

Speech and language functions that require a functioning Broca's area

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Abstract

A number of previous studies have indicated that Broca's area has an important role in understanding and producing syntactically complex sentences and other language functions. If Broca's area is critical for these functions, then either infarction of Broca's area or temporary hypoperfusion within this region should cause impairment of these functions, at least while the neural tissue is dysfunctional. The opportunity to identify the language functions that depend on Broca's area in a particular individual was provided by a patient with hyperacute stroke who showed selective hypoperfusion, with minimal infarct, in Broca's area, and acutely impaired production of grammatical sentences, comprehension of semantically reversible (but not non-reversible) sentences, spelling, and motor planning of speech articulation. When blood flow was restored to Broca's area, as demonstrated by repeat perfusion weighted imaging, he showed immediate recovery of these language functions. The identification of language functions that were impaired when Broca's area was dysfunctional (due to low blood flow) and recovered when Broca's area was functional again, provides evidence for the critical role of Broca's area in these language functions, at least in this individual.

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1. Introduction

Studies of chronic aphasia have indicated an essential role of Broca's area in various speech and language functions. The definition of "Broca's area" is controversial, and the precise neuroanatomical boundaries vary across individuals, whether the boundaries are defined by the cytoarchitecture or borders of sulci and gyri (Amunts et al., 1999; Rademacher, Caviness, Steinmetz, & Galaburda, 1993; Van Essen, Drury, Joshi, & Miller, 1998; Whitaker & Selnes, 1976). Nevertheless, Broca's area is sometimes defined as Brodmann's area 44 and 45—areas

of cytoarchitecture generally found in the left posterior inferior frontal cortex. Some investigators claim that Broca's area is essential for creating and maintaining traces or chains of movement in movement-derived sentences (e.g., passive and object relative clause sentences; Grodzinsky, 2000). Others argue that this area is more generally required for thematic role assignment or for verbal (semantic or phonological) working memory. Evidence for these hypotheses primarily comes from patients with chronic Broca's aphasia, who are assumed to have lesions involving Broca's area. For example, many studies have reported that individuals clinically diagnosed with Broca's aphasia understand simple active sentences, but fail to understand semantically reversible passive sentences (Friedmann & Shapiro, 2003; Grodzinsky, 2000; Schwartz, Saffran, & Marin, 1980). Some of these studies have found that they also understand subject relative clause sentences and sub-

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ject clefts, but fail to understand object relative clause sentences and object clefts (Caramazza & Zurif, 1976; Friedmann & Shapiro, 2003; Grodzinsky, 1989). The latter observation has led Grodzinsky and colleagues to claim that Broca's area is specifically involved in creating and maintaining traces of movement. However, the "trace deletion hypothesis" has also been criticized, leading to a lively discussion on the role of Broca's area in sentence comprehension (see Beretta, 2000; Berndt, Mitchum, & Haendiges, 1996; Caplan, Alpert, Waters, & Oliveri, 2000; Caplan, Hildebrandt, & Makris, 1996; Dick & Bates, 2000; Dickey, Choy, & Thompson, 2007; Draai & Grodzinsky, 2006; Draai, Grodzinsky, & Zurif, 2001; Hickok, 2000; Hickok & Avrutin, 1995; Kolk & Hartsuiker, 2000; Muller & Knight, 2006).

Other lesion/deficit association studies have implicated Broca's area in agrammatic speech (Caramazza & Hillis, 1990; Kolk & Friederici, 1985; Miceli, Silveri, Romani, & Caramazza, 1983), verb production (Hillis, Tuffiash, & Caramazza, 2002; Hillis, Wityk, Baker, Ulatowski, & Jacobs, 2003; Zingeser & Berndt, 1990), complex verb argument structure (Shapiro, Gordon, Hack, & Killackey, 2002; Thompson, Lange, Schneider, & Shapiro, 1997), or spelling (Hillis, Chang, & Breese, 2004; Hillis, Kane, Tuffiash et al., 2002). However, the evidence for some of these associations comes from patients selected for having "Broca's aphasia" (a controversial classification in itself, e.g., Caramazza, Capitani, Rey, & Berndt, 2001; Miceli, Silveri, Romani, & Caramazza, 1989), rather than patients selected for lesions involving Broca's area. There is not a one to one correspondence between Broca's aphasia and lesions in Broca's area. Some patients with damage to Broca's area do not have Broca's aphasia, and some patients with Broca's aphasia do not have lesions in Broca's area (Bramwell, 1898; Dronkers, 2000; Dronkers, Shapiro, Redfern, & Knight, 1992; Marie, 1906; Mohr, 1976; Willmes & Poeck, 1993). Furthermore, the majority of patients with chronic Broca's aphasia have large lesions involving additional areas, rather than damage specifically to Broca's area. Therefore, it is difficult to determine whether deficits are due to Broca's area or surrounding areas.

