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Neurobiological Mechanisms of Language Acquisition in Sturge Weber Syndrome

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In neurolinguistics, hemispherectomy has largely been discussed as a coherent, homogenous category, a circumstance providing the best population with which to study the potential of each, isolated hemisphere for language acquisition and language performance. However, a closer look at this population indicates that to understand the story hemispherectomies provide us regarding the linguistic potential of each hemisphere, we must subdivide this population by a number of clinical factors which distinguish them.

One major differentiating factor is etiology -- the pathogenesis of the disease leading to the resection of an entire hemisphere. There are two classes of neurological insults: 1) acquired insults (such as trauma, stroke) where damage is the result of external influences and the hemispheres have been allowed to develop normally in gestation, and 2) developmental insults, where an internal mechanism disrupts the course of neurological development during gestation. In the case of acquired disorders it is often possible to determine the time of insult, whereas with developmental disorders the character and time frame of the insult often remain obscure.

It has been widely accepted that developmental disorders lead to poorer cognitive development than acquired disorders. However, as we have argued previously (De Bode & Curtiss, 1998), contrary to a long-held belief, developmental abnormalities do not always lead to worse cognitive outcomes. This paper is devoted to elucidating part of the story regarding the different effects on language development of different developmental pathologies. We will attempt to account for the range of findings reported in the literature on the linguistic outcomes after hemispherectomy. Two kinds of findings in particular must be explained: 1) why so many right hemispherectomies fail to develop language and 2) why certain left hemispherectomies develop remarkably good language despite removal of the "language" hemisphere, and in contrast to many other left hemispherectomies.

We will present an account which centers on the characteristics of a particular developmental pathology; namely, Sturge Weber Syndrome (SWS), and the way it differs from other developmental pathologies, such that it allows for greater linguistic development than other etiologies.

Sturge Weber syndrome is secondary to an embryological abnormality which results after a vascular plexus around the cephalic portion of the neural tube fails to regress in the ninth week of gestation. In other words, the central nervous system develops from a primitive tube in the embryo. The blood supply develops in turn from a network of tissue that initially surrounds all of the developing nervous system, then is removed from selected areas where it is not needed. Sturge Weber syndrome results when part of this unnecessary primitive blood vessel network at the front end of the developing nervous system fails to be removed during the ninth week of pregnancy. This condition results in vascular tumor formation, or *angiomatosis*, for two of the cranial connective and protective tissue layers of the brain (leptomeninges: the pia matter and arachnoid,) lying over the cerebral cortex. Alterations in blood flow due to the angiomatosis lead to calcium deposits in the underlying cerebral cortex. This disorder is frequently associated with severe seizures, hemiplegia and mental retardation. These perinatal seizures usually prove to be resistant to anticonvulsant medication. However, early surgical resection, i.e., hemispherectomy, can significantly decrease risks of physical deterioration and improve chances for normal cognitive development (Shields, Duchowny, & Holmes, 1993; Wyllie, Comair, Kotagal, Raja, & Ruggieri, 1996).

Hemispherectomy for SWS began in the 1950's. In one of the earliest reports of hemispherectomy in the treatment of infantile hemiplegia associated with Sturge Weber, Cairns and Davidson in 1951 report on one child who underwent surgery at the age of 7 (Cairns & Davidson, 1951). Despite the lack of a detailed follow-up, the authors noted profound changes in behavior and "steady progress at school". In 1958, Peterman et al. report on 14 patients with SW syndrome seen between 1935 and 1956. 14 patients did very well and were leading independent lives, again implying substantial linguistic development in all cases (Peterman, Hayles, & Dockerty, 1958).

Most familiar to linguists is the seminal work on hemispherectomy carried out by Dennis and her colleagues (Dennis, 1980a; Dennis, 1980b; Dennis & Whitaker, 1976). The three hemispherectomized subjects reported on by Dennis were of average intelligence and performed at normal educational levels. The right hemispherectomy child underwent surgery at 4 1/2 years. The two left hemispherectomies had surgery before 5 months of age. Upon detailed linguistic examination, Dennis concluded that the isolated LH is superior to the right in relation to complex syntax and semantics. While the differences she found between the left and right hemispherectomies in linguistic performance are important findings, what we concentrate on today is the fact that she found that both isolated hemispheres developed fluent, fluid speech, and that all 3 cases were hemispherectomies consequent to SWS.

Ogunmekan and colleagues (Ogunmekan, Hwang, & Hoffman, 1989) report on 12 patients with Sturge Weber treated surgically. With the exception of two cases, surgery took place between the ages of 3 and 20 months. Though follow-up was not lengthy, and only seizure control and overall development were reported, not neuropsychological or linguistic development, the authors comment on an excellent outcome in all cases, again indicating good language development in both isolated hemispheres.

