Invited review

Clinical neurophysiology of language: The MEG approach

Riitta Salmelin *

Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, Espoo, Finland

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Abstract

Clinical evaluation of language function and basic neuroscience research into the neurophysiology of language are tied together. Whole-head MEG systems readily facilitate detailed spatiotemporal characterization of language processes. A fair amount of information is available about the cortical sequence of word perception and comprehension in the auditory and visual domain, which can be applied for clinical use. Language production remains, at present, somewhat less well charted. In clinical practice, the most obvious needs are noninvasive evaluation of the language-dominant hemisphere and mapping of areas involved in language performance to assist surgery. Multiple experimental designs and analysis approaches have been proposed for estimation of language lateralization. Some of them have been compared with the invasive Wada test and need to be tested further. Development of approaches for more comprehensive pre-surgical characterization of language cortex should build on basic neuroscience research, making use of parametric designs that allow functional mapping. Studies of the neural basis of developmental and acquired language disorders, such as dyslexia, stuttering, and aphasia can currently be regarded more as clinical or basic neuroscience research rather than as clinical routine. Such investigations may eventually provide tools for development of individually targeted training procedures and their objective evaluation.
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1. Introduction

In the clinical context, the question of language representation in the human brain is largely focused on pre-surgical mapping, in the form of noninvasive lateralization of language function and characterization of linguistic processes that are represented in the immediate vicinity of an area to be resected. Another topic of clinical interest is tracking of neural effects associated with rehabilitation after acquired language disorders, or with specific training programmes in the case of developmental disorders. All these applications critically depend on, or should depend on, information derived from basic research of the organization of language function in the human brain.

The successive and largely overlapping stages in language processing, from sensory analysis (visual, auditory, and tactile) to linguistic assessment, memory search, and motor function, can only be satisfactorily characterized and understood using combined spatial and temporal information. Whole-head magnetoencephalography (MEG) lends itself as an obvious tool in this endeavour as it allows fast tracking of brain activations at millisecond time resolution and reasonable spatial accuracy.

This paper discusses the neural organization of language function as it appears in MEG recordings. We will first outline neural processes of speech perception, reading, and speech production in healthy subjects and then proceed to consider how this information may be used in the clinical domain.

2. Speech perception

2.1. Sequence of activation

Speech perception is thought to proceed as follows: speech signals enter the ear as sound waves from which

* Tel.: +358 9 4512950; fax +358 9 4512969.
   E-mail address: riitta@neuro.hut.fi.

the brain extracts speech sounds and speech sound sequences which further activate the meaning of the word (Hickok and Poeppel, 2004).

At the level of the brain, activity is detected in the superior temporal cortex bilaterally (Fig. 1). All sounds evoke a prominent activation at about 100 ms, referred to as the N100 response, or N100m in MEG (Hari, 1990). When listening to natural speech, words, and sentences, the N100m response is followed by a sustained activation that starts at about 200 ms after stimulus onset, reaches the maximum at about 400 ms, and lasts until 600–800 ms (e.g., Biermann-Ruben et al., 2005; Helenius et al., 2002b; Marinkovic et al., 2003). This activation is often referred to as the N400 response, or N400m in MEG.

From the MEG (or EEG) point of view, with the limited spatial resolution (1–2 cm), all this activity is generated in the same general cortical area. However, based on a number of experiments, there are various processing stages reflected in this activation, at different times. Acoustic–phonetic features of speech modulate activity in non-primary auditory cortex from 50–100 ms onwards, as reflected in the N100m response (Kuriki and Murase, 1989; Obleser et al., 2004; Parviainen et al., 2005; Poeppel et al., 1996). Language-specific phonetic–phonological analysis starts by 100–200 ms after stimulus onset. In this time window, an MEG/EEG response associated with mnemonic functions of the auditory association cortex, i.e., the mismatch negativity (MMN, in EEG; cf. Näätänen et al., 2005) or mismatch field (MMF, in MEG) indicates access to phonological categories (Phillips et al., 2000; Vihla et al., 2000), and distinct processing of native vs. nonnative phonetic contrasts (Näätänen et al., 1997). From about 200 ms onwards, the superior temporal activation shows sensitivity to lexical-semantic manipulation (Helenius et al., 2002b; Kujala et al., 2004; Marinkovic et al., 2003). How may one extract this type of timing information? Let us consider examples of experiments that have been used for characterizing the stages of acoustic/phonetic analysis (N100m time window) and lexical-semantic processing (N400m time window).

2.2. Acoustic–phonetic analysis: example

Parviainen and colleagues (Parviainen et al., 2005) asked whether speech-specific analysis is reflected in the neural processing before the MMN/MMF time window, in the N100m response. The stimuli were synthetic vowels /a/ and /u/ and consonant-vowel syllables /pa/ and /ka/, and corresponding non-speech sounds. The complex non-speech sounds contained the dominant frequencies of the speech sounds (three formant frequencies, F1, F2, and F3), and the simple non-speech sounds one formant frequency (F2). For vowels, the frequency content remains essentially the same throughout the sound whereas for the consonant-vowel combinations there is a rapid frequency transition at the beginning. In this study, synthetic sounds were used (as opposed to natural speech) in order to control for acoustic properties as well as possible.

The strength of the N100m response in the left hemisphere was sensitive to the stimulus content, with strongest activation to speech sounds and weakest to simple non-speech sounds, similarly for vowels and consonant-vowel syllables (Fig. 2a). No such dependence on stimulus type was detected in the right hemisphere. Both the left and right superior temporal cortex were obviously involved in processing all sounds but the variation in the left hemisphere resulted in a leftward shift of hemispheric balance for speech sounds. The amplitude behaviour alone does not necessarily indicate a special role for speech sounds as the signal strength could reflect an effect of systematically increasing acoustic complexity of the stimuli, not speech-specificity per se. However, the timing of activation provides additional relevant information (Fig. 2b). For speech sounds, the build-up of the N100m response was significantly faster in the left than right hemisphere whereas for the non-speech sounds, simple or complex, no such difference in the ascending slope was observed. Speech seems to be special by 100 ms after stimulus onset.

These findings are in line with studies that have shown stronger N100m amplitude for vowels than piano notes or tones (Gootjes et al., 1999), longer latencies for vowels
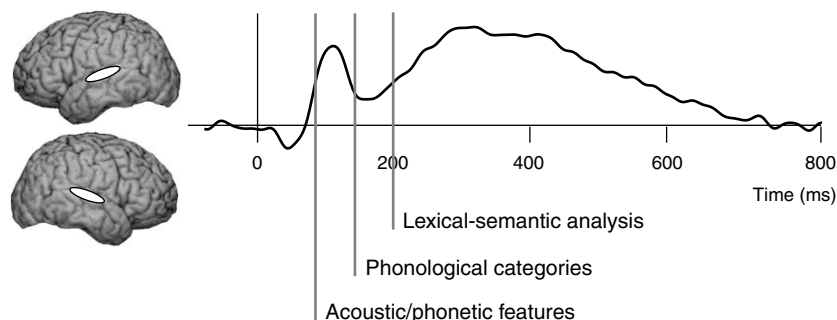

Fig. 1. Time course of speech perception in the superior temporal cortex, based on neurophysiological recordings.
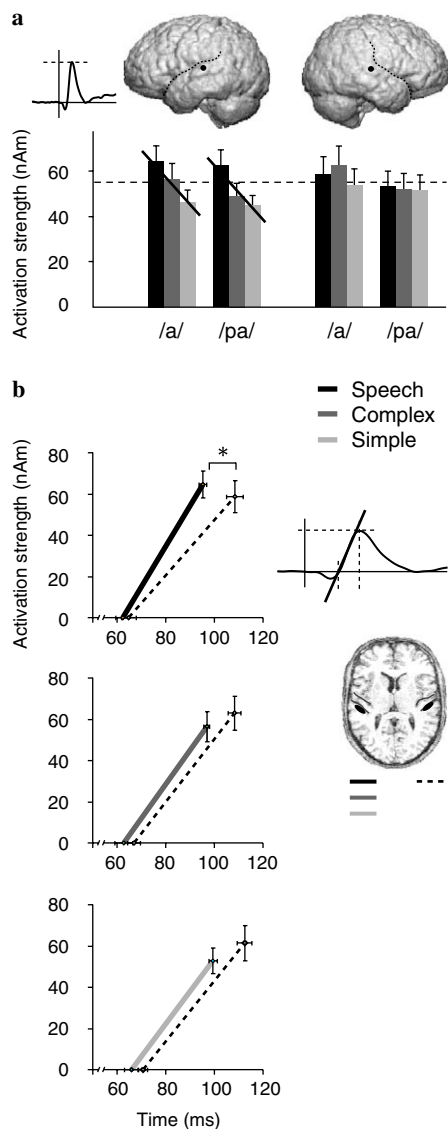
Fig. 2. Neural responses to speech and non-speech sounds. (a) Strength of the N100m response (mean + SEM) in the left and right superior temporal cortex to the /a/ and /pa/ stimuli and the corresponding complex and simple non-speech sounds. (b) Timing of the build-up phase of the N100m response, from onset to maximum, for the different stimulus types of the /a/ category. As the stimulus was given to the right ear the left-hemisphere response is systematically about 10 ms faster. Modified from Parviainen et al. (2005).

