Brain Activation During Reading in Deep Dyslexia: An MEG Study

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Abstract

■ Magnetoencephalographic (MEG) changes in cortical activity were studied in a chronic Finnish-speaking deep dyslexic patient during single-word and sentence reading. It has been hypothesized that in deep dyslexia, written word recognition and its lexical-semantic analysis are subserved by the intact right hemisphere. However, in our patient, as well as in most nonimpaired readers, lexical-semantic processing as measured by sentence-final semantic-incongruency detection was related to the left superior-temporal cortex activation. Activations around this same cortical area could be identified in single-word reading as well. Another factor relevant to deep dyslexic reading, the morphological complexity of the presented words, was also studied. The effect of morphology was observed only during the preparation for oral output. By performing repeated recordings 1 year apart, we were able to document significant variability in both the spontaneous activity and the evoked responses in the lesioned left hemisphere even though at the behavioural level, the patient's performance was stable. The observed variability emphasizes the importance of estimating consistency of brain activity both within and between measurements in brain-damaged individuals. ■

INTRODUCTION

Cognitive neuropsychological analysis of acquired language disorders has succeeded in identifying functionally coherent syndromes, which can be understood on the basis of models of normal language processes (e.g., Ellis & Young, 1988). A syndrome that has attracted considerable attention is a rare reading disorder labeled as deep dyslexia. In this disorder, oral reading is characterized by semantic errors (moon→"crescent"), visual errors (edge→"wedge"), morphological errors (typing→"type"), and by an inability to read nonwords. Moreover, reading success is related to the concreteness of the stimuli, as well as to word class (Coltheart, 1980). In cognitive neuropsychological models of reading, deep dyslexia is often interpreted as a simultaneous functional damage to two reading routes: The grapheme-to-phoneme conversion route is abolished and even the direct route via semantics is more or less disordered.

Deep dyslexic patients typically suffer from extensive left-hemisphere damage (Coltheart, 1980). This fact has been one motivation for the hypothesis that deep dyslexic reading reflects limited reading skills of the intact right hemisphere, which is assumed to be latent in normal reading (Coltheart, 1980; Weekes, Coltheart, & Gordon, 1997). Specifically, the right-hemisphere-reading hypothesis predicts that access-related stages of reading, orthographic and semantic processing are subserved by right-hemispheric structures in deep dyslexia. Word retrieval for oral output would then be performed by the left hemisphere as in normals (Weekes et al., 1997). This is an important issue, as shift of hemispheric control on crucial aspects of reading would mean that deep dyslexia could not inform us much about normal reading-related processes. The following sources of evidence support the right-hemisphere-reading hypothesis: (a) Some deep dyslexics have shown a left visual field (right hemisphere) advantage in word recognition (e.g., Saffran, Bogyo, Schwartz, & Marin, 1980); (b) In split-brain syndromes, the presentation of word stimuli in the left, but not in the right, visual field has led to oral reading responses resembling deep dyslexia (e.g., Michel, Henaff, & Intriligator, 1996); (c) In a deep dyslexic reported by Weekes et al. (1997), the regional

cerebral blood flow related to orthographic processing of words was relatively stronger in the right than in the left cortical areas.

Evidence against the right-hemisphere-reading hypothesis includes a case study by Roeltgen (1987). He reported the abolishment of deep dyslexic reading following a second left-sided damage in an aphasic patient, suggesting that the patient's deep dyslexic reading was dependent on the left-hemispheric structures. Price et al. (1998) recently reported reading-related brain activation patterns as measured by PET in two deep dyslexics. Even though the patients' right-sided activation patterns differed from those of normals, the patients' left-sided activation patterns (showing activation in areas that in normal readers have earlier been related to semantic and phonological processes) led the authors to conclude that their data do not support exclusive reliance on the right-hemisphere reading in deep dyslexia. Note, however, that they compared only resting state and single-word reading, making it difficult to reliably identify various subcomponents of reading in their particular data set. Finally, some follow-up studies have indicated that deep dyslexia can form a continuum with another reading disorder, phonological dyslexia (e.g., Laine, Niemi, & Marttila, 1990). If the right-hemisphere-reading hypothesis was correct, evolution of such patients' reading deficit during the first months of recovery should reflect rather rapid shifts of hemispheric reading control (normal left→deep dyslexic right→phonological dyslexic left), which may not appear likely. All in all, the issue of hemispheric control in deep dyslexic reading remains controversial.

A specific feature of deep dyslexic reading, the appearance of morphological errors (i.e., errors dealing with inflection, derivation or compounding), is especially interesting for morphologically rich languages like Finnish. In such languages, the speaker–hearer must constantly handle morphologically complex words: Each Finnish noun has over 2,000 inflectional variants (e.g., consider the form talo + i + sta + mme + kin "house + plural + from + our + even" = "even from our houses") and the number of verb forms exceeds 10,000. How is the mental lexicon organized to ensure fast and accurate access to this multitude of word forms? Previous behavioural evidence suggests that case-inflected Finnish nouns undergo morphological decomposition: As compared to monomorphemic nouns, they attract longer initial eye fixations in reading, require longer lexical decision latencies, and, as noted above, induce more errors in certain aphasic patients (Hyönä, Laine, & Niemi, 1995; Laine, Niemi, Koivuselkä-Sallinen, Ahlsén, & Hyönä, 1994; Laine, Niemi, Koivuselkä-Sallinen, & Hyönä, 1995; Laine & Koivisto, 1998; Laine, Vainio, & Hyönä, 1999; Niemi, Laine, & Tuominen, 1994). It would be of interest to know whether this processing cost, which we have seen quite dramatically in our deep dyslexic patient (Laine et al., 1995), is also linked to specific cortical activation patterns. Such patterns might inform us about the neural substrates of normal morphological processing, particularly if one is able to show that the hemispheric control of reading is not shifted in a deep dyslexic (see above).