If one were interested in identifying the language functions that critically depend on Broca's area, it would seem more straightforward to test language in patients with damage to Broca's area. However, many patients with damage to Broca's area (or any other perisylvian area) have language deficits initially, but recover over time, often after rehabilitation. Recovery may be due to reorganization; that is, other parts of the brain may assume functions of the damaged part. In other cases, rehabilitation may have provided alternative strategies or cognitive mechanisms for completing the task. In either case, some patients with damage to Broca's area might show normal performance, even on tasks that initially depended on Broca's area. To avoid these complications, one could test language functions immediately after damage to Broca's area, before reorganization or recovery.

However, neuroimaging of patients with acute stroke have demonstrated that surrounding acute infarction, there is an area of dysfunctional but potentially viable ischemic tissue that may be contributing to the observed deficits. For example, early studies using intracarotid xenon-133 cerebral blood flow indicated that aphasia in patients with subcortical lesions is generally due to hypoperfusion and functional loss in cortical language zones (Olsen, Bruhn, & Oberg, 1986). More recent studies using perfusion weighted imaging (PWI) have confirmed that aphasia only occurs after subcortical infarcts when there is concomitant hypoperfusion (Hillis, Wityk et al., 2002) and that language deficits in acute stroke are attributable to the entire region of dysfunctional brain tissue – the infarct plus the hypoperfused tissue (Croquelois, Wintermark, Reichhart, Meuli, & Bogousslavsky, 2003; Hillis, Barker et al., 2004; Hillis, Wityk et al., 2001; Hillis, Work et al., 2004; Reineck, Agarwal, & Hillis, 2005).

It has been demonstrated that a variety of interventions can restore blood flow to the hypoperfused tissue surrounding the infarct, with concomitant improvement in behavioral functions (Croquelois et al., 2003; Hillis, Barker et al., 2001; Hillis, Kane, Tuffiash, Ulatowski et al., 2002; Hillis, Ulatowski et al., 2003). For example, in a study of 44 patients with acute subcortical stroke, the patients who had aphasia all showed concurrent cortical hypoperfusion (Hillis, Wityk et al., 2002). Among the patients in this study who received intervention that successfully restored cortical perfusion, six out of six showed immediate resolution of aphasia. Interventions to restore perfusion have included intravenous and intra-arterial thrombolysis, stenting, urgent endarterectomy and other vascular surgical procedures (e.g., Wityk, Hillis, Beauchamp, Barker, & Rigamonti, 2002), and induced blood pressure elevation (Hillis, Ulatowski et al., 2003; Rordorf, Koroshetz, Ezzeddine, Segal, & Buonanno, 2001). The last intervention is based on animal studies showing that in hypoperfused tissue, there is a loss of autoregulation, such that increased blood pressure results in a linear increase in regional cerebral blood flow (Astrup, Symon, Branston, & Lassen, 1977).

Functional imaging studies have also identified activation in Broca's area (or parts of Broca's area) associated with a wide variety of language tasks and nonlinguistic or cognitive processes, not all of which can be reviewed in a case report. Some of these cognitive processes may be critical to the language functions that are impaired in Broca's aphasia. For example, a reliable finding from fMRI is activation in Broca's area and surrounding areas during tasks that demand phonological working memory (Fiez et al., 1996; Paulesu, Frith, & Frakowiak, 1993). A number of authors have proposed that phonological working memory deficits may underlie agrammatic speech and/or asyntactic comprehension that are frequently observed in Broca's aphasia (Stowe, 2000; Vallar & Baddeley, 1984). Other studies have shown activation in Broca's area associated with a variety of semantic

