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Cortical activation and language task difficulty in aphasia

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Abstract

Background—Previous research using functional MRI (fMRI) suggests changes in cortical activation as a function of increased task difficulty. This relationship has not been explored in persons with aphasia even though it may have significant implications for pre- and post-treatment interpretation of fMRI data.

Aims—The purpose of this exploratory study was to investigate the relationship between changes in language task difficulty and cortical activation in persons with aphasia.

Methods & Procedures—Four persons with chronic anomic or Broca's aphasia and four matched control participants underwent fMRI while performing a picture–word matching task.

Outcomes & Results—Compared to the more difficult task condition, all participants performed with greater accuracy on the easier condition. Moreover, greater mean blood oxygenated level dependent (BOLD) signal intensity and area recruitment were noted during the more difficult condition for three out of four persons with aphasia as well as three of the four controls. The increase in cortical activity was mainly noted in the superior temporal and posterior inferior frontal lobes.

Conclusions—The present findings mirror those found in previous studies of normal subjects in that cortical activation increased in parallel to task difficulty for most of our participants. It is unclear what mechanism accounts for this effect; this phenomenon might need to be considered in future fMRI studies of neural plasticity associated with aphasia treatment.

Functional neuroimaging has made it possible to investigate cortical regions associated with language processing in both normal and disordered populations. Supporting the views of classical neuropsychology, recent imaging studies of language processing have confirmed neural recruitment in the left inferior frontal gyrus—Broca's area (Stromswold, Caplan, Alpert, & Rauch, 1996)—and left superior temporal cortex—Wernicke's area (Binder et al., 1994; Mazoyer et al., 1993)—during various language tasks. Recent studies have also revealed increased neural activation, although to a lesser extent, in homologous areas of the right hemisphere during language processing (Bottini et al., 1994).

Similar to the present study, these previous investigations used fMRI and defined cortical activation as neural activity measured indirectly by assessment of localised increase in oxygenated blood flow (the BOLD signal). As increased neural activity requires increased delivery of glucose and oxygen, the BOLD signal is thought to mirror localised influx of cell nutrients. There are different ways to report changes in the BOLD signal but most reports include the signal intensity (compared to baseline when a given cognitive task is not being performed) and the extent of cortical areas where the BOLD signal reached some a priori determined intensity threshold.

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Although cortical activation patterns associated with language processing vary to some degree in normal persons (Burton, Noll, & Small, 2001), even greater variation is typically seen in persons with aphasia. It is not entirely clear why cortical activation varies more in the aphasic population, but it is likely that both cognitive and neurophysiological factors play a role. To better understand patterns of cortical activation as measured using fMRI, it will be useful to discern factors that influence the temporal and spatial aspects of the BOLD signal. One of these factors may be fMRI task difficulty. Recent studies utilising functional neuroimaging have demonstrated that brain activation is influenced by the complexity and difficulty of the experimental task—as task difficulty increases, so does cortical activation (Braver, Cohen, Nystrom, Jonides, Smith, & Noll, 1997; Carpenter, Just, Keller, Eddy, & Thulburn, 1999; Grasby et al., 1994; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). That is, greater task difficulty is commonly found to result in greater BOLD signal intensity as well as greater extent of neural activity. For example, Carpenter et al. (1999) presented subjects with a visuospatial task in which they mentally rotated one of two presented block figures to determine whether they were mirror images of one another. The degree of difficulty was varied by changing the angle of rotation between the two figures (i.e., 0°, 40°, 80°, 120°). Their findings revealed a relationship between increased cognitive effort and cortical activation.

To date, few studies have specifically investigated the effect of task difficulty on cortical activation during language processing. In one study utilising fMRI (Just, Carpenter, Keller, Eddy, & Thulburn, 1996) participants with normal language skills were presented with a sentence comprehension task that included three types of sentences of increasing difficulty—active conjoined clauses, subject relative clauses, and object relative clauses. Participants read four to five sentences of each type and, after reading each sentence, answered true-false questions about one of the clauses in the sentence. Results revealed a significant cortical activation increase in Wernicke's and Broca's areas as sentence complexity increased. A similar activation pattern was observed in the right homologous Wernicke's and Broca's areas, but to a lesser degree.

