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Adult Brain Plasticity Elicited by Anomia Treatment

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Abstract

■ We describe a study where a specific treatment method for word-finding difficulty (so-called contextual priming technique, which combines massive repetition priming with semantic priming) was applied with three chronic left hemisphere-damaged aphasics. Both before and after treatment, which focused on naming of a series of pictures, naming-related brain activity was measured by magnetoencephalography (MEG). Due to its excellent temporal resolution and good spatial resolution, we were able to track treatment-induced changes in cortical activity. All three subjects showed improved naming of the trained items. In all subjects, a single source area, located in the left inferior parietal lobe, close to the lesioned area, displayed statistically significant training-induced changes. This effect was of long latency as it started 300–600 msec after picture presentation. The change in activation was specific to training, as it could not be accounted for by variation of cortical dynamics associated with increased proportion of correct answers. Our interpretation is that the training effect reflects more effective phonological encoding and storage of the trained items through the engagement of a left hemispheric word-learning system. This is in line with recent functional imaging studies, which have linked left inferior parietal lobe activity to the phonological storage component of the verbal working memory, as well as with theoretical arguments stating that the primary role of the phonological loop is to acquire new words. Finally, the MEG results showed no evidence of increased right hemisphere participation following training, supporting the view that restoration of language-related networks in the damaged left hemisphere is crucial for anomia recovery. ■

INTRODUCTION

Both behavioral and brain imaging experiments have illustrated the plastic potential of the adult brain in healthy subjects (van Turennout, Ellmore, & Martin, 2000; Kopelman, Stevens, Foli, & Grasby, 1998; Poldrack, Desmond, Glover, & Garrieli, 1998; Raichle et al., 1994) as well as in brain-damaged individuals (Musso et al., 1999; Small, Flores, & Noll, 1998; Belin et al., 1996). However, the exact cortical mechanisms underlying recovery and rehabilitation of higher order neurocognitive disorders, such as aphasia, still remain poorly understood. In particular, the relationship between behavioral changes and co-occurring cortical changes is largely unknown. A better understanding of these mechanisms would be essential for the development of theoretically motivated treatment methods and their adaptation to specific cognitive disorders.

So far, functional imaging of recovery of language functions in aphasia has largely concentrated on spontaneous recovery (Warburton, Price, Swinburn, & Wise, 1999; Karbe et al., 1998; Buckner, Corbetta, Schatz, Raichle, & Petersen, 1996; Ohyama et al., 1996; Engelein et al., 1995; Weiller et al., 1995; Heiss, Kessler, Karbe, Fink, & Pawlik, 1993; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Demeurisse & Capon, 1987). The mechanisms of spontaneous recovery are likely to be different from those of training-induced recovery (cf. Johansson, 2000; Thompson, 2000). As regards cortical correlates of aphasia treatment, only a few studies have been published thus far (Musso et al., 1999; Small et al., 1998; Belin et al., 1996).

Furthermore, most of the functional imaging studies on language recovery have investigated group effects between aphasics and normal controls, rather than changes within subjects. The group study approach could give ambiguous results because brain responses in language tasks may differ markedly between individuals (Levelt, Praamstra, Meyer, Helenius, & Salmelin, 1998; Salmelin, Hari, Lounasmaa, & Sams, 1994). An aphasic individual may also show considerable instability in his/her task-related brain responses (Laine, Salmelin, Helenius, & Marttila, 2000). Moreover, the aphasic groups have mainly been selected by lesion localization, rather than according to their neuropsychological pattern. Furthermore, in most studies, the focus has been largely on overall language ability, rather than on changes in a single specific skill. Such an approach does not allow drawing clear conclusions as to which components of language are responsible for the treatment effects.

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Table 1. Subjects' Performance Level in Background Behavioral Tests (% Correct) in Pretraining (Pre) and in Posttraining (Post) Sessions and the Total Number of Items in the Tests (*n*)

	J. P.		*J. K.*		*H. H.*		
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*n*
General language performance and severity of anomia							
Tests tapping language comprehension (BDAE subtests)	94	92	82	90	90	90	119
Tests tapping reading (BDAE subtests)							
1. Reading comprehension	83	83	61	78	67	69	36
2. Reading aloud	93	58	58	60	53	55	40
Tests tapping speech repetition (BDAE subtests)	42	42	31	38	42	46	26
Tests tapping naming (BDAE, BNT, 106-item test)							
3. BDAE—visual confrontation naming	76	55	89	84	39	53	114
4. BDAE—responsive naming	67	37	80	73	53	40	30
5. BNT	28	28	43	55	32	33	60
6. 106-item naming test (naming only)	30	–	43	–	58[a]	–	106
Origin of anomia							
7. Knowledge of animate objects[b]	84	89	93	93	–	80	56
8. Knowledge of inanimate objects[b]	88	89	96	96	–	88	56
9. Identification of a superordinate[c]	93	–	43	–	88[a]	–	106
10. Identification of a semantic property[c]	79	–	93	–	96[a]	–	106
11. Length of the target word[c]	61	–	77	–	64[a]	–	106
12. Recognition of first syllable[c]	77	–	94	–	84[a]	–	106

BDAE = Finnish version of Boston Diagnostic Aphasia Examination (Laine, Niemi, et al., 1997); BNT = Finnish version of Boston Naming Test (Laine, Koivuselkä-Sallinen, et al., 1997); 106-item naming test = test encompassing 106 pictures of concrete objects. Tasks: naming objects, choosing corresponding superordinate out of eight alternatives, choosing best-fitting meaning-related statement out of four alternatives, judging how many letters the target word includes, choosing the first syllable of the target word out of five alternatives (Laine & Martin, 1996; Laine et al., 1992).

[a]Only 50 items out of 106 were studied.

[b]Mean value is based on odd-out, triad, and word–picture matching tests (Laine et al., 1992).

[c]Based on 106-item naming test (Laine & Martin, 1996; Laine et al., 1992).

The focus of the present study is on word retrieval in aphasia as measured by picture naming. Cognitive models of picture naming assume at least the following major subprocesses: visual recognition of the object, semantic processing (activation of object properties and attributes), phonological processing (retrieval of the word form and assembly of its constituent phonemes), and articulation (e.g., Goodglass, 1998; Levelt et al., 1998; Laine & Martin, 1996; Dell & O'Seaghdha, 1992). Aphasic breakdown may happen in any of these subprocesses (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Laine & Martin, 1996; Laine, Kujala, Niemi, & Uusipaikka, 1992; Kay & Ellis, 1987) or in information transfer between the subprocesses (Levelt et al., 1998; Dell et al., 1997; Laine & Martin, 1996; Schwartz, Saffran, Bloch, & Dell, 1994). In addition, aphasic breakdown could be caused by a general degradation of the lexical retrieval system limiting both speed and extent of lexical access (Gagnon, Schwartz, Martin, Dell, & Saffran, 1997; Nickels, 1997; Martin, Dell, Saffran, & Schwartz, 1994; Martin, Roach, Brecher, & Lowery, 1998).

In the present study, we trained picture naming in three chronic aphasic patients suffering from anomia. All patients had predominantly postsemantic anomia. For training, we used the contextual priming technique (CPT) (Martin & Laine, 2000; Laine & Martin, 1996), which is both theoretically motivated and structurally simple. We assessed the effect of CPT both behaviorally and using whole-head magnetoencephalography (MEG), which provides a good spatial and excellent temporal resolution of naming-related cortical dynamics. Our specific questions were as follows: (a) Is there a systematic effect of training on cortical activity? (b) If yes, is there a hemispheric preference for this effect? In addition, we tested (c) if and how brain activity differs for different forthcoming answer types (correct, incorrect,

and omitted responses). This information is needed to examine whether or not training effects, leading to higher rates of correct responses, fully overlap with cortical activation patterns differentiating correct from incorrect responses before training. If not, one has succeeded in identifying neural changes that are specific to training.

RESULTS

General Language Abilities

The results of the background behavioral language tests are shown in Table 1. Performance patterns were somewhat variable and two of the patients (J. P. and J. K.) had mixed (semantic and phonological) anomia. Nevertheless, one can conclude that in all patients, postsemantic deficits, that is, deficits located primarily within the phonological output system or in information transfer from the semantic to the phonological level, were the major factors underlying their anomia.

