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Right Hemisphere Participation in Aphasia Recovery: A Qualification of Incongruous Findings in the Literature

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Right Hemisphere Participation in Aphasia Recovery:
A Qualification of Incongruous Findings in the Literature

by

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Report

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Abstract

Right Hemisphere Participation in Aphasia Recovery: A Qualification of Incongruous Findings in the Literature

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Abstract: Neuroplasticity research yields mixed results for the differential contribution of perilesional and contralesional brain areas to language recovery in aphasia. This paper will outline variables that mediate the presence and degree of right hemisphere activity and may account for some of the inconsistent research findings. Factors include the site and size of left hemisphere lesions, the phase of recovery, and the language task type and complexity. The performance accuracy of tasks also will be explored to further qualify the nature of homologous activity. Results found right hemisphere activation to be modulated by the damage and preservation of specific brain areas as well as by the presence of large left hemisphere lesions. Right hemisphere activity also was more consistently evident in the acute phase of recovery and returned to the left hemisphere in the chronic stage. Additionally, homologous areas tended to be

more active during comprehension-based language tasks and during tasks of greater difficulty. In qualifying the nature of contralesional mechanisms, the activity appears to be more linguistic-oriented in less-recovered individuals with aphasia and more related to cognitive effort in well-recovered individuals. The nature of homologous activation depends on the brain's ability to reactivate left hemisphere language networks.

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Chapter One: *Background*

Aphasia is an acquired language impairment resulting from brain injury. Lateralization studies utilizing sodium amytal (Wada & Rasmussen, 1960) and fMRI (Desmond et al., 1995; Binder et al., 1996; Vikingstad, George, Johnson, & Cao, 2000), have determined hemispheric dominance for language expression, comprehension and use. Most right-handed individuals have relatively robust left lateralization for language although lateralization occurs on a continuum from left to right hemispheric dominance.

An important research question is the effect behavioral interventions have on the neural networks supporting language processing in aphasia. The ability of the brain to change structurally and functionally in response to new experiences throughout a person's life is termed neuroplasticity (Raymer et al., 2008). Merzenich et al. (1996) established the presence of neuroplasticity in language recovery although more traditional notions of neuroplasticity are associated with initial brain development. Merzenich et al. attributed functional recovery to the reappearance of cortical representation for a skill in areas responsible for other abilities prior to the brain lesion. For individuals with left hemisphere language lateralization, two brain areas have emerged as the hallmark contributors to neuroplasticity for language recovery: areas homologous to the left hemisphere in the right hemisphere (contralesional) and areas extending from the lesion site in the left hemisphere (perilesional) (Thompson, 2000; Grafman, 2001). The present paper will focus primarily on areas homologous to the left hemisphere in the right hemisphere and their role in the reestablishment of language functioning.

HISTORICAL OVERVIEW

As early as the late 19th century, the right hemisphere had a suspected role in the recovery of language function following damage to the dominant hemisphere. In 1877, Barlow reported that a ten-year-old boy, "must have had an attack of right hemiplegia…[and] had lost his speech." In a month's time it was reported that the boy, "…seems to have quite recovered…" However, after "he got an attack of left hemiplegia" the boy lost his speech once more (p. 103). Barlow's description suggests that the right hemisphere compensated for left hemisphere damage, allowing the boy to regain speech. Ten years later, Gowers (1887) reported, based upon clinical observation, that patients with initial speech recovery following left hemisphere damage would lose speech anew following right hemisphere damage. Gowers also speculated that the right hemisphere normally was involved in some elements of speech processes, and the role of the right hemisphere varies in different persons and at different periods of life.

Kinsbourne (1971) used intracarotid amobarbital injections to demonstrate dominance for residual language in the right hemisphere. In normal subjects, intracarotid amobarbital injection in the left hemisphere results in temporary arrests in expressive speech. In contrast, a contralesional injection leaves speech intact. However, Kinsbourne found in three individuals with acute left hemisphere damage, injection into the right, not the left hemisphere, resulted in temporary halting speech. Additionally, Basso, Gardelli, Grassi, and Mariotti (1989) reported results of two women who had partly recovered from global aphasia following a left hemisphere stroke, but demonstrated significant regression in language functioning following an additional stroke in the right hemisphere. The investigators concluded that the additional right hemisphere lesion caused the language deficit relapse, and thus it could be inferred that the right hemisphere had "taken-over" language functioning.

The development of neuroimaging techniques sensitive to blood flow fluctuations have provided more direct visualization of the anatomical and physiological changes in the brain following injury. Studies reviewed in this paper used either functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). These techniques have contributed to a more comprehensive knowledge-base of the neural mechanisms underlying language recovery in individuals with aphasia. However, reviewing the relevant research associated with contralesional participation in language recovery yields mixed results for the role of the right hemisphere in language recovery. Although neuroimaging studies have documented the presence of right hemisphere activation during language tasks, the nature of the contralesional activation remains unclear in part because of uncontrolled variables across studies.

PURPOSE

This paper will explore variables that have contributed to inconsistent findings for studies investigating neuroplasticity mechanisms in aphasia. Such factors include the site and size of left hemisphere lesions, the temporal phase of recovery, and the language task type and complexity. The performance accuracy of tasks associated with right hemisphere activation also will be explored to further qualify the nature of homologous activity.

Chapter Two: *Lesion Site*

The site of lesion in the left hemisphere determines post-stroke right hemisphere activation for language processing. The damage or preservation of left hemisphere structures can result in the presence or absence of right hemisphere activity during language recovery.

BACKGROUND

Generally, left hemisphere structures crucial for language expression and comprehension include the posterior portion of the third frontal convolution (Broca's area) and the perisylvian region (Wernicke's area). Damage to these brain regions produces language deficits. For example, damage to Broca's area results in non-fluent speech with impaired repetition and relatively intact comprehension. The relationship between site of lesion and resultant language deficits is not always transparent. Basso, Lecours, Moraschini and Vanier (1985) found that of 207 individuals classified by aphasia type, 36 (17.4%) subjects were exceptions to expected anatomo-clinical correlations of lesion site and resultant clinical presentation. One example is that some patients demonstrated nonfluent aphasia while the damage appeared confined to posterior temporal parietal regions.

Regardless of where language areas reside on an individual basis, neural reorganization can occur in the right hemisphere following left hemisphere damage to these areas (Thompson, 2000; Grafman, 2001). The right hemisphere assumes the language role of the left hemisphere because of a release of transcallosal inhibition. In transcallosal inhibition, cortical regions in one hemisphere inhibit activity in corresponding cortical areas in the opposite hemisphere through the corpus callosum, a bundle of nerve fibers at the longitudinal fissure that connects the left and right cerebral hemispheres. This active inhibition occurs because each hemisphere is optimized for certain tasks. The inhibition prevents the less optimized hemisphere from performing a given task and interfering with the activity of the specialized hemisphere. As long as left hemisphere regions are functioning, functional asymmetry is maintained by a left hemisphere actively inhibiting the linguistic operations in the right hemisphere, resulting in the seen pattern of increased activity on the left and decreased activity on the right during speech. Whenever left hemisphere regions are damaged, callosal fibers between the left and right regions are damaged, releasing the right hemisphere homologous areas from inhibition and allowing it to participate in language tasks (Ohyama et al., 1996; Abo et al., 2004; Xu et al., 2004). In the presence of left hemisphere damage, studies have identified specific structures that modulate right hemisphere activity. Some studies exploring the relationships between site of lesion and right hemisphere activity are provided in Table 1.

PARS OPERCULARIS

Blank, Bird, Turkheimer, and Wise (2003) qualified right hemisphere activation as being dependent upon the intactness of the left hemisphere's pars opercularis (POp), an anterior brain area important for the selection of words based upon semantic and syntactic features. The investigators hypothesized that infarction to the left POp would result in activation of the homologous POp in the right hemisphere. However, the investigators believed recovery would be linked with activation of the left POp if anterior

Table 1

Studies investigating the modulation of right hemisphere activity by damage to specific left hemisphere structures.