In a more recent study, participants with normal language-processing skills completed a task that comprised four experimental conditions of increasing syntactic complexity (Keller, Carpenter, & Just, 2001). Their results indicated that as task complexity increased—that is, with syntactically more complex sentences that also contained words of lower frequency of occurrence—reaction time increased and response accuracy decreased. Cortical activation associated with task performance was observed in the primary language areas of the left hemisphere, including Wernicke's and Broca's areas. More importantly, the BOLD signal intensity and cortical area recruitment increased as the task became more difficult. The most difficult condition, consisting of object-relative sentences with low-frequency words, resulted in the greatest volume of activation of the four conditions presented.

Anderson, Perera, Hilton, Zubin, Dela Paz, and Stern (2002) studied older adults' word recognition and found increased cortical activation associated with increased task difficulty. That is, higher cognitive demands associated with increased task difficulty (recognising lower-frequency words) resulted in greater BOLD signal intensity in areas activated during the baseline task. Further, area-specific activation not seen during the baseline task was also observed. These results further support previous findings that language task difficulty influences patterns of cortical activation as measured by fMRI.

The studies described above have implications for fMRI studies of neural reorganisation associated with aphasia treatment. To chart changes in the brain associated with aphasia treatment, it will be important to know whether change in cortical activation is consistent with that seen during performance of easier pre-treatment fMRI tasks. That is, if a language task becomes easier to perform as a result of aphasia treatment, will post-treatment cortical

activation resemble what would be seen before treatment on language tasks that were easier at that time? The results of such a study would provide important data to shed light on whether aphasia treatment results in strengthening of an existing cortical language network (cortical map expansion) or whether new areas have been recruited to support language (homologous area adaptation or cross-modal reassignment). Before such a study is conducted, however, it is pertinent to investigate the relationship between cortical activation patterns and task difficulty in persons with aphasia.

Although previous research supports an association between fMRI task difficulty and cortical activation in normal language users, this relationship has yet to be studied in persons with aphasia. The purpose of this exploratory investigation was to compare cortical activation associated with a picture-word verification task with two levels of difficulty in persons with aphasia and their normal counterparts. Our research question was: Is increased language task difficulty associated with increased cortical activation in persons with aphasia and in those with an intact language system?

METHOD

Participants

Four persons with aphasia who had suffered left middle cerebral artery ischaemic strokes were recruited for study participation from aphasia groups at the University of South Carolina Speech and Hearing Center (Table 1). Three of the four participants were men and all were native speakers of English. Time post-stroke varied between 12 and 141 months. In addition to aphasia, two participants (A1 & A2) had right hemiparesis. The Western Aphasia Battery (WAB; Kertesz, 1982) was administered to determine participants' aphasia type and severity. WAB Aphasia Quotients (AQ) ranged from 29.5 to 78.4; two persons had anomic aphasia and two had Broca's aphasia. Auditory comprehension sub-scores ranged from 4.45 to 9.5. Because this was an exploratory study, we did not control for type and severity of aphasia or site of lesion. These persons were studied because they could perform the task, and were available and willing to participate in this research

Four normal control participants were recruited and matched to the experimental group based on age, gender, race, and education. All participants demonstrated hearing and visual acuity (after correction, if needed) sufficient for task completion using pre-scanning screen where the task was presented using a laptop showing similar picture size and sound intensity to that experienced in the MRI scanner. Each participant gave signed informed consent approved by the University of South Carolina and the Medical University of South Carolina Institutional Review Boards for study participation.