J. P.'s naming disturbance was of moderate severity (Table 1; tests 3–6) and with a primarily phonological component indicated by difficulties in determining word length and first syllable of items (Table 1; tests 11–12). He had also some semantic impairment, as indicated by difficulties in detecting semantic properties related to objects (Table 1; test 10). Naming disturbance was not limited to a specific semantic category, and there was no dissociation between naming animate versus inanimate objects (Table 1; tests 7–8). In naming tasks, J. P. produced several semantic naming errors of which he was mostly unaware. He also produced phonological errors, which he was unable to correct.

J. K. suffered from moderate anomia (Table 1; tests 3–6). Its origin seemed to be mostly phonological (Table 1; test 11), but a semantic component was evident as well (Table 1; test 9). J. K.'s naming disturbance was not limited to a specific semantic category (Table 1; tests 7–8). In naming tasks, he produced some semantic and phonological errors. He seemed to be partially unaware of his semantic errors.

H. H. had moderate anomia (Table 1; tests 3–6). Its origin seemed to be phonological as performance on the semantic tasks was relatively well preserved (Table 1; tests 9–12). H. H.'s naming difficulty was not limited to a specific semantic category (Table 1; tests 7–8). He produced some semantic naming errors, but on most occasions was aware of his errors in advance. He did not produce phonological errors.

The patients' performances were relatively stable in all language tasks. On the basis of paired *t* tests, no statistically significant differences were found between

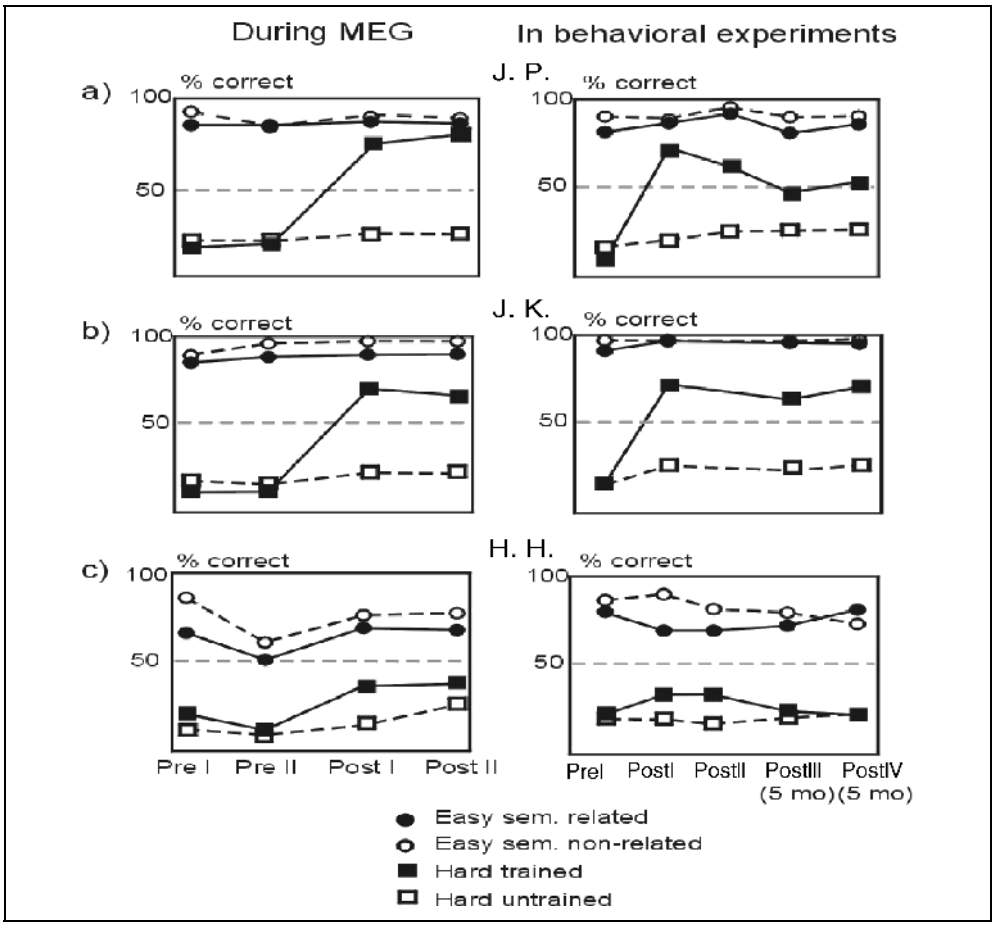

Figure 1. Performance in experimental items for (a) J. P., (b) J. K., and (c) H. H. during MEG measurements (left) and in the purely behavioral test sessions (right). The performance level is given as the proportion of correct answers of all studied items. In J. K., the second posttraining behavioral test was not administered, because of problems with the subject's time schedule.

the pre- versus posttraining screening sessions in naming or in speech comprehension. The subtle changes seen in a few subtests are most probably due to the commonly observed test–retest variability in aphasics when they face tasks difficult to them.

Naming of the Target Pictures

Picture naming for individually selected stimulus sets was evaluated before and after training, both during MEG and during purely behavioral sessions. The proportions of correct answers in pre- and posttraining measurements both during MEG and in the purely behavioral test sessions are illustrated in Figure 1. Each patient showed a significant increase in the amount of correct answers for trained items when pre- versus posttraining performance in the MEG measurements was compared by McNemar tests ($p < .001$ in J. P. and J. K.; $p < .01$ in H. H.; Siegel, 1956). J. P. and J. K. showed a statistically significant increase in the number of correct answers for trained items also in the purely behavioral test sessions ($p < .001$). The effect persisted up to the last behavioral measurement 5 months after the end of the training period ($p < .001$). None of the patients showed statistically significant changes in the amounts of correct answers in their control items, either in the MEG measurements or in the purely behavioral test sessions. The distribution of different answer types during the pretraining MEG sessions is shown in Table 2. The naming response patterns varied slightly across patients, with J. P. coming up with the highest proportion of semantic errors and H. H. having the highest percentage of omissions. The error analysis did not show any significant qualitative changes between pre- and posttraining measurements.

Table 2. Distribution of Different Types of Naming Responses (Percentage of All Answers) in the Three Aphasic Patients during the Two Pretraining MEG Measurements

Subject	*Correct*	*Semantic Errors*	*Omissions*	*Other Errors*
J. P.	53	18	18	10
J. K.	49	13	37	2
H. H.	37	10	50	2

Spontaneous Brain Activity

All patients showed strong pathological low-frequency activity, with the spectral maximum at about 5 Hz, in addition to the usual peaks around 10 and 20 Hz (Niedermeyer, 1990). The low-frequency activity was most prominent during the naming condition. The pathological rhythms were generated in the cortex surrounding the lesion. Particularly, H. H. (the patient studied in Laine et al., 2000) had abnormally strong slow-wave activity (<5 Hz) anterolaterally to the lesion, that is, in the left temporal and frontal lobes. Only for H. H. was it necessary to remove the signal produced by these slow-wave sources when analyzing the stimulus-locked evoked responses in the picture-naming condition.

Brain Activity during the Naming Task

The active cortical areas in each patient and their time behavior are shown in Figure 2 for the easy-to-name items and in Figure 3 for the hard-to-name items. The naming-related activation proceeded in a feed-forward pattern from one brain area to another, with no marked activation–deactivation–reactivation patterns. The occipital areas were active first, followed by signals in the posterior parts of the temporal lobes. The activation then proceeded to the inferior parietal and supramarginal areas, followed by post- and precentral area activation. Broca's area was not activated in any of our patients. In general, the anterior parts of the brain remained remarkably silent. Right hemisphere sources elicited rather strong responses as compared with left hemisphere sources in all patients. The chain of activation was similar for easy-to-name and hard-to-name items. The responses to both easy-to-name and hard-to-name items differed slightly between the two pretraining and posttraining measurements. The somewhat larger difference between the two posttraining than the pretraining measurements is probably due to a continued training effect. In easy-to-name items, there were no marked changes from pre- to posttraining measurements. However, in hard-to-name trained items, some differences were evident both in source strengths and latencies. Within measurements, the first and second presentation of the same stimuli did not differ significantly from each other in any of the categories.

In the signals averaged with respect to the vocalization prompt (not shown), activity was found mainly bilaterally in the primary motor cortex, the right hemisphere homologue of Broca's area, temporal cortex, and occipital cortex. Thus, some of the processes that were active after picture onset were apparently reactivated once the patients pronounced the name aloud. All three patients produced the answer within 500 msec after the onset of the vocalization prompt, that is, about 3.6 sec after picture presentation.