Study	*N*	Method	Time since stroke	Imaging task	Outcome
Blank et al. (2003)	7	PET	19-134 months	Narrative retell and counting	RH activity in the presence of LH POp damage
Kim et al. (2002)	6	fMRI	3-30 months (mean 14.8)	Auditory sentence completion	RH activity in absence of LH BG damage
Crosson et al. (2005)	2	fMRI	4 years; 8 months	Word production	RH activity in absence of LH BG damage

left hemisphere brain damage spared the POp. The investigators used PET scanning to study activation patterns for propositional speech during a narrative retell in contrast to automatic, non-propositional speech during counting. The study contained three subject groups, consisting of a non-brain damaged control group, and two additional groups with chronic aphasia as a result of damage to the left anterior perisylvian area. One group's area of infarction included the POp (POp+ group) and the other group was without left POp (POp- group) activity.

Blank et al. (2003) found for the typical participants strong activation in the left POp and significantly decreased activation in right homologous areas during the narrative retell. For the POp+ group, there was apparent increased activation in the right POp for both propositional and non-propositional speech as compared to a nonspeech condition.

They hypothesized that the right POp was involved in the assembly of sound structures for speech. For the POp- group, propositional speech activated the left POp in addition to the right POp. However, for right POp activation, there was no difference in activity between propositional, non-propositional speech and nonspeech. The investigators attributed this finding to a loss of transcallosal inhibition. Thus, in the POp+ group, the damaged left POp could no longer actively inhibit the right POp, so a take-over function by the right hemisphere would be possible. Callosal fibers would not preclude some damage between left and right POp even though the left POp remains intact in the POp- group. Right POp activation then is present because of an inability of the left POp to adequately suppress the right POp below the nonspeech baseline. In essence, the right POp was only able to take-over speech function when the left POp was damaged. Based on the results of Blank et al., the POp may be one structure in the left hemisphere important for speech production that can modulate right hemisphere activity.

BASAL GANGLIA

Another structure that mediates the presence of right hemisphere activation is the absence of damage to the left basal ganglia. Kim, Ko, Parrish and Kim (2002) identified bilateral lateral frontal activity during language production in nonfluent patients who had lesions in the left basal ganglia in addition to left frontal regions. In contrast, patients who presented with left frontal lesions in the absence of left basal ganglia damage displayed primarily right lateral frontal activity during language production. The same result was found by Crosson et al. (2005) during a word production task in two patients.

Consistent with findings of Blank et al. (2003), Crosson et al. attributed this effect to the right pre-SMA using the intact left basal ganglia to suppress left lateral frontal activity, making it possible for right hemisphere to take-over language functions.

CONCLUSIONS

The site of damage and preservation in the left hemisphere can determine the presence and site of activation in the right hemisphere. Blank et al. (2003) found that the right POp assumed a speech function only when the left POp was damaged. Kim et al. (2002) and Crosson et al. (2005) showed more pronounced right hemisphere activity with intact left basal ganglia, but not when the basal ganglia was damaged. Following a stroke, damaged structures are distributed throughout the left hemisphere and at times the extent of damage is unknown, making it difficult for studies to systematically control for lesion site. Moreover, right hemisphere activation may appear inconsistent across studies when in reality the activity is in response to the damage or preservation of specific left hemisphere structures.

Chapter Three: *Lesion Size*

The size of the lesion in the left hemisphere may account for the mixed results regarding the right hemisphere's role in language recovery as larger left hemisphere lesions tend to result in greater right hemisphere activation. Despite the findings of Kim et al. (2002), Blank et al. (2003), and Crosson et al. (2005), the assumption that across-study variability depends solely upon the presence or absence of lesions in discrete regions of the left hemisphere is simplistic, especially when considering that there is not always a one to one correlation between lesion site and the resultant clinical presentation (Basso et al., 1985). Thus, the results of Kim et al., Blank et al., and Crosson et al. may not be a result of POp or basal ganglia involvement, but rather of more global and involved lesions.

BACKGROUND

In keeping with the 'release from transcallosal inhibition' argument, larger left hemisphere lesions will have less ability to maintain inhibition over linguistic operations or interfere with right hemisphere processing than smaller lesions. Also, if specific structures require damage before this release occurs, there is a greater likelihood of the prerequisite damage in larger lesions. Studies (Heiss et al.; 1997; Cao et al., 1999; Rosen et al., 2000; Blasi et al., 2002) that identified correlations between larger lesion size in the left hemisphere and increased activation in the right hemisphere are listed in Table 2.

LARGE LEFT HEMISPHERE LESIONS

In a longitudinal study, Heiss et al. (1997) used PET to study six patients with aphasia at four weeks and again 12 to18 months after their left hemisphere stroke. The regional cerebral metabolic rate of glucose at rest and during a word repetition task was measured. A neuropsychological test battery determined the severity of the initial language impairment, and the Token Test (McNeil & Prescott, 1978) was used at the two different time points as a measure of improved language performance as related to patterns of regional glucose metabolic recruitment. Heiss et al. found that the three patients with large infarcts (lesion volumes of 66, 100, and 133 cm3) activated only right superior temporal cortex, while the patients with small infarcts (volumes of 40, 52, and 27 cm3) activated left superior temporal cortex adjacent to the infarct or reactivated the infarcted region.

Cao et al. (1999) used fMRI during lexical-semantic processing tasks in seven aphasic patients at least five months after their left-hemisphere stroke. Aphasia type and severity were assessed with the Aphasia Diagnostic Profiles (ADP; Helm-Estabrooks, 1991) between one and 14 days after stroke onset in five of the patients. For the remaining two patients, clinical presentations were documented and aphasia type determined with clinical bedside testing. At the time of testing, the patients demonstrated language function recovery. The fMRI results showed that in patients 1 and 2 who had severe left frontal damage, activation was primarily in the right hemisphere. In patient six, whose infarct spared the inferior frontal lobe, activation in the inferior frontal lobe was more bilateral. Thus, based on the findings of Cao et al., larger lesions were associated with greater right hemisphere activation than smaller lesions.

Blasi et al. (2002) used fMRI during a word stem completion task on eight patients at least six months post-stroke in addition to 14 age-matched controls.

Table 2

Studies demonstrating greater right hemisphere activation for larger left hemisphere lesions.

Study	*N*	Method	Time since stroke	Imaging task	Outcome
Heiss et al. (1997)	6	PET	4 weeks; repeated at 12-18 months	Word repetition	RH activity present for large infarcts (volumes of 66, 100, and 133 cm3)
Cao et al. (1999)	7	fMRI	≥5 months	Picture naming/ verb generation	RH activity increased for larger lesions; bilateral preferred to RH dominant activation for recovery
Blasi et al. (2002)	14	fMRI	≥6 months	Word stem completion	RH activity increased for larger lesions; reflects change in strategy
Rosen et al. (2000)	6	PET/ fMRI	≥6 months	Word stem completion	RH activity increased for larger lesions; reflects change in strategy or an anomalous response
Parkinson et al. (2009)	15	CT/ MRI	Mean 30.7 months	Naming	RH activity present for large lesions; better outcomes for large relative to moderately large lesions

Three of the patient participants with smaller lesions demonstrated perilesional activation while the patients with larger lesions showed more right-sided activation. For instance, in patient 6, who demonstrated a large frontal stroke, activation was found exclusively in the right IFG. This activation pattern is in contrast to patient 3, who presented with smaller more ventral lesions and activation in both left and right IFG.

LANGUAGE OUTCOMES

The results of Heiss et al. (1997), Cao et al. (1999), and Blasi et al. (2002) suggest that right hemisphere activation is mediated by the presence of larger left hemisphere lesions. Another consistent outcome across the studies was that the participants with larger left hemisphere lesions and right hemisphere activation also demonstrated poorer language outcomes. Heiss et al. found that the three patients who demonstrated good recovery had activation of perilesional areas. In contrast, the three patients with larger lesions who activated contralesional areas presented with persistent aphasia at follow-up. Additionally, Cao et al. found better language recovery to be associated with a more bilateral activation in the inferior frontal lobe than with activation that was primarily localized in the right hemisphere. Similarly, Blasi et al. discovered that the patients with perilesional activation and smaller lesions performed better overall on word stem completion than patients with contralesional activation and larger lesions. In a similar study, Rosen et al. (2000) used both PET and fMRI in six patients with infarcts centered in the left inferior frontal gyrus (IFG) during a word-stem completion task. They found the best language function for the two patients whose lesions were more restricted in the left IFG and who demonstrated brain activity near the infarct (perilesional).