MRI

All MRI scanning was conducted on a Philips Intera 3T system with parallel acquisition capabilities using an eight-element head coil. The fMRI sequence was collected using a time series of echo planar gradient-echo images and the following parameters: SENSE $r = 2$, TR = 10 s; TA = 1.647 s; TE = 30 ms; in-plane resolution 3.25×3.25 mm. A total of 32 axial slices (3.25 mm thick) covering the supratentorial brain were collected 120 times each. A TA of 1.647 s means that fMRI data were collected for only the first 1.647 s of each TR; therefore, the loud scanner noise associated with data collection was present for a total of only about 20% of the actual 20 minute fMRI sequence. Sparse scanning is useful for scanning persons with aphasia because it decreases the influence of the scanner noise on execution of the fMRI task. An anatomical reference for cortical activation was acquired using a rapid T1-weighted 3D FLASH acquisition, with magnetisation prepared by a non-selective inversion pulse: matrix size $256 \times 256 \times 160$, voxel size $1 \times 1 \times 1$ mm, 15 degree flip angle, TE = 5.7 ms, TR = 9.5 ms per

FLASH line, effective TI = 800 ms, frequency encoding head-foot with SENSE $r = 2$ applied in the left-right direction. MRI scanning lasted approximately 25 minutes.

Behavioural task

A picture-word verification task was used for the purpose of fMRI data collection. Stimuli consisted of recorded spoken words and pictured nouns identified as high-frequency words by Francis and Kucera (1982). The goal of the task was to determine whether a picture presented on an MRI-compatible computer screen matched a spoken word presented through air conduction type headphones. Difficulty of the task was varied between two conditions; during the easier condition participants were presented a series of two pictures for 2 s each. At the beginning of each picture presentation, a spoken word was presented—half of the spoken pictures and spoken words represented a correct match. To indicate whether a picture-word pair depicted a correct or incorrect match, participants pressed buttons on a response glove fitted on the left hand.

A response was recorded only when the picture was displayed on the screen. That is, participants had to respond to the correctness of picture-word pairs while each picture was in view. Once a new picture-word pair was presented, the time to respond to the previous stimulus pair was over. Therefore, the total time allotted for responding was the same as the time of each picture presentation (2 s for the easier condition). The more difficult condition was much the same; however, participants were presented with a series of three picture-word pairs for 1.333 seconds each. For the purpose of fMRI data analysis, a baseline condition consisted of abstract pictures and backwards speech. The baseline condition allows for extraction of neural activation associated with language processing rather than activation related to visual and speech processing. Participants pressed either the correct or incorrect response buttons during the baseline condition but were not required to make judgements regarding baseline items. The total number of stimulus blocks (each block representing either two or three picture-word pairs) was 40 for the two task conditions and their presentation order was randomised. Prior to fMRI data collection, all participants were screened using a short version of the fMRI task to verify that performance was above 50% accuracy on the easier condition. Auditory stimuli were recorded in a single session by the same male speaker. The experimental paradigm was constructed using E-Prime (2000) and presented during data acquisition using Integrated Functional Imaging System (IFIS; 2000).

The Automated Functional Neuro Imaging program (AFNI; Cox, 1996) was used to process the fMRI data. The data were realigned to correct for head motion and smoothed using an 8-point Hamming window, and low-frequency trends were removed. A correlation analysis was used to extract cortical activation associated with completion of the fMRI task. A correlation threshold of .31 ($p < .005$) was arbitrarily selected to account for 10% of the fMRI signal variance. Only two-voxel clusters were retained in the final functional maps. Functional maps were registered to standard space (Talairach & Tournoux, 1988) for comparison across subjects and to verify locations of cortical activation. MRIcro (Rorden & Brett, 2000), an MRI viewing software, was used for image display.

