Neural correlates of spontaneous language production in two patients with right hemispheric language dominance

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Abstract

Background: It is not conclusively explored what kind of reorganisation processes are set off after a stroke with resulting aphasia. Since the development of functional Magnetic Resonance Imaging (fMRI), linguistic processes and their neural representation have been researched, especially in aphasic patients after left hemispheric insult. The situation differs in aphasic patients with right hemispheric language dominance where only few studies have been carried out. In order to close this gap, the present study deals with the localisation of language functions in the brain of patients with right hemispheric language dominance.

Aim: The objective of the current study was to provide insights into the neural correlates of continuous aphasic language production of patients with right hemispheric language dominance. Based on the current state of research, a mirror image representation was expected.

Methods & Procedures: Two patients with fluent aphasia due to right hemisphere lesions, one presenting with crossed aphasia, described complex pictures. The continuous language output was transcribed and segmented into events, which were categorised according to a special evaluation scheme. The neural correlates of one important symptom category of both patients, the unsuccessful word-finding difficulties, were analysed using fMRI. The neural activation clusters were compared with the corresponding areas of a control group consisting of twelve patients with left hemispheric aphasia.

Outcomes & Results: The analysis of the behavioural data revealed unsuccessful word-finding difficulties as one of the most limiting factors in the spontaneous language output of the patients. The corresponding neural correlates were observed in four activation clusters both patients had in common. Each cluster was predominantly localised in the contralesional hemisphere. Compared to the corresponding areas of the control group, in general a mirrored image representation could be confirmed.

Conclusions: The combination of detailed linguistic analysis and fMRI confirmed the assumption of mirrored language organisation for anomia in continuous language production. Additionally, the study shed light on the contribution of the contralesional hemisphere to language recovery in right hemispheric aphasia.

Key Words

Crossed Aphasia, right hemispheric aphasia, fMRI, spontaneous language, anomia

1. Introduction

The question of the representation of language in the brain, in particular of hemispheric dominance, has been researched since the middle of the 19th century. Until Bramwell (1899) first mentioned the term "crossed aphasia", the so-called Broca's doctrine (1861) was generally accepted which attributed a left hemispheric dominance of language to right-handers and a right hemispheric dominance to left-handers. The increasing knowledge about the organisation of language-relevant areas in the brain led to the assumption that the linguistic processing takes place in the left hemisphere for more than 90% of the right-handed and up to 80% of the left-handed people (Springer, Binder, Hammeke, Swanson, Frost, Bellgowan, Brewer, Perry, Morris, & Mueller, 1999; Szaflarski, Allendorfer, Banks, Vannest, & Holland, 2013). Until the 1970s, the definition of crossed aphasia referred both to left- and right-handers. The current definition of crossed aphasia (now synonymously crossed aphasia in dextrals) thus includes aphasia, which occurs after a right hemispheric brain lesion in right-handed people (Coppens & Hungerford, 2001; Mariën, Paghera, Dedeyn, & Vignolo, 2004).

Crossed aphasia represents a rare form of aphasia with a prevalence of 1-2% of all right-handed stroke patients. Relative to all patients with right hemispheric insult, the prevalence of crossed aphasia is 3% (Schorl, Förster, Kropff, & Vasquez, 2017).

According to the consensus in the literature, the diagnosis of crossed aphasia is based on the following four criteria: (1) The patient has to be clearly aphasic and (2) strongly right-handed, (3) the lesion has to be located in the right hemisphere, and (4) the patient does not exhibit a previous brain damage (Coppens & Hungerford, 2001).

In order to gain a better understanding of the neural organisation of language function in patients suffering from aphasia due to right hemisphere lesions, the following sections address the neural representation of language in normal speakers and in aphasia patients with lesions in the left hemisphere.

1.1 Neural correlates of normal language processing

Neuroimaging studies of healthy language processing revealed activation mainly in inferior-frontal and temporal areas of the left hemisphere (Hickok & Poeppel, 2004; Wise, 2003). Vigneau et al. (2006) confirmed this result in their meta-analysis and additionally found a functional segregation for semantics, phonology and sentence processing. The main activations of phonological, semantic and morpho-syntactic processes were found in Brodmann areas 44 and 45 in the left inferior frontal gyrus (IFG), inferior temporal gyrus (ITG), the middle temporal gyrus (MTG), the superior temporal gyrus (STG) and the left angular gyrus (for reviews cf. e.g. Price, 2010, 2012; Hagoort & Indefrey, 2014; Friederici, 2017). Despite ongoing discussion about the functional segregation or integration of areas and their structural and functional connectivity, the notion of a bilateral but left-dominant brain network will suffice as a reference framework for the purpose of the present study.

1.2 Neural correlates of language processing in left hemispheric aphasia

The linguistic reorganisation after an insult occurs predominantly in preserved as well as in perilesional areas (Grande & Huber, 2007; Zahn et al., 2004). The contribution of the right hemisphere and the occurrence of co-activations to linguistic reorganisation processes are not sufficiently researched. In addition to left hemispheric activations in preserved language-relevant areas, activations of right homologues occurred in co-activations as a supporting effect. If the linguistic areas of the left hemisphere are affected, their functionality can to some extent be replaced by the homologous areas in the right hemisphere. Such compensatory activations leading to a functional replacement of the damaged left areas by contralateral homologues were also reported by Cao, Vikingstad, George, Johnson, and Welch (1999) and Saur et al. (2006).