The more recent study by Wyllie et. al. (1996) reports on, among others, 3 cases of infants with Sturge Weber syndrome who underwent functional hemispherectomies between 11 and 15 months of age. Duration of their postoperative follow-up varied from 13 to 34 months. Describing language development following surgery, the authors note that one patient at age 3;9 "had normal vocabulary", spoke in complex sentences and attended a regular preschool; another child (age 2.3) had more than 100 words used holophrastically, and the third child at age 2.5 used two-word phrases. This remarkably normal development in all 3 cases occurred despite the fact that one was a left hemispherectomy and two of the children had postoperative complications from which they eventually fully recovered.

More recently, Vargha-Khadem et al. (Vargha-Khadem et al., 1997) report a case of remarkable speech development in a nine-year-old boy. Alex, who underwent left hemispherectomy at age 8 1/2, had failed to develop speech prior to surgery. However, eight months post-surgically, Alex started uttering single words and within a few months developed "copious and appropriate sentences".

Finally, the most recent report by Mariotti et al. (Mariotti, Iuvone, Torrioli, & Silveri, 1998) presents a case of a patient who underwent early hemispherectomy because of Sturge Weber syndrome. Seventeen years postsurgically a woman is normal in any aspect of everyday verbal communication. No specific pattern of linguistic impairment was found in either linguistic domain (lexical semantic, phonological, morphosyntactic) though some generic reduction of linguistic competence is noted as for the subjects with comparable (low-normal) IQ.

From just this brief survey of the literature on SWS, we find numerous examples of considerable linguistic development after hemispherectomy of either hemisphere. In contrast, we are unaware of any literature reporting good language outcome after hemispherectomy for other developmental pathologies. Rossi and colleagues (Rossi et al., 1996) studied 28 children with different forms of cortical dysplasia. Cortical dysplastic lesions are cerebral malformations resulting from neuronal migration defects. They examined possible correlations between type and extent of the lesion as detected by MRI and the developmental progress, i.e. neuropsychological, psychiatric, and social outcomes. Language was evaluated with the Token test, qualitative and quantitative examinations of spontaneous language production, and tests of reading and writing. Though details of linguistic examination are not reported, the authors found that there was a tendency for expressive and receptive language to be correlated with the extent of lesion. Only two children showed normal cognitive development (their language status is not reported) with the rest of the group displaying differing degrees of mental retardation and impaired language. This is the only study to date that has examined systematic neuropsychological and linguistic outcomes in a group with cortical dysplasias.

To summarize, throughout the literature, almost all children with developmental insults who acquired remarkably or even reasonably good language had SWS.

In our own data, this, too, is proving to be the case. We have been studying a large pediatric hemispherectomy population. We have previously reported on some of our linguistic findings on this population (Curtiss & de Bode, 1998a; Curtiss & Schaeffer, 1997a; Curtiss & Schaeffer, 1997b). Today we focus on how the findings of our study relate to a possible model of the neurobiology underlying language acquisition.

Two cases will illustrate our findings. The first child, SM:, underwent surgery at 1;1,. had no surgical complications and remains seizure-free. He was initially language delayed, and the early course of his language development was slow and evidenced deficits with respect to I-system structures/features in particular (e.g., agreement, tense). By age 8, however, he demonstrated normal comprehension and production, both of which were investigated extensively and reported in Curtiss and Jackson, (Curtiss & Jackson, 1989). By age 8 he had a mature grammar with respect to functional category structure, and outperformed two CA controls in production of syntactically complex utterances. Some examples of his spoken language can be found in Table 1.

Table 1: Sample Sentences from SM

Example Sentences	Structures Illustrated
You ever see a balloon that's cut you mouth and popped?	rel. clause, reg. past tense
You know those stools who have one pole and another pole and then...	overt number agr. within the DP, def. DP, rel. clause
It would be a funny, it's a, it would be a a funny place for somebody to sit down there.	modal, for-to complement

Table 1: Sample Sentences from SM (cont'd.)

Example Sentences	Structures Illustrated
We weren't there when they did that.	s-v agr., adjunct CP
And you know, uh, you know why we were saying we have to take it home?	WH-movement, multiple object complements, s-v plural agr.
One day, when, and, when I was sleeping, I imagined I was walking in the mountains.	adjunct. clause, complement clause, reg. past tense, def. DP
It was made out of wood.	passive

The second child, VI, is a 7-year-old girl who underwent left hemispherectomy at age 1;5. She had no surgical complications and remains seizure free. She was mute until age 2, then began to produce single words, moving on to short sentences within about 6 months. Her developmental rate appears to have been somewhat slower than normal to date, yet she displays a rich range of grammatical structures in her speech and makes few errors, as illustrated in Table 2.