than tones (Eulitz et al., 1995; Tiitinen et al., 1999), or left-ward shift of hemispheric balance for natural vowels as compared with complex tones (Vihla and Salmelin, 2003). Apart from the study of Parviainen and colleagues (Parviainen et al., 2005), the stimuli have typically been sounds with stable frequencies (i.e., vowel type sounds) (Eulitz et al., 1995; Tiitinen et al., 1999; Vihla and Salmelin, 2003) or transition sounds (i.e., consonant-vowel syllable type of sounds) (Shtyrov et al., 2000) but not both. As natural language is a mixture of these sound types, it may be important to allow acoustic variation among the speech stimuli when evaluating cortical analysis of speech vs. non-speech sounds.

2.3. Lexical-semantic analysis: example

Here, we move from syllables to complete words, and to extraction of meaning in realistic speech perception. Bonte and colleagues (Bonte et al., 2006) explored emergence of lexical-semantic analysis in the analysis of spoken words. Their stimulus set was composed of a large number of natural spoken sentences from which both the initial words and the initial syllables were cut as separate stimuli. The initial syllables are potentially meaningful but only if followed by further speech. The perception of syllables was tested in two contexts. One sequence contained only syllables and, therefore, expectation for meaningful language was low. Another sequence included all stimulus types, syllables, words, and sentences, played in a random order. Accordingly, expectation for meaningful language was high as any syllable could signal the beginning of a sentence or word. This study thus varied the need for semantic analysis while equating phonetic/phonological aspects between the experimental conditions.

Fig. 3 displays the time course of activation in the auditory cortex to syllables played in isolation and to syllables played in context of words and sentences. The pattern was significantly different from about 200 ms onwards. For syllables in context, the sustained activation started earlier and was overall stronger than for syllables in isolation. In the ascending slope, the activation evoked by syllables in context coincided with that evoked by words and sentences. In potentially meaningful context auditory cortex thus seems to treat syllables as words and sentences, just in case. By about 300 ms, the system had determined that there was no information to follow the initial syllable and the signals started to diverge. Extraction of meaning, or potential meaning in syllables, thus seems to start at about 200 ms after stimulus onset.
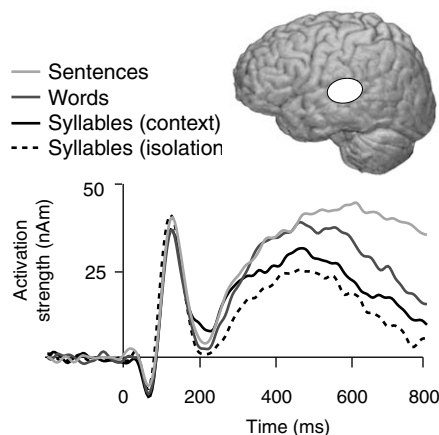

Fig. 3. Cortical effect of expectation for meaning. Time course of activation in the left superior temporal cortex for spoken sentences, sentence-initial words, and sentence-initial syllables. The syllables were presented either in context, as part of a sequence composed of all stimulus types, or in isolation, as a separate sequence. Modified from Bonte et al. (2006).

An efficient setup for characterizing neural correlates of lexical-semantic analysis is to use sentences that create a very high expectation for a certain final word, as in *The piano was out of tune*, and break that expectation in a number of ways (Connolly and Phillips, 1994; Helenius et al., 2002b); this experimental design was initially introduced in the domain of reading (Kutas and Hillyard, 1980). Fig. 4 illustrates the results from a study by Helenius and colleagues (Helenius et al., 2002b) where, in addition to the expected endings, the sentences could end with three different types of unexpected words. The sentence-ending word could be totally anomalous, as in *The pizza was too hot to sing*, or it could be unexpected but have a meaning that was plausible in the sentence context, as in *When the power went out the house became quiet* when most people would expect *dark*. Yet another type was a word that sounded correct in the beginning but had the wrong meaning, as in *The gambler had a streak of bad luggage*, instead of *luck*. The N100m response was not affected by the stimulus type. The responses to the different sentences started to differ at about 200 ms. There was a prominent N400m response to the semantically wrong endings, a weaker activation for the unexpected but semantically plausible final words, and the weakest response to the expected words, thus resulting in a pattern of activation systematically graded by semantic plausibility. Differentiation between word types was detected in both hemispheres. Overall, the unexpected sentence-ending words evoked stronger activation in the left than right hemisphere.

These data (Helenius et al., 2002b) and other MEG studies using sentences or semantically congruent vs. incongruent word pairs agree on involvement of the superior temporal cortex in lexical-semantic analysis of spoken words, starting at about 200 ms after stimulus onset (Kujala et al., 2004; Marinkovic et al., 2003). This is a consistent finding regardless of whether an active neuronal population is modelled as a focal Equivalent Current Dipole (ECD; Hämäläinen et al., 1993) which represents the centre of an active cortical patch and direction and magnitude of electric current therein, or displayed as a distributed probability map (e.g., Dale et al., 2000; Uutela et al., 1999). Distributed source modelling of MEG data (Marinkovic et al., 2003) suggests that neural activity underlying the N400m response may additionally extend into (left) anterior temporal and frontal areas. It is important to realize that focal ECDs and distributed probability maps produce exactly the same electromagnetic field outside of the head so they are both equally correct models of the underlying neural activity. The appearance of the result is determined by the choice of analysis method (model) rather than by the structure of active areas in the brain.

3. Reading

3.1. Sequence of activation

It is usually assumed that when we see a familiar word basic visual features must be processed first before the analysis can proceed to the content, apparently first at the level of single letters and then as a whole word which further activates the word's meaning and its sound form. According to the influential dual-route model (Coltheart et al., 1993) unfamiliar words or nonwords cannot be handled by this lexical route but, instead, we process them letter-by-letter, converting each grapheme to its corresponding phoneme, thus resulting in a phonological representation for the letter-string which may or may not evoke semantic associations. Both routes are thought to be activated but the dominance between the routes varies with the familiarity of the words. An alternative account is the distributed connectionist model (Plaut et al., 1996; Seidenberg and McClelland, 1989). Here, one assumes that both familiar and unfamiliar words are handled by exactly the same network, where orthography, phonology, and semantics are processed simultaneously in a single strongly interactive process, and it is the amount of exposure to letter-strings rather than their lexical status that influences the system behaviour. The existing theoretical models of reading are based largely on analysis of behavioural reaction times and error types in acquired and developmental reading disorders.

Fig. 5 summarizes the cortical dynamics of silent reading, as revealed by MEG. First, activation reflecting basic visual feature analysis is detected around the occipital midline, at about 100 ms. It is followed by left-lateralized activation of the occipitotemporal cortex at 150 ms, associated with letter-string analysis. This transient activation seems to indicate the first stage of language-specific processing or, more generally, category-specific analysis (Tarkiainen et al., 1999, 2002). It is taken to reflect pre-lexical processing as the response does not differentiate between words and nonwords, or even consonant strings (Cornelissen et al., 2003b; Salmelin et al., 1996; Wydell et al., 2003).
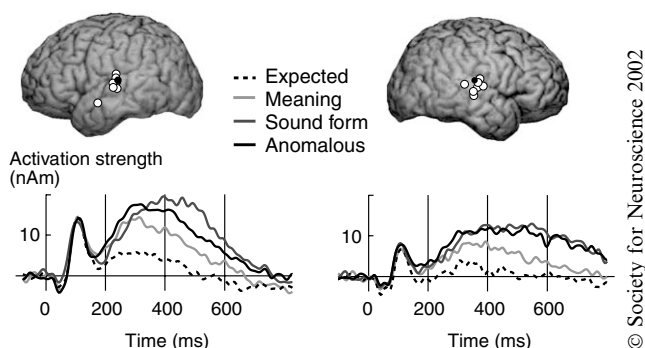