Meffert (2015) investigated the neural correlates of aphasic spontaneous language symptoms in patients with left hemispheric language dominance in an overt picture description study (for a parallel study with agrammatic patients cf. Schönberger et al. 2014). The main finding was that the occurrence of errors was associated with activations in additional areas in the right hemisphere, pointing to linguistic activity of the right hemisphere. Additional activation effects in the left hemisphere were attributed to extra-linguistic functions, such as monitoring and executive functions.

1.3 Neural correlates of language processing in right hemispheric aphasia

Based on the literature, in the case of crossed aphasia, two different laterality patterns for linguistic functions can be described. On the one hand, it is assumed that the language-relevant areas are mirror images of the corresponding left hemispheric representation. In contrast, there were also patterns deviating from the mirror image. The ratio of mirror image to non-mirror image distribution was given as 2:1 (Henderson, 1983; Schorl et al., 2017).

Only a few functional imaging studies were carried out investigating language production in right hemispheric aphasia, with none of the tasks going beyond oral naming. Khateb et al. (2004) studied the neural representation of language in a single case presenting with crossed aphasia by means of two receptive language tasks. The patient showed aphasic symptoms due to a right frontal meningioma combined with pronounced right-handedness. The cortical activations of this patient were compared with the activations of a healthy control group of 26 subjects. The task consisted of a rhyme and a semantic categorisation part. The fMRI analysis showed activations recruiting both left and right hemisphere areas. Nevertheless, the authors categorised the patient into the group of mirror-image crossed aphasia, because his language impairments fit into those usually observed in patients with a similar left hemispheric insult.

The examination of crossed aphasia by a language production task was object of investigation in the study by Della Rosa et al. (2014). They described functional regression in two patients with subcortical aphasia evoked with an oral naming task. Patient 1 suffered from aphasia after stroke in the left hemisphere, whereas Patient 2 presented with crossed aphasia. In a follow-up study design, the output of the two patients and the corresponding neural correlates were compared over three measurements. Regarding the patient with crossed aphasia, the results showed almost exclusively left-sided activation patterns. These were observed in left frontal (including Broca's region) and left temporo-parietal areas (fusiform and supramarginal gyrus). For both the patient with left hemispheric and the patient with right hemispheric insult, activation peaks for successful as well as for unsuccessful word finding difficulties were each located contralateral to the damaged hemisphere. Accordingly, the patient with crossed aphasia presented a mirror image representation of cortical activations and both patients showed up activation clusters in the contralesional hemispheres during correct and erroneous naming.

In regard to the few functional imaging studies dealing with right hemispheric aphasia and language production, studies investigating continuous language production in patients with right hemispheric aphasia are lacking. Consequently, there is no evidence on how functions of spontaneous language production are mapped to the brain of patients with right hemispheric aphasia.

2. Objectives

The aim of the present fMRI study was thus to investigate the neural representation of linguistic processes in the brain of patients with right hemispheric aphasia. The focus was on the correlation of erroneous language production, particularly the word-finding performance in aphasic patients with right hemispheric lesion compared to patients with left hemispheric lesion.

To this end, we used fMRI to assess the neural correlates of word-finding difficulties in the spontaneous speech production of two patients with fluent aphasia and right hemispheric language dominance. The neural activations of the two patients were compared with a control group consisting of twelve aphasia patients with comparable language deficits caused by lesions in the left hemisphere. All participants performed a picture description task previously developed and evaluated by Tillmanns et al. (2011), Meffert et al. (2011), Schönberger et al. (2014), and Grande et al. (2012) (for details cf. the Methods section below). Subsequently, the utterances of the two patients as well as those of the control group were evoked by fMRI to determine the cortical activations of the resulting aphasic symptoms.

3. Materials and methods

The study was approved by the ethics committee of the Medical Faculty of the RWTH Aachen University (Reference no. EK 040/47).

3.1 Participants

All patients were recruited from the aphasia rehabilitation ward of the University Hospital Aachen. They all had a normal or corrected-to-normal vision. All of them presented with fluent aphasia, as classified by means of the Aachen Aphasia Test spontaneous language syntax scale (Huber, Poeck, Weniger & Willmes, 1983; score 3-5 was assumed to represent fluent aphasia), and were able to perform the picture description task required in the scanner (see procedures section) while still showing enough aphasic symptoms for our analysis. Exclusion criteria were apraxia of speech to avoid movement artefacts in the scanner, a former psychiatric disease, premorbid language disorders or any contraindication for fMRI.

Informed consent was obtained from all participants according to the Declaration of Helsinki.

3.1.1 Patient A

Patient A was a 58-year-old native German man who showed aphasia due to an ischemic stroke affecting the right hemisphere. After ten years of education and an apprenticeship, he worked as a refrigeration plant mechanic. According to his own declaration he was a relearned left-hander. Based on the outcome of the evaluation with the Edinburgh Inventory (Oldfield, 1971), he was classified as ambidextrous with a laterality quotient of +67. Eleven months before participating in this study he suffered a cardiovascular accident that resulted in aphasia. Thus, at the time of testing, patient A was attributed to the late post-acute phase. Language was examined by means of the Aachen Aphasia Test (AAT) (Huber et al., 1983) and revealed an amnestic aphasia of mild to moderate overall severity (see Table 1 for details). His spontaneous language production was characterised by few word finding difficulties and few empty phrases, few phonemic uncertainties and some incomplete sentences. The structural MRI scan showed an infarction comprising the right superior and middle temporal gyrus (STG, MTG), particularly located at the end of the right STG at the transition to the right temporal lobe in the region of Wernicke's area (cf. Figure 1).

