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Clinical fMRI of language function in aphasic patients:
Reading paradigm successful, while word generation paradigm fails

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Abstract

Background: In fMRI examinations, it is very important to select appropriate paradigms assessing the brain function of interest. In addition, the patients' ability to perform the required cognitive tasks during fMRI must be taken into account.

Purpose: To evaluate two language paradigms, word generation and sentence reading for their usefulness in examinations of aphasic patients and to make suggestions for improvements of clinical fMRI.

Material and Methods: Five patients with aphasia after stroke or trauma sequelae were examined by fMRI. The patients' language ability was screened by neurolinguistic tests and elementary pre-fMRI language tests.

Results: The sentence-reading paradigm succeeded to elicit adequate language-related activation in perilesional areas whereas the word generation paradigm failed. These findings were consistent with results on the behavioral tests in that all patients showed very poor performance in phonemic fluency, but scored well above mean at a reading comprehension task.

Conclusion: It was concluded that the sentence-reading paradigm was appropriate to assess language function in this patient group and that the word-generation paradigm was inadequate. In addition, it is crucial to use elementary pre-fMRI language tests to guide the fMRI paradigm decision.

Keywords: fMRI, aphasia, language, word generation, sentence completion

Since the discovery of the Blood Oxygen Level Dependent (BOLD) effect in 1990 (1), functional Magnetic Resonance Imaging (fMRI) has developed from a pure experimental method for investigations of localized brain function into a useful clinical tool. One area of increasing interest for clinical fMRI is functional diagnosis and prognosis in patients with aphasia after stroke sequelae (2-10). However, fMRI examinations in this patient group are challenging. The patients do not only have language deficits but often also other kinds of cognitive impairments, such as reduced working memory and perception difficulties (11).

In order to map brain function using fMRI, the patient has to perform cognitive tasks during the examination. It is therefore essential to apply paradigms that trace the cognitive function of interest. Further, a high patient compliance is necessary in all fMRI examinations (12). That is to say, clinical paradigms should be suited for proper execution by patients that eventually are cognitive deficient. In general, paradigms should be kept short to prevent attention loss. However, longer presentation times may be required for patients with aphasia and it is therefore essential to adapt the paradigms for the intended patient population.

In this study, two types of paradigms, which are commonly used in clinical fMRI, were evaluated for their applicability in examinations of aphasic patients: 1) word generation and 2) sentence reading (12). These paradigms have been used in previous studies by us aiming to assess the correlation between brain activity and language performance (13). In healthy subjects, word generation results in activation in frontal language areas, predominantly in the left inferior frontal gyrus (Broca’s area) (14,15). However, activation in temporal language areas, *i.e.* the superior temporal gyrus (Wernicke’s area) and parietal areas, *i.e.* the supramarginal gyrus and the angular gyrus as well as the supplementary motor area in the medial frontal cortex is also observed. Paradigms involving sentence reading are considered to elicit more activation in Wernicke’s area compared to paradigms involving single word processing (12,15). In this study, we applied a word generation paradigm, where the task was to generate words beginning with a given letter, and a variant of a sentence reading task, where the patients were asked to generate the final word of a given incomplete sentence. The aim of the study was to evaluate two commonly used language paradigms in order to make suggestions for improvements of clinical fMRI in patients with aphasia after stroke or trauma sequelae

Material and Methods

Patients

Five patients (females/males = 1/4) with chronic aphasia after stroke or trauma sequelae were included in the study. Exclusion criteria were diseases that aggravate fMRI examinations, *e.g.* hemochromatosis and morbus Wilson. Patients with claustrophobia and reduced cognitive abilities, such as neglect, were also excluded. The patients had earlier been examined with CogniStat (16), NIH Stroke Scale (17) and a neuropsychology test battery to screen for cognitive disturbances. All patients had Swedish as their first and dominant language. The mean age was 53 years (range 26–74 years) and the mean time since lesion was 36 months (range 13–65 months). Four patients had left sided media infarction and one patient (Patient 2) had a traumatic brain injury. All patients were right-handed before lesion. Demographic data of the patients is found in Table 1.