tasks (Bookheimer, 2002) or selection of a response from semantic memory (Thompson-Schill, Aguirre, D'Esposito, & Farah, 1999; Thompson-Schill & Gabrieli, 1999; Thompson-Schill, Kurtz, & Gabrieli, 1998). Some studies also show activation of Broca's area during verb production (Tranel, Grabowski, Lyon, & Damasio, 2005) or spelling (Beeson et al., 2003; Rapp & Hsieh, 2001). Other functional imaging studies show that different subregions of Broca's area are responsible for different deficits. For example, a number of studies converge on the hypothesis that anterior Broca's area is critical for semantic tasks (Gitelman, Nobre, Sonty, Parrish, & Mesulam, 2005), while posterior Broca's area is critical for word recall and repetition (Buckner et al., 1995) or processing of letters or syllables (Booth et al., 2002; Poldrack et al., 1999).

Many other functions have been found to be associated with activation in Broca's area, with or without activation in its right hemisphere homologue. However, functional imaging studies can only show that Broca's area is engaged in a process, not that it is essential for the process (Chatterjee, 2005; Fellows et al., 2005). Ideally, functional imaging studies and lesion studies should be used together to identify areas that are necessary and sufficient for a particular cognitive function (Chatterjee, 2005; Muller & Knight, 2006; Price, Mummery, Moore, Frakowiak, & Friston, 1999). However, this recommendation has rarely been practiced.

One type of supporting evidence that an area is essential to a particular function in an individual is provided when a particular language function is impaired when the area is dysfunctional and recovers when that area becomes functional again. This sort of evidence can be obtained with temporary "lesions" (e.g., transcranial magnetic stimulation, direct cortical stimulation, or transient ischemia). To illustrate the last method, we previously reported that accessing orthographic word forms of verbs (but not nouns) for written naming was impaired in two patients with low blood flow in Broca's area, and recovered when blood flow was increased in Broca's area (in one case by carotid stenting, and in one case by blood pressure elevation) (Hillis, Wityk et al., 2003).

We hypothesized that other language functions, such as understanding and producing syntactically or semantically complex sentences are dependent on Broca's area (perhaps as one cog in a complex neural system) and will therefore be acutely compromised when the neural tissue within Broca's area is selectively hypoperfused. The following case report illustrates support for this hypothesis. We studied a variety of language functions in a patient with hyperacute stroke, who showed selective hypoperfusion, with minimal infarct, in Broca's area. Language testing was repeated after Broca's area was reperfused to confirm that language functions dependent on Broca's area in this individual recovered with reperfusion of Broca's area.

2. Case report

MJE, a 67 year old, right-handed man with atrial fibrillation developed sudden muteness at 4 AM, the day after a surgical procedure. Due to recent surgery he was not an appropriate candidate for intravenous thrombolysis.

Neurological examination took place 34 min after acute onset. MJE was found to be severely aphasic. Initially, he was mute, but within an hour he began to articulate words and phrases with numerous and varied off-target attempts, particularly with polysyllabic words (e.g., hospital-> [tas-pIdəl]...[hastIbəl]) despite normal strength, rate and range of movements of the muscles of articulation (consistent with apraxia of speech). He was alert and interactive, but his speech production was limited to short phrases or single words, and he made frequent paraphasic errors, mostly semantic in nature.

Although MJE could accurately follow simple commands, he was unable to repeat sentences and had difficulty naming objects. He described the "cookie theft" picture as "kis-kitchen...in kitchen...picture. The laundry running over...kid on the thing." Although the patient's sensation was intact and motor strength was normal in both upper and lower extremities, he could not form letters to write.

Immediate head CT was normal. On the same day, MRI scans were obtained at four hours post-onset of symptoms. MRI scans included sequences of diffusion weighted imaging (DWI), which is highly sensitive to infarct in the first hours of stroke, and perfusion weighted imaging (PWI), which shows areas of poor perfusion (low blood flow). Areas of hypoperfusion were defined by a time-to-peak (TTP) delay in arrival of contrast of >2.5–4.5 s compared to the homologous voxels on the right. MRI showed a very small (<3 mm) infarct in the left posterior frontal lobe, surrounded by a much larger perfusion deficit in a region that approximates Broca's area (an area in which we would predict the cytoarchitecture of Brodmann area (BA) 44 and 45 based on studies by Amunts et al., 1999 and others) (Figs. 1 and 2). The correspondence between his area of hypoperfusion and Broca's area defined in this way was confirmed by computational analysis of the percentage of voxel overlap with the probabilistic map of Amunts et al. (1999). To allow us to compute voxel overlap we registered the patient's diffusion and perfusion sequences to the MNI atlas, using a mutual-information maximization algorithm (Jenkinson & Smith, 2001) with the patient's high resolution spoiled gradient echo (SPGR) sequence obtained at the same time. Once we had registered the perfusion (TTP) map to the atlas, we could automatically locate the midsagittal plane, and thus could readily identify voxels that showed diminished perfusion relative to their counterparts in the right hemisphere. We placed these registered diffusion and perfusion maps and the Amunts et al. (1999) probabilistic map (already registered to the MNI atlas) into a brain-image database (BRAID; Herskovits, 2000) to calculate the percent overlap. Our patient's area of hypoperfusion overlapped with 85% of the voxels where

