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Age and Etiology as Predictors of Language Outcome following Hemispherectomy

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Hemispherectomy · Language · Language development · Plasticity · Linguistic outcomes

Abstract
We report on the effects of etiology and age on the linguistic outcomes in a large pediatric hemispherectomy population. Four populations were considered separately: cortical dysplasia (multilobar involvement), Rasmussen's encephalitis, infarction as a primary etiology and, fourth, children who failed to develop language, regardless of etiology. We argue against the 'the-earlier-the-better' hypothesis and propose our own hypothesis that weds maturational factors to etiological factors to predict language outcomes following pervasive brain insult. The implications of our 'critical impact point' hypothesis are discussed.

Introduction

How can we predict which children will do well linguistically following hemispherectomy? This question is not just of clinical interest in the treatment of epilepsy but is of key importance in our understanding of the linguistic potential of each isolated developing hemisphere and understanding which factors prevent or foster the instantiation of plasticity of language.

In this paper, we report on the linguistic outcomes of a large series of pediatric hemispherectomies, the largest population of pediatric hemispherectomies ever studied, and attempt to provide an account of our findings on the basis of two key factors: age and etiology (pathogenesis of the disease). The findings we present will, we hope, prove to be important parts of the complex story regarding language development following hemispherectomy.

Literature Review

There is increasing evidence indicating that at or even before birth, in the vast majority of individuals, the left hemisphere (LH) is prepotent to support language acquisition, that is, genetically programmed to serve as the neural substrate for language [Bates et al., 1992; Gallagher and Watkin, 1996; Molfese and Segalowitz, 1988; Witelson, 1985]. However, the picture is not entirely clear regarding the development of hemispheric specialization for language or the capacity of the right hemisphere (RH) to support language development. It is also not yet known

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whether the LH on its own, without the support of the RH, can mediate normal and complete language development.

Event-related potential studies of normal children in early stages of overt lexical acquisition and clinical studies of children with unilateral lesions lend support to the view that the LH is prepotent for language [Aram and Eisele, 1992; Cohen, 1992; Mills et al., 1994; Stark, 1997]. We will refer to this view as the 'prepotency' view. On this view, the prediction is that even with early damage to the LH, the RH will not support full, normal language acquisition.

A somewhat different view has been proposed which holds that despite this initial predisposition of the LH, the RH has an equal potential to subserve language. The continuing lateralization of language to the LH overrides this potential, however [Kinsbourne, 1974; Lecours and Joanette, 1985; Locke, 1997]. This view, an 'equipotential' view, is consistent with the Kennard principle [Kennard, 1940], which asserts that the earlier the brain damage, the better the outcome, as earlier damage to the LH would free the RH to realize its linguistic potential. Some studies of unilateral LH lesions in childhood have been used to support this position [Stiles and Thal, 1993; Thal et al., 1991]. In addition, some of these data have been interpreted to suggest that the RH plays a key role in language development and, if damaged, language development will be impaired. This equipotential account, then, makes three predictions: (1) that with significant early damage to the LH, the initially equivalent linguistic potential of the RH will be realized; (2) that the earlier the damage, the greater the potential which can be tapped, and (3) that damage to the RH may result in linguistic impairment.

Because so little is understood about the mechanisms responsible for inter- versus intrahemispheric language transfer after LH focal lesions [de Bode, 1998; Duchowny et al., 1996; Helmstaedter et al., 1994], studies of focal damage in children may not be adequate for determining the potential of the RH to serve as the substrate for the acquisition of grammar. It is often unknown whether impaired performance in these cases reflects the best efforts of the damaged LH, the linguistic performance of the RH or some combination of both. Moreover, findings regarding language transfer often conflict with each other regarding age, etiology and lesion location. Thus, it is the study of language development subsequent to hemispherectomy – the removal of an entire cortical hemisphere – that may best reveal which factors prevent or foster the instantiation of language plasticity.

The literature does not report consistent findings regarding the specific linguistic effects of hemispherectomy. A number of studies report greater capacity and proficiency of the LH over the RH for morphosyntactic comprehension, production and judgments [Day and Ulatowska, 1979; Dennis, 1980a, 1980b; Dennis and Kohn, 1975; Stark et al., 1995; Vargha-Khadem et al., 1991; Vargha-Khadem and Polkey, 1992] and for reading and spelling [Ogden, 1996]. Other studies [Riva and Gazzaniga, 1986; Strauss and Verity, 1983; Vargha-Khadem et al., 1997] report excellent, even normal linguistic abilities after hemispherectomy of either side.

