM, cortical stimulation mapping; fMRI, functional MRI; IAP, intracarotid amobarbital procedure; ICM, intracranial monitoring; MEG, magnetoencephalography; NTP, neuropsychological testing.

language tasks detects cortical areas of activation comparable to those from neuroimaging techniques.[66] Thus, the established paradigms for intracranial language mapping across many hospitals in the USA are verb generation and object naming.[66]

Differences in specific types of stimuli or in language task instructions affect the patterns of brain activation during language processing.[67] Also of note is the overlapping of receptive and expressive language activation patterns. Primary activation caused by auditory or visual stimulation is followed by activation of receptive language areas (including Wernicke's area). To activate expressive language processing and Broca's area supporting motor speech, patients should be instructed in an expressive task to covertly name objects or silently generate verbs. Examples of auditory stimuli can be found in Papanicolaou et al.,[43] while examples of the visual picture and word stimuli can be found in Bowyer et al.[6].

The Ideal Patient

For the most robust evoked brain activity, the patient needs to be in a state of wakefulness. This is *critical* for collecting data with a good signal-to-noise ratio. The occipital alpha rhythm in spontaneous ongoing MEG recordings can be used to monitor wakefulness during the study. The use of behavioral target stimuli interspersed in the task stimuli (e.g., "push a button when you see a solid circle or hear a tone") can be used to determine if the patient is awake and participating in the task. The technologist running the study can watch the behavioral response channel to determine if the patient pushes the button. Data segments associated with target stimuli and lateralized motor responses should not be averaged in the final MEG evoked responses.

Integrity of the Data

It is important to evaluate the integrity of basic auditory/visual responses at ~100 ms. Early evoked fields can be used for quality control (latency, topography). For example, if stimuli are presented acoustically, the auditory N100m responses should be symmetrical in topography, peaking around 100 ms and identified within the auditory cortex (superior temporal gyri). If visual stimuli are used, the peak N100m response should be easily identified in the occipital cortex. Epilepsy, tumors and other lesions can compromise *lateralization* of basic sensory (auditory/visual) processing if located in primary or secondary sensory (auditory/visual) areas. If core sensory processing (auditory/visual) is compromised, *caution* is needed in the interpretation of the long latency activity and may lead to inconclusive results.

Processing and Reporting MEG Language Mapping

The ACMEG CPG #2 provides all the necessary information for MEG data collection. Magnetoencephalography LEFs for *lateralizing* language has been shown to work extremely well using any of the described MEG imaging analysis techniques. As described above analysis techniques beyond the single ECD can be used to provide better language *localization*s.

The report of language *localization* and *lateralization* should include the stimuli used and the type of data analysis employed. Plotting of results should be on a spatially aligned individual patient MRI. Such plots may give the impression to neurosurgeons that areas without plotted activity are safe to resect. This type of error (false negative) cannot be excluded systematically, so qualifying statements may be appropriate.

CONCLUSIONS

In the clinical environment, MEG language mapping is used primarily for language *lateralization*[5] prior to a surgical resection. Validation of MEG for reliably detecting the dominant hemisphere of language processing in patients has occurred in over 25 studies with an average 85% concordance with Wada results (See table listing each validated MEG study). The *laterality* is based on the accurate *localization* of Broca's area and Wernicke's area activated during language processing. There are several tasks such as verb generation, picture naming, and auditory word presentation that have been used with success. These tasks can be expressive (where Broca's area is strongly activated) or receptive (where Wernicke's area is strongly activated). The Wada test mainly identifies the hemisphere in which motor speech is located. Magnetoencephalography studies that use expressive speech paradigms tend to match very well with Wada results. Since epilepsy may disrupt language networks involving only Wernicke's area or only Broca's area, it is wise to map both expressive and receptive language processing.

Understanding basic language functional brain areas can help identify abnormalities in patients with language disorders such as autism and dyslexia. In the future, identifying the dorsal and ventral[21] pathways that constitute the Language networks will provide insights into the underlying mechanisms of these disorders. The American Clinical MEG Society guidelines of 2011 provide the foundation for the best practice for imaging language processes.[4] This current review has provided pros and cons for the more complex analysis methods that can be used for language mapping. MEG has been shown to have strong reliability and validity for language mapping. The use of MEG neuroimaging can be used to detect altered language networks in patients and to provide identification of language eloquent cortices necessary for clinical care.

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