RESULTS

Task performance

All participants performed better than chance on the experimental task. For participants with aphasia (A1–A4), greater accuracy was observed on the two picture-word condition (2-PWC) than for the three picture-word condition (3-PWC) (Table 2). Accuracy ranged from 68% to 97% on the 2-PWC and from 53% to 85% on the 3-PWC. As expected, the normal control participants (N1–N4) performed the task with greater accuracy compared to their counterparts

with aphasia, with control participants performing at ceiling on the 2-PWC, and near ceiling on the 3-PWC with a range of 93% to 98% correct. Compared to the 2-PWC, the 3-PWC was reported as more difficult due to the shorter allotted response time by all participants.

Cortical activation

As shown in Figure 1, greater cortical activation was observed for three of the four persons with aphasia during the 3-PWC compared to the 2-PWC condition with regard to aerial extent and intensity of activation. Aphasic participant number three (A3) had a similar number of voxels activated for the two conditions; however, greater mean signal intensity was observed on the more difficult condition. A ratio of activated voxels was calculated to demonstrate the proportional activation change among the two conditions across all activation intensities. The total number of activated voxels during both conditions was divided by the number of voxels activated during the 3-PWC. Thus, a ratio of .5 would indicate equal number of voxels that reached statistical activation for the two experimental conditions. A ratio higher than .5 suggests greater activation associated with execution of the 3-PWC. The activation ratios are reported in Figure 1.

Cortical activation was primarily unilateral regardless of task difficulty. Mostly right hemisphere activation was observed for A1, A2, and A4 in the right superior temporal lobe while A3's functional scan showed primarily left temporal lobe activation (Figure 2).¹ With regard to activation loci, activation increase was noted primarily in the right superior temporal lobe of A1, A2, and A4. In addition, compared to the 2-PWC, greater cortical activation extent and signal intensity was noted in the right homologue of Broca's area for these participants on the 3-PWC. In contrast, A3 showed minimal change in the overall number of activated voxels across the two conditions. Note that in addition to a left parietal lobe lesion, A3 also had left thalamic damage.

Bilateral activation was observed in the control participants. This activation was primarily located in Wernicke's area as well as its right hemisphere homologue. Recruitment of left hemisphere regions was greater than that of the right hemisphere during completion of both experimental conditions.

fMRI data revealed greater overall activation in the control subjects than in the aphasic subjects (Figure 1). Similar to the persons with aphasia, three of the four controls showed more activation on the more difficult condition. Not surprisingly, the pattern of cortical activation was more consistent across these participants compared to their aphasic counterparts (Figure 2). The superior temporal lobe was activated in all four controls during both conditions with greater signal intensity and extent of activation seen during the more difficult condition. For N1, N3, and N4, the most notable increase in activation seen on the more difficult condition was in Broca's area (Brodmann's areas 44 and 45 including the anterior insula). It is important to note that N2 showed greater activation for the easier condition but Broca's area activation was similar across the two conditions.

DISCUSSION

Using a picture–word verification task with two levels of difficulty, the present research explored the association between language task difficulty and cortical activation in persons with aphasia and normal control subjects. Similar to that found in previous studies of normal participants, the results suggest that increases in cortical activation parallel that of language task difficulty (Anderson et al., 2002; Just et al., 1996; Keller et al., 2001).

¹For presentation purpose, slice thickness here is 6 mm but was 3.25 mm for EPI images and 1 mm for structural T1 scans. Therefore, only a small number of voxels that reached statistically significant activation are shown in these images.

Task accuracy was greater on the 2-PWC compared to the 3-PWC for all participants. This was not surprising and in agreement with others who have shown that reduced stimulus presentation rate and increased time allowed for response are directly related to greater accuracy on language tasks in both aphasic and normal persons (Pashek & Brookshire, 1982; Santo Pietro & Rigoordsky, 1982; Silkes, McNeil, & Drton, 2004). Silkes et al. found that error rate on a naming task increased when shorter response intervals were used. In fact, their participants produced some of the same naming errors seen in aphasia as allotted response time was decreased. Although the present study employed control participants, a direct comparison of cortical activation among the persons with aphasia and their normal controls was not feasible since the controls reached ceiling on the easier condition and were performing near ceiling on the more difficult condition. This was not the case for the participants with aphasia, who did not perform at ceiling level on either condition. It is possible, however, that the same mechanism was responsible for cortical activation differences within the two groups. The question remains as to why an increase in activation was observed during the more difficult condition for most participants. A number of factors could play a role, such as lexical access, stimulus presentation rate, and working memory load.