FIGURE 1 ABOUT HERE

3.1.2 Patient B

Patient B was a 47-year-old right-handed, native German man. After graduation he studied law and then worked as a lawyer until his stroke occurred. As opposed to patient A, he was strongly right-handed with a laterality quotient of 100 at the Edinburgh Inventory (Oldfield, 1971). The stroke occurred six months prior to the study. Thus, he was in the post-acute phase. According to the evaluation with the Aachen Aphasia Test (AAT) (Huber et al., 1983) he was diagnosed as suffering from amnestic aphasia with mild to moderate overall severity (see Table 1 for details). His spontaneous language production was characterised by very severe word finding difficulties, few phonemic uncertainties and some incomplete sentences. Because of his right-handedness and the right hemispheric lesion, by definition, patient B had a crossed aphasia. Similar to patient A, the insult was localised in the right STG as well as in the right MTG, but this time the entire anterior part of the temporal lobe was affected (cf. Figure 1).

TABLE 1 ABOUT HERE

3.1.3 Control group

The patients of the control group were reported in detail by Meffert (2015) and are reported here to provide a direct reference to a typical group of people with aphasia after left hemisphere damage. The group comprised twelve aphasic individuals, which suffered a left hemispheric cardiovascular accident 1-127 months (mean at 28.3 months) before participating in the study. They were all native German speakers. The mean age of the control group was 48.8 years. Five of the participants were female. The lesion foci were located in the left IFG and the left inferior parietal lobule (IPL) (cf. Figure 3).

FIGURE 2 ABOUT HERE

3.2 Materials

Nine black-and-white drawings were utilised to elicit the spontaneous language production of both patients as well as the control group. Each drawing showed a complex situation with a large number of people, objects and actions to ensure that there was a sufficient amount of propositions being depicted. These stimuli had been evaluated by Meffert et al. (2011) and had been used successfully for eliciting spontaneous language production in healthy participants and people with aphasia (Grande et al., 2012; Meffert, 2015; Schönberger et al., 2014; Tillmanns et al., 2011).

3.3 Procedure

The procedure has previously been described e.g. by Grande et al. (2012) or Schönberger et al. (2014). In preparatory sessions the patients described every image once outside the scanner to get familiarised with the stimuli and the paradigm. The task consisted of describing the nine black-and-white drawings one by one for three minutes each. Afterwards the patients got feedback regarding the length of the description only.

During the subsequent fMRI measurement, the nine black-and-white drawings were presented to the patients via goggles in randomised order for three minutes each while the entire linguistic output was recorded. Every presented picture was followed by a white screen indicating a rest of 55 seconds. Subsequently, a black fixation cross prepared the patients five seconds prior to the appearance of the next image.

3.4 fMRI data acquisition

The fMRI measurement consisted of the functional measurement (about 35 minutes) and the following anatomical image (about 10 minutes). Both measurements were performed on a 3T (Philips Achieva 3.0 T X-series) with a Philips SENSE Head Coil (8 Elements). Data was recorded from 42 sagittal slices using a fast-field-echo gradient EPI sequence with echo time = 30ms, flip angle = 90°, repetition time = 4s, field of view = 240mm, in-plane resolution = 3.75mm x 3.75mm, slice thickness = 3.75mm without inter-slice gap. In total 535 images were acquired for each patient.

Structural T1-weighted MP-RAGE images (resolution 1mm x 1mm x 1mm, FOV = 256mm, TR = 1s, TE = 4.6ms, flip angle = 8°) were subsequently acquired.

The paradigm was presented via video glasses (Resonance Technology Inc., Northridge, CA, USA) with *Presentation*® 11.0 (Neurobehavioural Systems Inc., Albany, CA, USA).

The linguistic output during the entire fMRI measurement was recorded with a directional microphone, consisting of a bell, a condenser microphone capsule (MCE-4000, Monacor, Bremen) and a function for feeding the trigger tone of the fMRI measurement using an external USB soundcard (SB0270, Creative Technology, Dublin, Ireland). It was recorded with the program Audition Version 1.5 (San Jose, CA, USA). A single trigger sound signalled the beginning of the paradigm and the functional record.

3.5 Behavioural data analysis

The language output evoked during fMRI was transliterated with the transcription and evaluation software *Aachener Sprachanalyse* (ASPA) (Huber, Grande, & Springer, 2005). The spontaneous language production including the aphasic symptoms was analysed in the transcripts and the speech files. In order to capture the spontaneous language processes on several levels simultaneously and to be able to compare them among each other, the linguistic data sets were analysed by means of an evaluation scheme developed for this purpose (Grande et al., 2012; Tillmanns et al., 2011).

Symptoms could be assigned to one of the following categories: sublexical, lexical, morphological and syntactic, depending on the linguistic level. Further symptoms were: fragments, incomplete utterances and formulaic language. Word-finding difficulties were assigned to the category "lexical". They were defined as pauses that lasts for at least two seconds, interjections of two words minimum (e.g. ehm ehm), a shorter pause (1-2s) and one interjection or the recurrence of at least one word (e.g. the the).

Moreover the utterances were categorised in incomplete phrases (U), sentence breakup (ABBR) and non-propositional language (AUT), i.e. speech automatisms or stereotypes. Unclear and mixed symptoms were assigned to the remaining category (REST).

The description of all nine black and white drawings was divided into events of one second. Every second was analysed and assigned to one category. After analysing the linguistic behaviour of the two patients, it was compared with the output of the left-hemispheric control group (n = 12), which had been examined with the same paradigm and evaluated in the same way. The most frequent distribution of events of the two right hemispheric patients was afterwards compared with the corresponding categories of the control group.