Given that hemispherectomy is performed in the treatment of intractable epilepsy, such variable findings may be accounted for only by considering the role of clinical factors on linguistic outcome [Gordon, 1996; O'Leary et al., 1983; Rossi et al., 1996]. However, little research has been carried out specifically addressing the effects of such factors on language. For example, the relationship between etiology of the underlying pathology and linguistic outcome in children with catastrophic epilepsy has yet to be established.

We have begun to address these questions by studying the language of our large series of hemispherectomized children and analyzing which of a number of clinical factors is predictive of their spoken language outcome [Curtiss and de Bode, 1998; Curtiss et al., 1999; de Bode and Curtiss, 1999]. We will review some of our initial findings before moving on to present work these initial findings have led us to focus on in some of our more recent research, which we present here in some detail.

Methods

Subjects

Our subject population consisted of 48 children who had undergone hemispherectomy as part of the UCLA Pediatric Epilepsy Surgery Research Program [for more details, see Peacock et al., 1996]. Patients were included in our sample if, among other criteria, they had catastrophic childhood epilepsy, their seizures were resistant to antiepileptic medications, they had surgery before 18 years of age, they were monolingual speakers of Standard American English or were in a Standard American English environment, and they were patients for whom follow-up information was available.

A breakdown of the subject population by side of damage, age at seizure onset and age at surgery is presented in each table.

Postsurgical Linguistic Evaluation

Because of the difficulty in establishing a common metric of comprehension across the age range studied, we concentrated our analysis on language production. At the point of assessment used in these analyses, all of our subjects were of an age to be expected to talk in the course of normal language development (i.e. 3 years or older).

Table 1. Distribution of SLRs as a factor of age at onset/sidedness/etiology for the entire group excluding the RE group

Side	Etiology	Age at clinical onset	SLR
Left	developmental	birth to 3 months	0–4.5
	acquired	birth to 11 months	0–5
Right	developmental	birth to 2;6 years	0–5
	acquired	birth to 8 months	0–4.5

Postsurgical data on the children's language production were collected by means of the MacArthur Communicative Development Inventories [Fenson et al., 1990] or via language sampling, as developmentally appropriate or possible. A question specifically asking for speech onset age was added to the MacArthur Inventories for our use. Language samples were collected by means of the Story Game from the Kiddie Formal Thought Disorder Scales [Caplan et al., 1989] or via naturalistic conversation with the examiner interviewing the patient on topics including family, friends, school, birthday, TV shows and favorite activities. These samples were recorded, transcribed and then analyzed for their grammatical and lexical content using a detailed grammatical analysis focusing on functional category structures, constituent structure and movement.

Based on these data, we assigned each child a spoken language rank (SLR), using a 5-point scale:

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: *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.

Some children's language appeared to fall between numerical ratings, and they received ranks reflecting these intermediate states (e.g. 3.5).

These rankings provided a global index of linguistic outcome. As the mean time after 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.

Results

We begin with some of our previous results in studying those factors which have predictive relationships to linguistic outcome [Curtiss et al., 1999]. Our first two hypotheses tested long-held assumptions regarding brain damage and its effects on language development. In our first hypothesis we addressed the assumption that it is the LH that is primarily involved in language development. We hypothesized, therefore, that removal of the LH should result in substantial linguistic deficits, particularly with respect to grammatical development compared to removal of the RH. Our second hypothesis addressed the assumption that 'earlier is better' [Kennard, 1940]. We thus hypothesized (a) that early onset can be expected to lead to better language outcome, particularly for left hemispherectomies, but (b) that age at onset will not be predictive of outcome for right hemispherectomies.

Our results were surprising. Our first hypothesis was not supported. We failed to find a significant correlation between side of surgery and linguistic outcome in terms of the qualitative and quantitative characteristics of speech production indexed by the SLR (left group mean, 2.60, right mean, 2.26; $F_i = 0.1777$, $p > 0.5162$) although an analysis of a subset of our hemispherectomy population looking at specific features of syntactic acquisition, namely functional category development of I and D system structures, did find the expected left-sided advantage [Curtiss and Schaeffer, 1997a, b]. Further investigation comparing hemispherectomies with respect to aspects of grammatical development is underway but will not be discussed here.

A second surprising finding was that a greater proportion of right hemispherectomies than left hemispherectomies failed to develop language: 41.2% (7 of 17) of the right hemispherectomies versus 17.2% (5 of 29) of the left – even long after their surgeries (from 3 years 9 months to 9 years 2 months after surgery). This result suggests a role for the RH in the earliest stages of language development, and we are currently considering the nature of that role but will not discuss this issue further here.