Training-Related Effects

The behavioral results showed facilitation of naming in the trained items only. Therefore, for a change in brain activity to be training-specific, the response should indicate a significant change with trained but not with untrained hard-to-name items. In each patient, only a single source area showed such pre- versus posttraining

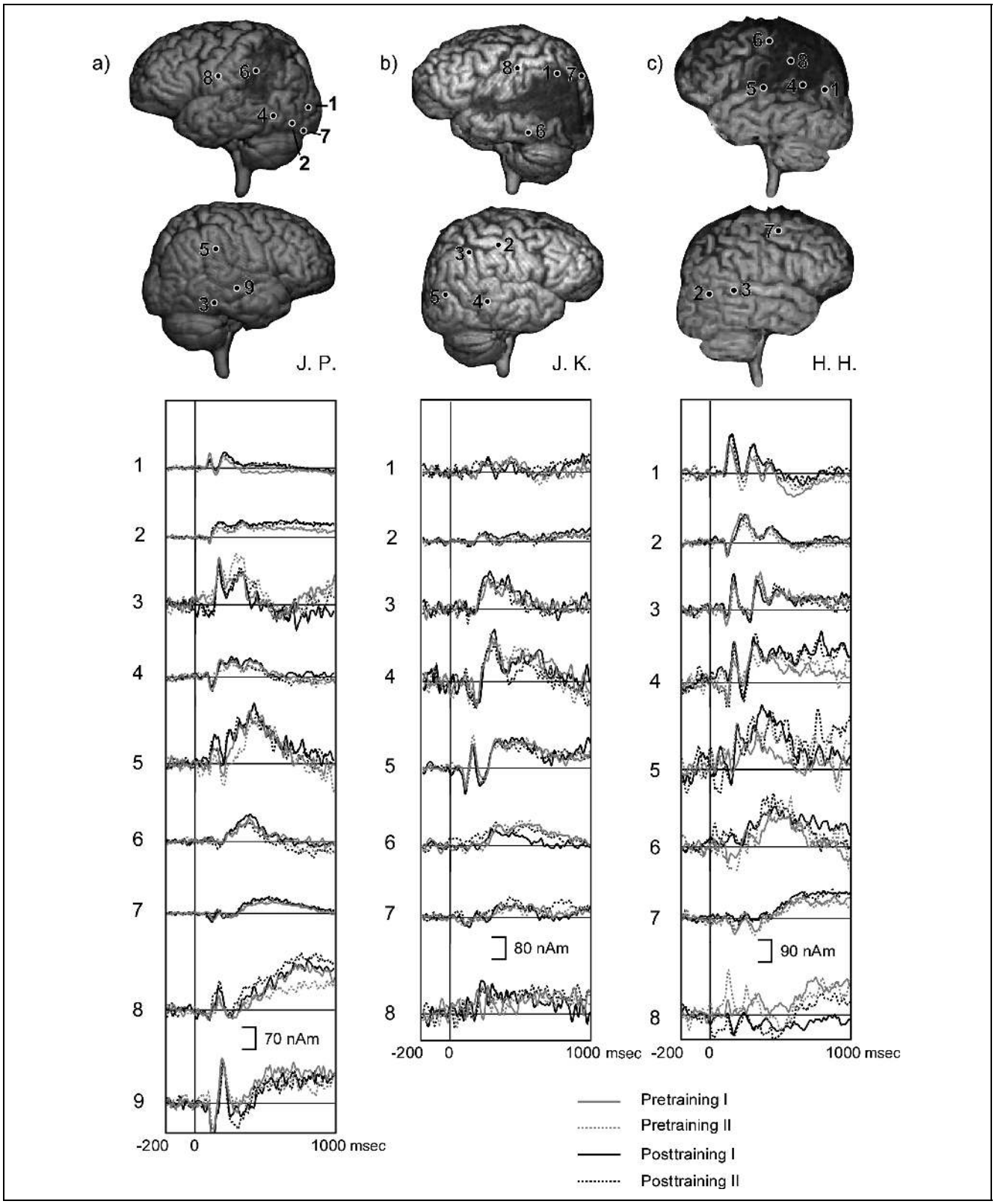

Figure 2. The activated source areas and time behavior of activation for easy-to-name semantically related items during the two pretraining (gray curves) and the two posttraining (black curves) MEG measurements in (a) J. P., (b) J. K., and (c) H. H. The location of each source is shown on individual surface MRIs. In the source models, the vertical axis displays the strength of the response in nanoampere meters (nAm) and horizontal axis the time in milliseconds (msec). The source model explained at least 80% of the measured magnetic field in the time window from 0 to 1000 msec with respect to stimulus onset.

changes that also reached our conservative criterion of statistical significance. As illustrated in Figure 4, this source area was located in the left inferior parietal lobe, in a region bordering the lesion. Patients J. P. and J. K. showed significant changes in trained items only. Patient H. H. displayed a significant training effect not only for the trained items but also for the semantically related easy items. In all patients, the training effect started to appear at around 400–700 msec after stimulus onset, and in J. P. and J. K. it lasted for at least 400 msec.

In the pretraining measurements, J. P. and J. K. showed a clear activation of the left inferior parietal cortex after 400 msec for the easy-to-name items, but a much weaker signal for the hard-to-name items. After training, the responses to trained items increased to the level of those for the easy items (J. P.), or even exceeded

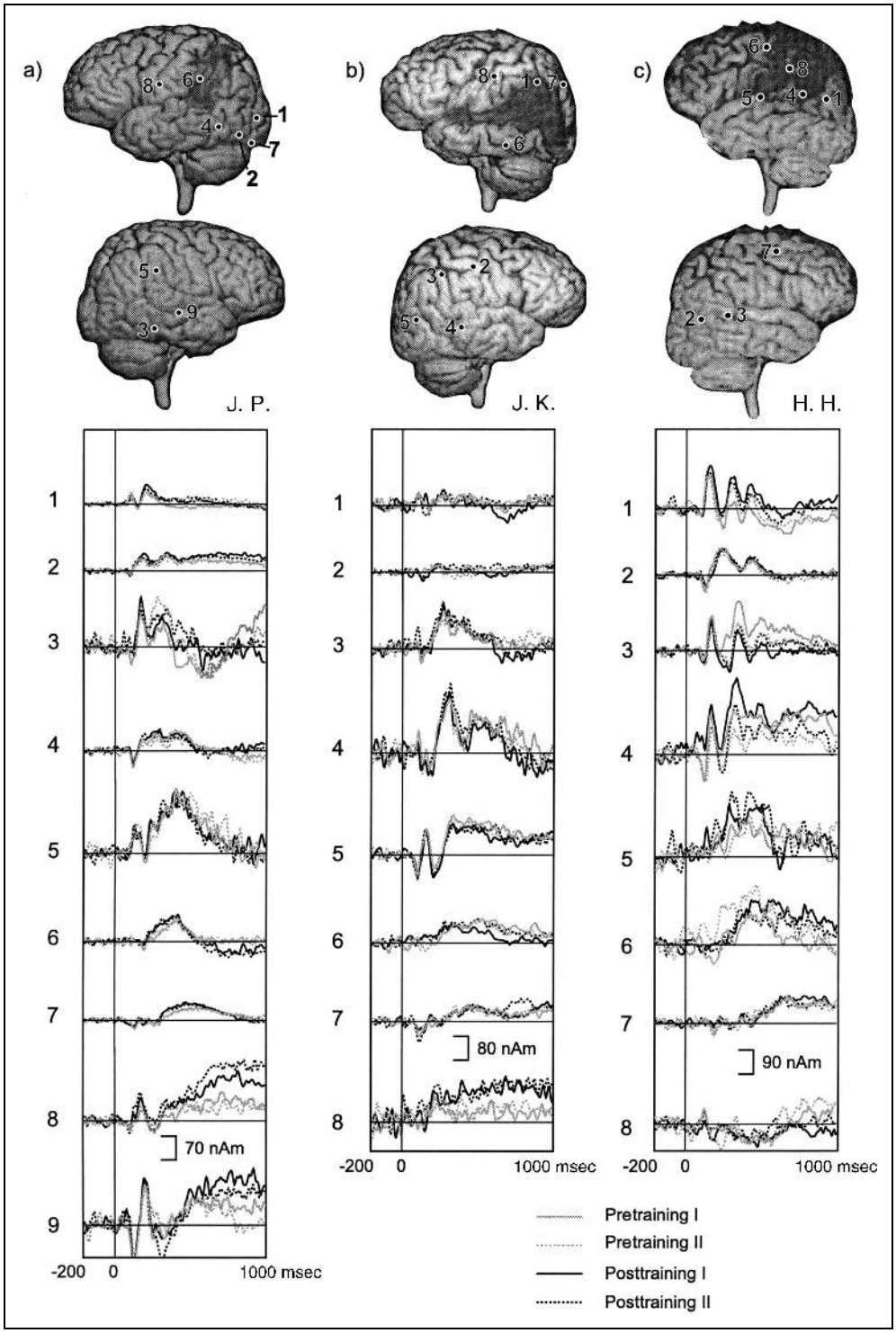

Figure 3. Time behavior of activation for trained items for all four measurements in (a) J. P., (b) J. K., and (c) H. H. See legend of Figure 2 for other details.