Fig. 4. Neural correlates of lexical-semantic processing in speech perception. The black dot indicates the location of the auditory cortex and each white dot the centre of the active cortical patch during the N400m interval, in one individual. The curves display the mean time course of activation in the depicted source areas. The semantically wrong endings (totally *anomalous*, expected *sound form* at the onset) resulted in a prominent N400m response. The signal was smaller for the equally unexpected words that had a plausible *meaning* in the sentence context, and weakest for the *expected* words. Modified from Helenius et al. (2002b).
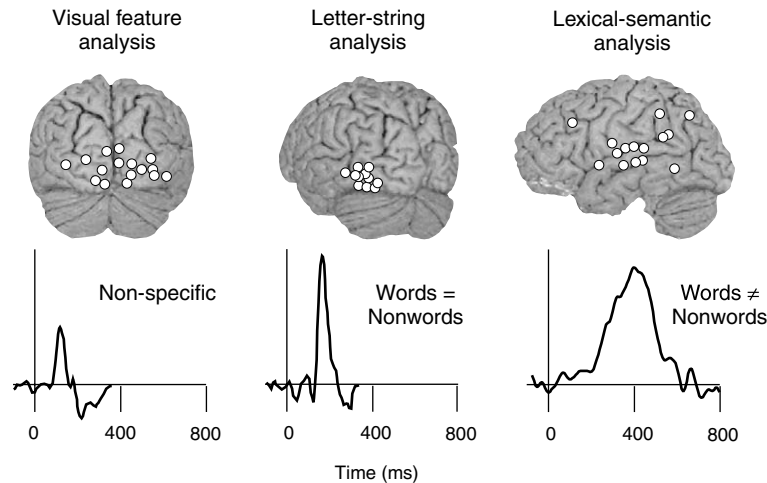
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Fig. 5. Cortical dynamics of silent reading. Dots represent centres of active cortical patches collected from individual subjects. The curves display the mean time course of activation in the depicted source areas. Visual feature analysis in the occipital cortex (∼100 ms) is stimulus non-specific. The stimulus content starts to matter by ∼150 ms when activation reflecting letter-string analysis is observed in the left occipitotemporal cortex. Subsequent activation of the left superior temporal cortex at ∼200–600 ms reflects lexical-semantic analysis and, probably, also phonological analysis. Modified from Salmelin et al. (2000a).

Reading comprehension is reflected in the subsequent activation of the left superior temporal cortex at 200–600 ms (Halgren et al., 2002; Helenius et al., 1998; Pylkkänen et al., 2002, 2006; Pylkkänen and Marantz, 2003; Simos et al., 1997). This sustained activation differentiates between words and nonwords (Salmelin et al., 1996; Wilson et al., 2005; Wydell et al., 2003). Apart from lexical-semantic aspects it also seems to be sensitive to phonological manipulation (Wydell et al., 2003).

As discussed above, in speech perception activation is concentrated to a rather small area in the brain and we have to rely on time information to dissociate between different processes. Here, the different processes are separable both in timing and location. Because of that, one might think that it is easier to characterize language-related processes in the visual than auditory modality. However, here the difficulties appear at another level. In reading, activation is detected bilaterally in the occipital cortex, along the temporal lobes, in the parietal cortex and, in vocalized reading, also in the frontal lobes, at various times with respect to stimulus onset. Interindividual variability further complicates the picture, resulting in practically excessive amounts of temporal and spatial information. The areas and time windows depicted in Fig. 5, with specific roles in reading, form a limited subset of all active areas observed during reading. In order to perform proper functional localization one needs to vary the stimuli and tasks systematically, in a parametric fashion. Let us now consider how one may extract activation reflecting pre-lexical letter-string analysis and lexical-semantic processing.

3.2. Pre-lexical analysis

In order to tease apart early pre-lexical processes in reading, Tarkiainen and colleagues (Tarkiainen et al., 1999) used words, syllables, and single letters, imbedded in a noisy background, at four different noise levels (Fig. 6). For control, the sequences also contained symbol strings. One sequence was composed of plain noise stimuli. The stimuli were thus varied along two major dimensions: the amount of features to process increased with noise and with the number of items, letters or symbols. On the other hand, word-likeness was highest for clearly visible complete words and lowest for symbols and noise.

At the level of the brain, as illustrated in Fig. 7, the data showed a clear dissociation between two processes within the first 200 ms: visual feature analysis occurred at about 100 ms after stimulus presentation, with the active areas around the occipital midline, along the ventral stream. In these areas, the signal increased with increasing noise and with the number of items in the string, similarly for letters and symbols. Only 50 ms later, at about 150 ms, the left inferior occipitotemporal cortex showed letter-string specific activation. This signal increased with the visibility of the letter strings. It was strongest for words, weaker for syllables, and still weaker for single letters. Crucially, the activation was significantly stronger for letter than symbol strings of equal length.

Bilateral occipitotemporal activation at about 200 ms post-stimulus is consistently reported in MEG studies of reading (Cornelissen et al., 2003b; Pammer et al., 2004; Salmelin et al., 1996, 2000b) but, interestingly, functional specificity for letter-strings is found most systematically in the left hemisphere. The MEG data on letter-string specific activation are in good agreement with intracranial recordings, both with respect to timing and location and the pre-lexical nature of the activation (Nobre et al., 1994).

3.3. Lexical-semantic analysis

To identify cortical dynamics of reading comprehension, Helenius and colleagues (Helenius et al., 1998) employed a
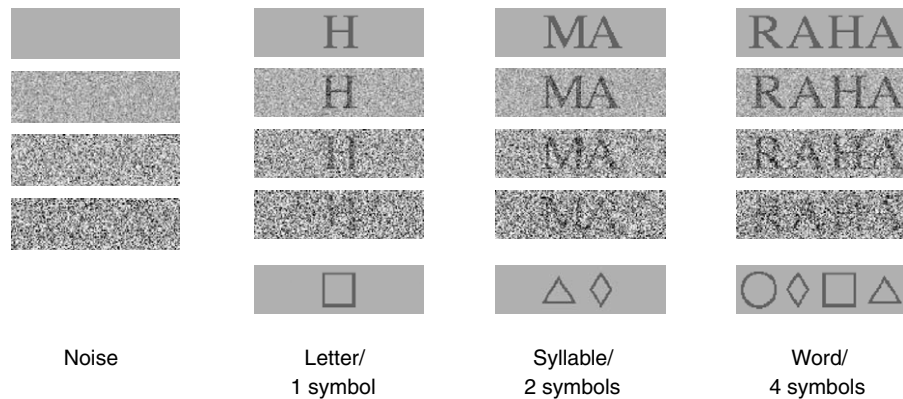
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Fig. 6. Paradigm for focusing on pre-lexical processes in reading. The amount of features to analyze (four levels of noise) and word-likeness of the stimuli (symbols; letters, syllables, words in Finnish) were varied parametrically. Modified from Tarkiainen et al. (1999).
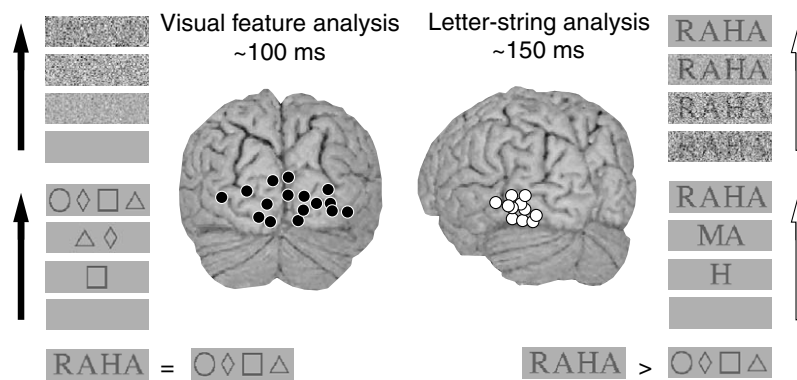

Fig. 7. Dissociation of basic visual feature and letter-string analysis within 200 ms post-stimulus. Dots represent centres of active cortical patches collected from the individual subjects. Arrows indicate increasing strength of activation. Amount of features to analyze (~100 ms) and content at the next stage (~150 ms).

visual version of sentences that create a very high expectation for a certain final word (see section on speech perception above). In these sentences, the final word was either the expected one or one of three types of unexpected endings: totally anomalous, unexpected but with an acceptable meaning in the sentence context, or semantically wrong but (deceptively) sharing its initial letters with the expected word.

Fig. 8 displays the average time course of activation for the sentence-ending words, with the left-hemisphere N400m activation graded by semantic congruity. The response was strongest and lasted longest for the semantically wrong word types and smaller and shorter-lasting for unexpected words with acceptable meaning. To the expected words there was no response that would have exceeded the noise level. In the right hemisphere, about half of the subjects showed a qualitatively similar sustained response but with much weaker differentiation between stimulus types. In reading, the neural signatures of lexical-semantic processing thus seem to be fairly strongly lateralized to the left hemisphere.