All subjects made informed consent to participate in the study, which was approved by the Ethics Committee at Linköping University.

MRI

Functional images were acquired with a BOLD-sensitive echo planar imaging (EPI) sequence using a Philips Achieva 1.5 T scanner (Philips Medical Systems, Best, The Netherlands). Following imaging parameters were used: TE = 40 ms, TR = 2.7 s, flip angle 90°, number of slices = 32, slice thickness = 3 mm, matrix = 80X80, FOV=24 cm. The slices were aligned between the floor of sella turcica and the posterior angle of the fourth ventricle and applied to cover the most relevant areas in the frontal and temporal lobes. T1W inversion recovery (IR) images were acquired applying the same geometry as the EPI images for an anatomical reference to the functional maps.

fMRI paradigms

SuperLab Pro software (Cedrus Corporation, San Pedro, Calif., USA) was used to present the language tasks in all sessions. The tasks were presented to the participants using MR-compatible video-goggles (Resonance Technology, Los Angeles, Calif., USA).

Word generation: In the word generation paradigm the subjects were asked to covertly generate as many words as possible beginning with a given letter. The presented letters were taken from the English alphabet, excluding C, Q, W, X, Y, and Z. Letters were presented in blocks for 5 s each and the number of tasks per block varied from 3 to 5 in a pseudorandom order. In the control task the following symbols were shown to the subjects with the same frequency as the letters: +, !, *, ? (Fig. 1A). Total task time was 5 minutes corresponding to 112 image volumes.

Sentence reading: The sentence-reading paradigm consisted of 4 blocks of 8 incomplete sentences, which should be completed using a single noun (13,18). The sentences contained 3–10 words fitted into one single row. In this study, the time for sentence reading and the interstimulus interval (ISI) were increased compared to a previous study on healthy subjects (13) in order to allow the aphasic patients more time to perform the task. Thus, each sentence was presented for 5 s followed by an ISI of 3 s, in which an *X* was presented on the screen. The participants were instructed to complete the sentences by covertly filling in suitable nouns during the ISI. The block duration was 64 s. During the control task the patients were instructed to passively observe the central *X* in a row of *Xs* (3 s) alternating with a single *X* (2 s) (Fig. 1B). Total task time was 7.6 minutes, corresponding to 169 image volumes.

The patients were asked to give their responses covertly in order to reduce movement artifacts.

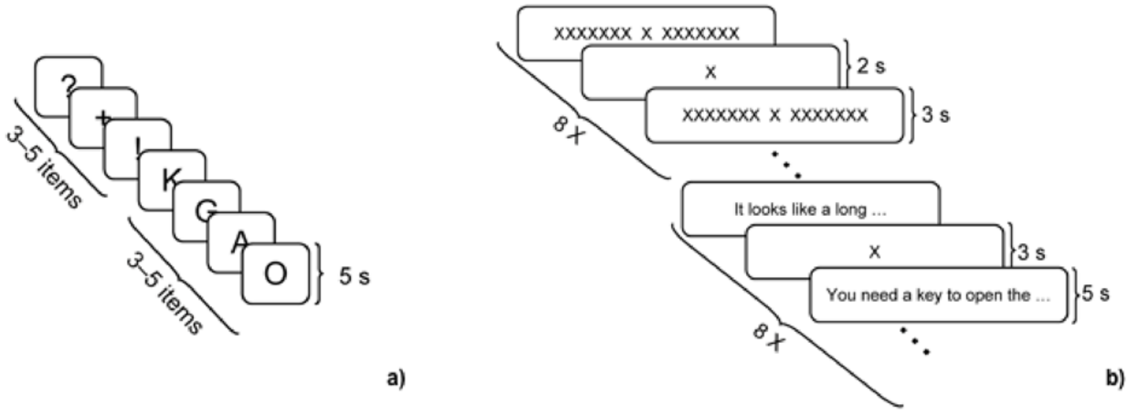

Fig. 1 *Schematic illustration of the word generation (A) and sentence reading (B) paradigms.*