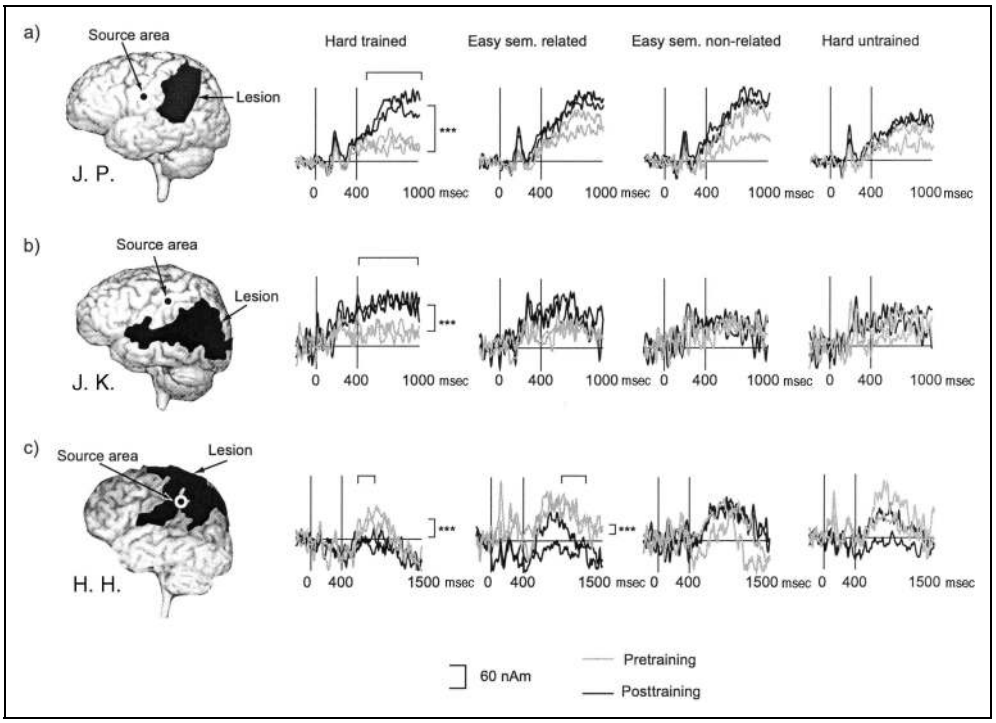

Figure 4. Left: The cortical area showing the training-induced changes of activation in (a) J. P., (b) J. K., and (c) H. H. The source area is marked with a single black dot on individual MR surface images. The lesioned area is painted in black. Right: The source waveforms for the different stimulus categories. The pretraining measurements are illustrated with gray lines and the posttraining measurements with black lines. The bars on top of the waveforms denote the duration of statistically significant differences in activation strength (***$p < .001$) between pre- and posttraining sessions. Note that the presented time window is from −200 to 1000 msec with respect to picture onset ($t = 0$) in J. P. and J. K., but from −200 to 1500 msec in H. H.

them (J. K.). The responses to hard untrained items, on the other hand, remained at their original low level. In H. H., however, the left inferior parietal response for the easy-to-name and for the hard-to-name items had originally been rather similar. Unlike in J. P. and J. K., training in H. H. resulted in a suppression of this response, instead of an enhancement, thus making the responses to semantically nonrelated easy-to-name control items and hard-to-name trained items highly dissimilar.

In motor responses, averaged with respect to the vocalization prompt, J. P. showed inconsistent changes between pre- and posttraining measurements in the left inferior parietal cortex and in the right hemisphere homologue of Broca's area at around 400 msec after prompt onset (not shown).

Answer Type-Related Effects

To verify that the training effects did not merely reflect the increased proportion of correct answers, we identified the cortical areas and time windows where source waveforms differentiated among correct answers, semantic errors, and omitted responses in the pretraining measurement. We focused on clear dissociations in source waveforms where one answer type differed significantly from the other two, or all three categories differed significantly from each other. These source areas were located in the posterior parts of the brain, including the left inferior parietal, posterior temporal, right middle temporal, and left occipital cortices, and in the right precentral area. The differences in amplitudes and latencies in these source areas started 150–800 msec after stimulus onset. The spatial distribution and time windows showed large individual variation. In J. K. and H. H., no effect of answer type was evident in the training-sensitive source area. In J. P., activation of altogether four cortical areas, including the training-sensitive source area, covaried with answer type.

In responses averaged with respect to the vocalization prompt, activations associated with forthcoming semantic errors were consistently weaker than those accompanying correct answers, apparently because the erroneous answers were produced at highly variable latencies. The motor areas were active even when the answer was going to be omitted.

DISCUSSION

We investigated training-related changes in behavior and in brain activation during picture naming in three aphasic patients suffering from anomia. This is the first study to investigate temporo-spatial aspects of neural function during a specific and theoretically motivated treatment of an acquired language deficit.

All patients showed pathological low-frequency activity around the lesioned area. Naming-related activation clustered on posterior parts of the brain, with right hemisphere source areas eliciting remarkably strong responses. It has been claimed that the right hemisphere plays either an inhibitory or facilitating role in aphasic language performance (e.g., Gainotti, 1993; Cappa & Vallar, 1992; Kinsbourne, 1971). However, as the right hemisphere is strongly involved in picture naming even in normal speakers (Levelt et al., 1998;

Salmelin et al., 1994), its involvement in our anomic patients cannot be considered a sign of fundamentally altered language processing.

Training-Specific Changes in Brain Responses

In all patients, the left inferior parietal cortex in the anterior border of the lesioned areas was the only region showing training-specific effects. The differences between pre- and posttraining responses started at 300–600 msec after picture presentation and continued for 200–700 msec.

Focal brain lesion studies have suggested that lesions in the left inferior parietal lobe lead to disturbances in spatial tasks (Mattingley, Husain, Rorden, Kennard, & Driver, 1998; Vallar, Sterzi, Bottini, Cappa, & Rusconi, 1990), in acquisition and retrieval of information from episodic memory (Shallice & Vallar, 1990; Shallice & Warrington, 1980), and in the phonological storage component of short-term memory (Vallar, Di Betta, & Silveri, 1997). Aphasiological studies have indicated that left inferior parietal lesions quite often lead to conduction aphasia, in which phonological output problems are remarkable, or to anomic aphasia (cf. van der Linde, Bastiaanse, & Gilbers, 1998; Nickels, 1997; Goodglass & Kaplan, 1983). Functional brain imaging studies have suggested the importance of the left inferior parietal lobe in encoding and retrieval of episodic information (e.g., Mottaghy et al., 1999), in repeating number sequences (Cowell, Egan, Code, Harasty, & Watson, 2000), and in spatial coding of letters (Jordan, Heinze, Lutz, Kanowski, & Jancke, 2001). Furthermore, recent functional brain imaging studies have strongly suggested that the left inferior parietal lobe has a crucial role in verbal working memory, namely phonological storage and encoding (Becker, MacAndrew, & Fiez, 1999; Paulesu, Frith, & Frackowiak, 1993).

Behavioral studies of picture naming have suggested approximate time windows for the main stages of picture naming (Levelt et al., 1998). For healthy individuals naming familiar pictures, the time window of 150–275 msec after picture onset is believed to be related to semantic processing, while the period of 275–400 msec would be related to phonological processing. Electrophysiological studies have suggested similar time windows for these processing stages (Schmitt, Munte, & Kutas, 2000; Levelt et al., 1998; van Turennout, Hagoort, & Brown, 1997). In addition, functional brain imaging studies in reading have shown that the left superior temporal cortex is sensitive to semantic manipulation, starting at about 200–300 msec after word onset in healthy subjects (so-called N400 effect; e.g., Helenius, Salmelin, Service, & Connolly, 1998; Kutas & Hillyard, 1984). The time window has mostly been verified with studies employing semantic incongruency in sentences. However, a similar N400 response was found also when a picture, rather than a word, was used as the last component of a sentence (Nigam, Hoffman, & Simons, 1992). Thus, at least, the time window of semantic processing does not seem to depend heavily on the stimulus type. Indeed, behavioral studies have also indicated roughly similar time windows for semantic and phonological processing of pictures and words (Smith & Magee, 1980).