When the active areas are modelled as focal ECDs, sources of the N400m response are consistently localized to the superior temporal cortex (Halgren et al., 2002; Hel-
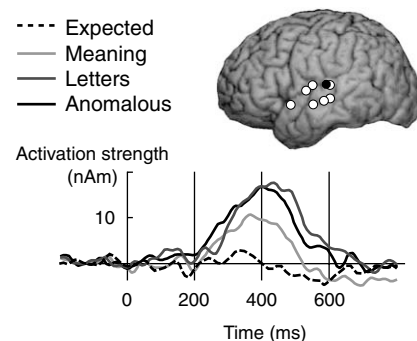

Fig. 8. Neural correlates of lexical-semantic processing in reading. The curves display the mean time course of activation in the left superior temporal cortex. The semantically wrong endings (totally *anomalous*, same initial *letters* as in the expected word) resulted in a prominent N400m response. The signal was smaller for the equally unexpected words that had a plausible *meaning* in the sentence context, and essentially non-existent for the *expected* words.

enius et al., 1998; Pylkkänen and Marantz, 2003; Pylkkänen et al., 2002; Salmelin et al., 1996; Simos et al., 1997), in the immediate vicinity of the auditory cortex (Helenius et al., 1998). Distributed source models suggest further spreading of activation to the anterior temporal and inferi-

or frontal cortex (Halgren et al., 2002; Marinkovic et al., 2003). Involvement of the left temporal pole in semantic processing would agree with previous intracranial recordings (Halgren et al., 1994; Nobre and McCarthy, 1995) which, however, did not probe the superior temporal cortex.

4. Speech production

Research into the neural basis of language production is complicated by the strong artefact signals that are generated by mouth and tongue movement and mask the cortical activity. Fortunately, those disturbing field patterns can often be removed from the MEG data (Salmelin et al., 1994, 2000b). Normally, there is considerable intertrial variability in timing from the trigger stimulus to actual speech production, and also from onset of mouth movement to actual speech onset (100–200 ms). This jitter makes it possible to dissociate the artefact signal from the cortical activity of interest. Let us consider two experimental setups that encompass speech production, vocalized reading and picture naming.

4.1. Reading aloud

Fig. 9 displays a sequence of activation during vocalized reading, collected from a group of 10 subjects (Salmelin et al., 2000b). Isolated words (German nouns composed of 7–8 letters) were presented for 300 ms. After a delay of 500 ms a question mark appeared for 2 s, prompting the subject to read the word out loud. The occipital and the left and right inferior occipitotemporal cortices were active within the first 200 ms. Based on the neural sequence in covert reading, outlined above, the early response close

to the occipital midline is likely to reflect, at least partly, the visual feature analysis, which is followed by letter-string specific processing in the left inferior occipitotemporal cortex. The largely visual nature of the right inferior occipitotemporal signal is emphasized by the second response to the question mark. Activation in the left superior temporal and inferior parietal cortices, starting at about 200–300 ms after word onset, and reaching the maximum at about 400 ms probably reflects semantic processing, as suggested by studies on silent reading (N400m). Activation of the left inferior frontal cortex, approximately Broca's area, however, is typically not observed in silent reading. The activity started at about 200 ms after word onset, and is likely to reflect access to phonological representation of the word for articulation (Fiez and Petersen, 1998). Activation of this region seems to be specific to vocalized reading.

The responses depicted in the two left-most columns fade out before the vocalization prompt. However, the activations depicted in the right-most column begin at about 200–300 ms after word onset and persist until actual vocalization and even beyond it. This seems reasonable as they arise from the left and right sensorimotor and premotor cortices and apparently from the supplementary motor area.

Event-related modulation of rhythmic cortical activity is less sensitive to disturbances caused by mouth movements than phase-locked evoked responses and may, thus, provide a useful tool for evaluating motor cortex involvement in speech production. The healthy human brain typically shows parieto–occipital rhythmic activity in the 10-Hz range, the α rhythm, and rolandic activity containing both 10- and 20-Hz components, the μ rhythm (Hari and Salmelin, 1997). The α rhythm is suppressed by opening the eyes,
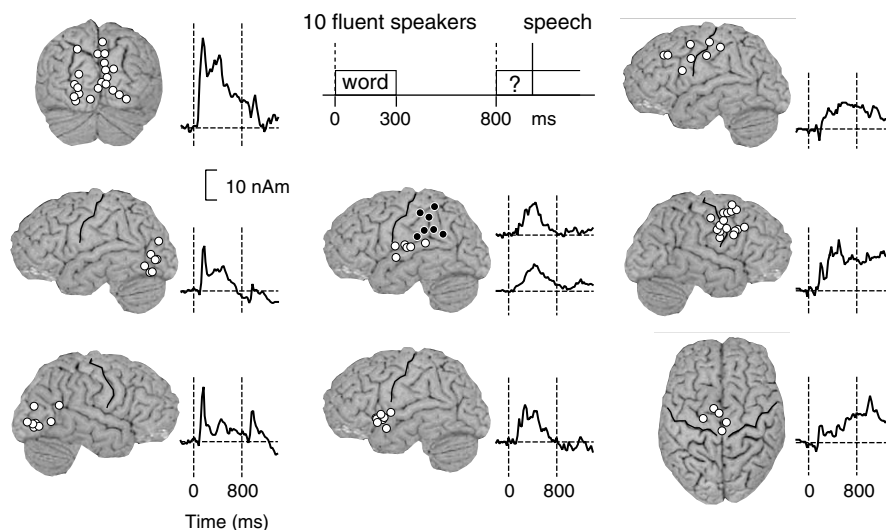
Fig. 9. Cortical dynamics of vocalized reading. Average cortical sequence of activation in 10 fluent speakers when they were reading isolated words out loud. The dots show the centres of the active cortical patches collected from the different subjects, and the curves the average time course of activation in those areas. The first vertical line indicates the word presentation and the second vertical line the onset of the question mark that served as vocalization prompt.

with little effect on the rolandic activity, and the μ rhythm by moving the left or right hand. In the resting brain, the sources of μ rhythm concentrate in and around the hand representation area in the central sulcus. The 10-Hz component originates largely in the somatosensory cortex, but also precentrally, whereas the 20-Hz component seems to be predominantly a motor cortical rhythm (Salmelin and Hari, 1994; Salmelin et al., 1995).

Importantly, for voluntary movements the motor cortex 20-Hz activity shows somatotopic organization (Salmelin et al., 1995), which means that one may use 20-Hz activity to evaluate functionality of different parts of the motor cortex, not only the hand area. In speech production, suppression of the 20-Hz activity, taken as a signature of cortical involvement in task performance, is detected in the mouth area bilaterally. In vocalized reading of isolated words the mouth-area 20-Hz activity is suppressed well before vocalization (Salmelin et al., 2000b). It turns out that this suppression is correlated with timing of the visual instruction rather than mouth movement onset, clearly pointing to involvement of motor cortex in cognitive processing, not simply motor control (Saarinen et al., 2006). These measures indicate no clear speech-specific lateralization at the level of the mouth motor cortex.

Interestingly, the hand areas appear to be involved in speech production as well although obviously much less than the mouth areas and only during the actual movement (Salmelin et al., 2000b). When the linguistic component of the output was varied from nonverbal kissing movement to silent articulation of the vowel /o/ and further to repeated vocalization of the same word and generation of new words the relative contributions of the hand and mouth areas were affected in a systematic fashion (Salmelin and Sams, 2002). In the mouth area, the 20-Hz suppression remained essentially the same for all tasks but in the hand area the suppression was diminished with increasing linguistic demands of the task. Accordingly, the mouth vs. hand area segregation in the motor cortex was stronger for verbal than nonverbal mouth movements (Saarinen et al., 2006; Salmelin and Sams, 2002), and this effect seems to be independent of sequence length or complexity (Saarinen et al., 2006). The main factor appears to be the verbal vs. nonverbal contrast, that is, the hand areas are more involved when producing nonverbal than verbal mouth movements.