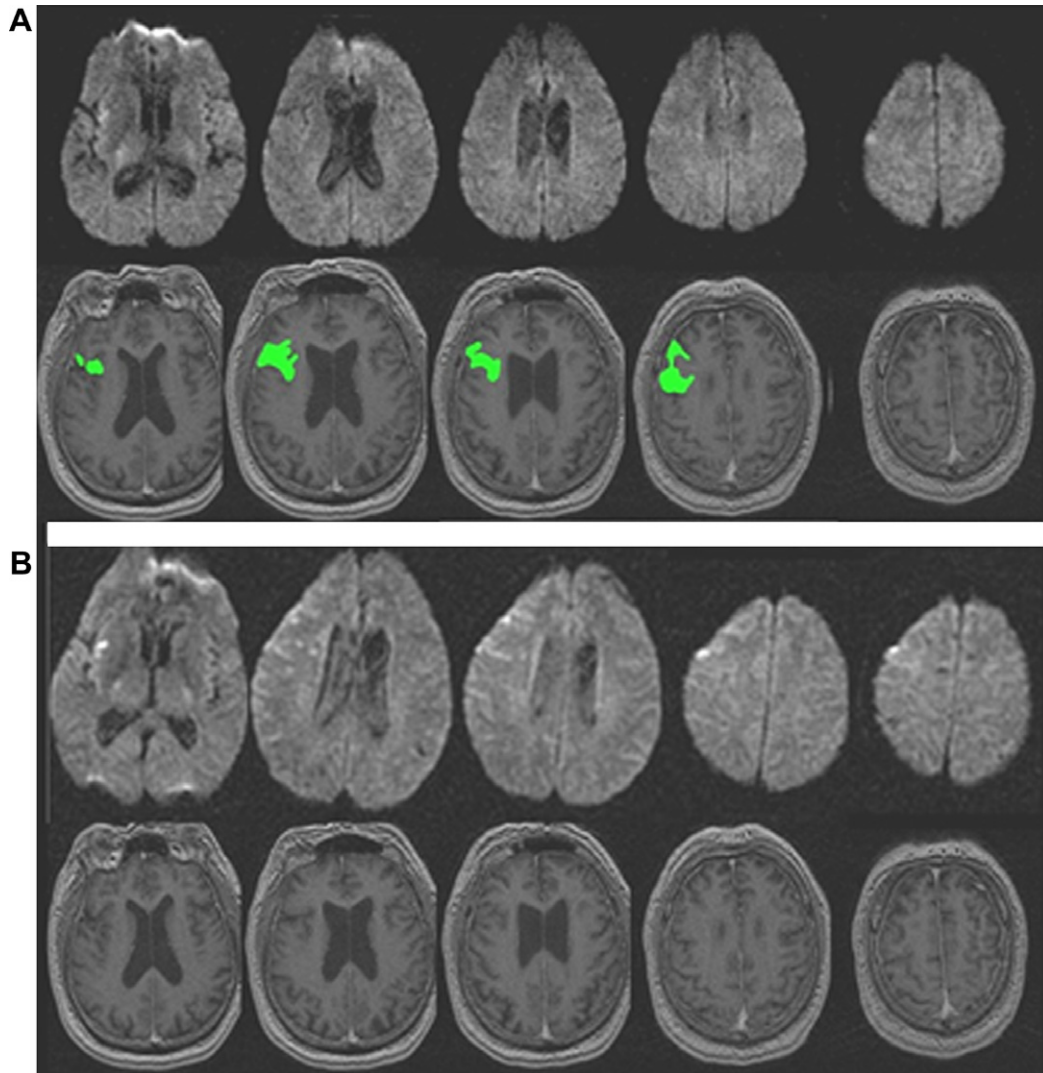


Fig. 1. DWI and PWI before intervention (Day 1) and after intervention (Day 2). (A) DWI (upper panel) and PWI (lower panel) obtained at 4 h post-onset of symptoms (pre-treatment). We show all slices that showed any lesion or hypoperfusion. PWI slices show substantial hyperperfusion (green areas) within Broca's area. (B) DWI and PWI obtained again at 36.5 h post-onset of symptoms (post-treatment). PWI scans were superimposed on the axial T1 weighted images, to show the sulci and gyri. These scans are in anatomical convention, with the left hemisphere on the left.

10/10 patients in the Amunts et al. study had cytoarchitecture of BA 45, and covered 47% of voxels where *any* patient in that study had cytoarchitecture of BA 45 (Fig. 2b). The area of cytoarchitecture of BA 44 in the Amunts et al. study was more variable; there was no area where all 10 patients in their study had BA 44. Our patient's area of hypoperfusion overlapped with 67% of the voxels where 7/10 patients had cytoarchitecture of BA 44, and covered 51% of the voxels where *any* patient had BA 44 (see Fig. 2a).

2.1. Pre-intervention language performance

Language tests were administrated at 5 h post-onset of symptoms (pre-treatment), and again 32 h post-onset of symptoms (post-treatment). The language battery included: oral and written naming, oral reading, spelling

to dictation, and repetition, with 17 or 34 word stimuli for each task, matched in word length and frequency across tasks and versions given on separate days. Additionally, 25 pseudowords matched in length in syllables and phonemes across sessions and across tasks were administered for oral reading and oral spelling to dictation. Norms for these lexical and sublexical processing tests were obtained from 50 neurologically normal subjects with a mean age of 64.7 ± 10.7 years. The median score for normal controls on all of the tests administered was 100% correct; no normal subject scored below 90%. Two film clip/sentence verification tests were administered; one with auditory and one with written sentences. Each of 13 film clips depicted a semantically reversible subject–verb–object relationship (e.g., the man pushed the girl). Each film clip was presented four times in counterbalanced order with: correct active sentence; correct passive sentence; incorrect active sen-

