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How the Brain Copes with a Phantom Hemisphere and Supports Language Development

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Introduction and Background

The literature to date does not report consistent findings regarding the specific effects of hemispherectomy on language development. A number of studies report greater capacity and proficiency of the left hemisphere (LH) over the right for morphosyntactic comprehension, production and judgments (Aram & Eisele, 1992; Mills, Coffey-Corina, & Neville, 1993; Molfese, 1989). Other studies, however, report excellent, even normal linguistic performance after hemispherectomy of either side (Ogden, 1988; Strauss & Verity, 1983; Vargha-Khadem et al., 1997). There are probably two major reasons for this inconsistency. First, the investigation into language outcomes in many of these studies lacks detailed or theoretically informed linguistic examination; and second, given that hemispherectomy is performed in treatment of intractable epilepsy, the role of clinical factors, such as disease etiology or lesion size, on linguistic outcome must be considered.

In approaching our own study of the effects of hemispherectomy on language acquisition, we based our original hypotheses on several assumptions. First, we assumed that the LH is prewired to be the neural substrate for language development and therefore hypothesized that removal of the LH should result in substantial linguistic deficits compared to removal of the right. Second, we adopted the "earlier is better" (Kennard, 1940) assumption; that is, that due to greater plasticity of the immature brain, earlier age at onset of clinical events would be expected to lead to better language than later insults to the LH.. Given the first assumption, that the left hemisphere is specialized for language development, we reasoned that in contrast, age at onset would not be predictive of language outcome for right hemispherectomies. Surprisingly, although our hypotheses were partially supported, our results painted a far more complex picture than would have been expected from these canonical assumptions (Curtiss & de Bode, 1998a). We found both surpassing linguistic recovery after left hemispherectomy and unexpected lack of language development following right hemispherectomy.

Our findings have led us to pursue two lines of research. First, we have conducted detailed linguistic analysis of the language production of our hemispherectomized subjects; focusing on an analysis of functional category

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status in the grammars of these children. Some of these findings have been reported previously (Curtiss & Schaeffer, 1997a; Curtiss & Schaeffer, 1997b), and further research on this question continues (e. g., Vasquez & Curtiss, 2000)

The second line of research has concentrated on dissecting the relationship between linguistic outcome and clinical factors associated with etiology, such as age at onset, age at surgery, seizure onset, and seizure outcome (Curtiss & de Bode, 1999; de Bode & Curtiss, 1999a; de Bode & Curtiss, 1999b). In the course of this investigation, we realized that the impact associated with each of these clinical factors was a reflection of the functional state of brain maturation at time of damage, i.e. the moment during which brain development was interrupted with respect to the unfolding of both the macro and micro neurodevelopmental programs and the relationship between this "moment" and those points in neurological development key to language. We refer to this insight as the *critical impact point hypothesis* (Curtiss & de Bode, 1999). This approach led us to abandon treating hemispherectomies as a homogenous group; and to adopt instead a theoretical approach in which language outcome was examined in relation to the state of the brain, namely, factors concerning *kind* of pathology and *extent* of pathology. Hence, we have explored the effect of well-defined etiologies and extent of damage on language outcome.

Addressing the issue of kind of pathology, we differentiated between developmental and acquired etiologies and divided the children in our series into two groups: 1) developmental - the children with cortical dysplasia (the CD group), and 2) acquired - the children without cortical dysplasia (the non-CD group). The CD group was further subdivided on the basis of the extent of pathology as a) CD of the entire hemisphere (hemimegalencephaly), and b) CD with multilobar (more than one lobe) involvement. The non-CD group was subdivided into two groups based on etiology: a) Rasmussen's encephalitis, and b) infarction. This division yielded a hierarchy of linguistic outcomes with the Rasmussen's group outperforming all other groups and those with hemimegalencephaly evidencing the poorest prognosis.

It is of note that the hierarchy we found based on linguistic outcomes maps closely onto the hierarchy reported for motor and seizure outcomes for the more than 300 pediatric hemispherectomies reported on worldwide in the literature with the best to poorest motor outcomes associated with Rasmussens encephalitis, infarct, multilobar cortical dysplasia, and cortical dysplasia of the entire hemisphere (hemimegalencephaly), respectively (Holthausen, 1998).

To better understand what our data are telling us, and to better account for the complex picture regarding the variability in language development following hemispherectomy, we have now begun to include an examination of motor function following hemispherectomy to provide us with an additional window into the status of the remaining hemisphere, the crucial factor underlying language recovery or development.

What is actually happening in the RH when its damaged counterpart becomes nothing but a phantom? The effect of the absent hemisphere on the

remaining one does not stop abruptly after surgical removal but continues for a considerable time. For this reason the RH cannot be considered completely normal after hemispherectomy. It is affected in the following ways: the first response of the remaining hemisphere is to eliminate toxic by-products of the injury itself (the surgery in our case) and then, through vascularization (new capillary growth), to provide appropriate nutrition for the remaining tissue (Stein, 1988). Various processes, each with its specific timing, are associated with this "*cleaning*" stage, e.g.