4.2. Picture naming

Object naming is a basic function of language that is thought to include all the main stages of word production from conceptualization to selection of a lexical item, phonological encoding and preparation for articulation (Levelt et al., 1999). Due to its apparent simplicity it is a frequently used task in clinical practice. However, from the neuroscience point of view the process of picture naming is far from simple. Unlike for reading and speech perception, it has been difficult to associate specific time windows and brain areas with processing stages assumed to be involved in picture naming. At present, there is only a small number of MEG studies describing the sequence of activation during overt picture naming (Levelt et al., 1998; Salmelin et al., 1994; Sörös et al., 2003). These studies give only indirect evidence on the timing and location of the cognitive subprocesses of word production, as experimental manipulations potentially differentiating the subprocesses were either not used (Salmelin et al., 1994; Sörös et al., 2003) or failed to reveal differences in activation (Levelt et al., 1998). Naming a set of pictures which were semantically related or not suggested priming effects in the left temporal cortex at around 200 ms post-stimulus, interpreted as a signature of lexical retrieval (Maess et al., 2002).

Indefrey and Levelt (2004) have compiled timing information obtained from behavioral and event-related potential studies (EEG) with spatial information provided by neuroimaging methods, mainly positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), including data from the small number of MEG studies available at present. The meta-analysis suggests the following approximate time windows and neuronal correlates for the subprocesses: (i) visual object recognition and conceptualization at 0–175 ms post stimulus, involving occipital and ventrotemporal regions; (ii) selection of the corresponding semantic-syntactic representation (a lemma) from the mental lexicon at 175–250 ms, associated with the mid-section of the left middle temporal gyrus; (iii) phonological code retrieval at 250–330 ms, involving posterior parts of left middle and superior temporal gyri (i.e., Wernicke's area); and (iv) preparation for oral output after 330 ms, engaging Broca's area in the left inferior frontal gyrus and bilateral sensorimotor areas. Further research combining MEG and careful parametric variation of tasks and stimuli is clearly needed to verify or correct this view.

As illustrated in Fig. 10, the context of picture naming may influence the observed pattern of activation. When naming stand-alone pictures of objects (Levelt et al., 1998; Salmelin et al., 1994) activation proceeded from the occipital cortex (<200 ms) to both temporal and parietal areas (>200 ms) and further to inferior frontal cortex (>300–400 ms) bilaterally. However, when naming objects or actions from simple drawings of events (Sörös et al., 2003) activation followed a route from occipital cortex (<200 ms) through the parieto–occipito–temporal junction (>200 ms) to the left dorsal motor/premotor cortex, in particular (>400 ms). The effect of stimulus and task on the neural correlates of overt naming needs to be addressed in future studies.

5. Pre-surgical mapping of language function

5.1. Language-dominant hemisphere

Based on the above, early stages of speech perception and analysis of written language would seem to show the clearest left-hemisphere lateralization in healthy right-handed individuals. Lateralization of the N100m response
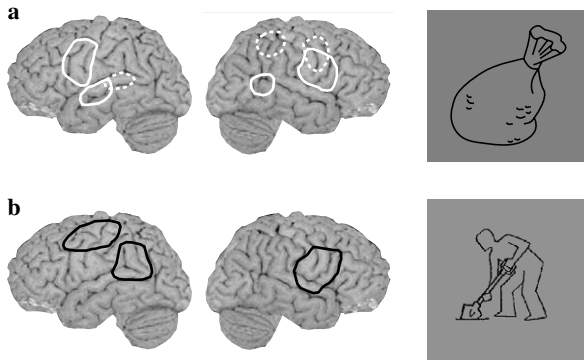
Fig. 10. Cortical activation in picture naming. (a) Activated areas when naming pictured objects. Solid and dashed lines indicate distribution of active areas as reported in Salmelin et al. (1994) and Levelt et al. (1998), respectively. (b) Activated areas when naming objects or actions from simple drawings of events as reported in Sörös et al. (2003).

to speech vs. non-speech sounds indeed shows promise for a clinical paradigm, as it is fast and easy to perform and simple to analyze. Probably the simplest approach was proposed by Gootjes and colleagues (Gootjes et al., 1999) who presented healthy right-handed subjects with pairs of tones, pairs of piano notes, and pairs of vowels in a random sequence. The subjects' task was to detect target pairs in which the two sounds were identical. The authors used no source modelling but compared the responses to speech vs. non-speech sounds by selecting, over each hemisphere, the sensor that showed the strongest N100m response; importantly, the MEG data were recorded using planar gradiometers that detect the maximum signal directly above an active cortical area. The relative strength of the N100m response to vowels vs. tones was consistently stronger in the left than right hemisphere in the right-handed individuals. Kirveskari and colleagues (Kirveskari et al., 2006) further evaluated this approach by simplifying the paradigm to only contain vowels and tones (Fig. 11) and including both right- and left-handed subjects. The authors demonstrated a difference in hemispheric dominance between right-handed and left-handed subjects that closely resembles the ratio of left- vs. right-hemisphere lateralization of language function suggested by previous invasive studies as well as by anatomical and functional comparisons between left- and right-handed individuals. This simple paradigm promises to be a reasonable candidate for comparison with the Wada test, and eventual clinical use.

The correspondence between MEG measures and the Wada test has been explored in a number of studies. Papanicolaou and colleagues have used a receptive language task, detection of repeated words, both in the auditory and visual modality. They focus on the late sustained activation (>200 ms) and model the distribution of activity with an ECD every 4 ms, separately in each hemisphere. A lateralization index is estimated from the total number of ECDs in the left vs. right hemisphere that pass a set of acceptance criteria developed over a series of related experiments (Breier et al., 1999a, 2000; Simos et al., 1998; Zouridakis et al., 1998). The authors report a high degree of concordance (>85%) between their MEG measure of lateralization and the Wada test (Breier et al., 1999b, 2001; Papanicolaou et al., 2004). Apart from the multiple studies on English-speaking subjects performed by Papanicolaou and colleagues the same paradigm and analysis approach have been tested on Spanish-speaking subjects, with comparable results (agreement between MEG evaluation and the Wada test in 7 of 8 subjects; Maestu et al., 2002). A similar analysis method has also been used to demonstrate lateralization in perception of vowels vs. tones (Szymanski et al., 1999). Accordingly, from the clinical point of view, the approach seems promising although further tests by other groups are clearly needed.

It is worth noting, however, that from the neuroscience point of view it is not immediately obvious why the number of acceptable ECDs should be a relevant or useful measure of lateralization (instead of the strength of the activation or its overall time course). For example, if two areas that are fairly close to each other but spatially separable are active simultaneously (see, e.g., Helenius et al., 1999a) one would not be able to account for their common pattern of activation with a single ECD that would pass any reasonable criteria of acceptance, which would potentially result in an erroneous description of laterality. Nevertheless, as Papanicolaou and colleagues focused on the time window >200 ms after stimulus onset and found the ECDs located essentially in the perisylvian region they seem to be focusing on the sustained N400m response. In many subjects, the number of acceptable ECDs (salient dipolar field patterns) may well serve as an indirect, approximate measure of the strength and duration of the N400m activation.