The studies reached different conclusions about the role of the right hemisphere in language recovery. Heiss et al. attributed right hemisphere activation to the unspecific activation of a global network in the effort to perform a complex task. In contrast, Cao et al. believed that right hemisphere activation contributed to recovery from aphasia. However, a bilaterally reorganized language network was deemed more efficacious than a right dominant network. Similarly, Blasi et al. attributed right frontal activation to reflect a change in strategy to a visual/orthographic strategy to accomplish the same linguistic task.

MODERATELY LARGE LEFT HEMISPHERE LESIONS

The findings of Heiss et al. (1997), Cao et al., (1999), Rosen et al. (2000) and Blasi et al., (2002), were further qualified by Parkinson et al. (2009), who examined 15 patients with left hemisphere stroke and aphasia who were a mean of 30.7 months post stroke onset. The investigators found greater improvement during naming tasks for large frontal lesions as opposed to moderately large lesions. The investigators attributed their counterintuitive results to the level of left hemisphere interference. In an argument similar to Blank et al. (2003), Parkinson et al. argued that in the cases of moderately large lesions, intact left frontal cortex activity was interfering or inhibiting right hemisphere activity. In the presence of larger lesions, the left frontal cortex would have incurred enough damage that it would be unable to interfere with recovery in the right hemisphere. Thus, this data suggests that poor outcomes as a result of larger lesions may not just be related solely to ineffective recovery mechanisms of the right hemisphere, but may also be a function of left hemisphere activity impeding a right hemisphere take-over function.

CONCLUSIONS

Lesion size provides one explanation for some of the variability in study outcomes. The results of Heiss et al. (1997), Cao et al., (1999), Rosen et al. (2000) and Blasi et al., (2002) showed a tendency for larger left hemisphere lesions to result in right hemisphere activation. Thus, the presence and volume of right hemisphere activation depends in part on the size of the lesion in the left hemisphere. These studies also found that the primary recruitment of contralateral areas does not appear to be the most effective strategy for language recovery. Additionally, per findings of Parkinson et al., poor language outcomes may not solely be related to ineffective right hemisphere function, but also may be a product of a damaged left hemisphere that is not ready to relinquish control of language processes.

Chapter Four: *Phase of Recovery*

The time post-onset of a stroke when the neuroimaging is conducted may influence the presence of right hemisphere neural activity. Images acquired during the acute stage of recovery tend to show more pronounced contralesional activity while images acquired during the chronic stage demonstrate a return of activity to the left hemisphere.

BACKGROUND

Following a cerebrovascular accident, certain physiological changes occur as the brain enters a “shutdown” mode. For instance, there is a bilateral reduction in volume of blood to the affected and unaffected hemispheres, a reduction in glucose metabolism, and an increase in the release of neurotransmitters. Also, brain swelling occurs, resulting in increased intracranial pressure. Within a relatively short period of time, these physiological changes will begin to return to premorbid levels, commencing the acute stage of the recovery process. Recovery that continues beyond three or four weeks is attributed to neuroplasticity, or reorganization, as the brain attempts to function despite damaged tissue. Brain reorganization occurs in part through the activation of parallel distributed pathways, changes in synaptic strength, and the formation of new synapse through axonal sprouting (Green, 2003). An individual progresses from the acute to chronic stage of recovery when spontaneous reorganization is completed. At this point, observed brain activity is reflective of the brain’s new structure. Neuroimaging must occur during the chronic phase of aphasia for the results to reflect neural reorganization and not a discrete stage of the recovery process.

Right hemisphere functioning may vary depending upon the underlying anatomical and physiological changes occurring at different points in time during recovery. Right hemisphere activity seen in images obtained in the acute or subacute phase provide evidence that right hemisphere activation changes occur rapidly after cerebral infarction. However, such rapid adjustments are inconsistent with the development of new anatomic pathways and should not be interpreted as neuroplastic changes (Blasi et al., 2002). Studies investigating right hemisphere activation during the acute stage are displayed in Table 3.

ONE MONTH POST-STROKE

Ohyama et al. (1996) used PET to investigate differences in regional cerebral blood flow (rCBF) between normal subjects and post-stroke aphasics during a word repetition task. Sixteen aphasic patients (10 fluent and six nonfluent) who had a single left hemisphere cerebral infarction were compared with six normal subjects. The stroke participants were studied at least one month post onset, and the investigators indicated they all had recovered to the point where they could repeat words. When examining the resting rCBF in the fluent and nonfluent aphasics, the repetition task elicited greater activation in the right posteroinferofrontal area (PIF) and right posterotemporal (PST). Ohyama et al. concluded that their results support the possibility of functional redistribution of language function and the importance of the contralesional hemisphere for language recovery in fluent and nonfluent aphasics.

Xu et al. (2004) compared fMRI results for three aphasic patients with six controls during a covert, event-related word generation task.

Table 3

Studies conducted during the acute stage of recovery that found greater contralesional activity.

Study	*N*	Method	Time since stroke	Imaging task	Outcome
Ohyama et al. (1996)	16	PET	≥1 month	Word repetition	Increased RH activity
Xu et al. (2004)	3	fMRI	10 days to 5 weeks	Word generation	Increased RH activity

The fMRIs were taken within 10 days to five weeks after the initial onset of symptoms in the acute stage of recovery. As compared to normal subjects, there were ostensible differences in the activation patterns seen in the individuals with aphasia. The word generation task elicited activation in the left inferior frontal gyrus in normal subjects while the left inferior frontal gyrus was not activated in any of the individuals with aphasia. Xu et al. attributed seen contralesional activation to the functional reorganization of language to the right hemisphere.

In both studies (Ohyama et al., 1996; Xu et al., 2004), the time post-stroke was inconsistent with time frames of language recovery. As many of the subjects were a month or less post-stroke, the right hemisphere activation patterns could not reflect language recovery, but rather a time sample of brain activity in the reorganizing process. To view the right hemisphere's role in language recovery, it is necessary to look at studies (Cappa et al., 1997; Thulborn et al., 1999) that specifically explored contralesional activation at later time points. Information for these two studies is displayed in Table 4.

SIX TO NINE MONTHS POST-STROKE

In a longitudinal study, Cappa et al. (1997) compared PET scans for eight patients with a left hemisphere stroke taken two weeks after the patient's stroke with scans taken six months post-stroke. Statistical comparisons were completed with 10 age-matched controls. A battery of standard language tests, including the Western Aphasia Battery (WAB; Kertesz, 1982), was administered at both time points. In comparison with the control subjects, patients in the acute phase following their stroke demonstrated hypo-metabolism in both left and right hemisphere brain areas that were structurally unaffected by the stroke.

At the second PET study, metabolic activity tended to normalize for all patients with glucose metabolism increasing significantly bilaterally in the basal frontal, lateral pre-frontal, and primary occipital cortex as well as in the basal ganglia. Nonetheless, an asymmetric hypo-metabolism remained in several left hemisphere brain areas with greater glucose metabolism identified in the right hemisphere for the premotor/motor cortex, parietal cortex and in the superior, middle/inferior and polar temporal cortex. A significant positive correlation was identified between changes in metabolic values of homologous right hemispheric regions contralateral to damaged left hemisphere regions and neuropsychological scores between the initial and follow-up examination, specifically the auditory comprehension score of the Western Aphasia Battery (Kertesz, 1982).

Table 4

Studies conducted at six to nine months post-stroke that showed greater right hemisphere activation.

Study	*N*	Method	Time since stroke	Imaging task	Outcome
Cappa et al. (1997)	8	PET	2 weeks; repeated 6 months	Language battery	Increased RH activity associated with the removal of functional depression.
Thulborn et al. (1999)	2	fMRI	P1:76 hours; repeated 6 months. P2: 3 months; repeated 9 months	Sentence comprehension task	Increased RH activity

The investigators concluded that recovery from aphasia in the first months following a stroke is associated with the removal of functional depression in structurally unaffected regions, especially the right hemisphere.