In our study, the differences in brain responses started 300–600 msec after picture onset. Although in aphasic subjects the temporal dynamics of processing stages might be different from those of healthy subjects, it is likely that this time window reflects phonological rather than semantic processing. In one of the patients (H. H.), brain responses to semantic incongruency have been measured earlier (Laine et al., 2000). In that study, the activation in the left superior temporal lobe started at 200 msec after stimulus onset, as in healthy subjects. However, H. H.'s activation continued up to 800 msec. In the present study, the pre- versus posttraining differences in H. H. started to appear at around 600 msec, that is, much later than his responses reflecting reading-related semantic processing (Laine et al., 2000). In addition, in all our patients, the sources showing training effects represented the final stages of synchronized stimulus-locked activation, which further supports a link with phonological processing.

The phonological interpretation of the training effect is in line with the fact that semantic processing was relatively better preserved in our patients than phonological processing. In addition, the to-be-trained items were selected individually in a way that the patients had semantic knowledge of them. Accordingly, in training, the task for the patients was to reacquire the phonological form for the word. In addition, our training technique uses semantic priming coupled with repetition priming, supposedly boosting spreading of activation to the phonological processing stage, and thus facilitating access to the corresponding phonological representations.

All in all, when taking into account location and time window of the training-specific responses, the behavioral status of our patients, selection of stimuli and paradigm, and the nature of our training method, the observed training-induced changes in cortical responses appear to reflect changes in phonological processing. In that case, the training effect could simply reflect the increased number of correct answers, that is, the larger number of available phonological output forms in post- than pretraining sessions. However, the training-specific cortical source did not distinguish among the three major answer types (J. K., H. H.) or was only one of many areas to do so (J. P.). The answer type effects showed considerable variability across the patients both in terms of timing and location, in contrast to the remarkably consistent training effect. We are thus observing a cortical effect specifically related to training.

We propose that the training effect observed in the left inferior parietal lobe may reflect learning-related phonological processing. The role of the phonological loop has indeed been shown crucial in learning new words (Baddeley, Gathercole, & Papagno, 1998). The fact that several other paradigms have indicated left inferior parietal lobe activity during verbal working memory tasks is in line with this interpretation. For example, repetition of number sequences, which was shown to activate the left inferior parietal lobe (Cowell et al., 2000), calls for phonological storage and articulatory loop components of verbal working memory.

The Role of the Lesion Border

In all our patients, the source area showing the training-induced changes was located at the border of the lesion. There are several reports supporting the notion that the neural tissue surrounding the lesion is crucial for recovery from aphasia. Warburton et al. (1999) reported that during a verb association task, chronic aphasics showed increased left hemisphere activation compared with controls, clustering in perilesional tissue. Similarly, Engelein et al. (1995) found activations in perilesional area during recovery from auditory agnosia. Furthermore, Heiss et al. (1993) demonstrated in their longitudinal functional magnetic resonance imaging (fMRI) study a reactivation of the areas surrounding the area of infarction. Thus, theoretically, one could argue that because all our patients had a left posterior lesion, it is quite natural that the source area showing pre- versus posttraining effect was located in the same brain region, on the anterior border of the lesion. However, such a view would obviously be simplistic. The lesions in our patients were nonidentical and extensive. The close spatial and temporal similarity of the training effect across patients is therefore quite remarkable and cannot be explained by general perilesional recovery effects.

Role of Right Hemisphere in Aphasia Recovery and Rehabilitation

In our patients, the naming-related activation in the right hemisphere was remarkably similar in pre- and posttraining measurements.

The role of the right hemisphere in aphasia recovery and rehabilitation was suggested already by Wernicke (1874; see also Nielsen, 1946; Gowers, 1893). Some case studies have also related the right hemisphere to language recovery (e.g., Cummings, Benson, Walsh, & Levine, 1979). Furthermore, more recent clinical studies have emphasized the role of the right hemisphere in spontaneous recovery of language (Thulborn, Carpenter, & Just, 1999; Mimura et al., 1998; Weekes, Coltheart, & Gordon, 1997; Ohyama et al., 1996; Weiller et al., 1995; Papanicolaou, Moore, Deutsch, Levin, & Eisenberg, 1988). Imaging results have shown shifts of activity to right hemisphere areas homotopic to the classical left hemisphere language areas (Ohyama et al., 1996; Weiller et al., 1995), overall stronger activity in the right than in the left hemisphere (Cao, Vikingstad, George, Johnson, & Welsch, 1999; Papanicolaou et al., 1988), or pronounced increase of right hemisphere activity during recovery (Thulborn et al., 1999). In all these studies, aphasic subjects were still in the process of spontaneous recovery (acute state). The right hemisphere hypothesis has been further supported by worsening of language capabilities in aphasics with a subsequent right hemisphere stroke (Basso, Gardelli, Grassi, & Mariotti, 1989; Gowers, 1893), temporary loss of speech in aphasics with anesthetized right hemisphere (Kinsbourne, 1971), or gradually enhancing speech comprehension capabilities after left hemispherectomy (Gott, 1973).

In contrast to the results emphasizing the role of the intact right hemisphere in aphasia recovery, Karbe et al. (1998) and Karbe, Kessler, Herholz, Fink, and Heiss (1995) found that the best predictor of recovery after aphasia was a high metabolic rate of the left Wernicke's or Broca's area in the poststroke acute state. In addition, in long-term recovery, recruitment of right hemisphere regions was less effective than the restoration of the left hemisphere network (Karbe et al., 1998). Similar results have also been reported by Heiss et al. (1993) and Cao et al. (1999). Furthermore, by measuring the same patients in acute state and 4 months after the stroke, Heiss et al. (1999) showed that an activational shift from the right to the left hemisphere corresponded to better behavioral recovery.

Several factors could explain these contradictory findings. First, the level of the right hemisphere recruitment might be individual and related to the premorbid level of lateralization (cf. Warburton et al., 1999). In addition, the type of aphasia may affect left versus right hemisphere activations (cf. Kertesz, 1995; Moore, 1989). Kertesz (1988) found that left hemisphere structures were more important for the complete and long-term recovery of motor output in verbal expressions, whereas for recovery of comprehension, right hemispheric compensation was more important. Similarly, Thomas, Alternmüller, Marckmann, Kahrs, and Dichgans (1997) concluded from their EEG study that Broca's aphasics and anomic patients showed a shift to left hemisphere dominance with recovery, whereas Wernicke's aphasics showed increased amplitudes over the right hemisphere. In addition, the size of lesion and its location probably have a great effect (cf. Kertesz, 1995). Right hemisphere involvement thus seems to be marked at the acute stage of recovery and later on when the patients are recovering from speech comprehension difficulties. Left hemisphere engagement seems to be associated with better long-term recovery, and it seems to play a role particularly in expressive

language disorders. Thus, the left hemisphere effects of successful treatment in our chronic aphasics are in line with earlier studies.

Training Effect and Patient-Specific Behavioral Patterns

In patients J. P. and J. K., the cortical responses to trained items, originally nonexistent, increased up to the level of easily named items. In H. H., however, the originally significant activation during the processing of the to-be-trained items was reduced to noise level by training. Furthermore, the activity for easy-to-name semantically related items decreased as well. Behaviorally, all patients displayed a statistically significant improvement in trained items, while the performance in the other categories remained at the original level. However, the pattern of behavioral improvement was dissimilar between patients. J. P. and J. K. showed a remarkable increase in the proportion of correct answers in all the posttraining test sessions. H. H. showed only a slight increase in the amount of correct answers, and the effect did not persist to the last behavioral test sessions, 5 months posttraining.

We can thus conclude that the training technique used was suitable for J. P. and J. K., but less so for H. H. Although postsemantic difficulties dominated in all our patients' anomia, both J. P. and J. K. had some semantic impairment as well. They both made several semantic errors in naming (see Table 2) and had difficulties in some of the tasks tapping semantic knowledge (see Table 1). In addition, based on behavioral observations, they were not always aware of their semantic errors. Our training technique that combined automatic semantic priming with repetition priming helped those patients. In contrast, H. H. was aware of his few semantic errors in naming, and did not have difficulties in tests tapping semantic information. In addition, in the analysis of cortical correlates of naming errors, H. H. showed a tendency towards a stronger response to correct answers in the left inferior parietal lobe. With training, the responses started to look much less like correct answers. Why did we then see changes in H. H.'s cortical responses after all? The most obvious reason is that our training technique tapped learning-related phonology that also affected H. H., although the training technique was not optimal for him. It might be that the behavioral effect seen in H. H. was only due to repetition priming, and the suppression in cortical response was caused by the disturbing effect of the semantic context (note also that for normals, naming in semantic context increases error rate; Martin, Weisberg, & Saffran, 1989). It is possible that H. H. would benefit from training requiring more conscious processing of the items.