We performed magnetoencephalographic (MEG) measurements while a chronic deep dyslexic Finnish patient was engaged in reading sentences and single words. MEG allowed us to combine accurate temporal and spatial resolution in charting the patient's reading-related cortical activation patterns. First, we wanted to determine hemispheric control of lexical-semantic processing in the patient by employing a semantic anomaly-detection task (sentence reading) during MEG. Semantic incongruity of sentence-final words has been extensively used in neurophysiological research to tap semantic processing (the so-called N400 effect, first reported by Kutas & Hillyard, 1980). Brain responses sensitive to deviant sentence-final words would enable us to identify neural correlates of lexical-semantic processing. In normals, semantically inappropriate and appropriate sentence-final words have recently been shown to differ predominantly in the left superior-temporal cortex (Helenius, Salmelin, Service, & Connolly, 1998). The right-hemisphere-reading hypothesis predicts that this processing stage is controlled by right-hemispheric structures in deep dyslexia. Accordingly, lexical-semantic processing should modulate right-sided cortical activity more strongly in a deep dyslexic patient than in normals. The alternative hypothesis states that lexical-semantic processing modulates predominantly left-sided cortical activity in both deep dyslexic and normal reading. Thus, deep dyslexic reading would reflect the residual capacities of the normally used, but damaged, predominantly left-sided cortical network, and not the engagement of a qualitatively different and normally latent right-hemisphere-reading system.

Second, we searched for possible cortical correlates of our patient's markedly differential treatment of inflected versus monomorphemic Finnish nouns. Our patient has marked difficulties in reading inflected words correctly (Laine et al., 1995; Laine & Niemi, 1997). Morphological processing was tested with a single-word oral-reading task. Third, we examined the consistency of the patient's behavioural and brain responses by administering most of our tasks twice with a 1-year interval. In a single case with disturbed brain function, repeated measurement may be particularly important in identifying those activation patterns that are stable.

Case Description

HH is a 46-year-old right-handed construction worker who suffered extensive left-hemisphere damage in
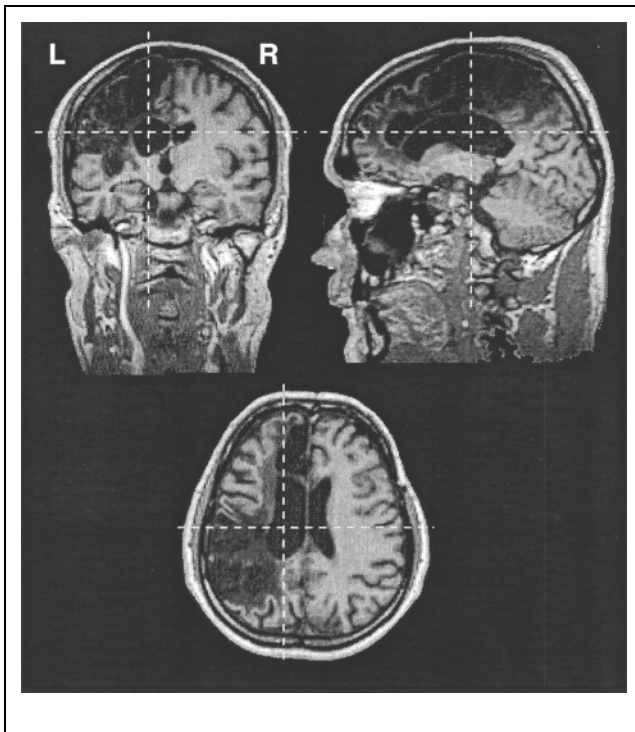
Figure 1. Anatomical magnetic resonance images of HH's brain. The dashed lines indicate the relative orientation of the three slices.

1985 following subarachnoidal haemorrhage and subsequent brain infarction. CT and MRI scans revealed extensive fronto-temporo-parietal damage with unusual lesion distribution (see Figure 1). The frontal part of the lesion was mostly medial while the temporo-parietal part extended to lateral-cortical areas as well. Broca's area was apparently intact while Wernicke's area was partly damaged. As a result of his lesion, HH exhibits chronic agrammatic Broca's aphasia and mild right-sided hemiparesis. Detailed testing of reading

skills has revealed the symptom complex of deep dyslexia: abolishment of nonword reading; concreteness/abstractness and word class effects in reading real words; and the appearance of semantic, visual, and morphological reading errors (Laine et al., 1995; Laine & Niemi, 1997). HH lives independently and drives a specially equipped car. He has a monolingual language background (Finnish), compulsory 8-year school education, and was a normal fluent reader prior to his illness (for additional background data, see Laine et al., 1995).

RESULTS

In a normal healthy individual, averaging MEG activity over 80–100 trials provides a good signal-to-noise ratio for both short- and long-latency responses (compare Helenius et al., 1998; Salmelin, Hari, Lounasmaa, & Sams, 1994; Salmelin, Service, Kiesilä, Uutela, & Salonen, 1996). A split-half division of the responses (i.e., responses to odd-numbered and even-numbered stimuli averaged separately) normally produces fully overlapping signals. However, in our brain-damaged subject HH, cortical networks in the lesioned left hemisphere generated continuous slow-wave activity (see Figure 2). These oscillations were of such low frequency and high amplitude that they seriously disturbed the analysis of the responses time-locked to stimulus or movement onset even after averaging over about 100 trials. In practice, the disturbance showed as major, local differences between the split-half responses. The spatial distribution of these differences agreed with that of pathological low-frequency activity in spectral analysis. The generators of the slow-wave activity were estimated from the continuous, nonaveraged MEG signals (cf. Mäkelä et al., 1998; Salmelin et al., 1994). When the effect of