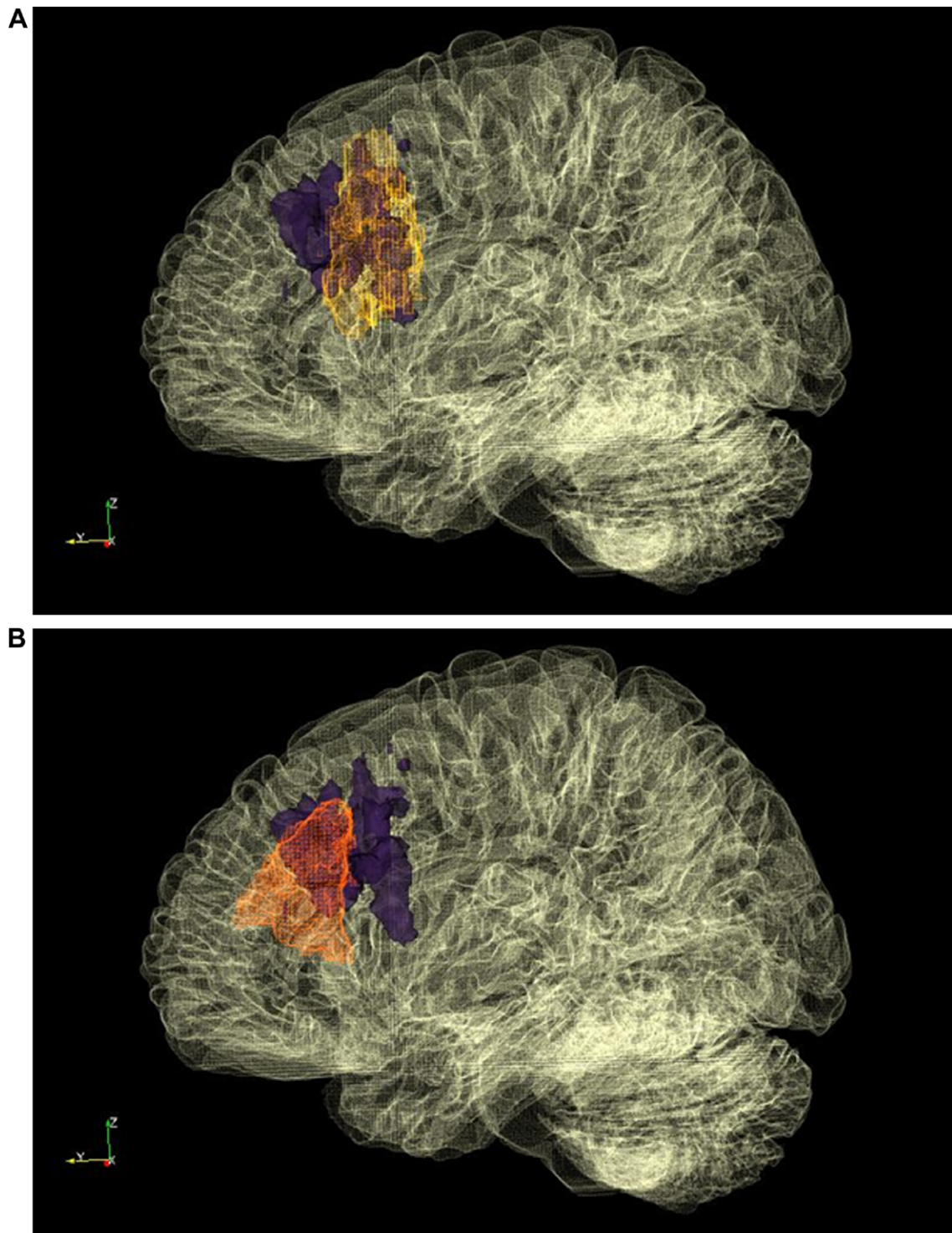


Fig. 2. Three dimensional reconstruction of the area of MJE's hypoperfusion at Day 1. (A) Overlap between MJE's area of hypoperfusion (shown in purple) and the area where any patient had cytoarchitecture of BA 44 in the probabilistic map of Amunts et al. (1999; shown in yellow). (B) Overlap between MJE's area of hypoperfusion (shown in purple) and the area where any patient had cytoarchitecture of BA 45 in the probabilistic map of Amunts et al. (1999; shown in orange).

tence; and incorrect passive sentence (semantically reversed forms), intermixed with other sentence/video pairs. Both auditory and written verification tasks required working memory, but sentence production was not required. Subjects were not required to produce a sentence; they were

asked to simply answer yes/no as to whether or not the sentence described the videoclip.

MJE scored normally on oral reading of words and pseudowords (57/59 or 96.6% successful trials; normal mean = 96.9 ± 5.3) and repetition of words and pseudo-

words (57/59 or 96.6% correct; normal mean = 99.0 ± 2.6), when his self-corrected articulatory (apractic) errors were not penalized. He was 100% correct in answering five simple yes/no questions (e.g., Do dogs fly?) that were semantically non-reversible. However, he performed poorly on other language tests (Fig. 3). Excluding self-corrected articulatory errors, he had mild impairment of oral naming (15/17; 88.2% correct; normal mean 99.2 ± 2.1). His errors were semantic paraphasias (e.g., bee named as “mosquito”). He was unable to form letters for written spelling to dictation, and had a moderate impairment in oral spelling to dictation (44/58 or 75.9% correct; normal mean = $98.7\% \pm 3.3$). His spelling errors were phonologically implausible nonwords, with deletions, substitutions, and transpositions of letters. On the remaining tasks his performance was not significantly different from chance. He scored 20% correct (1/5) in answering semantically reversible yes/no questions (e.g., Is a dog larger than an elephant?). On auditory sentence/film clip verification with semantically reversible sentences, he had 16/26 successful trials (61.5% correct) for passive sentences and 17/26 (65.4% correct) for active sentences. On the written form of this verification test, he was also at chance level: 11/26 or 42.3% correct for passive and 14/26 or 53.8% correct for active sentences.