Strength of cortical activation in the left vs. right hemisphere has also been compared with the Wada test. Bowyer and colleagues (Bowyer et al., 2005) used a current density imaging technique (MR-FOCUSS) to localize neural activation during two language tasks, verb generation and picture naming, that were performed mentally, without overt vocalization. Hirata and colleagues (Hirata et al., 2004) localized task-related suppression on rhythmic activity in the β (13–25 Hz) and low γ (25–50 Hz) band during a silent reading task, using Synthetic Aperture Magnetometry (SAM). In both studies, source analysis suggested involvement of multiple brain areas, including the posterior temporal (approximately Wernicke's area), inferior parietal, and inferior frontal cortex (approximately Broca's area). Lateralized activation of the inferior frontal cortex, as measured by increased current density of phase-locked evoked responses (Bowyer et al., 2005) or suppression of rhythmic activity (Hirata et al., 2004), was found to be in best agreement with the results of the Wada test (>90%). Left-lateralized activation in Broca's area (and Wernicke's area) in right-handed individuals has also been reported by Kober and colleagues (Kober et al., 2001) who used a spatial filtering method to study activation of posterior temporal and inferior frontal cortex during silent reading and picture
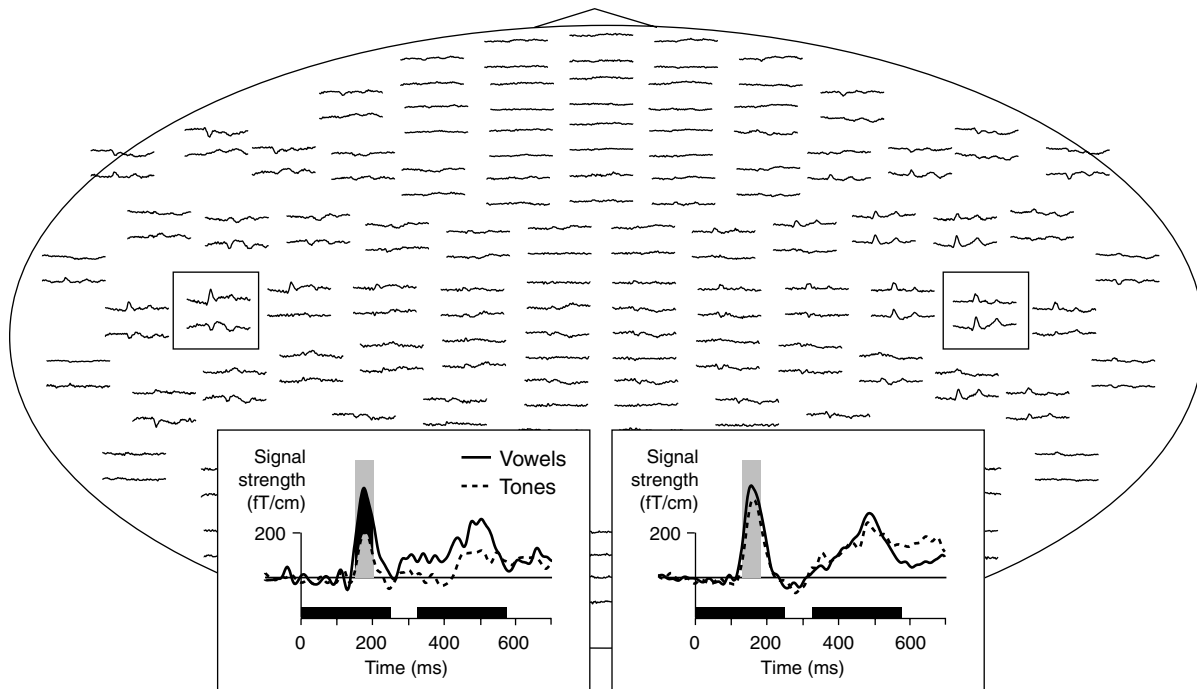
Fig. 11. Auditory responses to vowels vs. tones in one subject. The MEG measurement helmet is viewed from above, flattened to the plane. The curves show the variation of magnetic field as a function of time. This MEG system (Vectorview™, Elekta-Neuromag Ltd.) has planar gradiometers that detect the maximum signal directly above an active cortical area. At each measurement location there are two orthogonally oriented planar gradiometers. The rectangles over each hemisphere indicate the sensor pair that detected the strongest N100m response. The inserts depict the overall signal strength at those sites (vector sum, i.e., square root of the sum of the squared signal strength in the two orthogonal sensors). The N100m response in the left hemisphere is markedly stronger to vowels than tones whereas, in the right hemisphere, there is no clear difference. The analysis was performed by computing the mean signal strength in a 50-ms time window centred on the N100m peak latency (grey bar), and the ratio of signal strength for vowels vs. tones, separately in each hemisphere. The laterality index is obtained as the difference between left- and right-hemisphere ratios divided by their sum. The absolute values of the signal strength are thus irrelevant. Modified from Kirveskari et al. (2006).

naming in healthy subjects. Again, these techniques hold promise but more studies by different groups are needed to evaluate their practical feasibility and reliability.

5.2. Mapping activation in language tasks

A comprehensive mapping of areas involved in language processing becomes a relevant issue when the presence of a tumor or an epileptic focus necessitates operation on the language-dominant hemisphere and, more specifically, when the resection is likely to border on areas typically thought to be involved in language processing. The need for pre-surgical mapping – and post-surgical evaluation – of language areas is strengthened further if language deficits emerge in everyday interaction or if they are revealed in neuropsychological testing. Ideally, an MEG characterization of language function could help to plan and speed up the evaluation performed with direct cortical stimulation during actual surgery.

Providing a map of the language function for the neurosurgeon is far more problematic, both technically and conceptually, than localizing, e.g., the hand, foot, and mouth representation areas in the somatosensory and motor cortex (Mäkelä et al., 2001). There are several aspects to language function which may involve partly overlapping but also quite different cortical areas. This may be because the neural networks involved are different or because distinct parts of the same general network are emphasized in different tasks. Perception may occur via auditory, visual, or tactile pathways. Comprehension of single words, sentences, or continuous text or discourse may rely on slightly different networks. Semantic and syntactic processing are likely to have partly separate cortical representations. Also, language reception and production are two (partly) different things. Production can happen via speech, writing, or signing. The correct prosody, the rhythm and intonation, is a relevant aspect of speech production and comprehension. It is not immediately clear which aspect of language should be mapped for clinical purposes.

This process should probably be guided by a thorough neuropsychological identification of potential problems induced by tumor/epilepsy in specific aspects of language, say, speech comprehension. A targeted neuroscience-based parametric design could then be used for functional localization of brain areas involved in that particular processing stage (see above). Another possibility would be to develop a set of receptive and expressive language tasks that would be as general and realistic as possible to maximally engage the relevant neural networks which could then be tested with direct cortical stimulation; these are not necessarily experimental designs one would typically use in basic (non-clinical) research of language function.

At present, there are few published studies to address these issues. Simos and colleagues (Simos et al., 1999) reported that cortical areas activated during visual and auditory word recognition tasks, identified as clusters of ECDs fitted to the left- and right-hemisphere MEG patterns every 4 ms (see above for paradigms used to evaluate lateralization), were in good agreement with those detected during direct cortical stimulation. Kamada and colleagues (Kamada et al., 2004) tracked neural correlates of letter perception in a patient who underwent a radical resection of a mesial temporal glioma, involving the left fusiform gyrus. As anticipated by preoperative MEG mapping of letter perception the resection initially resulted in severe dyslexia, apparently due to the loss of the area specialized in early letter-string analysis (see above for section on reading). During a one-year follow-up the subject's reading skills were gradually improved. MEG data indicated concurrent overshoot of activity in the spared left superior temporal cortex (late letter-string analysis, lexical-semantic processing) but no compensatory activity in the right fusiform gyrus. Pataraia and colleagues (Pataraia et al., 2005) localized activation related to auditory word recognition/ repetition, with focus on Wernicke's area, before and after left anterior temporal lobectomy in patients suffering from intractable temporal lobe epilepsy. The authors compared the MEG findings with neuropsychological assessment and found that postoperative increase of right-hemisphere language activation was more likely to occur in patients who lacked clear hemispheric lateralization preoperatively than in patients who showed left-hemisphere dominance. Spatial distribution of language-related activation may be radically altered in epilepsy (Breier et al., 2005; Pataraia et al., 2004).

6. Language disorders

Published MEG research into the neural basis of developmental and acquired language disorders mostly falls in the realm of basic neuroscience rather than in the clinical domain. While there is genuine interest in understanding the neural underpinnings of these disorders, as a prelude to possible neuroscience-driven interventions, these deficits also provide essential information about brain areas and time windows that may be particularly relevant to successful language perception and production. Comparisons of cerebral implementation of language in subjects who have functional disorders in specific aspects of language without obvious structural deficits, such as dyslexia (reading) and stuttering (speech production), and in subjects with unimpaired language function have been highly informative in that regard.

Language disorders are efficiently diagnosed and characterized behaviourally. However, a detailed neuropsychological profile combined with a detailed description of language processing at the neural level in individual subjects could be a powerful tool. Eventually, it could help to identify specific subgroups of subjects within groups that are now pooled under a single label according to behavioural criteria or lesion site, facilitate development of methods for training or rehabilitation that would be optimally targeted for each individual, and provide objective means for evaluating the efficacy of a treatment.

6.1. Dyslexia

MEG studies on adult subjects have demonstrated that in dyslexic individuals visual feature processing is normal but reading is disrupted at the subsequent letter-string specific stage (Salmelin et al., 1996; Helenius et al., 1999b; Salmelin and Helenius, 2004). The non-existent or abnormally weak activation of the left inferior occipitotemporal cortex in dyslexia has been corroborated by later fMRI studies (Paulesu et al., 2001; Shaywitz et al., 1998). The subsequent left superior temporal activation, reflecting reading comprehension, is weaker and delayed in dyslexic individuals (delay 100 ms; Helenius et al., 1999a). In fluent readers, the letter-string-specific activation (∼150 ms) appears to be the gateway from visual to linguistic analysis, a fast route that automatically sets letter-strings apart from other objects and facilitates fast reading. The lack of this 'fast route' for written language is likely to be the immediate reason for the manifest difficulties in reading in dyslexia. The functional deficit at the level of category-specific occipitotemporal activation (Tarkiainen et al., 2002) seems to be related to written language, in particular, as processing of faces displays a normal pattern of activation in this area and time window (Tarkiainen et al., 2003).