It thus seems possible that the brain responses may actually inform us about the success and persistence of language treatment. In the case of H. H., the behavioral results suggested that the training technique was at least moderately beneficial for him. However, the brain responses rather suggested the opposite or that the positive effect was only temporary. The training method was deemed useful to H. H. based on the existing neuropsychological models of naming and H. H.'s behavioral performance pattern. This leads us to speculate as to whether more specific models of naming would have led to the choice of a different method for H. H.

Conclusions

Following successful treatment of picture-naming difficulties in three chronic aphasic patients, we found changes in naming-related cortical responses that were concentrated to the left inferior parietal lobe, starting at 300–600 msec after picture presentation. These changes were observed in all three patients. In contrast, analysis of same patients' correct versus erroneous answers demonstrated remarkable intersubject variability, which was both spatially and temporally distinct from the training effect. Accordingly, training-induced differences in the left inferior parietal lobe do not reflect merely the increased amount of correct answers for trained items. Based on timing and locations of the training-induced effects, as well as the neuropsychological profile of our patients, we conjecture that the changes probably reflect more effective phonological encoding and storage of the to-be-trained items through the engagement of a left hemisphere word-learning system.

METHODS

Subjects

The subjects were three chronic (2–14 years after onset) left hemisphere-damaged aphasic men, all originally right-handed, with a monolingual background (Finnish). They all gave their informed consent to participate in this study. The study was approved by the Ethical Committee of the Turku University Central Hospital. The patients had all suffered a cerebrovascular accident resulting in extensive lesions in the left hemisphere. Patients were selected based on their naming disorder: All suffered from moderate anomia. Background tests indicated that their anomic difficulties were predominantly related to phonological output problems.

Patient J. P. is a 46-year-old man who had suffered a cerebral infarct caused by dissection of arteria carotis interna 2 years before the current study. He does not have any other medical diseases. The 3-D MR image obtained just prior to our experiment shows a predominantly cortical left hemisphere damage, encompassing superior and middle temporal lobe, posterior parietal

lobe, and parts of the occipital lobe (see Figure 4). J. P.'s aphasia has evolved from conduction aphasia to residual aphasia coupled with marked anomia. His language disturbance is characterized by relatively good language comprehension but poor performance in naming and in repetition of sentences. Conversational speech is relatively fluent, but consists of paraphasic expressions and empty words. Phonological paraphasias occur quite often in speech output.

Patient J. K. is a 52-year-old man. Eight years before the current study, he suffered a hemorrage caused by a basilar artery aneurysm. The 3-D MR image obtained just prior to our experiment showed a left hemisphere damage, encompassing posterior parts of the temporal lobe, the superior portion of the temporal lobe almost completely, the inferior parietal lobe, and extensive regions of the occipital lobe (see Figure 4). J. K. suffers from a partial hearing loss (compensated by a hearing aid) not related to the cortical lesion, as well as partial loss of vision in the right hemifield. J. K.'s aphasia has evolved from Wernicke's aphasia to residual aphasia. His language disturbance is characterized by relatively good language comprehension and poor performance in naming and in repetition of sentences as well as more complex words. J. K.'s speech is fluent with commonly occurring simple expressions and empty words. Paraphasias are absent in conversational speech.

Patient H. H. is a 47-year-old man. He suffered from a subarachnoidal hemorrage and subsequent brain infarction 14 years before the current study. His 3-D MR image obtained just prior to our experiment shows extensive left hemisphere damage that encompasses posterior frontal parts of the left hemisphere medially, as well as large regions of the temporal lobe and the parietal lobe (see Figure 4). The posterior extension of the lesion is mainly cortical. H. H. suffers from right-sided hemiparesis. He does not have any other medical diseases. H. H.'s aphasia is a mild-to-moderate form of Broca's aphasia. His language disturbance is characterized by relatively good speech comprehension, poor naming performance, and good repetition capability. H. H.'s speech is nonfluent, consisting mainly of very short agrammatic utterances. However, articulation is well preserved.

Experimental Design

The design of this study is shown in Figure 5. Both before and after training, we assessed the level and pattern of performance on a number of language skills to ensure that any changes in picture naming were not confounded by simultaneous changes in other language skills.

In two behavioral pretraining picture-naming sessions (selection of stimuli I and II), 200 target pictures were selected for the experiment. Thereafter, those 200 items were administered to the patients to ensure the consistency of their naming performance (Behav exp pre). Because we had good reason to expect a more variable baseline for brain signals in aphasics than in healthy subjects (Laine et al., 2000), we performed two pretraining MEG measurements 2 weeks apart (MEG pre I and II) to determine the level of inherent variation in naming-related brain activity.

Training lasted for approximately 3 weeks. After the training period, patients' performance on 200 items was tested in order to ensure that the training had facilitated naming of the trained pictures (Behav exp post I and Ib). After that, two MEG measurements were performed (MEG post I and II) to identify possible stable and consistent changes in naming-related brain responses due to training. The first posttraining MEG measurement was done 2 weeks after the end of the training period, and the second 1–2 weeks after the first measurement. After the MEG measurements, a purely behavioral measurement was administered to further establish training effects on naming performance (Behav exp post II). In order to determine possible long-term effects on

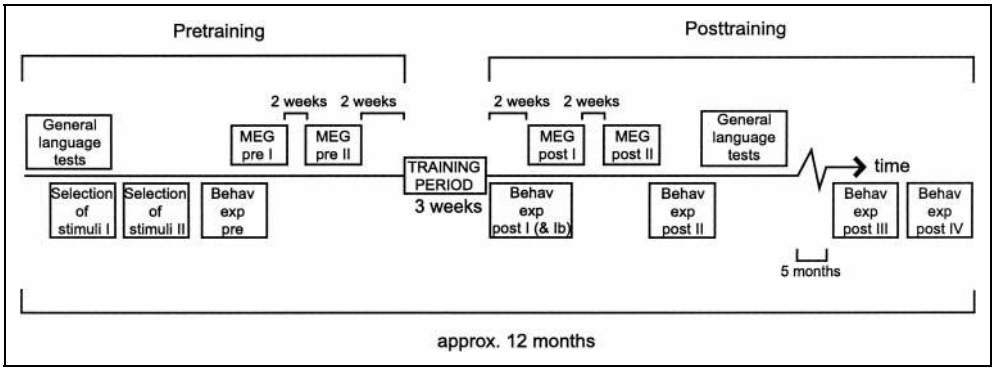

Figure 5. Design of the study. Performance in general language tests was tested before and after the training period. Performance in trained and control items was tested altogether 11 times, of which two were simply for selection of 200 stimuli out of about 800 pictures. Subsequent testing sessions, as well as the end of the training period and the first posttraining MEG session were separated at least by 2 weeks. The last testing sessions were performed five months after the posttraining tests. The training period lasted approximately 3 weeks for each subject.

naming, behavioral measurements were also performed 5 months after the training session (Behav exp post III and IV).

General Language Tests

General language abilities in our patients were tested before and after the training by both standardized and nonstandardized test batteries used in aphasia research (see Table 1). Individual test performance was compared subtest-by-subtest in pre- versus posttraining sessions.

The standardized Finnish version of the Boston Diagnostic Aphasia Examination (BDAE) (Laine, Niemi, Koivuselkä-Sallinen, & Tuomainen, 1997) and the Finnish version of the Boston Naming Test (Laine, Koivuselkä-Sallinen, Hänninen, & Niemi, 1997) were used to describe patients' general language performance and the severity of anomia.

Semantic versus phonological information of sets of pictures was probed to determine the origin of patients' anomia (semantic processing deficit vs. phonological processing deficit). Four tests tapping semantic and/or phonological/orthographic knowledge of target pictures were administered: an odd-out test (Laine et al., 1992), a triad test (Laine et al., 1992), a word–picture matching test (Laine et al., 1992), and a 106-item naming test (Laine et al., 1992; Laine & Martin, 1996).