Hypothesis 2 was also not supported. Earlier onset did not lead to a higher SLR for the left hemispherectomies as predicted. Table 1 illustrates both sets of findings. (The table also illustrates that the division of etiology simply into acquired vs. developmental can be too broad to predict language outcome).

Moreover, contrary to our predictions, age at onset *was* predictive of outcome for the right hemispherectomies. Early age at surgery led to lower SLRs in the right hemispherectomy group. This latter finding was in direct conflict with the received wisdom regarding age and developmental outcomes and has led us to direct our efforts to determine the basis of this surprising result. We turn now to this work.

Table 2. Children who have not developed language (SLR = 0)

Patient No.	Sex	Side	Age at surgery	Age at onset	Seizure control	Etiology/pathogenesis
1	M	left	3;4	8 days	no	CD/entire hemisphere
2	M	left	0;3	birth	yes	CD/entire hemisphere
3	F	right	2;5	6 months	yes	CD/entire hemisphere
4	F	right	2;2	5 days	no	CD/entire hemisphere
5	M	right	1;5	2 days	no	CD/entire hemisphere
6	F	right	0;5	birth	yes	CD/entire hemisphere
7	M	left	3;9	6 months	no	hydrocephalus, intraventricular hemorrhage
8	F	left	1;3	birth	no	diffuse CD, CC agenesis
9	M	left	9;0	11 months	no	infarct (MCA)
10	F	right	0;10	4 months	yes	CD, subdural hematoma

A Closer Look at Etiology as a Predictor of Language Outcome

Etiology

The most obvious confound bearing on our results concerning the right hemispherectomies may have been the fact that many of our right hemispherectomies with good language outcomes were patients with the specific etiology of Rasmussen's encephalitis (RE) and, what is more, that in this subgroup the patients' age at onset was considerably older than in the rest of the group. Therefore, realizing that our findings relative to hypothesis 2 might be an artifact of etiology, we devoted our attention to pathogenesis as a key factor in accounting for linguistic outcome. In this context, we specifically explored three areas: (1) the confound concerning RE and the RH results, (2) the etiologies of those children who failed to develop any language and (3) the effect of well-defined etiologies and extent of damage, such as hemimegalencephaly and other cortical dysplasias (CDs) on language outcome. Ultimately, of course, our objective is to determine whether or not there is a systematic relationship between underlying neuropathology and extent and patterns of linguistic development following hemispherectomy.

For questions regarding etiology, we based our analyses on 38 subjects whose etiologies fell into well-defined etiological groups which contained a large enough sample of children to be representative. Each child's etiology was diagnosed on the basis of examination of their entire medical history, including pathology report, PET, MRI scans, prolonged EEG monitoring, seizure history, drug history, interictal and ictal scalp EEG and assessment of neurodevelopment. Each diagnosis was rated by a neurosurgeon and a second rater (a neuropathologist) blind to the rating of the first.

Recognizing the importance of differentiating acquired versus developmental etiologies, the framework we adopted was to divide the children into two groups: children with CD and those without (the non-CD group). There were 8 children who were not included in this set of analyses: 2 with mild/focal dysplasia, 2 with herpes and varicella encephalitis, 2 with Sturge-Weber syndrome, 1 with Aicardi syndrome and 1 with a porencephalic cyst.

The CD group was further subdivided on the basis of extent of damage as follows: (1) CD/entire hemisphere (hemimegalencephaly; CD/entire hemisphere and hemimegalencephaly are used interchangeably throughout this paper); (2) CD/multilobar/diffuse involvement.

The non-CD group was subdivided into two groups based on etiology: (1) RE; (2) infarction.

Recall that in our original analysis, we were surprised to find that so many children with right hemispherectomies had failed to develop language. Indeed, we find that, in comparing the 10 children (5 left, 5 right) with SLRs of 0 considered here, there was a statistically significant difference in the degree to which the SLR performance deviated from expected SLR performance for the two groups (χ^2 test, $p < 0.025$), with the *right* hemispherectomies performing significantly worse than expected. However, even this result fails to capture the unexpected difference in the *proportion* of the full cohort of left and right hemispherectomies who failed to develop language, where our predictions were clearly that there would be a considerably larger proportion of left than right hemispherectomies who would fail to acquire language.