Figure 2. Continuous 10-sec recording of HH's magnetic cortical activity. The sensor locations (two orthogonal sensors in each block) are indicated on the schematic MEG helmet.
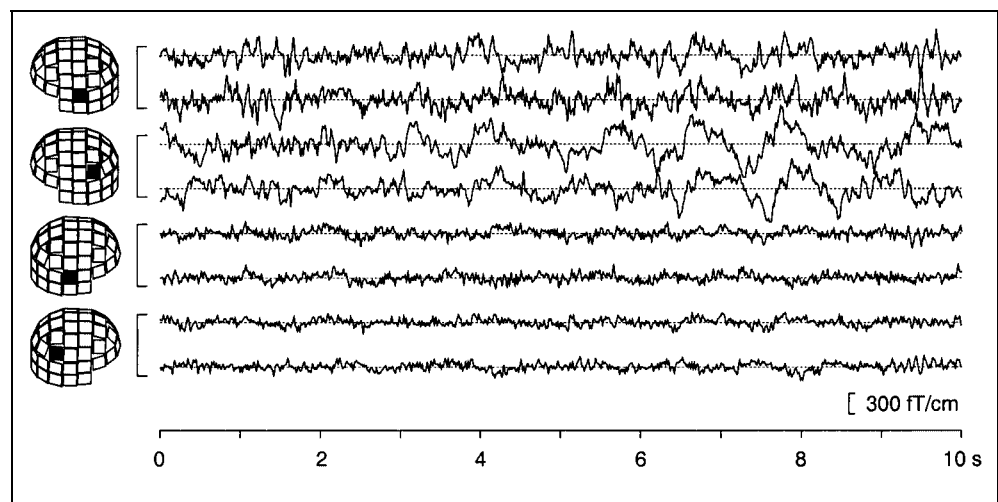
the slow-wave generators was removed from the time-locked evoked responses, the differences in the split-half averages vanished, supporting the assumption that the abnormally large variation was due to the background slow-wave activity arising from around the lesioned area. Thereafter, the cortical sources active during the auditory, finger movement, word reading, and sentence-reading tasks could be identified from data sets cleaned from background disturbance. In the final modelling, also the generators of the background activity were included when the time behaviour of all the source areas was estimated. For each task, the time behaviours were also evaluated separately for the split-half averages to obtain a statistical measure of the reliability of the source waveforms in this brain-damaged subject (see Methods for more detailed description of the analysis techniques and statistical assessment). In the following, we first describe HH's pathological low-frequency MEG activity, and then move on to the analysis of the evoked responses during auditory stimulation, voluntary finger movements, sentence reading, and single-word reading.

Spontaneous MEG Activity

As noted above, we assessed within-measurement reliability by comparing MEG responses to even-numbered versus odd-numbered items. Even and odd responses differed dramatically in all tasks, most prominently in single-word reading. This variation was mostly due to the presence of random high-amplitude low-frequency activity at about 1 Hz, superimposed on the time-locked evoked responses.

The spectral analysis of HH's spontaneous MEG activity on the opening of the eyes showed a normal suppression of occipital alpha activity in both recording sessions (e.g., Salmelin & Hari, 1994). However, in the left hemisphere, his spontaneous brain activity was characterized by exceptionally strong slow-wave (<6 Hz) activity (see Figure 2). Source modelling indicated that this slow oscillation originated from the tissue surrounding the left-sided lesion postero-laterally. The amount of low-frequency activity and the distribution of localizable sources were comparable in the two recordings.

The strong slow-wave activity, particularly in the 0–3 Hz range, interfered with the analysis of evoked responses. Therefore, we modelled the entire source clusters of 0–3 Hz activity with four generators, shown in Figure 3. We then employed the signal-space projection technique to remove all magnetic activity created by these sources from the time-locked responses (Uusitalo & Ilmoniemi, 1997). This clean-up procedure allowed source analysis of the MEG activity, which was systematically modulated by the task (tones, finger movement, single-word reading, sentence reading). Finally, all source areas, including the
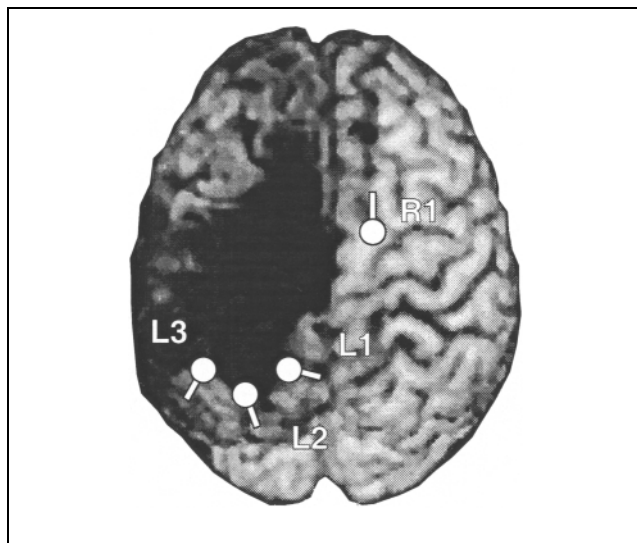

Figure 3. Mean locations and orientations of dipolar sources L1–L3 and R1 describing the spontaneous slow-wave (<3 Hz) activity, plotted on the top view of HH's brain.

four generators of the pathological 0–3 Hz activity, were entered in a multidipole model to determine, using the entire set of 122 sensors, how the activations vary as a function of time. This complete model was also employed to compare responses averaged to even versus odd stimuli. The same clean-up procedure was applied to all data sets, described in detail below. As expected, the sources of 0–3 Hz activity along the posterior bank of the lesioned area varied randomly (but see below for one exception), whereas the other source areas showed reproducible time locking to stimulus or movement.

Brain Responses to Auditory Stimulation

HH's MEG responses to auditory stimuli were located in the bilateral auditory cortices (Figure 4). On the left lesioned side, the ipsilateral- versus contralateral-evoked response showed an abnormally large latency difference in the first, but not in the second, recording (25 msec in the first vs. 10 msec in the second recording; for normal values see, e.g., Salmelin et al., 1998; Mäkelä et al., 1993). In addition, particularly the leftsided ipsilateral-evoked responses showed a decreased within-test consistency as revealed by comparison of responses averaged over odd-numbered versus even-numbered stimuli.

Brain Activity Associated with Voluntary Finger Movement

Self-paced movement of the left index finger elicited typical right-sided activation in the sensorimotor hand area, corresponding to both latency and localization to that found in normals (Salmelin, Forss, Knuutila, &
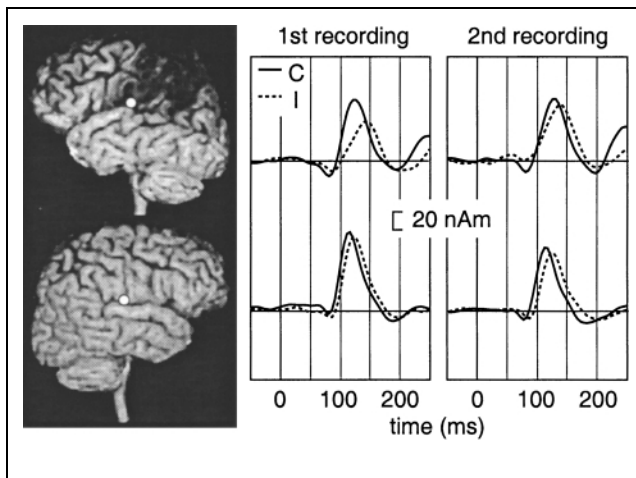
Figure 4. Time behaviour of the left (top) and right (bottom) auditory cortical activations in the first (left) and second (right) MEG recording. The responses to contralateral(C) and ipsilateral(I) stimulation are plotted with solid and dashed lines, respectively.