2.2. Intervention

Because his cortical infarct was so tiny, it was our clinical impression that it was very unlikely to be the cause of his deficits. Rather, it seemed clear that MJE’s significant language deficits were due to hypoperfusion of Broca’s area, and that the only way to restore function was to restore blood flow to this area of cortex. Although he presented within the 3 h window for intravenous thrombolysis, his very recent surgery made him a poor candidate for this

intervention (due to the risk of systemic bleeding). Instead, he was treated with intravenous saline to increase his blood pressure, to improve blood flow to the ischemic region. In addition, because he was in atrial fibrillation (a basis for cardioembolic source of stroke), he was anticoagulated with heparin to prevent recurrent stroke. Although there is some risk of hemorrhagic conversion of infarct with heparin, particularly after cardioembolic stroke, this risk was considered minimal in view of the tiny size of the infarct.

2.3. Evidence of reperfusion

Repeat MRI scans, including DWI and PWI sequences, were obtained 36.5 h post-onset of symptoms. DWI sequences showed a few punctuate bright areas, consistent with acute infarct, within Broca’s area. PWI showed complete reperfusion of Broca’s area (Fig. 1). The cause of reperfusion of the area is unknown; reperfusion may have been due to either spontaneous recanalization of the vessel supplying this territory or intervention resulting in reperfusion through collateral flow. The cause of the reperfusion is irrelevant to the current study, the purpose of which was to determine what language functions were impaired when Broca’s area was hypoperfused and recovered when the area reperfed.

2.4. Post-intervention language testing

Language tests were re-administrated at 32 h post-onset, after he had undergone treatment designed to improve blood flow to the hypoperfused region of the brain. He scored at ceiling (or at normal or above average levels) on all language tasks (Fig. 3). MJE’s spontaneous speech also returned to normal. He produced fluent, grammatical sentences in describing the “cookie theft picture”. He scored 100% (17/17 successful trials) on oral and written

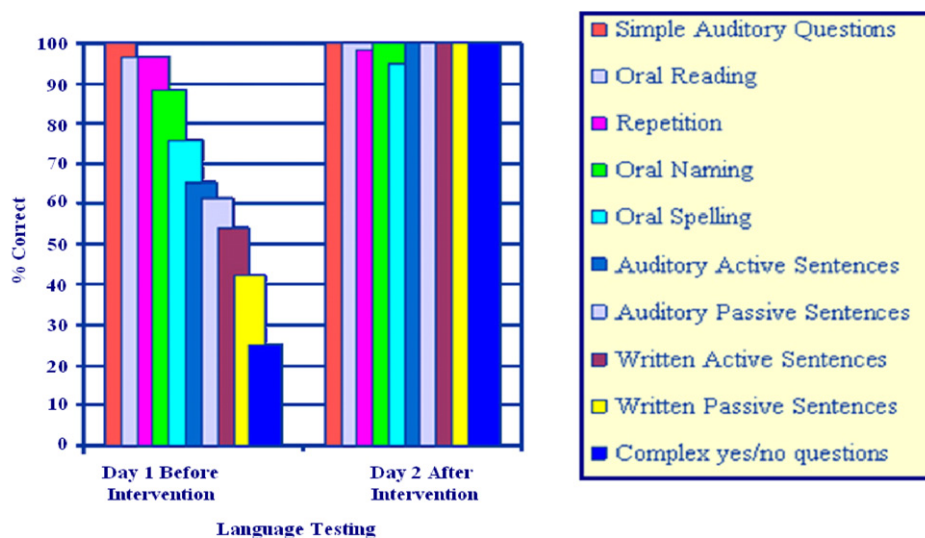


Fig. 3. MJE’s performance on language tests administrated on Day 1 (5 h post-onset of symptoms; pre-treatment), and again on Day 2 (32 h post-onset of symptoms; post-treatment).

naming, and at normal levels on repetition (58/59 or 98.3% correct; normal mean = 99.0 ± 2.6), oral and written spelling to dictation (both 56/59 or 94.9% correct; normal mean = $98.7\% \pm 3.3$). He scored 100% correct on auditory and written sentence/film clip verification for passive and active sentences, and 10 yes/no questions (semantically reversible and non-reversible).