- neuronal death (the death of neurons that were not directly affected by injury),
- glia proliferation (population of cells that nurtures and supports neurons)
- glia scar formation, a restitution of a boundary between the CNS and the rest of the organism and repair of blood vessels.

The next stage is a *reactive response* associated with

- neurotrophic factor production (much more efficient in the developing brain),
- sprouting and reactive synaptogenesis (synaptic proliferation caused by injury) that allows for the partial re-innervation of deafferented cells.

The last component is the *modification* of on-going normal developmental events, for example the reversal of the events of axon retraction and sometimes neuronal loss.

Out of all of these processes, the last one is better understood than the others, primarily based on a number of animal studies. Neurons that are initially produced in excess and later die as well as axons that spread exuberantly in the beginning and later retract in the course of normal development can persist and partially compensate for the loss of tissue in case of brain insult (Janowsky & Finlay, 1986). These alterations caused by early brain damage are hypothesized to underlie the process of recovery especially effective in the immature brain.

This phenomenon is in essence, the **reversal** of the normal developmental mechanisms of the "sculpturing" period of normal brain development that eliminates extra, exuberant connections in the young normal brain. Specifically, when axons are deprived of their transcallosal targets, that is, when hemispherectomy removes the targets through the corpus callosum to areas in the contralateral hemisphere they were programmed to connect to under normal circumstances, the axons may nonetheless persist and re-innervate **homologous ipsilateral** areas, and in some cases, both ipsilateral and contralateral areas (if any are left). If thalamic structures are left intact in the removed hemisphere in cats, for example, there is evidence for abnormal axonal sprouting when both thalami are innervated from the remaining cortex of a single hemisphere. Development of new dendritic fields and reversal of the process of synaptic pruning have also been shown in animals after hemispherectomy (Schmanke, Villablanca, Lekht, & Patel, 1998; Villablanca, Carlson-Kuhta, Schmanke, & Hovda, 1998). Again, in cats when comparing young hemispherectomies to the

adult ones, the most significant difference is in the number of neurons in the remaining hemisphere. These studies receive some converging evidence from research of metabolism following hemispherectomy on humans (first reduced, then increasing to normal and higher values) (Chugani & Jacobs, 1995; Muller et al., 1999).

The important point here, then, is that these processes documented post-hemispherectomy, may result in the reversal of pre-programmed cell death and axonal retraction in the remaining hemisphere, making possible some degree of ipsilateral compensation and recovery.

By addressing the issue of motor development consequent to hemispherectomy, we are testing how effective brain reorganization is in terms of establishing new and strengthening already existing but weak ipsilateral motor connections. Since it is known that language development will depend on the integrity of the remaining neocortex, we can use regained motor function as an indirect index of the integrity of the remaining hemisphere, providing us with an additional window into understanding the source of the variability in the extent of language development after hemispherectomy that we are finding.

Methods

Subjects

Our subject population consisted of children (monolingual speakers of Standard American English) who had undergone hemispherectomy as part of the UCLA Pediatric Epilepsy Surgery Research Program. Hemispherectomies were performed in treatment of catastrophic childhood epilepsy. The findings reported in the beginning of this paper were based on 37 hemispherectomies.

Language assessment

We concentrated our analysis on language production. Spoken language was assessed through analysis of spontaneous speech samples. These samples were recorded, transcribed and then analyzed for their grammatical and lexical content. Based on these data, each child was assigned a SLR, spoken language rank, using a five-point scale. Some children's language appeared to fall between numerical ratings, and they received ranks reflecting these intermediate states (e.g., 3.5).

0 = no speech
1 = has fewer than 20 words
2 = has more than 20 words but no word combinations
3 = constructs short telegraphic utterances
  a. *Helping the monkey*
  b. *Him brown*
4 = is a fluent speaker, but does not yet have the target grammar

a. *Because Sammy was growned up first, so he is the biggest and I growed up and Chris growed and Ruben was last.*

5 = has the target grammar

a. *I forgot to tell them what I want*
b. *I hope I have my iron cast off*
c. *I hope it's off by Thanksgiving because I love to downhill ski*

These rankings provided a global index of linguistic outcome. As the mean time post-surgery was 5.28 years for the left hemispherectomies and 6.31 years for the right hemispherectomies, these rankings represent at least a medium-term outcome.

To begin this investigation into the relationship between residual or redeveloped motor control and language outcomes, we selected 11 left hemispherectomies all with language, but with varying degrees of language. Moreover, these 11 children are representative of the majority of the larger sample from which they were drawn. They have different etiologies, different ages at surgery, some have achieved seizure control, some not, they range in age from 5;8 to 15, and their spoken language ranks (SLRs) vary from 2 to 5.
Table 1 presents the SLRs and other clinical information for the 11 subjects focused on here.

Table 1.