Hari, 1995). In addition, an unusual source area with highly variable activity both within and across recordings was identified at the ventral end of the left central sulcus (data from this task are not depicted in the figures).

Sentence Reading

Figure 5 shows the three long-latency sources identifiable in the sentence-reading task, two in the left temporo-parietal areas and one in the right posterior-temporal lobe. This pattern is similar to that observed in healthy subjects (Helenius et al., 1998). The two semantically incongruent conditions (last word semantically inappropriate; last word semantically inappropriate, but phonologically related to a high-probability target) resulted in an MEG response that was reliably different from the nondeviant high-probability control sentences. With regard to location, it was the left superior-temporal gyrus region in the vicinity of the auditory cortex that showed clearest sensitivity to semantic incongruency of the sentence-final words in HH. The onset of this effect (around 200 msec) was comparable to that seen in normals, but it lasted somewhat longer (up to 800 msec). Nevertheless, it is understandable that for HH, evoked responses are inevitably less clearcut than in normals. First, all our measures indicate that his brain activity, in general, was more variable in the left than in the right hemisphere. Second, given his severe dyslexia, he probably missed the gist of some sentences, which would reduce the semantic-incongruency effect. In any case, the semantic-incongruency effect gives us an important spatio-temporal landmark about the lexical-semantic processing stage, which can be used in the analysis of single-word reading results.

Single-Word Reading

Behavioural Data

HH's overall reading pattern has remained quite stable over the last decade or so (compare Laine et al., 1995; Laine & Niemi, 1997). The rate of semantic paralexias has always been low, but HH continues to occasionally produce them and also shows all the other major features of deep dyslexia. During the present 1-year follow-up, his reading success was equivalent on both sessions (McNemar = .59, df = 1, p = ns) (Table 1). HH's characteristic difficulty in reading aloud inflected versus monomorphemic word forms was readily observable in both recording sessions as he read correctly only a small fraction of the inflected items (Table 1). In contrast to previous studies, where case substitutions to inflected items were common (Laine et al., 1995; Laine & Niemi, 1997), he now produced most of the incorrectly read inflected forms in the uninflected nominative singular form, i.e., uttering the stem only. This may be a strategic effect reflecting the speeded nature of the single-word-reading task employed in this MEG study.

Evoked Responses as Measured by MEG

In order to examine the time course of brain activation in the single-word-reading task, we analyzed evoked responses both from stimulus onset (emphasis on word input) and from the onset of the articulation prompt (emphasis on word output). We averaged data from correct responses to monomorphemic items and incorrect responses to inflected
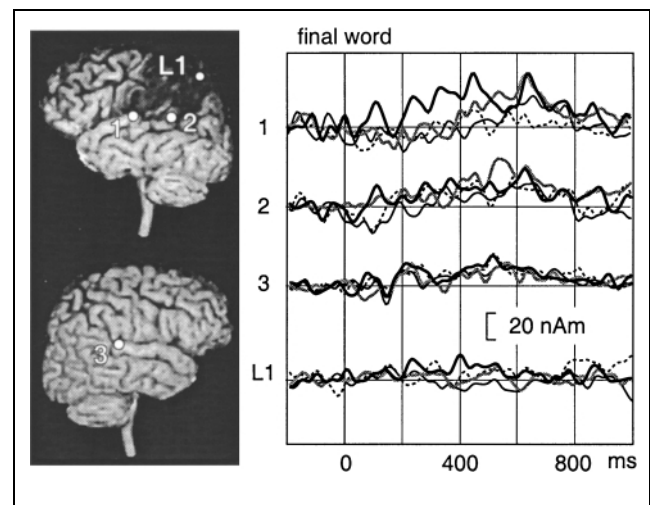
Figure 5. Time course of activations in the left (sources 1 and 2) and right (source 3) superior-temporal cortex to sentence-ending words, which were either probable (thin dashed line), rare but semantically appropriate (thin solid line), semantically incongruous (thick black line), or semantically incongruous but sharing the initial letters with a highly probable sentence-final word (thick gray line). Activation of the L1 source of slow-wave activity (see Figure 3) is also shown.

Table 1. Oral Reading of Monomorphemic and Case-Inflected Nouns During the Two MEG Sessions

	Monomorphemic (n = 85)	Inflected (n = 85)
First testing		
Total correct	67	1
Error distribution		
Morphological	0	54
Visual	5	0
Semantic	1	0
Visual + morphol.	0	12
Visual + sem.	0	0
Omission	11	18
Other	1	0
Total errors	18	84
Second testing 1 year later		
Total correct	63	5
Error distribution		
Morphological	0	47
Visual	1	0
Semantic	0	0
Visual + morphol.	0	9
Visual + sem.	1	0
Omission	19	24
Other	1	0
Total errors	22	80

items, as these categories covered most of HH's responses (see Table 1). Omissions were excluded from the analysis. In each measurement session, the same source areas participated in the processing of both monomorphemic and inflected items. However, partly different sets of brain areas were active for perceiving (stimulus onset) and producing the word (question mark onset). Most of the source areas were similarly active in both measurements (1 year apart), and their locations did not differ from each other (see Methods).

Evoked Responses from Stimulus Onset

Altogether, eight source areas, indicated in Figure 6 (together with the four sources describing the 0–3 Hz background activity, Figure 3), gave a sufficient ac-

count for the reading-related variance of MEG activity in the two recordings. In the following, we will discuss only the most reliable and theoretically relevant sources. Note that Figure 6 also includes one of the slow-wave activity sources, L1, which turned out to be important when evoked responses were analyzed from the articulation prompt (see below). In the present analysis, however, this activity was highly variable both within and across recordings. The earliest response (source 1), localized in the occipital cortex, was highly reliable across the recordings and showed clear reactivity to both stimulus onset and offset, suggesting that it is essentially visual in nature.

In the temporal areas, we were able to identify three sources that appear to correspond both in spatial distribution and in temporal order to the ones observed in the sentence-reading task. The left superior-temporal sources (6 and 7) preceded the right superior-temporal activation (8) by 100–150 msec. Source 6, located in the middle part of the left superior-temporal gyrus and reacting within the time window of 350–800 msec, corresponds rather closely to the source most clearly related to lexical-semantic processing in the sentence-reading task (source 1 in Figure 5).