Table 2: Sample Sentences from VI

Example Sentences	Structures Illustrated
My mom told me to close my eyes and I did.	small clause, definite DP, regular plural VP ellipsis with *do*
I don't know, I don't know what's his name.	WH-complement, *SAI in nonroot clause
You just get on it, walk on the stairs, find a seat, sit on it, then they take you to another one to pick up somebody else...	purpose clause, appropriate use of determiners
You get mad if I do.	adjunct clause
Is it a lot of work, mom?	SAI, s-v agreement with *be*
How'd you know that?	SAI with WH question and do-support
Cause you, you could take yourself to see Chucky's Bride.	modal, anaphor, small clause

Table 2: Sample Sentences from VI (cont'd.)

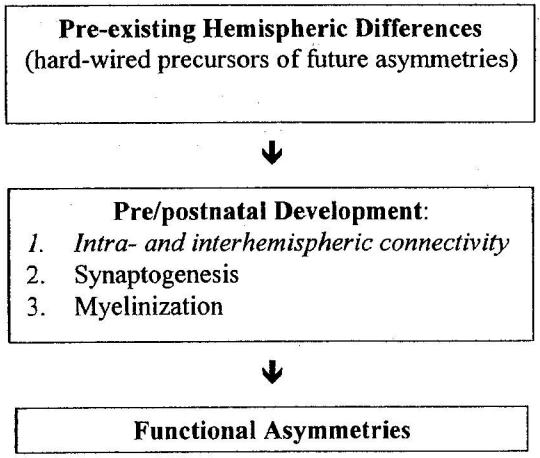
Example Sentences	Structures Illustrated
My tooth popped out.	reg. past tense
They're my childrens	s-v pl. agr, nom. & gen. prons, pl. error

Both of these children had SWS.

Thus, in our own hemispherectomy study (Curtiss & de Bode, 1998b) out of 21 children with defined dysplastic lesions, only 3 children are developing good language. Two of them have SWS, and only one of them has cortical dysplasia throughout the hemisphere, or *hemimegalencephaly*. The overall picture, then, is one of poor linguistic outcome after developmental pathologies other than SWS.

Our specific hypothesis is that within the heterogeneous group of developmental pathologies, SWS represents a separate population distinguished by an increased chance of developing normal language and less impaired language and cognition than other developmental disorders, for example, hemimegalencephaly. We suggest that this is because in SWS, until resection, interhemispheric connectivity and inhibition are still functional, in contrast to disorders affecting neuronal migration. We propose an account of the neurobiology underlying language acquisition in which interhemispheric inhibition and axonal loss contribute critically to the process of language acquisition and lateralization in both clinical and normal populations. Our hypothesis rests on the following assumptions: first, each hemisphere has its own hardwired, predetermined program for functional specialization. Second, to instantiate this predetermined program as functional asymmetries, normal prenatal and postnatal neurobiological development is crucial. We hypothesize that part of this normal development is establishing normal interhemispheric connectivity. Our account regarding the hemispherectomy findings, and more generally, regarding the neurobiology of language acquisition thus encompasses 3 related hypotheses, presented in (2), which rest on the assumptions presented schematically in (1) below.

(1)



(2)

a. Interhemispheric connectivity and the resulting pattern of excitation and inhibition and axonal loss, contribute critically to the process of language acquisition and lateralization.

b. In Sturge Weber Syndrome (SWS), interhemispheric connectivity and inhibition are still functional, leaving intact neurological conditions favorable to language development.

c. In SWS, the peculiar combination of preserved interhemispheric connectivity and abnormal stabilization of corpus callosum fibers prevents the instantiation of lateralization, thus allowing both hemispheres to remain plastic with respect to language development.

Because our model places a lot of weight on interhemispheric connectivity, let us briefly go over what interhemispheric connectivity entails and how it is or fails to be instantiated in developmental disorders. First, the main prerequisite for normal interhemispheric connectivity is normal intra-hemispheric cortical organization. Second is the prenatal establishment of connections with homotopic areas in the other hemisphere. This requires that normal homotopic areas be available; otherwise aberrant connections result in random connections with heterotopic areas (Cook, 1990; Trevarthen, 1990). Third, normal, postnatal axonal loss appears to be a crucial component of establishing functional asymmetries in the developing brain (Witelson & Pallie, 1973). Let us note that in the normal case, we are born with an excess of axonal connections passing through the corpus callosum. Later in the process of normal development, the number of these connections shrinks and the corpus callosum reaches its adult values. It has been proposed that it is this axonal loss which fixes predetermined functional asymmetries in place (Hines, McAdams, Chiu, Bentler, & Lipcamon, 1992; Njiokiktjien, De Sonnerville, & Vaal, 1994).