Patient	DOB Etiology Age at Surgery	Seizure Control	SLR
1F	6-23-92 Infarct 6;9	yes	3.5/4
2M	4-10-93 Infarct 2;7	no	2.5
3M	12-05-90 Cortical Dysplasia 1;5	yes	5
4M	2-22-91 Cortical Dysplasia 2;10	yes	3.5/4
5M	9-23-84 Cortical Dysplasia 1;5	no	2
6F	7-15-92 Cortical Dysplasia 0;5	no	4
7M	3-24-94 Cortical Dysplasia 1;0	yes	3.5/4
8F	5-07-90 non-diagnosed 1;0	yes	3.5
9M	11-14-91 Hemimegalencephaly 2;3	yes	3.5/4
10M	8-30-90 Rasmussen's Encephilitis 2;5	yes	3.5/4
11F	06-03-88 Rasmussen's Encephilitis 10;0	yes	3.5/4

Motor Function

To assess motor function we developed a weighted scale to evaluate leg, arm and hand function on the side contralateral to the resected hemisphere (i.e., evaluated use of the right limbs after left hemispherectomy.)
Scores intermediate between other scores reflect only partial ability to perform the requisite activities to obtain the next highest score.

Use of affected leg, 0 - 4

0 = none, paretic (paralyzed)
1 = poor: walks w/brace and/or limp
2 = limited: walks w/limp and is able to perform some other motor activity (e.g., kick, jump, ride a 3-wheel bike)
3 = good: walks, runs and is able to perform some other motor activity (e.g., kick, jump, ride a 3-wheel bike, climb stairs)
4 = excellent: age-appropriate activities

Our subjects' leg motor function scores ranged from 0.5 - 3.5.

Use of affected arm, 0 - 3
0 = none
1 = poor: raises arm
2 = limited: raises, bends
3 = good: raises, bends and is able to carry objects and/or put clothes on

Our subjects' arm motor function scores ranged from 0 - 3.

Use of affected hand, 0 - 3
0 = none
1 = poor: only able to open and close
2 = limited: is able to grasp or hold an object
3 = good: is able to grasp or hold an object and to perform some other motor activity (e.g., brush hair or teeth)

Our subjects ranged in hand function from 0 - 2, with 9/11 receiving a score of 0.

Results

Through parental report and in some cases personal observation, we derived motor scores for each child using the total score achieved for the three components together, as the child's motor score. We then compared the SLRs and the motor scores for each child. These results are presented in Table 3.

Table 2: Spoken Language Rank and Motor Scores

Patient	SLR	Motor score
1F	3.5/4	6.5
2M	**2.5**	**5.5**
3M	5	7.0
4M	3.5/4	5.0
5M	2	1.0
6F	4	5.0
7M	**3.5/4**	**1.5**
8F	3.5	5.0
9M	3.5/4	5.0
10M	3.5/4	5.0
11F	3.5/4	5.0

For the most part, the two scores correspond rather closely. In fact, the correlation between the two scores nearly reaches significance, despite the small n ($F = 4.676$; $p < 0.059$). In general, then, those children with the highest SLR have achieved the greatest motor function. This relationship holds for 9 of the 11 children so far assessed. However, for two of the children this relationship does not hold: one child has a SLR of between 3.5 and 4, yet has a motor function score of only 1.5, far lower than the 5 other children with the same SLR. Conversely, another child has a SLR of only 2.5, yet has a motor function score of 5.5, a score higher than all but two of the other children.

Note that although our focus here is on motor function, we also included information regarding seizure control in Table 1. We did this because our previous research has indicated that seizure control is an important clinical variable to consider in predicting language outcome. Specifically, in our examination of our larger sample of 49 children, we found that seizure control was strongly correlated with SLR ($F = 7.610$; $p < 0.0082$). Although we do not take up the role of seizure control in this paper, we consider seizure control to be an important indicator of the integrity of the remaining hemisphere, and as such, these findings further support our predictions about language recovery after left hemispherectomy being crucially dependent upon the state of the remaining right hemisphere. Our future research will investigate whether combining the two variables of motor function and seizure control will result in more precise prediction of extent and quality of language development following left hemispherectomy.

Returning to our findings on motor function in this preliminary sample, we see two results worthy of mention. First, for the majority of children we find a direct relationship between language rank and motor outcome, such that the higher the SLR, the higher the motor score and vice-versa. This findings suggests that motor function may indeed be usable as an indirect index of the integrity of the remaining hemisphere, and thus may provide one means by which we can further explore our complex findings regarding language development following hemispherectomy.

Second, however, this relationship is not constant. Two of the children in our sample show a notable distinction between language and motor outcomes following hemispherectomy, in one case language having developed to a much greater degree than motor function, in the other, just the opposite. These children, while a minority of the sample, nonetheless remind us that language and motor abilities are two quite distinct domains of cortical function, one not dependent on the other.

Finally, it becomes possible to use the structural patterns of language development, itself, as a means of delimiting the specific neurodevelopmental processes which have been disrupted, thereby allowing us to tie developmental pathogenesis with specific language outcomes. Such a mapping, of

developmental language processes onto brain development, would address the very essence of developmental neurolinguistics.

Endnotes

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