In another longitudinal study, Thulborn et al. (1999) used fMRI to measure temporal changes in activation patterns in two adult patients with aphasia as compared to six normal adults during a sentence comprehension task. In normal controls, the activation pattern for language comprehension was predominately left-sided, involving a comprehensive network that included both Wernicke's and Broca's area.

In patient 1, who had a lesion to Broca's area, the fMRI results at 76 hours revealed an uncharacteristic, right-sided laterality ratio for Broca's area. By six months, this change in cerebral dominance in Broca's area evolved to be solely right-sided.

Additionally, Wernicke's area, which was structurally intact following the stroke, remained entirely left dominant at both measurement intervals. The retention of left hemisphere dominance for unaffected areas is consistent with other study outcomes (Ohyama et al., 1996; Abo et al., 2004; Xu et al., 2004), suggesting that right hemisphere reorganization is restricted to areas homologous to the damaged left hemisphere regions. Patient 2, who presented with a lesion affecting Wernicke's area, showed a pattern of laterality ratios that evolved from a left hemisphere dominance pattern prior to onset, toward a weak right dominance at three months, followed by a significant right hemisphere shift at nine months. In contrast with findings for patient 1, patient 2 demonstrated a minor shift from weak right dominance to weak left dominance in Broca's area at nine months. The results of Thulborn et al. demonstrate a reorganization of language comprehension function to the right hemisphere that occurred in a relatively short period of time and progressed over a span of several months as performance became more normalized.

Thulborn et al. (1999) and Cappa et al. (1999) found right hemisphere activation during language tasks between six and nine months post-stroke. Thulborn et al. also identified the retention of left hemisphere dominance for undamaged areas. However, the obtained neuroimages may not reflect neural reorganization as their subjects may have been within the spontaneous recovery period as evidenced by persistent hypo-metabolism and the presence of early indicators of a shift back to left hemisphere dominance. Moreover, quantitative group studies of recovery identified the transition from acute to chronic to be approximately 12 months post-onset (Code, 2010). Thus, studies exploring neural activation at one year post-stroke will need to be reviewed to determine if right hemisphere activation remains predominant in the chronic stage. A list of studies conducted on subjects at approximately 12 months post-onset is provided in Table 5.

TWELVE MONTHS POST-STROKE

Longitudinal studies that visualized brain activity one year post-stroke include Heiss et al. (1997), Karbe et al. (1998), Fernandez et al. (2004), Saur et al. (2006), and van Oers et al. (2010). The findings of Heiss et al. will be reviewed once more because the investigators acquired PET scans during the chronic stage at 12 to 18 months after a left hemisphere stroke. In contrast with conclusions of Thulborn et al. (1999), and Cappa et al. (1999), Heiss et al. found that the three patients who displayed the most language recovery had activation of left hemisphere perilesional areas at follow-up. It was only the three patients who primarily recruited contralesional areas for both PET scan sessions who demonstrated persistent aphasia. Right hemisphere mechanisms did not appear effective to allow recovery from aphasia. Based on the results, the investigators found mixed hemispheric participation in long-term language recovery, but attributed favorable language outcomes to the sparing or reactivation of perilesional areas.

A similar result was found by Karbe et al. (1998), who like Heiss et al. (1997) used PET to measure metabolic changes at rest and during a word repetition task. PET measurements were acquired three to four weeks post-stroke in 12 patients, with an additional PET study conducted on seven patients one year post-stroke. For these seven patients, the investigators noted interesting activation pattern changes between the initial and follow-up PET scans. In the initial scans from the subacute phase, additional activation was observed in right hemispheric regions, such as the right SMA and the right inferior frontal cortex. In the follow-up study investigating the long-term reorganization of the speech-relevant network, right hemisphere activation had disappeared in some patients, while the left-hemispheric superior temporal activation had recovered. The study's results suggested that recovery of left superior temporal regions nullifies the long-term compensatory activity of right hemisphere. However, the presence of permanent loss of left hemisphere regions reinforces the compensatory activity of right hemisphere. Like Heiss et al., the investigators found poorer outcomes to be associated with contralesional activation and a positive long-term prognosis to be associated with the recovery of the left superior temporal cortex.

Fernandez et al. (2004) used fMRI to examine brain activation in 10 healthy subjects as compared to an aphasic patient named PL. The investigators utilized two language tasks denoted as "rhyme" and "semantic" to delineate specific language component involvement based upon the network which had incurred damaged. The group of healthy controls underwent two fMRI sessions to evaluate the replication of results. The patient with aphasia, PL, was scanned at one month and then again one year after his stroke. Results displayed "intersubject robustness and intrasubject reproducibility" (p. 2174), which the investigators believed established the validity of results found for the patient at follow-up.

For patient PL there were evident spatiotemporal changes in brain activation from the initial to follow-up scan that correlated with language recovery. Brain reorganization was found to implicate both hemispheres, but activation was characterized by initial

Table 5

Studies conducted ~12 months post-stroke showing a return to left hemisphere functioning.

Study	*N*	Method	Time since stroke	Imaging task	Outcome
Heiss et al. (1997)	6	PET	4 weeks; repeated at 12-18 months	Word repetition	Mixed hemisphere activity; better outcomes associated with LH activity
Karbe et al. (1998)	7	PET	3-4 weeks; repeated at 12 months	Word repetition	RH activity in acute phase; RH activity nullified by LH recovery in chronic stage
Abo et al. (2004)	2	fMRI	60 months	Word repetition	Activation only in the RH
Fernandez et al. (2004)	10	fMRI	1 month; repeated at 12 months	Word-picture rhyming; Word-picture semantic matching task	RH activity in acute phase; LH activity in chronic phase
Saur et al. (2006)	14	fMRI	Mean 1.8 days post stroke days; repeated at mean 12.1 dps; repeated at mean 321 dps	Auditory comprehension task	Minimal. LH activity in acute stage; greater bilateral activity in subacute phase; LH activity in chronic phase
van Oers et al. (2010)	13	fMRI	1.3-4.7 years	Word-picture matching; Semantic decision; Verb generation	RH activity normal in chronic stage; recovery correlated with LH activity

contralateral activity with later left hemisphere activation at 12 months. Specific areas of right hemisphere activation included the parietotemporal region, an area homologous to damaged left areas, as well as bilateral prefrontal areas. Activation of the right pre-frontal cortex was attributed to nonspecific attentional and executive control functioning since PL had more difficulty performing the language tasks as compared to the control subjects. The investigators believed their hypothesis was supported by a reduction of right prefrontal activation when PL presented an improvement of language abilities at 12 months. The investigators' finding of greater left hemisphere activation in long-term language recovery was consistent with that of Heiss et al. (1997) and Karbe et al. (1998) even though the study by Fernandez et al. only consisted of one individual with aphasia.

Saur et al. (2006) conducted a slightly more extensive investigation than Heiss et al. (1997), Karbe et al. (1998), and Fernandez et al. (2004) by using fMRI to scan 14 patients with aphasia at three time intervals in an attempt to capture the acute, subacute and chronic stages of the recovery process. In conjunction with each fMRI examination, a battery of language tests was administered as a measure of recovery from aphasia. An auditory comprehension task was used in an event-related design on the patients with aphasia as well as an age-matched control group. Based on their fMRI data results, the investigators identified a progressively changing activation pattern associated with the three phases of language recovery.