3.6 fMRI data analysis

The data sets of the event-related fMRI measurement were analysed using SPM12 (Wellcome Department of Cognitive Neurology, UK) running on MATLAB 9.0 (The Mathworks Inc., Natick, USA) in combination with the SPM Anatomy Toolbox (Eickhoff et al., 2007) for the localisation of effects.

In order to analyse the 535 images per patient, all steps of pre-processing were realised. In the first and most important step, the realignment, the functional data sets were motion-corrected. Head movements occurring during the measurement were eliminated. Furthermore a mean image for each patient was calculated. In the second step of pre-processing, the anatomical and functional images were superimposed and normalised. Finally, a smoothing process was applied to distinguish real activations from interfering signals, using a Gaussian kernel of 8mm FWHM and a high-pass filter of 1/128 Hz.

The pre-processing of the functional data sets was followed by the 1st level analysis, which included at least 15 events in the statistical analysis. Then the statistical evaluation for the calculation of contrasts was conducted. Based on the result, the functional activations of each category were compared within both patients and finally with the control group.

4. Results

4.1 Behavioural performance: occurrence of symptoms

For patient A, in sum 1573 events of language output were included in the analysis splitting up into 954 events of unimpaired and 345 events of impaired language. Patient B showed a similar quantity of 1588 events in total, which were divided into 569 events of unimpaired and 432 events of impaired language.

The two most frequent categories in the language of both patients were unsuccessful word-finding difficulties and hesitation phenomena in between CLUs. The largest symptom category in the group of impaired language of patient A were hesitation phenomena in between CLUs with 159 events, followed by unsuccessful word-finding difficulties with 103 events. Patient B showed 102 events of hesitation phenomena in between CLUs and 120 events of unsuccessful word-finding difficulties. Patient A presented 91 events of successfully solved word-finding difficulties and patient B 58 events.

TABLE 2 ABOUT HERE

The statistical values of the control group are presented in Table 2 and were taken from Meffert (2015). The largest symptom category of the control group (n = 12) was hesitation phenomena between CLUs with an average of 347 events, followed by unsuccessful word-finding difficulties with 143 events.

4.2 Functional imaging data

The focus of the investigation was laid on the symptom category with the highest amount of events. The word-finding problems represented one of the most limiting factors in the language of patient A and B as well as in the control group. The events assigned to unimpaired language (cf. Table 2) were compared with all events of the highest symptom category “Unsuccessful word retrieval” of patient A and B. This category revealed left-dominant activation clusters for both patients.

For patient A, seven activation clusters were found in total (cf. Table). The cluster with the largest extent was located in the left hemisphere. It reached from the MTG over the insula lobe and the Rolandic operculum to the STG. The second cluster was located in the right precuneus and the right middle cingulate cortex. Further effects were found in the left postcentral gyrus, left paracentral lobule, left basal ganglia (putamen), left precentral gyrus, left inferior parietal lobule and in the left angular gyrus. The reverse contrast showed no BOLD effects for events assigned to “Unsuccessful word retrieval“ versus “Unimpaired language“ (see Table 3 for details).

TABLE 3 ABOUT HERE

For patient B, all in all nine activation clusters were observed. The largest cluster was located in the left putamen and the left pallidum. The next smaller cluster was found in the left middle and superior occipital gyrus (SOG) and in the left angular gyrus as well as in the left MTG. A third activation cluster was found in the left cuneus, left calcarine sulcus as well as in the left precuneus. The fourth cluster was located in the left middle cingulate cortex, in the left precuneus as well as in the right middle cingulate cortex. A further BOLD effect was located in the left fusiform gyrus and in the left lingual gyrus. Another cluster was observed in the left rolandic operculum. The next cluster had its maximum in the left inferior temporal gyrus (pars triangularis). The penultimate cluster appeared in the left ITG and a last cluster showed up in the left MTG. The reverse contrast revealed no BOLD effects for events assigned to “Unsuccessful word-finding difficulties“ versus “Unimpaired language“ (see Table 4 for details).

TABLE 4 ABOUT HERE

When contrasting unimpaired language to unsuccessful word-finding difficulties, it was found that patient A and B had four activation clusters in common. They showed up in the left angular gyrus, in the left temporal lobe, in the left and right precuneus and in the left putamen (Figure 3).

FIGURE 3 ABOUT HERE

The common activation clusters of the two patients were compared to those of the control group presented by Meffert (2015). In contrast to patient A and B, the control group showed activation clusters in the angular gyrus of the right hemisphere (Meffert, 2015). The activation patterns of the control group in the temporal lobe were located in both hemispheres, i.e. bilateral effects could be observed. In the precuneus, both patients showed midline-like structures that were most far away from the lesion and were observed in both hemispheres. In comparison, the activations of the control group were observed in the right-sided precuneus. A final BOLD effect was located in subcortical structures, in the putamen of the two right hemispheric patients. Here, congruent structures were observed in the left hemisphere of both patients. The control group showed no such effects.

5. Discussion

In the present fMRI study the neural correlates of continuous language production of two patients with aphasia after right hemispheric lesion were studied and afterwards compared with the neural correlates of a control group of patients with standard, uncrossed aphasia (n = 12). In both single cases as well as in the control group the language output was elicited by a complex picture description task. The corresponding neural correlates were afterwards examined with respect to word-finding difficulties. The main finding was the mirrored representation of activation clusters, which will be discussed together with the behavioural data in the following paragraphs.