It could be argued that the language processing demands of the task were greater during execution of the 3-PWC, leading to the increased activation. As participants had less time to consider the correctness of a picture–word match, they had to work faster, and perhaps harder, to arrive at a conclusion. In the case of aphasia, lexical access is frequently impaired and we could expect greater proportional change in cortical activation between the two conditions than in the normal participants who possess normal lexical access and performed at or near ceiling on both conditions. This was not the case as the mean proportional difference in activation among the two conditions was similar for the two study groups (aphasia = .62; normals = .66). Moreover, when the study task was piloted for the present study using only one picture–word pair per stimulus block, mostly left superior temporal lobe activation was noted in the absence of left inferior-posterior frontal lobe activation in three normal persons. Although we cannot discount a purely language processing based explanation of the present findings, an activation increase in the right homologue of Broca's area in the persons with aphasia and in Broca's area for the normals would perhaps suggest an explanation based on increased working memory load, since Broca's area is frequently activated during working memory based fMRI tasks.

Previous research suggests that working memory and language impairment coexist in some persons with aphasia (Caspari, Parkinson, LaPointe, & Katz, 1998) while others have implicated posterior-inferior frontal lobe activation on both verbal and non-verbal working memory tasks (Coull, Frith, Frackowiak, & Grasby, 1996; Gaschler-Markefski, Yoneda, Kaulisch, Brechmann, & Scheich, 2003; Postle, Berger, Goldstein, Curtis, & D'Esposito, 2001). The pilot data showed no such activation during a single picture–word matching task as opposed to consistent activation associated with the 3-PWC in both study groups. It is possible that increased working memory load could account for these findings.

As discussed by Chein, Ravizza, and Fiez (2003), the embedded-processes model of working memory suggested by Cowan (1999) is particularly suitable for explaining results of neuroimaging studies of working memory. In his model, Cowan describes one memory store, likened to long-term memory, in which feature-based representations are held. Information in this memory store is made available in one of two ways: (1) information can temporarily be placed at a heightened level of activation; and (2) specific focus of capacity-limited attention can be placed on a limited subset of this information. Cowan suggested that heightened level of activation acted like a spotlight on information in long-term memory and was supported by the inferior-posterior prefrontal cortex. Increased demands on this process should result in increased neurological activation in cortical areas that support the process. Chein et al. (2003) further postulated that Broca's area is involved in heightening activation of

phonological information. Consequently, it is possible that the increase in Broca's area activation seen in the normal participants, and the right homologous Broca's area in three of the four persons with aphasia, was the result of faster scanning rate of the "spotlight" in lexical-semantic memory. That would mean that persons with Broca's area damage would perform particularly poorly on a task requiring picture-word matching. However, the only participant (A2) in the present study with damage to Broca's area performed the task as well or better than the other aphasic participants. It should be noted that this person was also the furthest post-stroke and his aphasia type had progressed from initially being global to current type of Broca's. Nevertheless, it is possible that increased activation observed during the more difficult condition could be accounted for by increased working memory demands, even though the present data do not allow for such a definitive conclusion.