3. Discussion

This case confirms the hypotheses that adequate function of Broca's area was necessary for a number of language comprehension and production tasks for this individual. Results suggest that Broca's area played an essential role in his comprehension and production of semantically reversible sentences, spelling, and motor planning/programming of speech articulation. Acute hypoperfusion of Broca's area was associated with severe impairment in comprehension of active and passive semantically reversible sentences, and moderate impairment of motor speech, grammatical sentence production, and spelling, without impairment of comprehension of semantically non-reversible sentences. Restoration of normal blood flow to Broca's area resulted in immediate recovery of these functions. These results provided evidence that deficits in these language functions can be due to hypoperfusion of Broca's area in at least some patients and that reperfusion can restore these functions in the same individuals. These functions might have relied on Broca's area or on areas functionally connected to Broca's area that were compromised when Broca's area was dysfunctional.

When Broca's area was hypoperfused, MJE's performance was no better than chance in understanding semantically reversible questions and sentences, but was above chance in understanding non-reversible sentences. Because reperfusion was achieved very quickly, we did not administer enough tasks to determine if his sentence comprehension impairment was due to a general problem with thematic role assignment, working memory, semantic comparison, or more generally due to impaired selection of a response from semantic memory.

MJE was also impaired in motor planning and/or programming of speech articulation, manifest as numerous and varied off-target attempts at articulating polysyllabic words. This finding is consistent with studies indicating that acute lesions in Broca's area are associated with apraxia of speech (Hillis, Work et al., 2004; Mohr, 1976). Studies of chronic stroke have shown variable areas of overlap (including the anterior insula; Dronkers et al., 1992) in patients with chronic apraxia of speech. However, this result may reflect the fact that patients with chronic speech deficits have large infarcts, which often include the insula.

Finally, MJE was profoundly impaired in writing, and moderately impaired in oral spelling when Broca's area was hypoperfused. His deficit in oral spelling was not due to his motor speech impairment, since his rare errors in

articulating names of letters were not penalized. Rather, he seemed impaired in accessing orthographic representations for output, or in maintaining the representations in the graphemic buffer while motor plans for writing or oral spelling were articulated. Again, there was not sufficient time to tease apart these deficits. Of note, though, his errors in spelling were not phonologically plausible, indicating that he was not able to rely on sublexical phonology-to-orthography conversion to spell. His impairment in forming letters may have been due to impaired retrieval of letter-shape specific motor plans or converting from graphemes (abstract letter identities) to letter shapes, with a particular case and font (see Rapcsak & Beeson, 2004; Rapp & Hsieh, 2001). A similar deficit was previously reported in patients who all had lesions or hypoperfusion involving parts of Broca's area and Brodmann's area 6 (Hillis, Chang et al., 2004; Hillis, Rapp, & Caramazza, 1999). It became clear the day following treatment that his deficits in spelling and writing were not premorbid, since he recovered these functions with reperfusion.

In summary, this case provided the unique opportunity to identify the speech and language functions that were compromised when neural tissue in Broca's area was dysfunctional in this individual, before substantial reorganization or recovery. It is possible that MJE's transient impairments had a single underlying cause. Each of the impaired tasks (comprehending semantically reversible sentences, grammatical sentence production, spelling, and motor planning/programming of speech articulation) requires maintaining the sequential order of elements for output or for further processing. One can speculate that Broca's area was essential for maintenance of the serial order of phonemes, graphemes, and other linguistic and motor elements (see Knutson, Wood, & Grafman, 2004 for evidence consistent with this hypothesis). Alternatively, Broca's area may include functionally distinct cortical areas with different connections as well as specializations (see Grodzinsky & Amunts, 2006 for extensive discussion; see also Hillis, 2006).

MJE's transient deficits occurred when there was temporary hypoperfusion of an area of left posterior inferior frontal cortex, often described as Broca's area. Although we do not know the cytoarchitecture of the hypoperfused region, it generally corresponds to an area within which 10 individuals studied at autopsy had cytoarchitecture of Brodmann's areas 44 and 45 (Amunts et al., 1999). A single case cannot provide evidence for a hypothesis about structure–function relationships, since there is almost certainly some individual variability in such relationships, at least within heteromodal association cortex (or all areas other than “primary” or unimodal cortex, such as striate cortex and Heschl's gyrus). Nevertheless, a series of studies of additional patients with focal areas of tissue dysfunction caused by ischemia or transcranial magnetic stimulation of parts of Broca's area would complement functional imaging studies of normal subjects in sorting out the various roles of Broca's area in language comprehension and

production across individuals. Moreover, this case provides clear evidence of rapid recovery of language when blood flow is restored to areas critical for language.

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