The study found minimal activation in the left IFG in the acute phase (1.8 days post-stroke) with only peak voxel activation in the pars orbitalis and triangularis. The subacute phase (mean: 12.1 days post stroke) was characterized by strong bilateral activation with the strongest increase in activation in the right IFG or Broca-homologue and in the supplementary motor area (SMA). Additionally, increased activation in these areas also correlated with improved performance on the language battery. In the chronic phase (mean: 321 days post stroke), Saur et al. (2006) noted a normalization of activity with a return of activation to the left hemisphere language areas, which also was associated with further language improvement. Similar to Fernandez et al. (2004), Saur et al. believed right inferior frontal activation during the subacute phase could be attributed to cognitive processes such as attention. An alternative explanation was that altered left-hemispheric functioning merely resulted in a temporary reduction in trans-hemispheric inhibition. As left hemisphere language areas recovered, it once again exerted its inhibitory influence. Also, similar to Karbe et al. (1998), the investigators postulated that the activation patterns of patients with extensive left language area damage would continue to resemble those of patients in the subacute phase because of an inability of the left hemisphere to recover and because of the absence of left hemisphere transcallosal inhibition. Although the results of Saur et al. are consistent with those of Heiss et al., Karbe et al., and Fernandez et al., only half of the patients included in the chronic phase could be classified as being12 months post-stroke.

van Oers et al. (2010) examined 13 individuals with aphasia and 13 controls with fMRI during three language tasks, picture word matching, semantic decision and verb generation. In contrast to Heiss et al. (1997), Karbe et al. (1998), Fernandez et al. (2004) and Saur et al. (2006) who utilized two or more temporally separated fMRI scans, the investigators only performed one fMRI scan between 1.3–4.7 years post-stroke. The investigators measured recovery from aphasia from the subacute (within two months) to the chronic phase using differences in confrontation naming ability per the Boston Naming Task (Kaplan et al., 1978) or the naming subtask of the Aachen Aphasia Bedside Test (AABT; Biniek, Huber, Glindemann, Wilmes, & Klumm, 1992) in addition to the Token Test (de Renzi & Vignolo, 1962; McNeil & Prescott, 1978) scores. Test scores were only correlated with fMRI data in the chronic phase since a measure of contralesional activity in the acute phase was not obtained.

Results identified a normalization of right hemisphere participation in the chronic stage of aphasia, consistent with previous study results (Heiss et al., 1997; Karbe et al., 1998; Fernandez et al., 2004; Saur et al., 2006). Also, in agreement with previous findings, van Oers et al. found language recovery from the subacute phase to the chronic phase to be correlated with a higher relative activation of the left as compared to the contralesional hemisphere. Specifically, improved naming ability was correlated positively with activation in the left inferior frontal gyrus (IFG) during the semantic decision and verb generation language tasks. For the same language tasks, recovery on the Token Test positively correlated with activation in both left and right IFG, suggesting the right IFG contributed more during auditory sentence comprehension than during picture naming.

The finding of greater right hemisphere activation during the comprehension tasks is consistent with the conclusions of Cappa et al. (1997), who identified a significant positive correlation between changes in metabolic values of homologous right hemispheric regions and the auditory comprehension score of the Western Aphasia

Battery (Kertesz, 1982). Furthermore, van Oers et al. (2010) concluded from this data that in the chronic stage of aphasia, activation of the left IFG is associated with improvement of picture naming and sentence comprehension. However, similar to the conclusion of Fernandez et al. and Saur et al., the investigators believe right IFG activity may reflect non-linguistic cognitive processing, such as making inferences to compensate for increased processing load.

AGGREGATE FINDINGS

A pattern emerged when chronic aphasia is defined as being "12 months or more post-stroke" in studies conducted on patients during the acute versus the chronic phase. The neuroimaging was performed during either the acute or sub-acute stage for most of the studies that found a supportive role for the right hemisphere in language recovery, (Cappa et al., 1997; Ohyama et al., 1996; Thulborn et al., 1999; Xu et al., 2004), whereas the studies that identified more pronounced left hemisphere activation were completed during the chronic phase (Karbe et al., 1998; Fernandez et al. 2004; Saur et al., 2006; van Oers et al., 2010). Another interesting finding is that Thulborn et al. (1999) found an unexpected minor shift in Broca's area from weak right dominance to weak left dominance in the neuroimages for patient 2 at nine months. This shift possibly suggests the beginnings of a return to left hemisphere dominance. Patients also presented with large left peri-sylvian lesions and poorer outcomes in most studies that did find right hemisphere activation in patients in the chronic stage (Heiss et al., 1997; Cao et al., 1999; Blasi et al., 2002).

Nonetheless, exceptions to this pattern exist as seen in a study by Abo et al. (2004). The investigators compared fMRI results during a repetition language task between six controls without brain damaged and two participants, one with a lesion in Broca's area and the other with a lesion in Wernicke's area. When the fMRIs were taken, both individuals with aphasia were 60 months post stroke in the chronic stage of recovery. Both participants demonstrated complete recovery from their aphasia following therapy. The study found that the individuals with brain damage only demonstrated activation in the unaffected or right hemisphere. The results of Abo et al. confirm that other factors other than phase of recovery can mediate the presence of contralesional activation.

CONCLUSIONS

The right hemisphere has a more active role in language recovery in the initial period following a stroke. However, good language outcomes are associated with the ultimate reactivation of damaged areas and/or the distribution of functioning to perilesional areas in the left hemisphere. If language functioning is unable to return to the left hemisphere because of the extent or specific local of damage, language functioning remains in the right hemisphere but retains dysfunctional elements.

Chapter Five: *Language Task Type*

Another explanation for discrepancies in the presence or degree of right hemisphere activation is related to the type of language task utilized by the researchers. The linguistic processing requirements of comprehension-based tasks may more readily activate right hemisphere regions.

BACKGROUND

Language tasks used in fMRI studies should reflect realistic linguistic-based processes as they probe the residual language abilities of post-stroke patients across the recovery interval (Crosson et al., 2007). These criteria are not consistently met as researchers do not consider well-tested psycholinguistic models of the processes involved in executing a particular task, resulting in tasks that have only an indirect relationship to natural language performance (Postman-Caucheteux et al., 2010). Activation in the contralesional hemisphere could reflect the right hemisphere's use of nonlinguistic mechanisms in performance of linguistic tasks. Also, for imaging results to be sensitive to neural mechanisms operating in aphasia and changes during recovery, researchers must consider the type of aphasia with which the task will be utilized. For instance, Thulborn et al. (1999) used a sentence comprehension task to measure recovery in patients with Broca's aphasia when a production-based task would likely have been more sensitive to recovery in these patients.

AUDITORY COMPREHENSION TASKS

A common theme among studies that found language task effects related to contralesional activation (Cappa et al., 1997; Musso et al., 1999; van Oers et al., 2010) was greater activation on tasks involving auditory comprehension. These studies are displayed in Table 6. In a previously discussed longitudinal study, Cappa et al. compared PET scans for eight patients with a left hemisphere stroke taken two weeks after the patient's stroke with scans taken six months post-stroke. A battery of standard language tests, including the Western Aphasia Battery (Kertesz, 1982), were administered at both time points. The investigators identified a significant positive correlation between changes in metabolic values in contralesional regions and neuropsychological scores at the initial and follow-up examination for the auditory comprehension score of the Western Aphasia Battery.

Heiss, Kessler, Thiel, Ghaemi and Karbe (1999) used PET on 23 right-handed aphasic patients at two and eight weeks post-stroke in addition to an 11 member control group. A word repetition task was used during scanning and flow changes were calculated in 14 regions representing perilesional and contralateral homotopic areas. The investigators classified patients according to the site of lesion (frontal, subcortical, temporal). At both time points, a battery of neuropsychological tests was administered to the participants with aphasia. Results showed that the temporal-lesion group activated Broca's area and the supplementary motor areas at two weeks. At the second scanning, the participants showed greater activation of precentral gyrus bilaterally as well as the right superior temporal gyrus (STG), but did not reactivate the left STG. On the neuropsychological test battery, the temporal-lesion group only showed improvement in word comprehension, indicating a relationship between right hemisphere activity and improvements in comprehension measures.

Table 6

Studies identifying an association between contralesional activity and comprehension.

Study	*N*	Method	Time since stroke	Imaging task	Outcome
Cappa et al. (1997)	8	PET	2 weeks; repeated 6 months	Language battery	Correlation between RH activity and comprehension score on the WAB
Heiss et al. (1999)	23	PET	2 weeks; repeated 8 weeks	Word repetition task	Activation of precentral gyrus bilaterally and the right STG associated with improvements in comprehension
Musso et al. (1999)	4	PET	6, 9, 9, and 18 months	Subtest of the Aachen Aphasia Bedside Test	Correlation found between increased blood flow in the RH during the comprehension task and scores on the Token Test
van Oers et al. (2010)	13	fMRI	1.3-4.7 years	Word-picture matching; Semantic decision; Verb generation	Normalization of RH activity in chronic stage; recovery correlated with a higher activation of LH; recovery on the Token Test correlated with activation in both hemispheres

However, overall the temporal-lesion group had the most severe language disturbances at initial scanning and the most persistent deficits at follow-up, suggesting that contralesional activity is present in response to more severe left hemisphere deficits and does not necessarily contribute to more global improvements in language functioning.