It could also be argued that because rate of presentation and response time are the only differences between the two levels of the experimental task, simply seeing more pictures and hearing more words could have resulted in the activation increase. However, previous functional neuroimaging studies of cortical activation associated with changes in rate have yet to show a universal pattern of activation increase coupled with rate increase (Dhamala, Pagnoni, Wiesenfeld, Zink, Martin, & Berns, 2003; Riecker, Wildgruber, Mathiak, Grodd, & Ackermann, 2003). For example, Dhamala and colleagues (2003) used fMRI to identify cortical regions and extent of activation associated with varying rates of finger tapping. Increased rate of finger tapping resulted in greater activation in the cerebellum and thalamus, but less activation in the basal ganglia. Here, increased rate was not consistently correlated with increased cortical activation. These findings suggest that increased rate alone may be an insufficient explanation for the present findings.

It is important to note that the change in cortical activation was not uniform between the two conditions across aphasic and normal participants. As explained by Aguirre, Zarahn, and D'Esposito (1998) there is considerable variability in the amount of cortical activation seen on fMRI across different participants performing the same task. Therefore the locus of activation is usually similar among a group of participants even though the amount and intensity of activation may vary. This phenomenon is probably more pronounced in persons with aphasia where greater inter-subject variability can be expected with regard to language performance and neurological status compared to the normal population. For example, Fridriksson, Rorden, Morgan, and Baylis (2005) suggested that the BOLD signal has a later onset in the case of chronic hypoperfusion compared to a healthy blood supply. Finally, as is evident on the T1 structural scans, the lesion location varied among the experimental group, something that directly influences what areas are available for task processing.

Even though we cannot definitively confirm why there was a difference in cortical activation between the two task conditions, the present study suggests a factor that may need to be considered when using fMRI to measure neural plasticity associated with treatment-assisted aphasia recovery. Future studies may benefit from calibrating the difficulty of the fMRI language task used before and after treatment in order to highlight new areas that have taken over language function or become more activated as a result of aphasia treatment. In addition, it may be important to investigate the influence of varying difficulty of other kinds of language tasks used in fMRI studies such as overt picture naming and sentence parsing. Intuitively, such studies should mirror that of the present investigation. However, as our findings suggest, there is much fMRI signal variability even within just a few participants.

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A1 (AR=.60)

A2 (AR=.71)

A3 (AR=.50)

A4 (AR=.65)

N1 (AR=.74)

N2 (AR=.43)

N3 (AR=.61)

N4 (AR=.85)

Figure 1.

Extent of cortical activation (measured in number of voxels that reached significant activation) and BOLD signal intensity associated with performing the two experimental task conditions by persons with aphasia (A1–A4) and control participants (N1–N4). The light grey bars represent the two picture–word condition and the dark grey the three picture–word condition. Activation ratios (AR) are reported for each participant.

Figure 2. Cortical activation for the two task conditions in participants with aphasia and control subjects. Images are shown in radiological view (left–right reversed) and were selected for display to highlight activation differences between the two experimental conditions.

TABLE 1
Participants' biographical and aphasia-related information

	<i>Gender</i>	<i>Age</i>	<i>Race</i>	<i>Years of education</i>	<i>Months post stroke</i>	<i>Aphasia type</i>	<i>AQ¹</i>	<i>Cortical areas affected by the stroke</i>
Participants with aphasia								
A1	Male	45	AA	10	20	Anomic	78.4	L parietal lobe
A2	Male	67	Cauc.	12	141	Broca's	29.5	Entire L MCA distribution
A3	Male	78	Cauc.	13	18	Anomic	65	L thalamus & parietal lobe
A4	Female	51	AA	16	12	Broca's	53.4	L posterior-lateral frontal lobe
Normal controls								
N1	Male	48	AA	11				
N2	Male	65	Cauc.	12				
N3	Male	77	Cauc.	12				
N4	Female	46	AA	18				

¹ AQ = Aphasia Quotient on the Western Aphasia Battery.

TABLE 2

Task accuracy for the two experimental conditions

<i>Participant</i>	<i>Two picture– word matches</i>	<i>Three picture– word matches</i>
A1	97%	85%
A2	92%	79%
A3	86%	56%
A4	68%	53%
N1	100%	97%
N2	100%	93%
N3	100%	98%
N4	100%	96%