Table 3. SLRs of children with CD/multilobar involvement (developmental insult)

Patient No.	Sex	Side	Age at surgery	Age at onset	Seizure control	SLR	Comments
1	M	left	1;8	6 weeks	yes	3	+ cortex thinning + other
2	F	left	1;5	birth	yes	4	pachygyria
3	M	left	2;10	birth	yes	3	pachygyria, lissencephaly
4	M	left	1;5	birth	no	2.5	+ complications
5	M	left	1;0	birth	yes	1	
6	M	left	1;8	birth	yes	4.5	
7	F	left	0;5	birth	yes	3	+ prenatal infection
8	M	left	0;8	2 months	yes	3	n. fibromatosis
9	M	left	2;7	3 months	no	2	diffuse atrophy of LH
10	F	right	1;1	birth	no	1	
11	F	right	0;9	5 months	no	3.5	

Examining further the group of children who have failed to develop language, we find that a majority of the right hemispherectomies with no language (4/5) have an etiology of CD/entire hemisphere, as illustrated in table 2. Note the variability between seizure control and language outcome.

For the left hemispherectomies the picture is somewhat different. Two of the 5 also have CD/entire hemisphere, but 3 have different etiologies. However, we find it noteworthy that all but one have developmental etiologies, and looking at the group overall, we find that the failure to develop language is largely predictive of pervasive developmental pathology and, most particularly, hemimegalencephaly. Six of the 8 children who have failed to develop language have CD with an entire hemisphere involved. Thus, our first finding regarding the relation between etiology and language development following hemispherectomy is that hemimegalencephaly, a developmental pathology involving an entire hemisphere, appears to have the severest impact on linguistic prognosis.

There are children with similar pathology, however, who appear to be exceptions to this pattern. Two children with hemimegalencephaly, 1 right hemispherectomy, 1 left, have started to develop language. In both cases the children are language delayed, but it is still too early to delimit the linguistic growth they will display.

CD/Multilobar/Diffuse Involvement

The children who fell into this etiological subgroup were quite heterogeneous as far as linguistic outcome is concerned, ranging from 1, a few words, to 4.5, fluent, nearly normal language development. These results are illustrated in table 3.

Table 4. Children with RE

Patient No.	Sex	Side	Age at surgery	Age at onset	Seizure control	SLR
1	M	left	4;7	3;4	yes	3.5
2	M	left	5;5	2;5	yes	3.5
3	F	left	5;11	5;7	no	4
4	F	right	17;3	12	no	5
5	F	right	14;1	5;0	no	5
6	F	right	5;11	4;6	yes	5
7	M	right	3;5	2;0	yes	4

We find, then, that despite pervasive, developmental pathology, those children with multilobar CD but not CD involving the entire hemisphere have a notably better linguistic prognosis. Even with 4 children not doing as well as the others within this etiological subgroup (the mean SLR of the multilobar subgroups is 2.77), 7 of 11 evidenced an SLR of 3 or better. Two of these children with multilobar damage have displayed remarkably normal grammatical development, and 4 others appear at this point to be on the road to good language development as well. Despite their initial language delay, these latter 4 all achieved SLRs of 3–3.5 while still preschoolers. We expect to see further linguistic progress, i.e. higher SLRs, in all 4 at the next evaluation.

It is striking to find such remarkable linguistic development in the face of such catastrophic neurodevelopmental pathology. Note, however, that in cases where language progress was poorer, there is evidence that the remaining 'good' hemisphere was itself damaged. Using continued

Table 5. SLRs of the children with a pre/postnatal stroke (acquired insult) as a primary etiology

Patient No.	Sex	Side	Age at surgery	Age at onset	seizure control	SLR	Comments
1	M	left	8;6	birth	yes	3	+ CD
2	M	left	6;2	10 months	yes	4	
3	F	left	4;0	birth	yes	4	+ complications
4	F	left	11;5	3 weeks	no	3	+ complications
5	F	left	6;8	birth	yes	4	+ complications
6	M	left	9;8	6 months	yes	5	
7	M	right	7;9	birth	yes	4	
8	M	right	2;2	8 months	yes	4.5	
9	F	right	5;1	2 months	no	2.5	+ CD + CC agenesis

seizures following hemispherectomy as a global metric in determining the status of the nonresected hemisphere, the child with the intraventricular hemorrhage and the child with corpus callosum agenesis are clear examples of children who fared less well linguistically and who evidenced signs of a problematic remaining hemisphere. Clearly the integrity of the remaining hemisphere plays a key role in the potential for linguistic development subsequent to hemispherectomy.

Rasmussen's Encephalitis

Of all the etiological subgroups, those children with RE demonstrate the best linguistic outcome. The SLRs and other variables of the RE subgroup are displayed in table 4.