5.1 Behavioural data

The analysis of the aphasiological profiles of both patients revealed two issues, which were most frequent in the language production of both patients. These were the unsuccessful word-finding difficulties and the hesitation phenomena in between clause-like units (CLUs). While the biggest symptom category of patient A was hesitation phenomena in between CLUs, the main limiting factor of patient B were unsuccessfully solved word-finding difficulties, followed by hesitation phenomena in between CLUs. The big amount of unsuccessfully solved word-finding difficulties was due to the fact that patient B showed longer phases of lexical search, which then often ended successfully. The many incomplete phrases in the language of patient B were associated with syntactic difficulties.

The symptoms displayed by these two patients included the associated difficulties that typically occur in fluent aphasia. The six most common symptom categories were the same as those of the control group. Similar to patient A and B, the two main symptom categories of the group were hesitation phenomena in between CLUs and unsuccessful word-finding difficulties. Both patients and the control group were therefore comparable in their deficits as expected in the light of the similar phenomena of interest they all had to fulfil, i.e. the pattern of spontaneous language production (fluent aphasia, many aphasic symptoms). Both patients were in the same remission phase, i.e. in the post-acute stadium, which additionally increased the comparability.

5.2 Functional data

The comparison of all events assigned to the category of unimpaired language to unsuccessful word-finding yielded four activation clusters patients A and B had consistently in common: the left angular gyrus, the left temporal lobe, the precuneus, and the left putamen. The comparison with the group of control patients with left-hemisphere lesions revealed a mirror pattern for the angular gyrus, a mirror pattern for the middle temporal lobe with also ipsi-lesional involvement in the control patient group, and a mirror image for one of the two patients in the precuneus. These different clusters in combination with the degree of involvement in language processing are discussed in detail in the following sections.

5.2.1 Functional activation cluster in the angular gyrus

The activations shown up during word-finding difficulties in the continuous language production of the two patients revealed BOLD effects in the angular gyrus of the left hemisphere. Comparing these patterns with the functional images of the control group, which showed up BOLD effects in the angular gyrus of the right hemisphere, both patients displayed mirrored activation clusters confirming the hypothesis of mirror image representation.

The contribution of the left angular gyrus to language production in healthy speakers was stressed out by Seghier (2013), who described the angular gyrus to be involved in comprehension and reasoning processes. The study mentioned several abilities that were involved in picture description, such as the implementation of conceptual knowledge, refocusing the attentional system to relevant facts, retrieving information for problem solving and introducing stored memories and experiences into external events. Additionally, Grande et al. (2012) revealed effects in the angular gyrus for normal speakers during error production in the spontaneous language. Symptoms related to conceptual planning in between CLUs in contrast to unimpaired language were correlated with bilateral posterior superior parietal activations including the angular gyrus and the precuneus.

5.2.2 Functional activation cluster in the temporal lobe

Activations in the temporal lobe could be observed in the left hemisphere of both patients with right hemispheric language dominance. In contrast, the control group with standard left hemispheric aphasia presented activations in the temporal lobes of both hemispheres.

Although this represents a rather unexpected imaging, thus, the patients showed contralateral effects indicating a mirror image representation.

In general the temporal lobe was found to be responsible for many language associated functions, such as single word or sentence processing. In picture naming it was relevant for lexical selection, i.e. naming objects of semantically heterogeneous categories (Maess, Friederici, Damian, Meyer, & Levelt, 2002). Besides the conceptually driven lexical selection, the temporal lobes were also mentioned in error-related mechanisms, such as self-monitoring in single word production (Indefrey & Levelt, 2004). Additionally, activations in the temporal lobe were involved in error production in fluent aphasic language (Tillmanns et al., 2011). The temporal lobe was activated for lexical retrieval, possibly reflecting control processes in semantic concepts and the correct word form. This is in accordance with Kircher, Brammer, Levelt, Bartels, and McGuire (2004) who stress the left STG to be correlated with lexical retrieval especially in connected speech and the correlation with pauses particularly occurring within utterances.

5.2.3 Functional activation cluster in the precuneus

Another common activation cluster of both patients was located in the precuneus positioned near the mid-line of the brains. The activations of the control group were observed in the right-sided precuneus. As expected for a patient with distinct right hemispheric aphasia, the activation of patient B was located in the precuneus of the opposite hemisphere compared to the control group. Unexpectedly, Patient A showed activations in the right precuneus as well. It should be noted, however, that these effects are all very close to the mid-line and thus at a comparably wide distance from the lesion in the lateral parts of the brains. In the literature, activation of the precuneus was attributed to mental imagery and mental representations of a text, i.e. to conceptual planning (Grande et al., 2012). It was also associated with perspective-taking during story processing (Vogeley & Fink, 2003). Based on these findings, the activations in the precuneus of patient A and B probably reflected active conceptual planning connected with imagery processes.

5.2.4 Functional activation cluster in the putamen

A supplementary BOLD effect was found in the putamen of the two patients. Corresponding activation clusters were observed in the left hemisphere of both patients. Based on the findings in the previously mentioned areas, the activated cluster of the putamen matches with the expected left hemispheric activation. In contrast, no BOLD effects were observed in the putamen of the control group.

The putamen is a subcortical structure, but is also involved in some aspects of language, e.g. in the generation of sentences, grammatical processes and semantic processes. According to Seghier and Price (2010) the putamen as a part of the basal ganglia plays a non-negligible role in speech production. The results of the study of Viñas-Guasch and Wu (2017) indicated the relevance of the putamen in reading and naming in aphasic language. These results led to the assumption that the putamen of patient A and B is also involved in producing intelligible speech and thus in word-finding processes meanwhile.