These difficulties in learning to read are often thought to derive from impaired processing of phonemes (Bradley and Bryant, 1983). MEG studies have shown that in dyslexic individuals the strength of the superior temporal activation evoked by spoken words diverges from the normal pattern by about 100 ms after stimulus onset (Helenius et al., 2002a,b; Parviainen et al., 2005), i.e., in the time window when phonetic information is extracted (Parviainen et al., 2005). Differences in activation strength between dyslexic and control groups from 100 ms onwards have been reported for processing of non-speech sounds as well (Fisher et al., 2006; Nagarajan et al., 1999; Parviainen et al., 2005; Renvall and Hari, 2002, 2003). In speech perception, the stage of lexical-semantic processing is delayed in dyslexic adults (50 ms; Helenius et al., 2002b) but clearly less than in reading.

Simos, Breier and colleagues have studied the neural correlates of speech perception and reading (Simos et al., 2000a,b) in dyslexic and non-reading-impaired children, using the word recognition paradigm and analysis methods developed for evaluation of language lateralization (see above). They report increased involvement of the right temporoparietal region and decreased involvement of the left temporoparietal region compared with the pattern observed in controls. When children were asked to discriminate between speech sounds (syllables from /ga/-/ka/ continuum) an increased relative activation of the right

temporoparietal areas was found to be correlated with reduced performance in phonological tasks (Breier et al., 2003). Comparison of word reading and picture naming tasks in dyslexic vs. control children points to abnormalities in neural processing in dyslexic individuals that are specific for reading (Trauzettel-Klosinski et al., 2006).

In addition to activation strength or timing or number of accepted ECDs, interhemispheric symmetry in the location of the active areas has also been reported to differentiate between groups of dyslexic and non-reading-impaired subjects. Normally, the centre of activation during the auditory N100m response is located 5–10 mm more frontally along the supratemporal plane in the right than left hemisphere (e.g., Pantev et al., 1998; Salmelin et al., 1999). In dyslexic subjects, however, the N100m response in adults (Heim et al., 2003a) and the early auditory activation in children (Heim et al., 2003b) did not show the expected spatial asymmetry. The degree of the reduced hemispheric asymmetry, suggested to be related to an anatomical asymmetry of the planum temporal, appeared to be correlated with phonological abilities (Paul et al., 2006). For these early auditory responses, the neural current flows perpendicular to the course of the sylvian fissure. As the spatial resolution of MEG is best in the plane oriented orthogonally to the direction of current flow, where small changes of source location result in large changes in the magnetic field pattern, the small differences in source location along the supratemporal plane may be relevant. For most purposes, however, the particular strength of MEG is in the powerful combination of accurate timing with approximate (1–2 cm) location.

In both reading and speech perception cortical processing in dyslexic individuals apparently starts to differ from the normal pattern at the earliest language-specific processing stage and there is a dramatic difference in timing by the stage of semantic analysis, which is particularly emphasized in reading. These observations would seem to point to impaired integration of auditory and visual information in dyslexia. Because the problems in dyslexia appear so early on in the cortical sequence, it seems essential to study these neural processes in children who are in the process of learning to read.

Parviainen and colleagues (Parviainen et al., 2006) investigated neural correlates of visual perception of letter-strings in 7-year-old children who were on the first grade of the elementary school, using a simplified version of the letters-in-noise paradigm originally developed for adults (cf. Fig. 6). Based on a set of standardized behavioural tests, these children were expected to become fluent readers. In children, the sequence of activation was functionally quite similar to that in adults, with visual feature analysis in the occipital cortex followed by letter-string-specific activation in the left occipitotemporal cortex, and finally sustained activation in the left superior temporal cortex. However, all stages were delayed in time, by about 50 ms at the stage of visual feature analysis and by about 100 ms at the stage of letter-string analysis. A letter-string-specific response was detected in about half of the children, which is clearly less than in fluently reading adult subjects (>90%). In those children who did show letter-string-specific activation its strength was correlated with behavioural measures of phonological awareness. As phonological skills are seen as a prerequisite for reading acquisition, this is an intriguing finding. Simos and colleagues (Simos et al., 2002b) found, in English-speaking children, that a risk for developing reading problems was accompanied by reduced engagement of the left superior temporal region and increased activation of the corresponding right-hemisphere region. The authors reported a normalization of this aberrant pattern following remedial training (Simos et al., 2002a).

There is an obvious need for controlled studies of the effects of intervention on reading skills in children and adults that are based on choices of training paradigms informed by neuroscience. A combination of behavioural and neural measures should be used for evaluation of the results. The occipitotemporal letter-string activation seems like one promising candidate for this purpose but more research is clearly needed into its development and role in reading acquisition.

6.2. Stuttering

When fluent speakers read aloud isolated words the sequence initially follows that observed in silent reading (see above). In addition, activation is observed in the left inferior frontal cortex when preparing to speak, probably reflecting access to the phonological representation of the word for articulation, and in the left and right motor and premotor cortex and supplementary motor area during actual speech production (Salmelin et al., 2000b). Intriguingly, these are the very areas in which the timing and strength of activation in developmental stutterers has been found to differ from that in controls, thus indicating abnormalities in processes specifically involved in overt speech production rather than core linguistic analysis (Salmelin et al., 2000b; Walla et al., 2004). Furthermore, activation of these same areas was affected also when stutterers simply listened to spoken sentences that they needed to repeat or transform after a short delay (Biermann-Ruben et al., 2005). Tracking of anatomical connectivity with MRI supported the view of a defective interplay between the left inferior frontal cortex and motor/premotor areas (Sommer et al., 2002). Task-related suppression of the motor cortical 20-Hz rhythm during overt reading has further demonstrated a strong involvement of not only the face but also the hand areas when stutterers produce speech (Salmelin et al., 2000b), suggesting that motor cortical specialization for verbal mouth movements may not have developed normally in individuals who stutter. A functional deficit in the interplay between auditory and motor systems during speech production, suggested to underlie stuttering (Fairbanks, 1954), finds some support in MEG data (Salmelin et al., 1998).

A wealth of techniques has been proposed to improve fluency in stutterers (Bloodstein, 1995). MEG should be an excellent tool for evaluating the neural correlates of fluency training but again, as in the case of dyslexia, it is essential to first gain a better understanding of the neural processes underlying stuttering and of detailed neuropsychological description of the training methods. From the neuroscience point of view, stuttering is a somewhat problematic phenomenon as it is typically not present when producing isolated words. More realistic situations of speech production, ideally continuous free discussion, would be needed to fully assess stuttering. Such approaches will require new techniques for signal analysis that rely on neural timing rather than on stimulus timing.

6.3. Aphasia

MEG research on aphasia, clinically a highly relevant topic, is currently quite limited. The entire language network may be drastically affected by the lesion. For example, a dissociation between naming actions (verbs) and objects (nouns) has been reported in aphasia and thought to reflect different cerebral representations for accessing these lexical categories (Caramazza and Hillis, 1991). Recent MEG data, however, showed an essentially identical sequence of activation for verb and noun retrieval in healthy subjects but clear divergence in an aphasic patient with specific difficulties in naming nouns. It thus seems that dissociation of verb and noun production at the cortical level may only emerge when the normal language network is disrupted (Sörös et al., 2003); note, however, that the question of noun vs. verb dissociation at the neural level in normal subjects is far from settled, and the results also seem to influenced by the task (e.g., picture naming, lexical decision, semantic categorization of written words).

In the presence of lesions one cannot simply assume that the neural responses display the normal spatiotemporal distribution, and there is plenty of individual variation in healthy subjects as well. Therefore, functional localization is particularly important in patient studies. Fig. 12 shows an example of such a procedure in patient HH who had an extensive lesion in the left hemisphere, reaching to the left superior temporal cortex (Laine et al., 2000). Based on neuropsychological findings the lesion affected his reading comprehension. More specifically, he showed a rare syndrome known as deep dyslexia where extensive left-hemisphere damage results in specifically semantic errors in reading (e.g., "moon" read as "crescent"). It has been thought that these errors reflect shifting of semantic analysis to the right hemisphere. Patient HH was tested using a set of semantically constrained sentences that ended with expected or unexpected words (see above for section on reading). The data demonstrated that in HH lexical-semantic processing was still subserved by the damaged left hemisphere as in unimpaired subjects.

Spatiotemporal patterns of activation in a spoken word recognition task were compared between six chronic apha-sics and six control subjects (Breier et al., 2004). The data indicated decreased involvement of areas typically associated with receptive language function, including the left superior temporal gyrus, but increased involvement of the surrounding areas. The authors suggested that better recovery may be associated with normalization of the premorbid language areas rather than recruitment of adjacent cortex.