fMRI analysis

The fMRI images were preprocessed and analyzed using SPM5 software (Wellcome Department of Imaging Neuroscience, University College, London, UK). All functional images were re-aligned to correct for movements during scanning, coregistered to the T1W anatomic images and smoothed using 8 mm Gaussian kernel. Functional images were analyzed applying the hemodynamic response function and a high pass filter with a cutoff period of 128 s. Movement parameters from the re-alignment procedure were included as regressors in the analysis in order to diminish the effects of movements during scanning. The threshold (T-value) was individually adjusted for each patient and each paradigm. The choice of individual thresholds was based on the best possible adoption to following criteria: 1) No spurious activation in non-cortical regions and 2) Visible activation clusters in frontal and/or temporal language areas. In addition an extent threshold of 10 contiguous voxels was applied in all images.

Linguistic tests

All patients underwent two elementary language tests prior to fMRI scanning in order to be familiarized with the procedure. The tasks were chosen to resemble the tasks used in the fMRI study. In the first test (phonemic fluency), the patients were asked to generate as many words as possible during 1 minute beginning with A and F, respectively. One credit was given for each word produced. In the second task, the patients were presented with four random sentences from the sentence reading paradigm. The task was to fill in the last missing word in each sentence. The time for sentence completion was noted.

After fMRI scanning, the language ability of the patients was assessed with the Swedish neurolinguistic aphasia test A-ning (19). A-ning is used in Swedish clinics to assess language function in patients with aphasia after acquired brain lesion. The test is standardized for patients with Swedish as their first language and contains the following tasks: informative speech, repetition, auditory comprehension, reading comprehension, overt reading, dictation, and writing.

Results

fMRI

Word generation: Following individual thresholds were chosen for the word generation paradigm: Patient 1 (T=4.2), Patient 2 (T=3.1), Patient 3 (T=3.4), Patient 4 (T=3.0), and Patient 5 (T=3.4). The uncorrected p-values were less than 0.0005 for all patients. The ambition was to select thresholds that minimized non-cortical false positives. However, for Patient 1, spurious activation in the ventricles and the frontal pole remained even after a rather rigorous threshold of T=4.2 (Fig. 2). These false activations were probably due to task-related movements, which was consistent with the behavior outside the scanner during the efforts to generate words. The findings of activation in left temporal and frontal regions are therefore questionable to interpret. Only one patient (Patient 2) showed activation in left frontal language areas at word generation. The other patients showed activation clusters in regions, *e.g.* the anterior and posterior cingulate cortex, which are related to but not uniquely coupled to language function. Representative findings for each patient are visualized in Fig. 2.

Sentence reading: In contrast to the word generation task, sentence reading induced activation in language areas in all patients ($p<0.0005$). In particular, activation in regions adjacent to the lesion in the left frontal, temporal, and parietal lobes correlated to the reading task performed during fMRI. Representative findings, as described below, are shown in Fig. 2. The threshold T-values are indicated in parenthesis for each patient.

Patient 1 (T=4.0): Language stimulation with sentence reading generated activation adjacent to the lesion in the left supramarginal area in the parietal lobe. Activation was also found in the left middle temporal lobe. The putamen and globus pallidus were activated bilaterally. In the right hemisphere, slight activation in the middle frontal lobe was observed (not shown in

Fig. 2). In addition, the left motor cortex (not shown) and the posterior cingulate cortex were activated.