Musso et al. (1999) specifically investigated short-term improvements in language comprehension in four patients with left temporoparietal lesions and Wernicke's aphasia. The investigators utilized PET to measure regional cerebral blood flow (rCBF) at 12 consecutive measurements. During PET scanning, a subtest of the Aachen Aphasia Bedside Test (Biniek et al., 1992) was used to activate language comprehension areas. After each scan, comprehension was measured directly with a shortened version of the Token Test (McNeil & Prescott, 1978) created by the investigators. In the intervals between scans, patients participated in language comprehension training. Ultimately, the study found significant improvement in all patients, and the investigators correlated increased blood flow in the right superior temporal gyrus and the left precuneus during the language comprehension task with scores achieved on the Token Test. The results suggest a proclivity for the right hemisphere to aid in comprehension-based tasks although the investigators also acknowledge the results reflect only short-term processes and the increased contralesional activation may not be present in long-term recovery.

van Oers et al. (2010) examined 13 individuals with aphasia and 13 controls with fMRI during three language tasks, picture word matching, semantic decision and verb generation. The investigators measured aphasia recovery from the subacute to the chronic phase by observing differences in confrontation naming ability per the Boston

Naming Task (Kaplan et al., 1978) or the naming subtask of the Aachen Aphasia Bedside Test (Biniek et al., 1992) in addition to Token Test (de Renzi & Vignolo,1962; McNeil & Prescott, 1978) scores. Test scores then were correlated with fMRI data for subjects in the chronic phase. The investigators found a positive correlation between recovery on the Token Test and activation in both left and right inferior frontal gyrus (IFG). The investigators concluded that the right IFG contributed more during auditory sentence comprehension than picture naming provided that right IFG activation was not seen during semantic decision and verb generation language tasks.

CONCLUSIONS

Contralesional areas may more readily aid comprehension relative to production-based tasks. This effect could be due to more complex patterns of reorganization for comprehension as compared to production-based tasks or the processes involved in comprehension-based tasks being more responsive to utilizing different cognitive strategies to perform the same task. Consequently, studies utilizing a comprehension-based task may identify correlations between contralesional activity and improvements in language functioning where production-based tasks may not see a similar effect. However, right hemisphere activation also has been identified during other language tasks including overt repetition (Ohyama et al., 1996), silent word generation (Blasi et al., 2002) and overt word generation (Cardebat et al., 2003), suggesting that right hemisphere activation is not limited to comprehension-based tasks and other influencing factors are present (e.g. lesion site/size, phase of recovery, etc.). Inconsistency of task type across studies is an additional factor that has complicated the comparison of language-related activation results and has limited the ability to generalize conclusions about the nature and degree of contralesional activation for language.

Chapter Six: *Language Task Difficulty*

Activation in the contralesional hemisphere could also be a product of task difficulty and the resultant greater processing demand (Just, Carpenter, Keller, Eddy, & Thulburn, 1996; Keller, Carpenter, & Just, 2001; Anderson et al., 2002; Fridriksson & Morrow, 2005). Studies that found greater right hemisphere activity in response to greater task difficulty are listed in Table 7.

BACKGROUND

Increased effort to perform a task can result in a global increase in blood flow throughout the brain. More challenging tasks may result in an increase in blood flow to the right hemisphere as a byproduct of greater general cognitive effort not specific to right hemisphere language processes.

TASK DIFFICULTY EFFECTS IN NORMALS

Just et al. (1996) conducted an fMRI study on 15 college-aged participants with normal language abilities. The stimuli consisted of visually presented sentences including three sentence types of increasing complexity: active conjoined clauses, subject relative clauses and object relative clauses. Participants were instructed to read four to five sentences of each type presented in succession followed by true-false questions as a comprehension measure. The study identified significant cortical activation levels in Wernicke's and Broca's areas as a function of increases in sentence complexity. A similar activation pattern was observed in the homologous areas though to a lesser extent.

In a similar study, Keller, Carpenter, and Just (2001) utilized fMRI with 30 participants with normal language-processing skills. Sentences were constructed based on the stimuli utilized in the Just et al. (1996) study with both conjoined active and object-relative clauses. The investigators created four experimental conditions with increasing syntactic complexity by crossing the conjoined active and object-relative sentence types with nouns of either high or low lexical frequency. Five sentences of the same type were presented sequentially with true or false probe questions after each sentence presentation. This procedure was completed four times for each of the four experimental conditions. The results identified cortical activation levels associated with task performance in the primary language areas of the left hemisphere. The greatest activation was present during the most difficult task condition, object-relative sentences with low-frequency words. Results showed the blood-oxygen-level-dependent (BOLD) signal intensity and cortical area recruitment increased and involved a more extensive neural network as the task became more complex. The right hemisphere showed a consistent main effect for lexical frequency and a lesser effect for syntactic complexity.

TASK DIFFICULTY EFFECTS IN THE ELDERLY

Just et al. (1996) and Keller et al. (2001) identified increased activation for more linguistically complex stimuli, but both study's participants were limited to young adults. In an additional study, Anderson et al. (2002) used fMRI to investigate the effects of low and high linguistic demand in four cognitively intact elders (average of 76 years old). The participants performed a word recognition task with both a low demand and high demand condition titrated to each subject's ability (titrated demand). To determine each participant's titrated demand, the researchers selected words from a word list that the subject achieved 75% accuracy in recognizing the day before scanning.

Table 7

Studies identifying increased right hemisphere activity in response to more difficult tasks.

Study	*N*	Method	Time since stroke	Imaging task	Outcome
Just et al. (1996)	15	fMRI	N/A	Comprehension of sentences of increasing complexity: active conjoined clauses, subject relative clauses and object relative clauses	LH activity increased as a function of increases in sentence complexity; pattern observed in RH to a lesser extent
Keller et al. (2001)	30	fMRI	N/A	Same as Just et al. (1996) crossed with nouns of either high or low lexical frequency	Greatest LH activation present for the most difficult task condition; RH had a consistent main effect for lexical frequency and syntactic complexity
Anderson et al. (2002)	4	fMRI	N/A	Word recognition with low and high demand	Increased activity of bilateral cortical areas for the high versus low demand condition
Fridriksson & Morrow (2005)	4	fMRI	12-141 months	Picture-word matching task with variations in presentation frequency and length of presentation time	Greater activity present in the RH for the more difficult task for three of the four individuals with aphasia

Study results revealed that in the titrated demand relative to the low demand condition the elders demonstrated increased activation of bilateral cortical areas, including the left medial frontal, right superior temporal and right superior parietal cortices. Findings could also reflect Hemispheric Asymmetry Reduction in Older Adults (the HAROLD model). Neural activity during verbal recall tasks tends to be less lateralized and more bilateral in older than in younger adults. This effect may be a result of functional compensation (Cabeza et al., 1997; Cabeza, 2000). Although the HAROLD effect may account for some of the increase in right hemisphere activity, the relative greater activation in the titrated versus low demand condition in Anderson et al. suggests that the brain recruits additional regions, including right hemisphere networks, when a subject attempts to maintain performance when confronted with greater cognitive demand. These results further support previous results (Just et al.; Keller et al.) and suggest that language task difficulty can influence patterns of cortical activation in the right hemisphere in individuals with normal language skills regardless of age. However, the exact nature (e.g. linguistic, cognitive) of activation in the right hemisphere is not known.