Selection of the Experimental Stimuli

Black and white line drawings of concrete objects served as stimuli. Based on individual naming results, 200 target pictures were selected for the experiment. The selection was based on naming performance in two separate occasions at least 1 week apart using a pool of about 800 black and white drawings of objects collected from various sources (e.g., Roach, Schwartz, Martin, Grewal, & Brecher, 1996; Snodgrass & Vanderwart, 1980). The pictures were shown on a computer screen for 150 msec, and each presentation was followed by a blank screen for 30 sec, which was allowed for naming. If the patient named the picture earlier, the experimenter proceeded immediately to the next item. Of all the images tested, we first selected items that the patients were consistently able or unable to name. For each patient, we then chose 100 hard-to-name pictures, that is, pictures that he could not name or the naming latencies exceeded 10 sec, but for which he could describe the use and/or produce the name of the semantic category. The 100 hard-to-name pictures were divided into two matching 50-item stimulus lists. There were semantically corresponding items in the two lists (e.g., a lion in one list and a tiger in the other), the same semantic categories were used, and the word frequencies of the object names were comparable, as defined by a lexical database program that utilizes an unpublished corpus of 22.7 million word tokens from a major Finnish newspaper (Laine & Virtanen, 1999). One 50-item list was trained during the training period, while the other one served as a control. In addition, we selected 100 easy-to-name items, that is, pictures that were named correctly within 6 sec. Easy-to-name pictures were divided into two lists as well. Fifty represented exactly the same semantic categories as the hard-to-name item lists. Another list of 50 easy-to-name pictures was not semantically related to the other three lists. The easy-to-name semantically related versus unrelated control pictures were included to determine whether any training-related generalization effects to semantically related items could be seen in the brain responses.

Training Procedure

In training, we used the CPT, illustrated in Figure 6 (cf. Martin & Laine, 2000; Laine & Martin, 1996). The technique is a spin-off of theoretical research focusing on word production models. In this method, the patient is asked to name, after the researcher, items set in matrices of semantically (or in some other versions phonologically) related pictures. The names are repeated several times. At predetermined intervals, the researcher asks the patient to name the items himself. The training effect is supposed to be mediated by two mechanisms: repetition priming, which activates target word forms, and context effects (semantic priming) boosting target-related lexical–semantic representations, with secondary facilitative effects on phonological encoding (cf. legend of Figure 6). Previous research (Martin & Laine, 2000; Laine & Martin, 1996) has suggested that semantic relatedness among to-be-named pictures can boost naming performance of an anomic patient, at least when the underlying deficit is postsemantic. As semantic abilities were better preserved in our patients than their phonological output, we employed semantic relatedness among to-be-trained items.

For training purposes, the 50 to-be-trained pictures were divided into 10 matrices, each containing five pictures semantically related to each other. The semantic categories included both living and nonliving items, such as domestic animals, fish, clothing, and fruit. Within one training session, baseline performance was obtained by asking the patient to name the pictures in a matrix spontaneously. Then he repeated the names of the five pictures after the experimenter, four times in a random order. While uttering each name, the experimenter pointed to the corresponding picture. After this, the naming performance was tested again. If the patient could not name all the pictures, the repetition rounds were readministered and so forth. After five repetition rounds (or earlier if the patient managed to name all items in the matrix), the experimenter moved to the next matrix even if the patient could still not name all the pictures spontaneously. On a single training session,

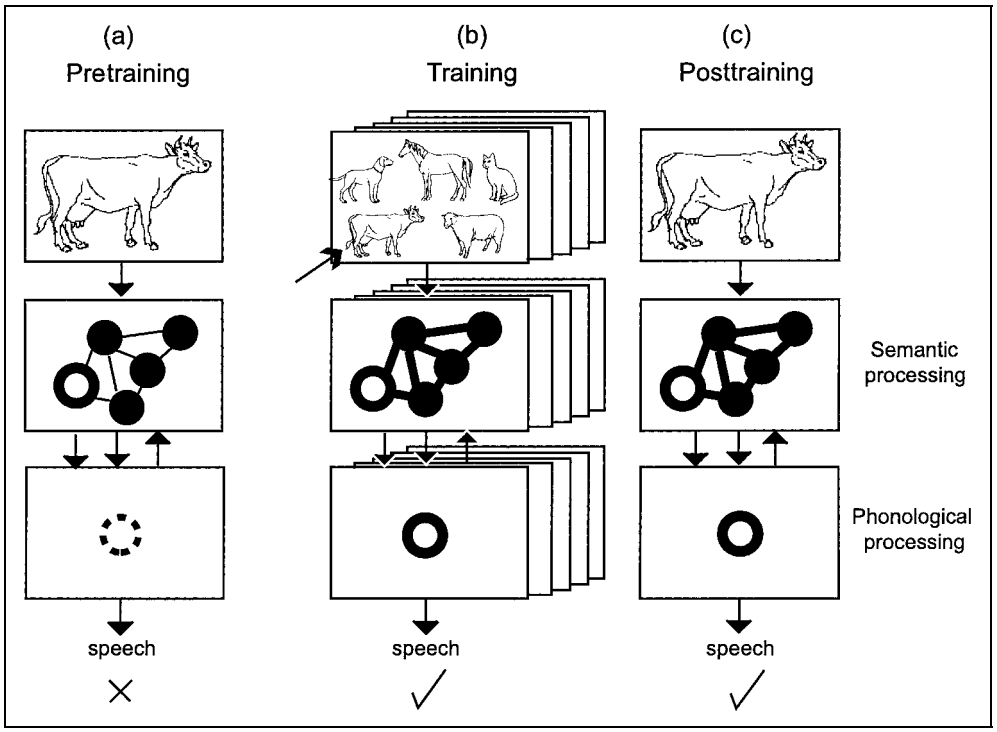

Figure 6. Training technique. In this technique, massive repetition of target names is coupled with semantic priming to facilitate target naming. The assumption behind the employment of semantic relatedness is that it increases activation of the target representation at the semantic processing stage. This increase boosts activation spreading to the phonological processing stage, leading to better phonological encoding and, subsequently, more successful naming. In this concrete example, when the picture of a cow is presented in isolation to an anomic patient, the semantic node representing "cow" is activated (a). Activation from that node spreads to other items that are semantically related to it, for example, domestic animals like "horse" and "dog." These nodes would then feed back to the target node "cow" due to the bilaterality of the connections. However, the spreading is not particularly strong, and there may be too little boost for the target representation to overcome dysfunction at the phonological level, and naming fails. During training (b), the semantic network representing domestic animals is activated because the picture of the cow is presented in the context of other semantically related items. This enhanced activity in the semantic network facilitates transfer of activity from the semantic to the phonological stage, and naming may succeed. Furthermore, multiple repetitions of target items during training is assumed to have a long-term effect by strengthening the connections between the semantic nodes and the corresponding phonological representations. After training (c), the reinforced connections between the semantic representation of the target and the corresponding phonological form enable successful naming of the target item.

five matrices were trained. In addition, matrices including all the control pictures were shown to the patient in each session in order to obtain comparable visual exposure. Half of the matrices were shown in one session, the second half in the next session, so that the same control pictures were shown in every other session. The control pictures were set in matrices randomly, avoiding semantic relatedness among pictures. The patient was asked to look at the figures carefully without attempting to name the objects.

Training was carried out three times a week (approximately 1 hr per session). Each patient underwent at least nine training sessions. If the patient could not name at least 70% of the trained items spontaneously within 6 se, training was continued beyond the nine sessions. This was the case with one of our patients (H. H.) for whom training was continued with six additional training sessions.

Tasks in Behavioral and Imaging Experiments

During the behavioral experiments and the four pre- and posttraining MEG measurements, the patients performed a delayed naming task. The patients' vocal reaction times in naming tasks were typically longer than 6 sec. However, the face muscle movements related to effortful naming tended to start immediately after stimulus presentation. A delayed paradigm was chosen in order to minimize these movement artifacts, but with a delay that was clearly shorter than the patients' reaction times, and thus, should not affect the naming process per se. In both behavioral experiments and MEG measurements, one picture at a time appeared on the screen for 150 msec (short presentation time to avoid eye movement artifacts that would disturb MEG data analysis). Then the picture disappeared and after 3 sec, a question mark appeared indicating that the object had to be named aloud. The question mark remained on the screen for 2 sec, and then it disappeared, indicating the end of the trial. A blank screen was shown for 1 sec to stabilize brain activity before the next epoch. All pictures were shown twice during the MEG session. The pictures were presented in six blocks with short breaks in between. The same randomized sequences were used in all MEG recordings. During the purely behavioral measurements, pictures were shown in a different randomized order than in the MEG measurements. Here, all pictures were shown only once with two breaks in between, with the same randomized sequence in all behavioral experiments.