None of the sources identified from stimulus onset showed sensitivity to morphological structure of the stimuli in a reliable fashion.
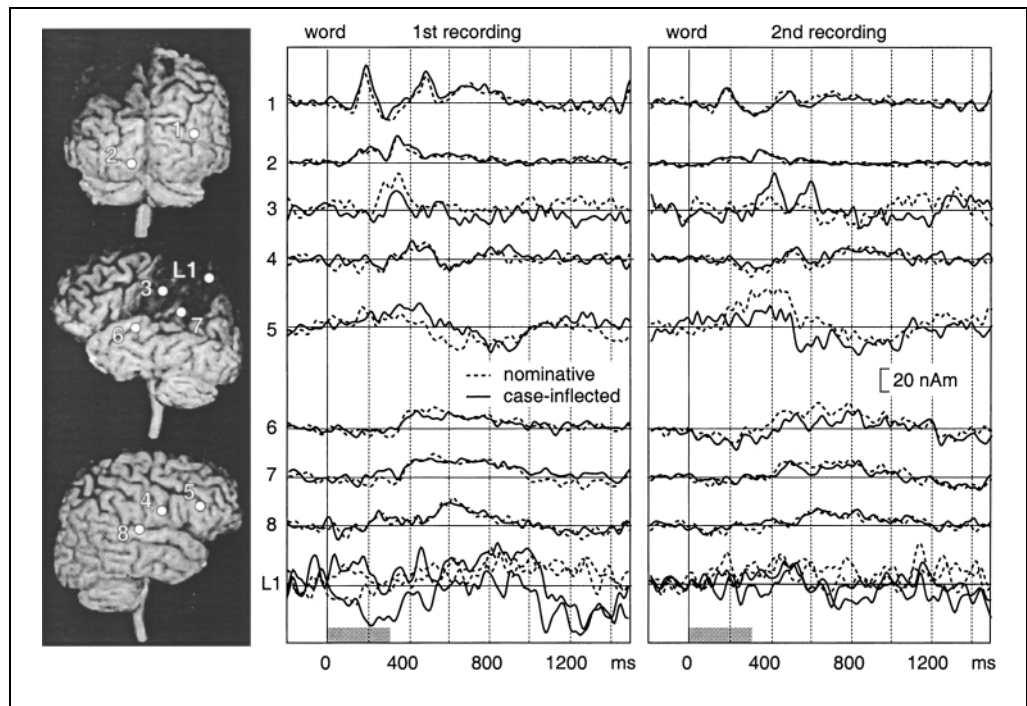
Evoked Responses from the Articulation Prompt

A sufficient account of production-related variance in brain activity in the two recordings was reached with seven generators, singling out the significant sources of 0–3 Hz background activity (Figure 7). As with the onset of word stimuli, the appearance of the visual articulation prompt elicited an early right-occipital onset response (with no offset response because the question mark stayed on for 2 sec).

Again, we could identify three superior-temporal generators (sources 5, 6, and 7) closely corresponding to the ones observed with both the sentence-reading task and the single-word-reading task analyzed from stimulus onset. Unlike in the latter analysis (reflecting input-related lexical processes), right-temporal activity (source 5) now preceded left-temporal activation. Here, generator 7 appears to correspond to the one that was most sensitive to semantic incongruency in the sentence-reading task.

In the first recording, sources 5 and 6 in the right and the left superior-temporal cortex, respectively, showed significantly stronger activation for nominative than case-inflected word forms. Moreover, we also observed that the slow-wave source L1 in the posterior wall of the lesioned area was reliably sensitive to morphological structure, responding vigorously to case-inflected words. This effect started about 200 msec after question mark onset. In the second

Figure 6. Spatial and temporal distribution of the eight source areas activated by seeing words in the first (left) and second (right) MEG recording. Responses to words in the nominative form are plotted with dashed lines and responses to inflected forms with solid lines. For the slow-wave source L1 (see Figure 3), responses averaged over every other stimulus (even vs. odd) are overlaid. The word appeared at time 0 and was displayed for 300 msec (gray bar).

recording, source 3 in the left-frontal cortex, present only when brain responses were averaged from the articulation prompt, showed sensitivity to morphological structure. The apparently stronger response of source L1 to case-inflected than to base form stimuli did not reach significance in the second recording.

To summarize, the activation pattern differed between the two recording sessions. In the first recording, the temporal sources 5 and 6 and the slow-wave source L1 made a clear distinction between nominative and case-inflected word forms. In the second recording, however, these areas remained relatively

Figure 7. Spatial and temporal distribution of the seven source areas associated with vocalization, prompted by the question mark, in the first (left) and second (right) MEG recording. Responses to words in the nominative form are plotted with dashed lines and responses to inflected forms with solid lines. For the slow-wave source L1 (see Figure 3), responses averaged over every other stimulus (even vs. odd) are overlayed. The question mark appeared at time 0 and was displayed for 2 sec (gray bar).
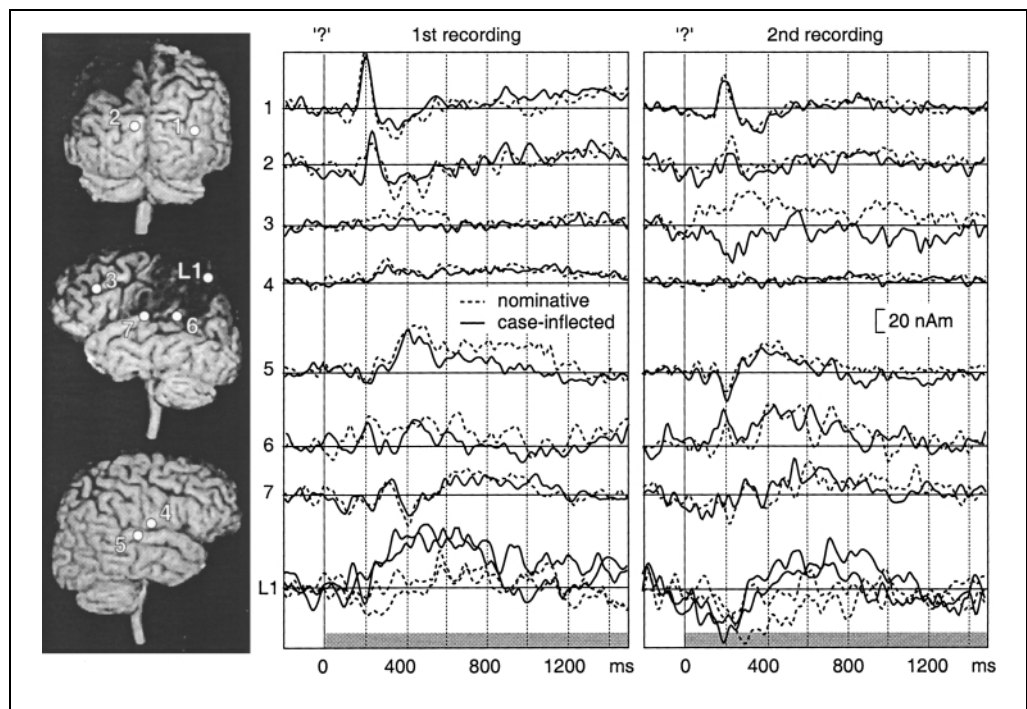
inactive while only source 3 in the left-frontal cortex showed prominent sensitivity to morphology.