Now let us contrast this normal pattern with the developmental pattern of cortical organization in SW and other developmental disorders. As we go through this description, it may be helpful to look at (3) below.

Because our hypothesis contrasts the possibilities for linguistic growth in SWS with prognosis after other developmental etiologies, we will support our analysis by examining postnatal development in the two groups, most specifically, with respect to interhemispheric connectivity. To illustrate this comparison, we will focus on HM, which resembles Sturge Weber in that it is also a unilateral malformation; that is, a malformation confined to one hemisphere[1]. At the same time, hemimegalencephaly is characteristic of other cortical dysplasias with cortical disorganization which includes both neuronal and glial abnormalities (O'Kusky, Akers, & Vinters, 1996; Robain & Gelot, 1996).

In nontechnical terms, with cortical dysplasia, there is disorganization throughout the six layers of the cortex, with no systematic organization regarding which kinds of cells inhabit each of these layers, and the cortex is abnormally thick. In addition, while in the normal brain we see a clear demarcation of white and gray matter, in cortical dysplasia such a demarcation is not found. Moreover, neurons are scattered throughout white matter.

The most prominent feature of HM, specifically, is abnormal cortical lamination, that is lack of alignment in the horizontal layers of the cortex and an indistinct demarcation between gray and white matter. Also, there are abnormal, giant neurons extensively distributed throughout the cortex and subcortical white matter. The most interesting finding to which we will refer later is that an increased size of these giant neurons is associated with increased size of their dendritic tree and an increased number of dendritic branches. This coupled with a significant increase in the total number of synapses due to increased cortical thickness leads to synaptic dysgenesis. In other words, cortical inter- and intra-

connectivity in HM is highly abnormal due to the increased number of synapses. In contrast, a pathological examination of SWS often demonstrates normal cortical organization despite microscopic foci of calcification in the cortex and widespread angiomatoses of the meninges. There may or may not be cortical disorganization but it is never as severe as in cortical dysplasias (Vinters, 1998).

To summarize, the first condition for normal connectivity, preserved cortical organization, is not met in HM, but is in SW. As the next step critically depends on normal cortical organization, we can deduce that SW but not HM will support the establishment of normal connections between the hemispheres. However, the third condition, axonal loss leading to functional asymmetries, will not be met in either condition because seizures appear to prevent axonal diminution (Grigonis & Murthy, 1994). It has been shown that epileptic cortical activity stabilizes immature callosal projections which are normally eliminated during development. Thus, functional asymmetries will not be established in SWS and, as a result, both hemispheres will stay 'on line', by virtue of extensive interhemispheric connectivity which fails to progress into a normal pattern underlying functional asymmetries. It is this failure which keeps lateralization from progressing, which in turn fosters the linguistic potential of the right hemisphere. On this account, what seem like surprising findings, good language development after hemispherectomy of either side in cases of SW, become predicted, neurolinguistic findings.

(3) Neurobiological mechanism leading to the unique cognitive outcome in SWS

Neuropathology of Hemi Megalencephaly	**Normal Brain Development**	**Neuropathology of Sturge Weber**
Abnormal (much thicker cortex, neurons in the white matter result in the increased # of synapses)	I. *Intra*hemispheric cortical organization	Normal or mildly abnormal (despite vascular tumor formation of the two protective brain tissue layers)
	II. *Inter*hemispheric connectivity	
Abnormal (due to a significant increase in the total number of synapses)	1. Establishing connections between homotopic areas of the two hemispheres (pre- & postnatally)	Normal
Does not occur	2. Postnatal axonal loss (fixes predetermined functional asymmetries in place)	Does not occur due to the known effect of seizures on corpus callosum fibers
↓	↓	↓
Aberrant connectivity prevents a healthy hemisphere from normal functioning even after resection	Functional Asymmetries	Functional asymmetries fail to get established but both hemispheres stay "on-line" due to extensive and normal connectivity. Surgical resection releases inhibition and allows a remaining hemisphere to develop normally.

Notes

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1. Although bilateral involvement in SWS has been reported, it is more often confined to one hemisphere.

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