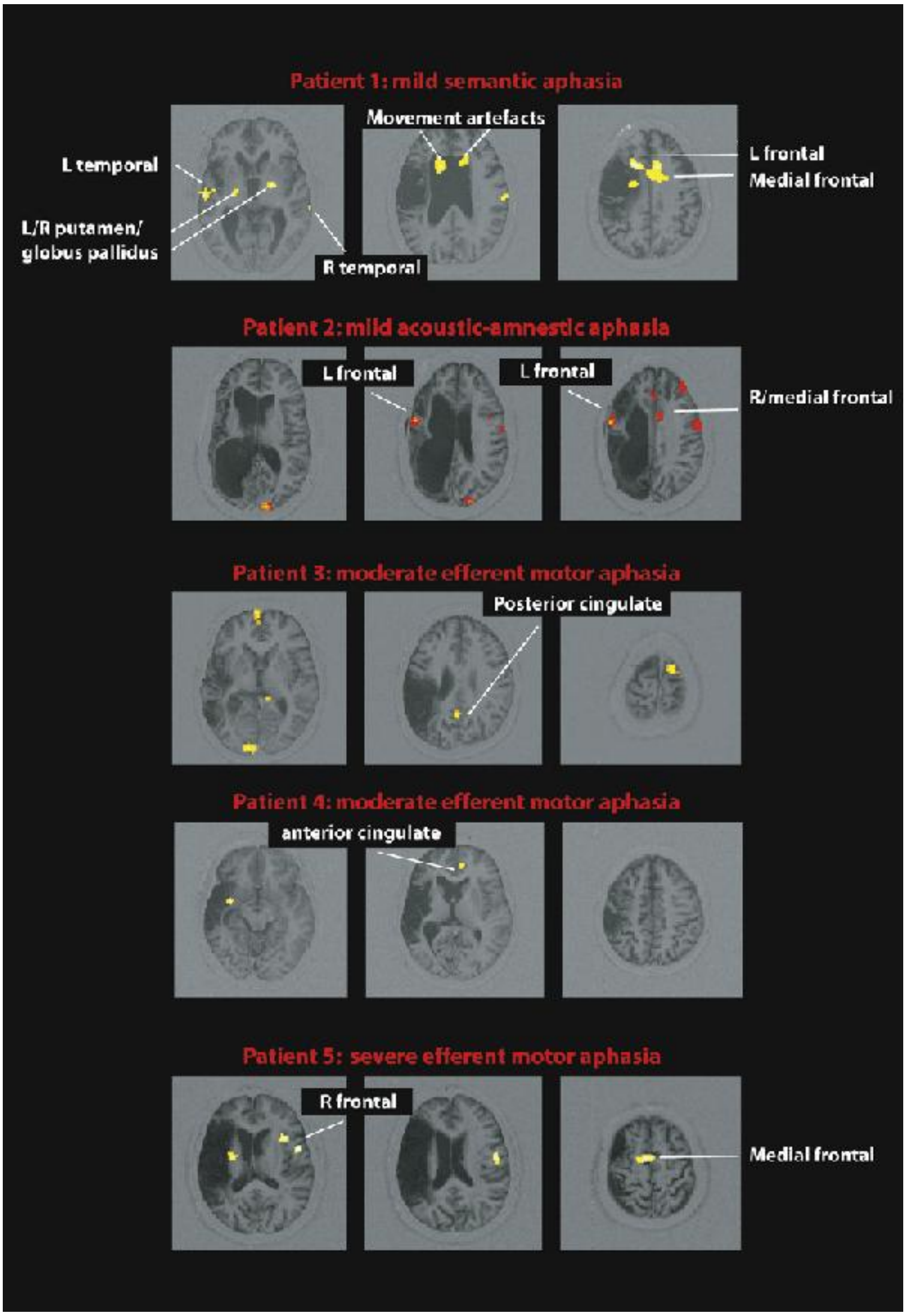

Fig. 2 *Results from the word generation task showing three representative slices for each patient. T-value thresholds: Patient 1 = 4.2, Patient 2 = 3.1, Patient 3 = 3.4, Patient 4 = 3.0, and Patient 5 = 3.4.*

Patient 2 (T=3.1): This patient had language-related activation in the left frontal and temporal lobes. The reading paradigm induced additional activation in the inferior parietal lobe adjacent to the lesion. In the right hemisphere, activation was observed in the supramarginal area.

Patient 3 (T=3.6): This patient activated a large area in the left hemisphere including parts of the frontal and temporal lobes at sentence reading. In addition, activation in the medial superior frontal lobe (*i.e.* the supplementary motor area) and the left precuneus was found.