5.2.5 Neural correlates in the contra-lesional hemisphere

The effects observed for unsuccessful word-finding difficulties for patient A and B as well as for the control group were mostly found in the contralateral hemisphere to the lesion side. In the literature the contribution of the right hemisphere to recovery processes in aphasia after left hemispheric insult was a matter of debate. Some studies observed a hindering role of the right hemisphere in successful recovery (Naeser et al., 2004; Rosen, Ojemann, & Ollinger, 2000). An important question was, whether the right hemisphere takes over functions of the left hemisphere and consequently has a beneficial contribution in language recovery (Winhuisen et al., 2005). Other studies suggested the contribution of the right hemisphere as unrelated to language production (Rosen et al., 2000).

Regarding the neural correlates of error production, additionally to increased effects in the left hemisphere, right hemispheric activations were observed for uncrossed aphasia (Grande et al., 2012). Meyer, Friederici, and von Cramon (2000) associated activations in the right hemisphere in patients with left hemispheric insult with silently repairing errors during the presentation of receptive sentences. They assumed the increased activity in the right hemisphere to reflect the greater demand of context processing or global intent of language.

Meffert (2015) pointed out that right hemispheric homologues of language relevant areas play an important role in spontaneous language error production and revealed effects in the contralesional hemisphere. These results are in accordance with the present study where in both patients with right hemispheric language dominance the functional representation of word-finding difficulties was mainly located in the left hemisphere. This conclusion matches the assumption that language relevant areas in the right hemisphere were compensated by contralateral areas in the left hemisphere.

In order to examine the regression of crossed aphasia, Della Rosa et al. (2014) researched the differences in functional recovery in a patient with crossed aphasia compared to a patient with uncrossed aphasia concerning the productive performance on naming level. Similar to the results of the current study, they observed functional activations contralateral to the side of the lesion both in the patient with crossed and uncrossed aphasia. They concluded that language recovery in crossed aphasia was presented in the homologous hemisphere compared to uncrossed aphasia.

Consequently, the results of the present study were in accordance with the literature suggesting that recovery from crossed aphasia is generally comparable to recovery from aphasia after left hemispheric lesions (Hindson, 1984; Mariën et al., 2004). Additionally, the results of previous studies examining crossed aphasia were confirmed.

6. Conclusions

Crossed aphasia or aphasia after an insult in the right hemisphere is a rare acquired speech disorder. So far language production in crossed aphasia was only reported for single word processing. For the first time the clinical picture of crossed aphasia was examined using a continuous language fMRI paradigm.

Four common areas were found for patient A and B as well as the control group. Compared to the control group, the analysis of the functional data showed similar reorganisation processes in the homologous areas in the two patients. The activation clusters of the patients with right hemispheric aphasia as well as the activation clusters of the control group were mostly located in the contra-lesional hemisphere. Hence, error production seems to be correlated with contra-lesional activations not only for left hemispheric but also for right hemispheric patients.

The nature of crossed aphasia is not satisfactorily understood and should be further investigated using functional imaging techniques and naturalistic language tasks. By using such methods, not only a better understanding of neurocognitive language lateralisation in general could be achieved, but also a deeper understanding of neural correlates of explicit linguistic processes. Additional neurofunctional knowledge could improve therapeutic approaches and provide an optimum therapy for the patients. The current method of combining fMRI data and specific linguistic parameters seems to be a suitable method.

Due to the fact, that in the current study only two patients were examined, further research should include a greater sample size to obtain more significant results and to validate the results of this study.

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Disclosure of interest

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The authors have no other conflict of interest to report.

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Table 1: Performance of Patient A and B in the Aachen Aphasia Test Subtests (AAT, Huber et al., 1983). AAT percentile ranks are based on norms for the aphasic population (n=376)

Subtest	Patient A		Patient B	
	Score achieved/max	Percentile	Score achieved/max	Percentile
Token Test	15/50	74	4/50	94
Repetition	133/150	64	148/150	97
Written language, production	78/90	86	82/90	91
Naming	108/120	91	74/120	47
Comprehension	113/120	99	103/120	89
Middle profile height/overall aphasia severity	59.96/mild to moderate		56.80/mild to moderate	

Table 2: Behavioural data: number of events per category. The values for the control group were taken from Meffert (2015).

Symptom	Patient A	Patient B	Control Patients (Mean)
Unimpaired Language	954	569	711
Hesitation phenomena in-between CLUs	159	102	347
Unsuccessful word retrieval	103	120	143
Successfully solved word-finding difficulties	91	58	82
Unnoticed unsuccessful morphological errors	27	21	12
Successfully solved sub-lexical errors	26	23	26
Unnoticed unsuccessful incomplete CLUs	36	43	24

Table 3: Patient A: Unimpaired language vs. unsuccessful word retrieval, reported at P = .001 uncorr., extent threshold k = 50 voxels. The coordinates (x,y,z) refer to anatomical MNI space. Abbreviations: L: left; R: right; T_{max}: maximum value in the anatomical structure. Overlap with cytoarchitectonic areas obtained from the SPM Anatomy Toolbox

Cluster	Cluster sizes (voxels)	Local maxima in macroanatomical structure	MNI coordinates			T_{max}	Overlap with cytoarchitectonic areas
			x	y	z		
1	546	L Middle Temporal Gyrus	-50	-20	-8	4.23	Areas OP1, OP2, OP3, Ig1, Ig2, Id1, TE1.0
2	395	R Precuneus	8	-58	40	4.11	
3	141	L Postcentral Gyrus	-36	-22	32	4.06	Areas 2, 3a, 3b, 4p
4	96	L Paracentral Lobule	-14	-12	52	3.52	
5	65	L Basal Ganglia (Putamen)	-16	6	-12	3.78	Area BF (Ch4)
6	62	L Precentral Gyrus	-40	6	46	3.70	
7	56	L Inferior Parietal Lobule	-32	-72	48	3.38	Areas PGa, hIP3, 7A

Table 4: Patient B: Unimpaired language vs. unsuccessful word retrieval, reported at P = .01 uncorr., extent threshold k = 50 voxels. The coordinates (x,y,z) refer to anatomical MNI space. Abbreviations: L: left; R: right; $T_{max:}$ maximum value in the anatomical structure.