During MEG recordings, the pictures were projected on a back-projection screen (Neuromag) with a VistaPro

(Electrohome) data projector. A Macintosh Quadra 800 computer and MacProbe software were used to generate the stimuli. The patients viewed the screen binocularly from a distance of 1 m. The pictures appeared in the middle of the screen and spanned a visual angle of 8°. In the purely behavioral measurement sessions, the pictures were shown on a computer screen, using the RunWord stimulus presentation program (Kello & Kawamoto, 1998). The patients were seated at the distance of approximately 1 m from the screen, fixating to the middle of the screen. The oral-naming responses were tape-recorded in the MEG measurements; during the purely behavioral measurements, they were coded on-line manually. The patients were instructed to try to find as accurate an answer as possible. They were instructed to start searching for the answer in their mind immediately when they saw the picture and to produce the oral response after the appearance of the question mark. In addition, during the MEG measurements, the patients were specifically asked to remain completely silent if they did not know or were uncertain about the correct answer.

We also recorded the patients' spontaneous brain activity and studied its intrinsic variability in sessions where patients were sitting relaxed with their eyes open (3 min) and closed (3 min).

Magnetoencephalography Recording

Magnetic fields were recorded in a magnetically shielded room with an assisting person sitting next to the patient, but not visible to him. A 306-channel whole-head neuromagnetometer (Vectorview, Neuromag) was used. The device employs 204 gradiometers and 102 magnetometers, which are arranged in a shape of a helmet. In this study, only the gradiometer data were used in the analysis. There are two gradiometers at each recording site, which measure derivatives of magnetic field both along longitudes and latitudes. Planar gradiometers detect the largest signal directly above a local current source.

The measured signals were band-pass filtered at 0.1–200 Hz in patient H. H. and at 0.03–200 Hz in the other patients and digitized at 600 Hz. In the naming task, responses to different stimulus categories were collected on-line only to monitor the signal-to-noise ratio and further averaging to relevant categories was done off-line. MEG signals, vertical and horizontal electrooculograms, and left hand muscle (right hand muscle in J. P.), as well as lip muscle electromyograms were collected continuously.

Analysis of the Behavioral Data

The possible changes in performance in background behavioral tests across similar subtests were estimated with paired samples *t* tests within each patient. In both the behavioral experiments and in the MEG experiments, the number of correct answers was calculated, and possible changes in behavioral performance were evaluated using the nonparametric McNemar test (Siegel, 1956). In addition, the number of semantic errors, omissions, and other errors was calculated. Correct answers were those in which a patient produced the correct name or a fully acceptable synonym. Semantically erroneous answers were those in which a patient produced a single word from the same semantic category and from the same ordinate level as the target (e.g., duck vs. goose). Only trials in which the patients remained completely silent were determined as omissions. The heterogeneous category of other errors included such responses as phonological paraphasias, formal paraphasias, multiword expressions, neologistic expressions, and single sounds.

Magnetoencephalography Data Analysis

The MEG signals were reaveraged off-line for the different stimulus categories from 200 msec before to 3000 msec after stimulus onset. The MEG signals were also reaveraged based on the question mark (−500 to 1000 msec with respect to the question mark onset), which served as the vocalization prompt. In addition, the responses were reaveraged according to the answer type (correct answers, semantic errors, omissions, other errors) for the pretraining measurements (from 200 msec before to 3000 msec after picture onset, as well as −500 to 1000 msec with respect to the question mark onset). The pretraining measurements were considered to be a baseline situation for each patient, and were therefore assumed to give the most realistic picture of the patients' cortical activity for successful and erroneous naming. In addition, because the error type distributions did not show behaviorally any significant qualitative changes between pre- and posttraining measurement, we could restrict our detailed analysis on pretraining measurements. For the final analysis, a minimum of 80 averages was required for each response type. Because of the low number and heterogeneity of the answer types in the category of other errors, they were discarded from further analysis. MEG signals were also averaged with respect to blink onset, and the corresponding field pattern was projected out using the signal-space projection method (Uusitalo & Ilmoniemi, 1997). The few epochs contaminated by horizontal eye movements or hand movements were discarded from averaging.

Before source analysis, the MEG data were further low-pass filtered at 40 Hz. All patients' data and all different average categories were analyzed individually. The active cortical areas were modeled as equivalent current dipoles (ECDs), which can be determined from the magnetic field distribution. The location of the ECD reflects the center of gravity of the active cortical area

(Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). The amplitude of the ECD describes the amount of synchronous activity of neurons within the cortical patch. Each active area was identified at the time point where the magnetic dipolar field pattern was clearest and there was least interference from other sources, using a subset of sensors.

A fast Fourier transformation (FFT) was performed to determine the frequency distribution of patients' cortical activity. A 3-sec time window was shifted forward in 1.5-sec steps, and the FFTs were averaged over the whole measurement time. Pathological slow-wave activity (<5 Hz) was seen in all patients. These slow rhythms may seriously disturb the analysis of the stimulus-locked responses, and thus should be removed if possible (cf. Laine et al., 2000). The source areas of the pathological rhythms were identified in each patient from the data recorded during the resting condition (cf. Laine et al., 2000; Salmelin & Hari, 1994). When necessary, the effect of these source areas (one to two in each patient) was removed using signal-space projection method (Laine et al., 2000; Uusitalo & Ilmoniemi, 1997) by selecting a representative ECD from each source cluster.

In each patient, all average categories (stimulus types, answer types) showed similar activation patterns, and a single set of ECDs could therefore be selected for each patient (eight to nine ECDs in each patient). The time behavior of activation in the source areas was determined by introducing the identified set of ECDs simultaneously to a multidipole model. The locations and orientations of current flow were kept fixed while the source strengths were allowed to vary to best explain the MEG signals recorded by all the 204 gradiometers. The identified sources accounted for 80–90% of total variance.

Evaluation of the Training Effect

The training effect was evaluated by comparing the source waveforms between pre- and posttraining measurements and also by comparing the responses to different stimulus categories within each measurement.

The intrinsic variability of cortical activity in each patient was determined from the variation of the MEG activity during the prestimulus baseline (−200 to 0 msec) in the pretraining signals. For the pre- versus posttraining comparisons, the standard deviation (*SD*) was calculated from the standard deviations of the baselines in the two pretraining recordings (*SD*1, *SD*2) as $SD = \sqrt{SD1^2 + SD2^2}$. The training effect was considered as significant only when the signals for both posttraining measurements differed from the mean signal of both pretraining measurements by at least 3.29**SD* (corresponding to $p < .001$). The comparison of the source waveforms was done for each time point in the time interval of 0 to 1500 msec. The difference had to continue for at least 150 msec to be considered as significant. Furthermore, both posttraining measurements were required to differ from both pretraining measurements by at least twice the difference between pretraining source waveforms at those time points.

Evaluation of the Answer Type Effect

Because the source waveforms in the two pretraining measurement sessions were essentially identical, they were averaged together to improve the signal-to-noise ratio for the statistical analysis. The significances of the differences between response categories were tested in pairwise comparisons, that is, two answer types were compared with each other at a time. For the comparison of two source waveforms, the standard deviation (*SD*) was calculated from the standard deviations of the baselines (−200 to 0 msec with respect to stimulus onset) of the two waveforms (*SD*1, *SD*2) as $SD = \sqrt{SD1^2 + SD2^2}$. The further comparisons of the two waveforms and statistical requirements were similar to the analysis of the training effect (see above).

Alignment of Magnetoencephalography and Magnetic Resonance Images

The anatomical MR images of the patients' brains, with 1-mm spatial resolution, were acquired at the Department of Radiology, Turku University Central Hospital. The head coordinate system for both anatomical MRI and MEG was specified using clearly identifiable fiducial points in front of the ear canals (*x*-axis, from left to right) and at the nasion (positive *y*-axis), with the *z*-axis oriented towards the vertex. The MRI and MEG coordinate systems were aligned by attaching four small coils on the patients' head. The location of the coils was first determined with a 3-D digitizer in the head coordinate system. With the patients' head in the MEG system, the coils were energized briefly and their locations were computed with respect to the magnetometer. The identified source locations were first viewed on the individual 3-D MRI slices, and then projected along the head radius to be displayed on MRI surface renditions (see Figures 2–4).

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