Patient 4 (T=3.8): Sentence reading elicited significant activation in the left prefrontal cortex adjacent to the lesion. This patient also had perilesional activation in the left temporal pole, the left fusiform area and in the left superior medial frontal cortex (not shown in Fig. 3).

Patient 5 (T=3.4): The most prominent activation was found in the left inferior parietal lobe and in the supramarginal area adjacent to the lesion. Additional activation was found in the supplementary motor area in the medial frontal cortex.

Linguistic tests

Results from the elementary language tests showed a pronounced difficulty in phonemic fluency. The word generation capacity ranged from 0 to 6 words in one minute (Table 2). The mean number of words produced during one minute was 3.1. The shortest time for sentence completion ranged from 5 to 20 s and two out of five patients were not able to complete all of the 4 presented sentences (Table 2).

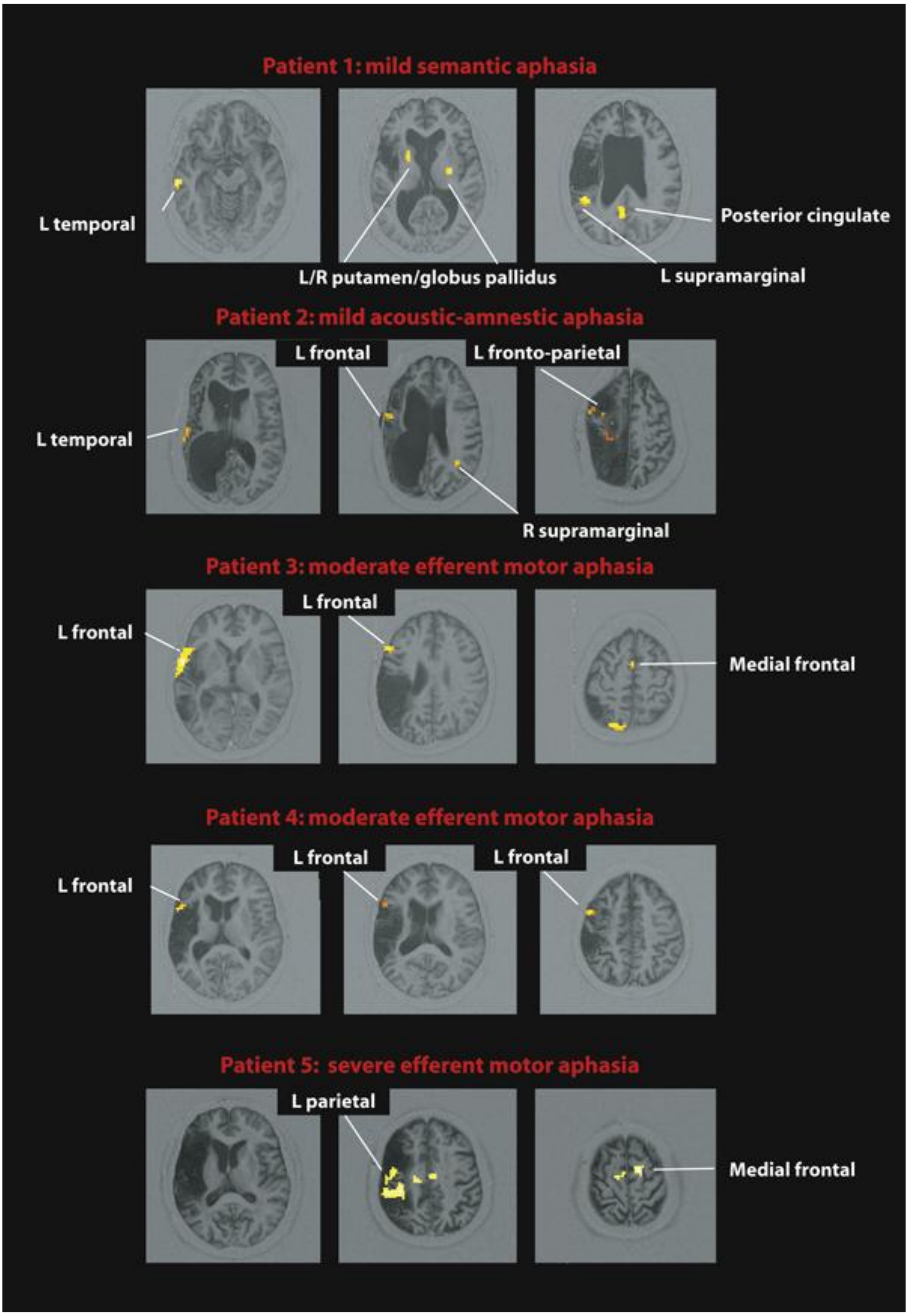

Fig. 3 *Results from the sentence reading task showing three representative slices for each patient. T-value thresholds: Patient 1 = 4.0, Patient 2 = 3.1, Patient 3 = 3.8, Patient 4 = 3.6, and Patient 5 = 3.4.*

Aphasia grading was based on the mean scores for the A-ning test. Max score for all A-ning subtests is 5.0. Two patients with mild aphasia (Patients 1 and 2) had the highest A-ning mean scores of 4.4 and 4.3, respectively. Two patients with moderate aphasia (Patients 3 and 4) scored 3.1 and 2.9, respectively. The remaining patient (Patients 5) had severe aphasia and consequently the lowest A-ning mean scores of 1.8. Scores for the A-ning subtests are presented in Table 3.

Discussion

This study aimed at improving fMRI paradigms for future clinical examinations of patients with aphasia after stroke or trauma sequelae. For that purpose, five patients with aphasia were examined applying two commonly used clinical fMRI paradigms: word generation and sentence reading. The resulting brain activation patterns were interpreted using both elementary tests and a full-scale aphasia test.