Cluster	Cluster Size (Voxels)	Local maxima in macroanatomical structure	MNI coordinates			T_{max}	Overlap with cytoarchitectonic area
			x	y	z		
1	628	L Putamen	-32	0	-2	3.87	Thal: Premotor, Thal: Prefrontal, Thal: Motor, Thal: Somatosensory
2	581	L Middle Occipital Gyrus (Cluster extends into the L Angular and L Middle Temporal Gyrus)	-34	-80	30	3.66	Ara PGp, Area hOc4d, Area PFm
3	358	L Cuneus (Cluster extends into Precuneus)	0	-66	24	3.22	
4	333	L Middle Cingulate	0	-46	44	3.02	Area 7A
5	199	L Fusiform Gyrus	-18	-40	-16	3.01	Cerebellar Lobule V, Lobule VI, Area FG3, Subiculum
6	83	L Rolandic Operculum	-52	2	12	3.14	Area 44
7	64	L Inferior Frontal Gyrus	-48	28	24	2.79	Area 45
8	64	L Inferior Temporal	-46	-52	-12	2.69	Area FG4
9	60	L Middle Temporal	-52	-14	-10	2.92	Area Id1

Figure Legends

Figure 1:

MRI scans of the two aphasic patients with right hemispheric lesions.

Figure 2:

Brain lesions of the control group (from Meffert, 2015).

Figure 3:

Activation clusters for the contrast “Unimpaired > Unsuccessful Retrieval” (in colour), superimposed on the Jülich probabilistic brain atlas (grey-shaded) by means of the SPM Anatomy Toolbox (Eickhoff et al. 2007). The top and middle panel show the effects for Patient A (purple) and Patient B (red), the lower panel shows the effects in the left hemispheric control patients from Meffert (2015). Effects were observed in the angular gyrus (first panel form left), middle temporal gyrus (second cluster from left), precuneus (third panel from left), and (for Patients A and B) also in the putamen. Note the mirror or partly mirror images in the right-hemispheric patients A and B vs. the left-hemispheric control patients.