DISCUSSION

In the present study, we tested the hypothesis that deep dyslexic reading (up to the lexical-semantic level) is subserved by the intact right hemisphere (e.g., Coltheart, 1980; Saffran et al., 1980; Weekes et al., 1997). By locating the sentence-final semantic-incongruency effect in the left superior-temporal gyrus, we are able to conclude that a central component in reading, lexical-semantic processing (meaning integration), is subserved predominantly by the left-temporal structures in our patient. In normal readers, the same task has produced similar results (Helenius et al., 1998). Left superior-temporal location of brain activity related to lexical-semantic processing is in line with HH's single-word-reading results. Also during single-word reading, we could identify spatio-temporally overlapping left superior-temporal gyrus activation both in an analysis emphasizing word input (i.e., averaged from stimulus onset) and in an analysis that presumably tapped word output (i.e., averaged from articulation prompt). Salmelin et al. (1996) observed similar, predominantly left-sided temporal activations in normals engaged in silent reading of single words.

Even though MEG and PET are fundamentally different measures of brain activity, it is of interest to note that Vandenberghe, Price, Wise, Josephs, and Frackowiak (1996) recently observed left superior-temporal gyrus activation (together with the left-anterior middle-temporal gyrus and the left inferior-frontal gyrus activation) with semantic tasks using word stimuli. In general, PET studies have suggested several neuroanatomic correlates of semantic processing, most notably inferior frontal, temporal and parietal cortices in the left hemisphere (for a recent review, see Price, 1998). Aphasia case studies have shown that damage to the left superior temporal gyrus (particularly its posterior part) and adjacent areas is associated with the syndrome of Wernicke's aphasia, where lexical-semantic difficulties are common. However, more inferior and posterior left temporal and temporo-parietal areas have also been implicated in lexical-semantic disorders following brain damage (e.g., Tranel, Damasio, & Damasio, 1997).

Clearly, our results are in conflict with the right-hemisphere-reading hypothesis. Instead, they are in line with Roeltgen (1987) who reported a patient whose deep dyslexic reading had been dependent on the remaining left-hemispheric structures. A solution to this controversy may be that the question should be stated differently: It could be that hemispheric control of written word recognition, in fact, varies in deep dyslexic patients (compare, e.g., the reading-related rCBF results of Weekes et al., 1997

and the present findings obtained with MEG), depending on factors that are as yet unidentified. One possibility is premorbid individual variability in hemispheric abilities. Second, the extent and the location of the left-hemisphere lesion may play a role as well. Third, it might be worth examining whether the key deep dyslexic features themselves may be related to hemispheric control of written word recognition. Specifically, the rate of semantic paralexias (which is quite low for our patient) is one such factor. Finally, one could speculate that even language structure may play a role here (in contrast to, e.g., English, Finnish has a practically fully regular orthography).

It is worth pointing out that our results do not indicate that the right hemisphere plays no role in HH's reading. On the contrary, several right-hemisphere sources were identified during reading performance. It is only that none of these sources showed sensitivity to sentence-final semantic incongruency, which was at the focus of our study. The longer-latency right-hemispheric sources in single-word reading (averaged from stimulus onset; Figure 6) and in sentence reading (Figure 5) were, in fact, quite similar in location to those found in neurologically intact subjects (Helenius et al., 1998; Salmelin et al., 1996). This strengthens the conclusion that HH's reading-related cognitive mechanisms, while being seriously disturbed after his lesion, were mainly subserved by the same neural systems as in normals.

Another reading-related issue we examined were the brain activation correlates of HH's morphological processing difficulties. Empirical evidence obtained for Finnish suggests that case-inflected Finnish nouns are recognized on the basis of their morphemes, yielding a processing cost as compared to monomorphemic words (for a review, see Niemi et al., 1994). In a recent visual half-field study performed in Finnish (Laine & Koivisto, 1998), it was concluded that both hemispheres are capable of morpheme-based access, but that this mechanism is more accurate in the left hemisphere. A hemispheric difference in morphological processing is also indicated by aphasia case studies, where morphological disorders are almost invariably elicited by the left-sided brain damage (e.g., Vanier & Caplan, 1990; for HH, see Laine et al., 1995). Accordingly, it was of interest to search for brain activation correlates specific to HH's reading of inflected words. Following the articulation prompt, we found a left-frontal source close to Broca's area, which showed sensitivity to morphological structure. Even though the effect was clearcut in one recording only, it is in line with recent arguments about the importance of the left anterior language areas in the processing of rule-based morphology (Ullman et al., 1997). Note that the Finnish inflectional system, although complex, can be described by rules and it does not include such irregularities as, e.g., English. There is also evidence

from a recent PET (oxygen-15) study conducted with right-handed normals, where memorization of inflected versus monomorphemic Finnish nouns elicited stronger activation, particularly in Broca's area (Laine, Rinne, Krause, Teräs, & Sipilä, 1999).

To our surprise, one of the slow-wave sources not modulated by morphology immediately after stimulus presentation, nevertheless, showed a response specifically to inflected forms when the data were analysed from the articulation prompt. Given HH's strong lesion-related slow-wave activity, it was intriguing to observe that this source was consistent and well synchronized to specific stimulus type. One could speculate that this synchronous activity might represent a nonspecific response to an increased processing load induced by morphological decomposition. Be that as it may, this phenomenon certainly raises interesting questions for further analyses of evoked activation patterns in brain-damaged individuals.