Language training in aphasia, its efficacy, and its cortical correlates are questions of major clinical importance. Cornelissen and colleagues (Cornelissen et al., 2003a) investigated the neural correlates of re-learning in three anomic patients. Based on extensive behavioural testing, these patients were assumed to have weak semantic associations, thus resulting in an input to the phonological processing stage that was not coherent enough to produce the word. During training, pictures were shown in matrices which also contained other semantically related items, e.g., a cow together with other domestic animals. Repeated training of naming on this type of matrix structure is expected to strengthen the connections in the semantic system. After training, single objects should be easier to name with the help of the stronger semantic network. In all three subjects, the left inferior parietal cortex was the only area showing effects of training. Behavioural improvement was associated with increased cortical activation, approaching the level of activation to initially easy-to-name items. Based on location and timing, on the training procedure, and on the subjects' behavioural profile this activation was interpreted to reflect more effective phonological encoding of the target words. There was no evidence of increased right-hemisphere participation after training.

In aphasic patients, the neural responses may show considerably more intersession variability than in healthy controls. In order to reliably evaluate training effects it is important to test the subject with the same paradigm at least twice both before and after training (Cornelissen et al., 2003a). Presence of abnormally abundant slow rhythmic activity (<6 Hz), often detected in brain areas bordering a structural lesion (Butz et al., 2004; de Jongh et al., 2003), also contributes to the apparent variability (Cornelissen et al., 2003a). On the other hand, the aberrant low-frequency activity may also serve as a measure of the efficacy of a training procedure. Meinzer and colleagues (Meinzer et al., 2004) found that the amount of perilesional low-frequency activity was correlated with the training-induced behavioural improvement in language abilities; it remained unclear, however, why the magnitude of rhythmic activity was increased in about half of the patients and decreased in the other half. Accordingly, it is feasible to track and quantify neural changes associated with re-learning of language abilities in aphasia. An essential step will now be to gain better understanding of language learning in the healthy brain in order to take full advantage of the possibilities in the clinical domain.
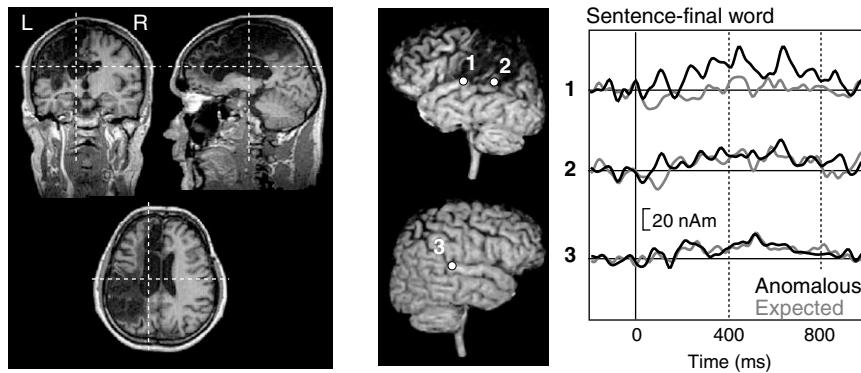
Fig. 12. Characterization of lexical-semantic analysis in an aphasic patient. Patient HH had an extensive lesion in the left hemisphere, apparently encompassing the superior temporal cortex. Nevertheless, when tested with the sentence-reading paradigm designed to focus on lexical-semantic analysis HH had two centres of activation (dots) in the left superior temporal cortex, with the anterior one showing a salient difference between the responses to the semantically anomalous and expected sentence-ending words, a pattern interpreted as reflecting lexical-semantic analysis and similar to that observed in healthy controls. No difference between sentence types was detected in the right superior temporal cortex. Modified from Laine et al. (2000).

7. Conclusion

A reasonable amount of information has begun to be available about the cortical dynamics of basic processes of speech perception, reading, and speech production to support clinical MEG studies of language function. For estimation of the language-dominant hemisphere multiple experimental designs and analysis approaches have been proposed which will need to be further tested in practice. Ideally, the test should be fast and easy for both the subject and the experimenter, and extraction of the result should not require source estimation which takes time and may be influenced, to some degree, by the analysis method and choices made by the person performing the analysis. One example of such a paradigm was described above.

When seeking to describe language representation in more detail experimental design is a key issue. Both functional disorders and structural lesions may severely alter neural processing. Functional localization with careful parametric variation of stimuli and/or tasks is particularly important in patients as one cannot simply assume that the responses display the normal spatiotemporal distribution – and there is plenty of interindividual variation in the healthy population as well. Parametric designs tend to increase the duration of the experiments, thus emphasizing the need for careful neuropsychological testing to guide the MEG experiments for optimally tapping the specific problems in language performance of individual patients. If a growing tumor starts to degrade speech comprehension it would seem particularly relevant to map that specific function in detail (functional mapping using a parametric design) to guide the possible resection, or decision about a resection, and combine it with an overview provided by another, more general language task that would encompass both reception and production (e.g., picture naming, vocalized reading) without detailing specific functional subcomponents.

From the neuroscience point of view, although much information has been gathered, we are only starting to grasp how language may be organized in the human brain, and each finding raises new questions. Questions that also hold considerable clinical interest include the neural correlates of language learning and re-learning in children and adults and the overall development of language function from childhood through adolescence to adulthood. At present, the different components of language function are typically probed using isolated stimuli that allow good control of the task and stimulus properties but obviously create rather unnatural experimental situations. While this is a well-grounded and necessary approach, the brain correlates of language processing may appear quite different in natural performance which the brain is tuned for. Moving towards increasingly realistic experimental designs will be a intriguing challenge not only conceptually but also methodologically as it will require new approaches for data analysis. Tools for extracting networks of brain areas with correlated time courses of activation, instead of isolated active areas, have been introduced and successfully applied to analysis of the motor system, also in the domain of clinical research (Gross et al., 2001, 2002; Schnitzler and Gross, 2005). These methods are currently being developed for use with cognitive tasks (Kujala et al., 2006; Salmelin and Kujala, 2006) which may, eventually, lead to clinical applications as well.

The present review was focused on the contribution and usability of MEG in basic research and clinical evaluation of language function. Research in this domain is also actively done using EEG (for recent reviews see, e.g., Friederici, 2005; Hagoort, 2003; Kutas and Federmeier, 2000), fMRI and PET (for recent reviews see, e.g., Démonet et al., 2005; Jobard et al., 2003; Matthews et al., 2003; Price and Crinion, 2005; Vigneau et al., 2006) and transcranial magnetic stimulation (TMS) (e.g., Dräger et al., 2004). The specific importance of the MEG method is in the way it merges good spatial accuracy with accurate real-time tracking of cortical activity, revealing both the sequential structure of neural activation and the frequently observed overlap between time courses of activation in distinct brain areas. Combined spatiotemporal information is a valuable asset in functional neuroimaging and, in particular, when

identifying the neural correlates of functional disorders. For example, as discussed above for dyslexia, it is important to know that the neural abnormality in reading appears as early as 150 ms after stimulus onset, at the point when the brain first begins to treat visual stimuli as specific entities, such as letter-strings or faces. Location-based analysis using fMRI/PET points to abnormalities in the same general brain area in dyslexia (Paulesu et al., 2001), probably in word-form analysis (Cohen et al., 2000) – but based on location only the exact functional role of this activation, or the significance of its absence in dyslexia, is difficult to resolve (Price and Devlin, 2003). A more detailed comparison of MEG and fMRI/PET data reveals small but intriguing differences in anatomy and function of the left occipitotemporal activation in reading, suggesting that MEG detects the onset of letter-string-specific analysis which is not detected in or does not dominate the hemodynamic signal. fMRI/PET, on the other hand, may detect subsequent activation along the ventral stream where neurons would be increasingly sensitive to the word-likeness of the letter-strings but their activation would be less strongly synchronized or less rigorously time-locked to stimulus presentation and might thus go undetected in MEG (or EEG) (Cornelissen et al., 2003b; Salmelin and Helenius, 2004). As regards the subsequent processing stages in reading, namely, semantic and phonological analysis, the agreement between MEG findings and hemodynamic measures (see Jobard et al., 2003 for a meta-analysis of 35 fMRI/PET studies) is not impressive. It is currently not known whether the amount of activity (fMRI, PET) or its synchronicity (MEG, EEG) is more relevant to human behaviour. Clearly, for a comprehensive picture of the neural representation of language function it will be essential to understand and capitalize on the similarities and differences between hemodynamic and neurophysiological measures.

Acknowledgements

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