TASKS DIFFICULTY EFFECTS IN INDIVIDUALS WITH APHASIA

Previous findings (Just et al., 1996; Keller et al., 2001; Anderson et al., 2002) suggest that right hemisphere cortical activation can increase in response to greater task difficulty. However, the studies were conducted on individuals with normal language skills, precluding generalizations to individuals with aphasia because of structural brain differences. For instance, individuals with aphasia may have a more robust response in the right hemisphere provided that their compromised left hemisphere is now unable perform a language role. Fridriksson and Morrow (2005) investigated the relationship between changes in cortical activation and language task difficulty in individuals with aphasia. The study included four subjects with either chronic anomic or Broca's aphasia with the time post-stroke varying between 12 and 141 months in addition to four matched control participants. Subjects underwent fMRI while performing a picture-word matching task requiring the participants to determine whether a picture matched a spoken word presented through headphones. Task difficulty was manipulated by the number of pictures presented in a series in addition to the length of presentation time. The easier condition consisted of a series of two pictures presented for two seconds each. For the more difficult condition, subjects were presented with a series of three pictures for 1.333 seconds each.

For the more difficult task condition, greater mean blood oxygenated level dependent signal intensity and area recruitment were noted for three of the four individuals with aphasia as well as for three of the four controls. Mostly right hemisphere activation in the right superior temporal lobe was observed for three of the participants with aphasia. The fourth subject's functional scan showed primarily left temporal lobe activation and minimal change in the overall number of activated voxels across the two conditions. However, this participant had additional left thalamic damage, which may have impacted his scan results. The results of Fridriksson and Morrow (2005) are consistent with those in previous studies utilizing subjects with normal language skills in that cortical activation increased in response to task difficulty for most of the study's participants.

The neural mechanisms that account for increased activation in the right hemisphere during more complex tasks are unclear. The right hemisphere could be performing a language role in the individuals with aphasia as Fridriksson and Morrow (2005) primarily found increased activation in the right hemisphere for individuals with aphasia as compared to other studies (Just et al., 1996; Keller et al., 2001; Anderson et al., 2002) who found more pronounced left hemisphere activation in normals. Another possibility would be that increased activation does not reflect a language restoration function of the right hemisphere, but rather the requirement of additional cognitive processes (e.g. attention) to perform the task given that both normals and individuals with aphasia had some degree of right hemisphere activation. Individuals with aphasia may rely more on these cognitive processes than normals, resulting in greater right hemisphere activation. Fridriksson and Morrow recognized that a purely language processing based explanation should not be discounted. However, the investigators also recognized that an activation increase in the right homologue of Broca's area in persons with aphasia and in the same area for normals could suggest an explanation based on increased working memory load, since Broca's area frequently is activated during working memory based fMRI tasks. Additionally, Anderson et al. (2002) suggested that bilateral activation may represent greater attention and monitoring demands needed for the more demanding condition as compared with the low demand condition. The nature of right hemisphere activity will be further addressed in the following chapter.

CONCLUSIONS

Research has demonstrated that task difficulty can influence the presence and degree of right hemisphere activation, a factor that may need to be considered when assessing post-stroke neuroplasticity. For instance, the selection of a more difficult task during imaging may result in images that exaggerate the level of right hemisphere participation. Differences across studies in the selection of difficulty level may account for some of the discrepant results of right hemisphere activation during the language recovery process. Variations in task difficulty across studies have limited the comparison and generalization of conclusions about right hemisphere activation in recovery from aphasia.

Chapter Seven: *The Nature of Homologous Activity*

This paper has identified several factors that modulate right hemisphere activity following left hemisphere damage. The presence of activation, however, does not necessarily indicate function. Questions remain concerning the nature of right hemisphere activity (e.g. linguistic, cognitive) and the correlation between right hemisphere activity and poorer language outcomes. An examination of the relationship between performance accuracy on a task by task basis and homologous activity would provide additional insight into the right hemisphere's role in language recovery. Results suggest that in less-recovered patients, activation of contralesional areas is associated with accurate performance while in more recovered patients, right hemisphere activity is correlated with inaccurate responses. Studies investigating the relationship between right hemisphere activity and performance accuracy are displayed in Table 8.

BACKGROUND

Right hemisphere activation has been attributed to a range of nonlinguistic functions, such as inefficient mechanisms, continuous brain background activity in addition to a variety of cognitive processes (Weiller et al., 1995; Rosen et al., 2000; Blasi et al., 2002; Blank et al., 2003; Fernandez et al., 2004). Weiller et al. noted that right hemisphere activation may result from the maintenance of sustained attention for the perception and comprehension of stimulus nouns, and/or the exaggerated need for monitoring within working memory to perform the language task. Conversely, the right hemisphere has some capacity for a language take-over function provided certain circumstances, as evidenced by improved language outcomes and right hemisphere activity (sometimes exclusively) (Barlow, 1877; Gowers, 1887; Basso et al., 1989; Cappa et al., 1997; Heiss et al., 1997; Cao et al., 1999; Musso et al., 1999; Thulborn et al., 1999; Blank et al., 2003; Abo et al., 2004). However, better outcomes have been associated with the reactivation of left hemisphere dedicated language networks, while poorer outcomes are correlated with right hemisphere activity (Heiss et al., 1997; Heiss et al., 1999; Rosen et al., 2000; Blasi et al., 2002; Perani, et al., 2003; Winhuisen et al., 2005). In spite of this correlation, it remains unclear if right hemisphere activity is reflective of maladaptive effort or if homologous areas are simply less skilled at language processing.

To characterize the nature of right hemisphere recruitment and the relationship between contralesional activity and poorer outcomes, monitoring of performance accuracy would be needed on a single-trial basis during image acquisition to facilitate error analysis. Until recently, both PET and fMRI imaging limitations prevented the acquisition of images on a single-trial basis. For instance, PET scans are limited to measures of overall accuracy, and in fMRI studies, tasks must be performed covertly to avoid articulatory motion confounds, requiring performance level to be assessed off-line (Postman-Caucheteux et al., 2010). Studies (Saur et al., 2006; van Oers et al., 2010) also have utilized group analysis of scans where information about individual patterns of activation could be lost through averaging of patient brain images.

A positive correlation between right hemisphere activity and accurate performance on a language task would suggest that homologous areas are performing a language role (possibly through nonlinguistic mechanisms) on a task by task basis. The overall language outcome may be poor as a result of a less-skilled right hemisphere even though the homologous areas are contributing to language recovery. If the correlation is found between right hemisphere activity and inaccurate performance, it would be less likely that the right hemisphere is contributing positively to language recovery outcomes. The question would then be does inaccurate performance result from maladaptive effort as the right hemisphere attempts to compensate for a severely impaired left hemisphere or is the right hemisphere activity actually the source of patient errors.

PERFORMANCE ACCURACY

In one of the first studies notable for acquiring overt picture-naming responses, Martin et al. (2005) used an fMRI block design that utilized a hemodynamic response delay allowing for task-related information to be obtained after the task, which minimized motion artifacts. Five chronic aphasia patients participated, with four of the participants classified as having mild- moderate non-fluent aphasia and one patient classified as severely nonfluent. The four mild -moderate patients, who correctly named 88–100% of the pictures during fMRI, had a greater activation in the left supplementary motor area. In contrast, the severe patient, who was unable to name any pictures, activated almost twice as many voxels in the right SMA as the left SMA. The investigators concluded that more left-sided activation was present in patients with high naming accuracy and more right-sided activation in the poorly performing patient. However, the investigators did not allow for direct comparison of accurate to inaccurate

Table 8

Studies exploring the relationship between performance accuracy and right hemisphere activity.

Study	*N*	Method	Time since stroke	Imaging task	Outcome
Martin et al. (2005)	5	fMRI	1-10 years	Overt picture naming	More LH activation for patients with high naming accuracy and more RH activation in the poorly performing patient
Meinzer et al. (2006)	1	fMRI	2 years	Overt picture naming	Greater RH IFG activation for correct as compared to incorrect responses
Postman-Caucheteux et al. (2010)	3	fMRI	≥3 years	Overt picture naming	RH activation only present in individuals with aphasia; incorrect responses were associated with RH activity

responses. The nature of the right hemisphere activation of the severe patient could not be evaluated because the patient never produced a correct response.