As HH shows dramatic difficulties in processing inflected word forms, we certainly expected to see stronger sensitivity to morphology in his brain activation patterns. One reason for the modest findings is suggested by HH's oral responses during MEG recordings: As noted earlier, he produced most of the inflected items in nominative (uninflected) form, which has not been the case in clinical test situations. It may, thus, be that the speeded nature of our single-word-reading task elicited a strategy, where HH effectively processed word stems only, avoiding a major part of the processing costs related to inflected words. Indeed, a post hoc analysis of success in stem reading (irrespective of success with the case ending) indicated rather similar performance for monomorphemic and inflected nouns in both MEG recordings (first recording: 67/85 monomorphemic stems and 56/85 inflected stems correct, Yates corrected $\chi^2 = 2.94$, $df = 1$, $p = .09$; second recording: 63/85 monomorphemic stems and 51/85 inflected stems correct, Yates corrected $\chi^2 = 3.22$, $df = 1$, $p = .07$).

Our repeated measurements enabled us to study the stability of both spontaneous and evoked brain activity in a chronic brain-damaged patient. The overall conclusion is that in spite of HH's behavioural stability, both spontaneous and evoked brain activation patterns showed considerable variability in the lesioned hemisphere. The methodological lesson to be learned is that it may not be safe to base interpretations of functional imaging patterns of a brain-damaged individual on a single measurement only, even if the patient has apparently reached a stable state and is free from medication. Only by taking into account both intra- and inter-measurement consistency, reliable activation patterns can be identified.

METHODS

Two language and two nonlanguage tasks were administered to HH during MEG measurement. Moreover, HH's magnetic brain activity associated with three of the four tasks (oral reading of single words, listening to simple tones, and finger movement) was recorded twice, 1 year apart.

The Reading Tasks

We employed two reading tasks: silent reading of sentences and oral reading of single words. The first task manipulated the probability and semantic appropriateness of sentence-final words. As noted earlier, sentence-final semantic incongruity has been extensively employed in neurophysiological studies on semantic processing, and semantically inappropriate versus appropriate target words have recently been shown to elicit different brain responses predominantly in the left superior temporal cortex in normals (Helenius et al., 1998). The sentence-reading task was administered during the second MEG recording only. The second task was an oral-reading task that included monomorphemic and case-inflected nouns. A comparison of these two types of words might reveal brain activation patterns related to morphological processing, which is significantly impaired in HH (Laine et al., 1995; Laine & Niemi 1997).

Sentence-Reading Task

This task included 4×100 Finnish sentences, presented visually one word at a time. HH was instructed to simply attentively follow the unfolding sentences and to read the words silently. No overt response was required. Each word was presented for 330 msec with a 750-msec blank inter-stimulus interval. The appropriateness of the sentence-final word was systematically manipulated. It was either appropriate and highly probable (e.g., of the type "Fred put the worm on a hook"), appropriate but of low probability (e.g., "When the power went out, the house became quiet" instead of "dark"), semantically anomalous (e.g., "The pizza was too hot to sing"), or semantically anomalous but sharing the initial phonemes with the high-probability alternative (e.g., "The gambler had a streak of bad luggage"). The presentation order of the sentences was randomized. The four sets of sentences were comparable by average number of words, average final word length in letters, distribution of different word classes, and by the cloze probability of the most often suggested ending (see Helenius et al., 1998, for details).

Single-Word–Reading Task

We devised two lists of Finnish nouns, both containing 85 items. The first list included monomorphemic (nominative singular) forms (e.g., AMMATTI "profession",

KATTILA "pot"), whereas the other list had bimorphemic, case-inflected noun forms (e.g., SOHVA + STA "sofa + from", LEIRI + SSÄ "camp + in"). The two lists were matched by average cumulative stem frequency (mean 16.4 for List 1 and 16.5 for List 2; source: Saukkonen, Haipus, Niemikorpi, & Sulkala, 1979), length in letters (mean 6.3 for List 1 and 6.4 for List 2), and average bigram frequency (mean 1136 for List 1 and 1147 for List 2; source: Laine & Virtanen, 1996). Stimuli were randomized and presented visually in lower case. Each target word was exposed for 300 msec; and 1,000 msec later, a question mark appeared, prompting HH to say aloud the written word form. The question mark remained on the screen for 2,000 msec. The screen then went blank for 3,000 msec, after which the next target word was presented. Due to the low intensity of HH's voice, a microphone setup (enabling definition of the onset of articulation) could not be employed. Instead, his responses were registered by a researcher present in the magnetically shielded room.

Basic Auditory and Motor Functions

In order to locate the hand sensorimotor cortex, brain responses to self-paced left-index-finger lifts were recorded; HH cannot move his right-hand fingers. The primary auditory cortex was identified by recording responses to 50-msec 1-kHz tones (approximately 70 dB HL), which were delivered once per sec alternately to the left and the right ear via plastic tubes. These activation measures served two purposes. First, they provided functional neuroanatomical landmarks that aid in the identification of cortical areas involved in the cognitively more complex reading tasks. Second, their within-test and test–retest consistency gave a baseline measure for the stability of HH's brain responses, particularly in the damaged left hemisphere.

Spontaneous Brain Activity

We also recorded magnetic background activity of HH's brain while he was resting, relaxed with eyes closed (2 min) and eyes open (2 min). The observed frequencies and their spatial distribution, as well as the reactivity to opening versus closing the eyes, are good general indicators of brain function or dysfunction.

MEG Recording

Concerted activation of thousands of cortical neurons produces an electric current that can be detected outside of the skull by means of the magnetic field associated with it. We recorded the cerebral magnetic signals with a Neuromag-122™ whole-head magnetometer (Neuromag, Helsinki, Finland). This device has 122 planar gradiometers in 61 locations, arranged in a hel-

met-shaped array (Ahonen et al., 1993). It detects maximum signal immediately above an active cortical area. The MEG signals were recorded using a 100-Hz low-pass filter and digitized at .4 kHz, thus providing a time resolution of 2.5 msec. Horizontal and vertical electrooculograms were recorded simultaneously for on-line rejection of epochs contaminated with eye movements.