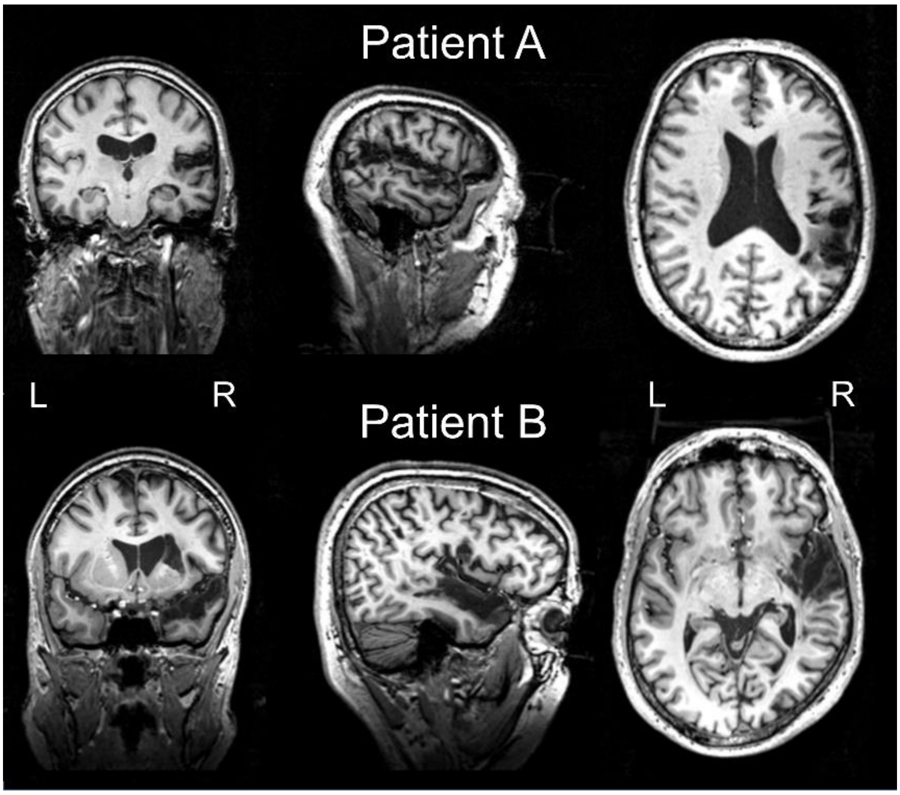

Figure 1

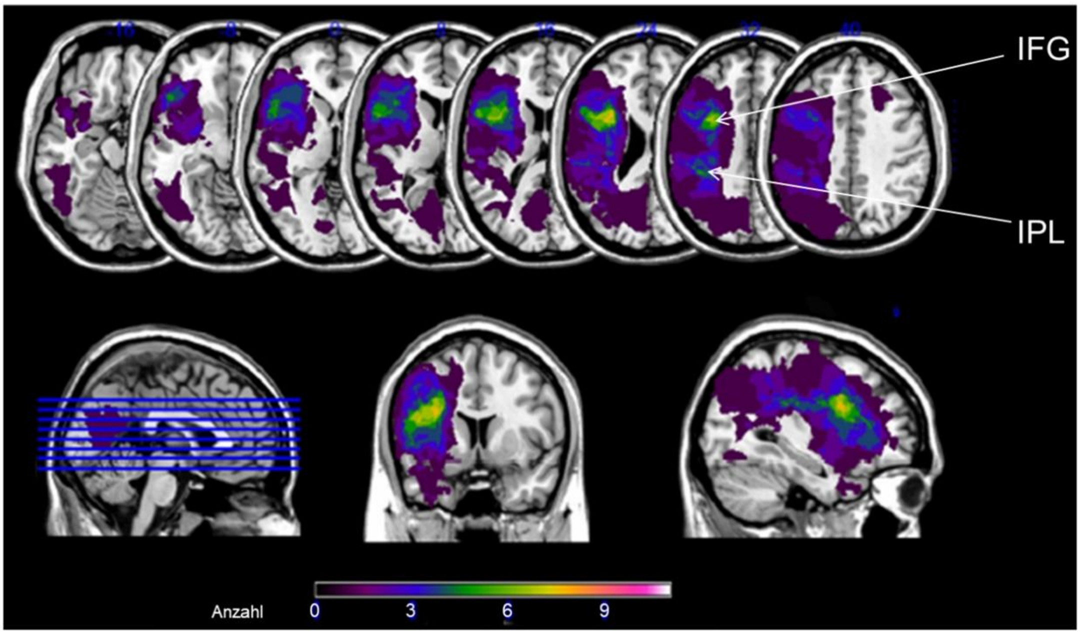

Figure 2

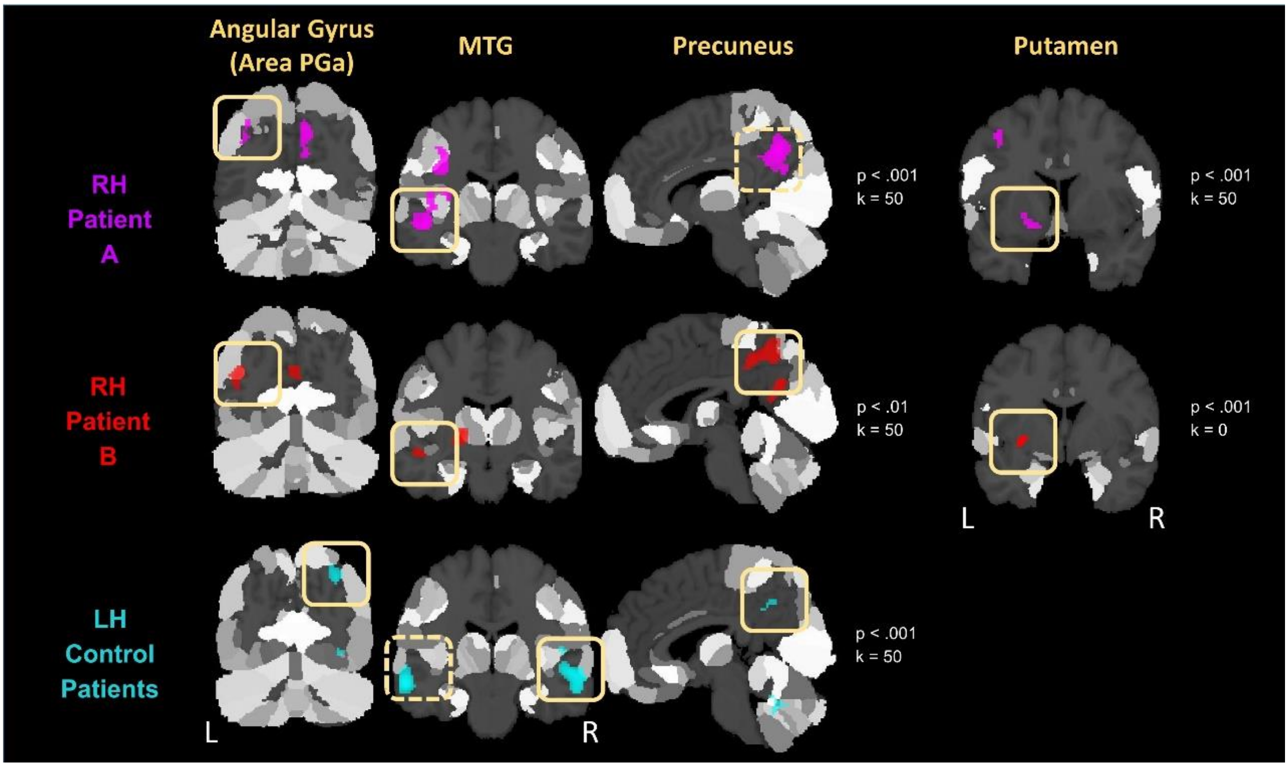
Angular Gyrus (Area PGa)
MTG
Precuneus
Putamen
RH Patient A
p < .001
k = 50
p < .001
k = 50
RH Patient B
p < .01
k = 50
p < .001
k = 0
L
R
LH Control Patients
p < .001
k = 50
L
R

Figure 3