Meinzer et al. (2006) separated correct and incorrect responses in a single patient. The investigators acquired two fMRI scans, one prior to the onset of constraint induced language therapy and another following treatment two weeks later. When comparing the two scans the investigators found significantly greater right inferior frontal gyrus activation for correct as compared to incorrect responses, a result inconsistent with the findings of Martin et al. (2005). The activation of the right IFG increased between scannings and was associated with improved naming performance. The results highlight the importance of homologous regions for the recovery of naming performance in this particular patient and suggest that the right hemisphere is performing a language role. The investigators qualified improvements by indicating the patient's performance remained low, suggesting a less than optimal compensatory activation pattern.

Postman-Caucheteux et al. (2010) conducted an fMRI study where overt responses were recorded in an event-related experimental design, allowing comparison of individual responses within a single scan session. The investigators utilized continuous echo planar imaging (EPI) for the first time with patients with aphasia, overcoming complications due to articulation artifacts. The study consisted of three participants with aphasia who were at least three years post-stroke prior to testing in addition to four neurologically intact controls. Two patients were classified as anomic and one as conduction based on the Western Aphasia Battery (Kertesz, 1982). An overt naming task was utilized with responses categorized as correct, paraphasia, omission, or other error type.

The results revealed that neurologically intact controls achieved almost 100% accuracy while aphasic patients achieved 53% to 76% correct responses. Right hemisphere activation in regions opposite the left hemisphere damage was observed in all aphasic subjects, a striking point of distinction between patients and controls. When accurate and inaccurate trials were compared, both response types activated left-sided regions, with no difference in magnitude. In contrast, incorrect responses were associated with activation of contralesional prefrontal areas, primarily in the right inferior and middle frontal gyri. Even though past studies (Heiss et al., 1997; Rosen et al., 2000; Blasi et al., 2002; Perani, et al., 2003; Martin et al., 2005; Winhuisen et al., 2005) identified a correlation between right hemisphere activity and poorer outcomes of patients, this study was the first experiment to find evidence of contralesional activation in response to inaccurate performance.

Postman-Caucheteux et al. (2010) found evidence of contralesional activation in response to inaccurate performance, making it less plausible that right frontal activation underlies an effective compensatory mechanism in chronic aphasia. However, the investigators emphasized that contralesional activity is not the source of patient errors. Instead, the investigators believe that contralesional activation reflects an increased, but ineffective search and selection process recruited when perilesional areas are inadequate.

CONCLUSIONS

Postman-Caucheteux et al. (2010) found right hemisphere activity to be associated with inaccurate performance and reflective of increased effort. In contrast, Meinzer et al. (2006) found homologous activation increasing with accuracy, suggesting a language role for the right hemisphere. Though the results of the two studies are contradictory, they may not be fully comparable. In Meinzer et al., the patient classified as having Wernicke's aphasia achieved less than 30% accuracy in naming and produced a number of neologisms. Participants in the Postman-Caucheteux et al. study achieved 50% correct responses and no neologisms. The study differences may result because right frontal activation is more essential for patients with less recovery than for the well-recovered, consistent with results related to lesion size (Heiss et al., 1997; Cao et al., 1999; Rosen et al., 2000; Blasi et al., 2000) and phase of recovery (Karbe et al., 1998; Fernandez et al. 2004; Saur et al., 2006; van Oers et al., 2010). Both patients with large lesions and patients in the acute phase of recovery (less-recovered) tend to show greater right hemisphere activation and have poorer outcomes.

In regards to the nature of homologous activity, it appears dependent upon the reactivation of left hemisphere language networks. Language functioning will remain in the right hemisphere if the damage in the left hemisphere remains severe after spontaneous recovery. Patients will be expected to have poorer outcomes given that the right hemisphere is not optimized for language tasks. However, if the left hemisphere regains predominance, right hemisphere activity is then reflective of increased, maladaptive effort whenever perilesional areas are insufficient. In this scenario, contralesional activity is related to task difficulty effects and a global increase in blood flow not specific to language networks. Essentially, right hemisphere activation is reflective of language functioning in less-recovered patients and indicative of effort in well-recovered patients with level of recovery being determined in part by the reactivation of left hemisphere language networks.

Chapter Eight: *Discussion*

ADDITIONAL CONSIDERATIONS

This paper has attempted to qualify some of the discrepant findings in the neuroplasticity literature with regard to the right hemisphere's role in language recovery. Nevertheless, additional confounding factors exist. For instance, differences in right hemisphere activation have been identified in relation to age (Nass, 1997; Bates & Roe, 2001) and gender (Vikingstad et al., 2000). For example, right hemisphere regions likely would more readily and successfully take-over language functioning in children because of their relatively more plastic brains. Also, methods of fMRI data collection and analysis can yield different results. Crosson et al. (2007) explored methodological challenges for fMRI imaging of language in aphasia: the mitigation of motion-related artifacts, the use of stimulus onset versus response onset in fMRI analyses, and the reliability and stability of fMRI images across sessions. Also, the use of multi-voxel pattern analysis (MVPA), where patterns of activation in fMRI BOLD signal data are considered as opposed to overall measures of increases in volume and area, have allowed investigators to recognize discrete signal changes that are predictive of task stimulus conditions. Although some variables have been explored, there are multiple known and unknown variables that will influence findings of right hemisphere participation in language recovery.

GENERAL FINDINGS

Research has provided some insight into contralesional activation during language recovery in individuals with aphasia. Right hemisphere activation can be dependent upon the involvement or preservation of specific left hemisphere structures. This paper discussed outcomes related to the POp and basal ganglia though other structures likely exist. Additionally, lesion size provides another factor accounting for some of the variability in results as the presence and degree of right hemisphere activation is modulated in part by the size of the lesion in the left hemisphere. Larger lesions are more likely to evoke a right hemisphere response though the primary recruitment of contralateral areas is not the most effective strategy for language recovery. Additionally, based on the findings of Parkinson et al. (2009), evidence suggests that in the presence of moderately large lesions, activity in the left hemisphere interferes with recovery of language function in the right.

Another confounding factor is the finding that the right hemisphere has a more active role in language recovery in the initial period following a stroke. Conversely, poorer outcomes result if language functioning remains in the contralesional hemisphere during the chronic phase. The right hemisphere also may more readily aid comprehension-based tasks because the processes involved in performing such tasks are more responsive to utilizing different cognitive strategies. Greater right hemisphere activation is present for tasks of greater difficulty. The nature of increased activation partly depends upon the reactivation of left hemisphere language networks and the patient’s level of recovery.

The finding of Meinzer et al. (2006) that the right hemisphere contributes to accurate performance in less-recovered patients is in contrast to Postman-Caucheteux et al. (2010) who found evidence of contralesional activation in response to inaccurate performance in well-recovered patients. Postman-Caucheteux et al. emphasized that the right hemisphere is not the source of patient errors, but rather that right hemisphere activity reflects an increased, but ultimately ineffective search and selection process in patients with chronic aphasia. Essentially, the right hemisphere is the brain's less capable alternative when damage severity prevents the ultimate return of language processes to the left hemisphere.

DIRECTIONS FOR FUTURE RESEARCH

Future research studies should consider some of the variables outlined in this paper. Attempts should be made to fully outline and describe all implicated structures and the degree of involvement even though aspects of lesion site and size cannot be controlled. More comprehensive descriptions will aid in the discovery of patterns of contralesional activity and improve generalizability of results to other studies. Additionally, investigators should ensure that subjects included within the study are in the chronic stage for the results to be reflective of language recovery. During task selection, researchers should consider well-tested psycholinguistic models of the processes involved in executing a particular task. Investigators must ensure that task selection results in images sensitive to neural mechanisms involved in language recovery and are not reflective of increased effort. More research is needed examining activation patterns on a single-trial basis to further establish the impact of contralesional activation on accuracy for less- and well-recovered subjects.

CONCLUSIONS

The relationship between the loss of language in the left hemisphere and the redistribution of language functioning to the right hemisphere is not linear. Instead there exists an interplay between left and right hemisphere networks as the brain attempts to optimize language performance in individuals recovering from aphasia. The right hemisphere assumes a language role when left hemisphere areas are inadequate. However, better outcomes are associated with the reactivation of left hemisphere language networks. Furthermore, the focus of future research should not be on if language functioning can be reestablished in the right hemisphere, but rather on the parameters that predict contralesional participation.

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