The experiments were performed in a magnetically shielded room. HH was seated on a chair, resting his head against the MEG helmet. Signals were averaged on-line, time-locked to stimulus (tone to left or right ear, monomorphemic or case-inflected word, four different types of sentence-final words) or finger movement onset, until 80–100 artefact-free epochs had been collected. The MEG signals were recorded continuously during all experimental conditions, and stored on a magneto-optical disk for further off-line analysis. The tone and finger movement paradigms lasted for about 5 min each. Responses to single words were collected in two 9-min sessions, interleaved by a 2-min pause. Sentences were presented in four 10-min sessions with a longer 10-min pause between the second and third sessions.

Data Analysis

Spectral Analysis

The spectral content of HH's brain activity was estimated by calculating fast Fourier transformations (FFTs). A 3.4-sec time window was shifted forward in 1.7-sec steps, and the FFTs were averaged over the whole recording time, separately for all experimental conditions.

Response Categories

Based on the behavioural data in the single-word–reading task (Table 1), the signals were averaged off-line into two categories: correct responses to monomorphemic items and incorrect responses to case-inflected items.

Source Analysis

In analysis of both time-locked averaged responses and background activity, an active neuronal population was modelled as an equivalent current dipole (ECD), which is both physiologically and physically reasonable approximation of current flowing in a limited cortical structure, being recorded from a distance of several centimeters (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). The three-dimensional location, orientation, and amplitude of the ECD, representing the center of the active cortical area and the mean direction and total strength of current flow therein, can be determined from the magnetic field distribution. Each active area was identified at the time-

point, where the dipolar field pattern was clearest and there was least interference from other sources, using a subset of sensors. In the analysis of time-locked responses, the time behaviour of activation in the source areas was determined by introducing all the identified ECDs simultaneously to a multidipole model (Hämäläinen et al., 1993). The locations and orientations of current flow were kept fixed while the source strength was allowed to vary to best explain the MEG signals recorded by all the 122 sensors. The identified sources accounted for 80–90% of the total variance.

Spontaneous Activity

For both recordings, continuous nonaveraged data in the word-reading condition were filtered through .3–3 Hz and 3-6 Hz, coinciding with distinct maxima in the frequency spectra. Thereafter, dipolar patterns were searched automatically every 10 msec in 2 min of data, using four subsets of sensors covering the left temporal and rolandic areas, the right temporal and rolandic areas, the posterior parietal and the occipital cortex, and the vertex (cf. Mäkelä et al., 1998; Salmelin et al., 1994). Whereas in normal subjects, sources of frequencies below 6 Hz can be rarely localized in HH, such sources formed prominent clusters along the posterior wall of the lesioned area. The separate clusters were adequately represented by 4 ECDs, three in the left hemisphere and one in the right hemisphere, close to the vertex.

Evoked Responses

The data were first modelled separately for each recording, and also separately for the responses to monomorphemic and inflected nouns. The accuracy for localization, estimated from the noise level in the prestimulus baseline, was within 5 mm (95% confidence limit) when a timepoint could be found, where essentially only one area showed strong activity. Otherwise, the accuracy was 5–10 mm. Both short- (<400 msec) and long-latency (>400 msec) sources could be localized with the same accuracy. Localization of simultaneously active source areas is usually successful if the source locations differ by at least 2 cm (identical orientations), if the orientations of current flow differ by at least 40° (identical location), or with smaller differences if both locations and orientations of the sources differ. Within each measurement, the magnetic-field patterns evoked by monomorphemic and inflected nouns were highly similar and the source areas differed from each other less than the accuracy of localization. The same was true across the two recordings, 1 year apart (differences of 5–10 mm in localization and 10–20° in orientation).

To compare the responses across recordings and experimental conditions (word type), a single set of sources was collected for each task, with each ECD taken from that data set where the localization had been most reliable. A small number of sources was identified in one recording only. These sources were included in the final set of ECDs after their effect had been checked in the other data sets. Fortunately, the inclusion of the additional inactive sources did not affect the time behaviour of the other ECDs, nor did the added sources show spurious activity. In single-word reading, separate sets of ECDs had to be formed for responses averaged with respect to word onset and question-mark onset.

Stability of Responses

A noise estimate of each MEG response and source waveform is obtained as the standard deviation (SD) of amplitude during the prestimulus baseline interval. A response was taken to differ significantly from zero, at $p < .05$, if the amplitude exceeded 1.96 times the baseline SD, at $p < .01$ if the amplitude exceeded 2.58 times the baseline SD, and at $p < .001$ if the amplitude exceeded 3.29 times the baseline SD. Differences between two waveforms were considered significant when they differed from each other at the selected confidence level, based on the root-mean-square of the SDs of the waveforms. To remain on the conservative side in evaluating this highly variable data set, we required a confidence level of $p < .001$ for all comparisons.

To estimate stability within each recording, we reaveraged the responses to every other stimulus (or movement) separately. The even and odd responses were calculated for all experimental conditions. We first tested (i) if the responses differed significantly from signal variation in the baseline interval (−200–0 msec for words and sentences, −100–0 msec for tones, and −800...−400 msec for finger movements), for a period of at least 100 msec. We then proceeded to evaluate (ii) the within-measurement stability, i.e., we tested whether the even and odd responses were similar enough. The response was judged unreliable if the even and odd waveforms differed from each other for a period longer than 50 msec during the nonzero response (as determined in (i)) or—if the nonzero response lasted for more than 250 msec—for more than 20% of this interval, or if all difference intervals summed up to more than 10% of the total time span of the response.

For single words, we then compared the responses to nominative and case-inflected word forms against the baselevel variation. For sentences, the difference between responses to semantically inappropriate final words versus the expected final words served as an

indicator of lexical-semantic processing. In both cases, the curves were judged to differ if they separated for a period of at least 100 msec during the nonzero peak signal (as determined in (i)), or for 50% of the nonzero response if it was shorter than 200 msec. We performed this test if at least one of the waveforms to be compared was nonzero and if at least one of the waveforms was definitely stable in the even versus odd evaluation.

Alignment of MEG and MRI Images

The location of the sources is defined in head co-ordinates, set by clearly identifiable fiducial points in front of the ear canals (x-axis, from left to right) and by the nasion (positive y-axis); the z-axis is oriented towards the vertex. The position of the head within the magnetometer was found by attaching three small coils on the subject's head, measuring their location in the head coordinate system with the help of a 3-D digitizer, and energizing them briefly to obtain their locations in the magnetometer coordinate system. Finally, the MEG and MRI coordinate frames were aligned by marking the fiducial points in the MR images as well.

Acknowledgments

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