The patients were able to produce 3 words per minute, in average. This corresponds to the number of words a healthy subject is anticipated to produce during 5 s (result from a pilot study at our lab). Five seconds is also the given time for word generation during fMRI. As a comparison, the normative value for Swedish people at ages from 30 to 64 with ≤12 years of education is 42 words/minute (20). In addition, the test with sentence reading and completion outside the scanner showed that most patients probably did not have enough time to complete the sentences during the given time for fMRI scanning, which was 3 s. However, in most cases they were able to find a suitable word. This implicates that they could understand the content of the sentences even though they were not able to produce the completion word during fMRI. In addition, all patients scored well above mean in the reading comprehension part of A-ning (Table 3).

This study clearly showed that the classical word generation paradigm failed to give adequate language activation in this group of patients. Only one patient (Patient 2) elicited unambiguous activation in left frontal areas, which could be attributed to word generation activity. This patient had mild aphasia and was also the youngest in the group (26 years). Results from the pre-scanning phonemic fluency task indicate that the word generation task during fMRI was not suited for this patient group, in that all patients needed more time than provided to generate words. One way to overcome this problem is to allow patient-adopted presentation times, which in the current patient population could be 20–30 seconds/letter instead of the present 5 seconds. An alternative way is to select other variants of word generation paradigms, *e.g.* verb generation where the subjects are asked to generate verbs from a given noun. In a recent study, Eaton *et al.* used a verb generation together with a semantic decision paradigm and found high inter-scan reliability for repeated measures both in aphasic patients and healthy controls (21).

On the other hand, all patients with mild or moderate aphasia elicited language related activation adjacent to the lesion in the left frontal and temporal lobe at sentence reading. Perilesional activation in the parietal lobe was observed in the patient with severe aphasia (Patient 5). This result could have been predicted from the pre-scanning sentence reading and completion task in that all patients succeeded to find at least one suitable word to complete the presented sentences if they were given enough time. In addition, the results from the reading comprehension part of the neurolinguistic test, A-ning, indicate that this patient group performs relatively well at reading.