Six of the 7 children in the RE group have SLRs of 4 or 5; none have SLRs lower than 3.5. Moreover, the child with the SLR of 3.5 has had the shortest time between surgery and evaluation. We expect that at the next data collection point he will have progressed and, like his cohort, display an SLR of 4 or better.

How do we explain this uniform result of good language outcome following RE? This finding bears directly on questions regarding functional plasticity for language, in particular, with respect to its temporal dimension. All of the left hemispherectomies became globally aphasic after hemispherectomy, confirming that resection was indeed affecting their 'language' hemisphere. Yet even at ages where fluent, nearly mature language would have developed – ages 4;7, 5;5, 5;11 – the brain displayed the capacity to reorganize itself in such a way as to ensure successful language development. What is clearly called for is a more refined understanding of RE and the effect it has on neural development.

Infarction as a Primary Etiology

Considering those children who did develop language, the children with pre- or postnatal infarction also demonstrate good linguistic outcome, with a mean SLR of 3.77. A breakdown of this subgroup is presented in table 5.

Although at first examination, it looks as if the linguistic outcomes of the children with infarction confirm the 'the-earlier-the-better' view, when the entire population is considered, we can see that this is the only group for which this hypothesis holds. We will revisit this point below.

A Closer Look at Age as a Predictor of Language Outcome

Our findings with respect to age at onset and language outcome were not what we had originally predicted; however, they are in line with a different view regarding the relationship between age at insult and resultant outcome, a view we might term the 'critical impact point' hypothesis. On this view, early insults could be predicted to have equally deleterious effects as later insults, depending on the point in both neurological and functional maturation at which the insult is suffered. If an insult is sustained at some critically defined point in maturation, at which both the subsequent neurological and cognitive development requisite to support normal or relatively intact function are affected, a poor outcome may be predicted, despite the insult's occurring at an early age. On this scenario, if age at damage corresponds to a maturational point at which critical neurological and cognitive developments have yet to occur (or are in the process of taking place), the establishment of the neural base to support a given function and development of the cognitive function itself may be permanently disrupted.

What would constitute 'critical impact points' for language development? Candidates would surely include both prental and postnatal 'events'. Prenatally, candidate 'impact points' would include points at which key events in neurobiological maturational processes are disrupted, such as periods of neuronal migration. Postnatally, reminiscent of Kolb's findings [Kolb, 1990; Kolb and Whishaw, 1998], we hypothesize that candidates would include points at which intra- and interhemispheric connectivity are established as expressed in periods of dendritic proliferation, changes in callosal connections and potentially others.

Our hypothesis is not altogether at odds with Dennis's [1989] proposal suggesting that an earlier insult may have a more deleterious impact on cognitive development than a later insult. In Dennis's proposal, presented in the terminology and framework of skill development (from emerging, to developing, to established), the earlier the developmental process is disrupted, the greater the impact because the greater the number of skills yet to be acquired made vulnerable by cerebral insult. The findings from a number of studies lend support to her proposal [Anderson and Moore, 1995; Anderson et al., 1997; Chapman et al., 1992; Dennis and Barnes, 1990; Hemphill et al., 1994].

Our hypothesis is fundamentally different in two respects, however. First, we take issue with view of language acquisition as 'skill development', and work within a theoretical framework within which language is very simply part of the human genotype (akin to being bipedal), with language acquisition a largely hard-wired, maturationally constrained and timed biological endowment whose normal growth and expression nonetheless require appropriately timed and specified neurological events. Second, as we failed to find a correlation between early age and outcome in either direction (note especially that we failed to find the significant correlation between earlier insult and poorer outcome that Dennis [1989] would predict), our hypothesis goes beyond characterizing age as a predictor of outcome in isolation, separate from the specifics of neural development.

The 'critical impact point' hypothesis weds maturational factors to etiological factors. Thus, what on first analysis were surprising findings regarding age and linguistic outcome become predicted neurolinguistic findings. Our findings appear to confirm our hypothesis, in that those children with good linguistic outcomes (for example, the RE and infarction groups) did not sustain damage at such 'critical impact points', whereas those with poor outcomes (e.g. children with hemimegalencephaly) did.

The next step in our analysis will be to feed our data into this framework and thus test our hypothesis against the totality of our data, including careful consideration of the integrity of the remaining hemisphere. Our hope is that this framework will lead to a clearer understanding of the relationship between neurological factors and linguistic development, and will prove to be of help to clinicians in predicting ouctome.

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