Despite the successful results at sentence reading, some improvements are suggested for future studies. Firstly, the length of the sentences could be shortened and the sentences are preferably presented in 2–3 rows instead of one single row in order to facilitate the reading. Secondly, the timing of the paradigm could be adjusted for individual performance. In this study, the presentation time for each sentence was prolonged leading to a block time of 64 s, which might not be optimal. Normally, the block lengths in fMRI are 20–30 s. Therefore; if longer presentation times are required the block lengths should be adjusted by using fewer sentences/block.

Problems with image artifacts emanating from general and/or task related movements are not unusual in fMRI. In this study, such artifacts were eliminated or reduced by incorporating movement parameters in the model at the image analysis. That is to say, a matrix composed of the translational (x, y, z) and rotational parameters (pitch, roll, yaw) was included in the model for the exploratory variables. Including movement parameters as regressors in the model resulted in reduced artifacts. Despite of this, spurious activation in the ventricles and the frontal poles remained for Subject 1 at word generation. From the movement parameters it could be deduced that these artifacts emanated from behavior during efforts in word production, so called task-related movement. It was therefore concluded that this type of artifacts could be expected also in other patients with similar behavior. Thus, in order to improve fMRI in aphasic patients the problems with motion artifacts have to be diminished for example using restraining head fixation. This is particularly important in the clinical situation where sophisticated analysis tools, such as multiple regressor modeling, are not available.

In conclusion, the word generation paradigm was not appropriate for language assessment in this group of aphasic patients since they were not given enough time for task completion during scanning. In contrast, language stimulation with sentence reading generated adequate language activation in perilesional areas in all patients. It was concluded that the sentence-reading paradigm was appropriate to assess language function in this patient group, which performed comparatively well at sentence reading. This result could have been predicted from language tasks outside the scanner. Therefore, patient screening using elementary pre-fMRI language tasks is crucial to guide the fMRI paradigm decision.

Acknowledgements

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Tables

Table 1. Age, time since lesion, site of lesion, and aphasia status for five patients that were included in the fMRI study. Patient 3 is female. The other patients are males.

Patient	**Age** (Years)	**Time** (Months)	**Site of lesion**	**Aphasia status***
1	53	55	Frontal, anterior temporal and parietal	Mild semantic
2	26	65	Frontal, temporal, parietal, occipital	Mild acoustic-amnestic
3	54	30	Temporal, parietal	Moderate efferent motor
4	41	35	Frontal, temporal, parietal	Moderate efferent motor
5	64	15	Frontal, temporal, parietal	Severe afferent motor

* According to A-ning that uses Luria taxonomy (semantic/acoustic-amnestic aphasia ≈ anomic aphasia, efferent motor aphasia ≈ Broca’s aphasia, afferent motor aphasia ≈ conduction aphasia).

Table 2. Results on language tests outside the scanner for fMRI-patients: Number of produced words during 1 minute beginning with the letters A and F, respectively, number of completed sentences of 4 given, minimum and maximum time for sentence completion.

Patient	**A/min**	**F/min**	**Sentences**	**Min–max** (s)
1	5	2	4	8–15
2	4	4	4	10–75
3	6	5	4	5–20
4	2	2	3	14–∞
5	1	0	1	20–∞

Table 3. Results on the Swedish neurolinguistic aphasia test, A-ning, for fMRI-patients. Informative Speech (IS), Repetition (R), Auditory Comprehension (AC), Reading Comprehension (RC), Overt Reading (OR), Dictation (D), Writing (W), and mean score. Patients with aphasia score lower than maximal score, which is 5.0.

Patient	**IS**	**R**	**AC**	**RC**	**OR**	**D**	**W**	**Mean**
1	4.9	5.0	4.8	4.6	4.8	4.3	1.3	4.4
2	4.8	3.8	3.6	4.9	4.8	4.3	3.8	4.3
3	3.4	2.3	2.9	4.1	4.5	2.3	2.3	3.1
4	3.0	2.5	3.9	3.4	2.8	2.0	1.8	2.9
5	1.6	0.5	3.4	3.3	0.5	0.8	0.5	1.8

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