Exploring Neuronal Plasticity: Language Development in Pediatric Hemispherectomies

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Abstract

We investigated the categories of neural plasticity and the genesis of the neural representation for language in population of 43 pediatric hemispherectomies. We have chosen to correlate language outcomes with the stages of neuronal plasticity rather than age at insult because of the unavoidable confound between the latter and etiology (Curtiss and de Bode, submitted). We argue that by examining the neural substrate for language and language outcomes post-hemispherectomy, it is possible a) to investigate the progression of neural representation from pluripotential and distributed to localized and specialized and b) to accurately predict language outcomes.

Introduction and Rationale

It is still unclear whether neural systems underlying adult organization for language crucially differ from their respective counterparts in the young brain. Though the assumption of complete and rapid recovery of children after brain lesions has been abandoned by the majority of researchers, there is no question that the rate and extent of reorganization in children differ from adults recovering from similar insults. The two most obvious hypotheses explaining this phenomenon make two different sets of assumptions. First, it is possible that language representation in a young brain is not identical to its adult counterpart. Indeed, more diffuse brain organization of the immature brain is suggested both by recent brain imaging studies and language acquisition research in clinical and normal populations ((Dapretto, Woods, & Bookheimer, 2000; Mills, Coffey-Corina, & Neville, 1993; Papanicolaou, DiScenna, Gillespie, & Aram, 1990). Under this hypothesis faster recovery rates in children may be explained by the fact that functional localization and cortical commitment have not yet reached their peak, i.e. their adult pattern. An alternative explanation does not need to assume brain organization that is different from adults. Empirical support for this hypothesis is provided by investigations of childhood acquired aphasia. This research indicates the presence of adult-like neural representation for language and similar consequencies of brain damage in children and adults (Paquier & Van Dongen, 1998). Thus it is possible that more efficient reorganization is achieved due to neural plasticity of a young brain, in other words, with the help of the same mechanisms that are already in place guiding and supporting brain maturation in the first decade of life.

The two accounts need not be mutually exclusive. It is possible that what seems like wider functional distribution is, in fact, the reflection of both exuberant neuronal connectivity and increased neuronal excitation characteristic of an immature brain. This suggestion is supported by the findings of some recent brain imaging studies. Dapretto et al. (2000) demonstrated that both phonological and semantic conditions activated similar though not completely identical areas in adults and children. Furthermore, cortical areas activated only by specific linguistic tasks in adults showed reliable activation during *all* tasks in children. The authors interpret these findings in terms of increased functional specialization with development and redundancy in the neural system subserving language early in development. Taking these conclusions one step further, we suggest that the dichotomy of 'pluropotential and distributed' versus 'specialized and localized' exists only on the functional level. On the neurobiological level, language representation in children is similar to adults, but this similarity is masked by diffuse connectivity and exuberant synaptic proliferation that characterize the young brain.

For the purpose of this paper we assume that an innate endowment and cortical representation for language are present from birth. We also assume that *quantitative differences of an immature cortex lead to some qualitative differences (such as pluripotential*

cortex and distributed functional organization in infants) but represent a developmental continuum within the framework of similar language representation in children and adults. What do we attribute to the processes underlying quantitative differences between the young and mature brains? Similar to animal research, morphometric and brain imaging studies (EEG, glucode metabolism, blood flow volumes, etc.) in humans imply the presence of the period of massive overproduction of synapses, dendritic arbors and exuberant connectivity. This period, known as the Critical Maturation Period, leads to the next stage of development - the process of elimination when neuronal/synaptic numbers, density, connectivity are adjusted to their respective adult values. Though there is no complete data regarding the exact timetables of these events for the entire brain, it is known, for example, that these overproduction/adjustment processes in the frontal lobes continue into adolescence (Huttenlocher, 1993). The outline of our hypothesis is shown in Table. 1:

Table 1. Rationale for our hypothesis

	Young brain	**Adult brain**
Neurobiological level	**Similar language representation**	
	Morphological/Quantitative changes underlying brain maturation (synaptogenesis, dendrtic proliferation, neuronal volume adjustment)	
Functional level	**Pluripotential & distributed**	**Specialized & localized**

Methods

Subjects consisted of 43 patients who underwent hemispherectomy for intractable seizures at the UCLA Medical Center. Etiology was catalogued according to the following breakdown: developmental pathology - 28 subjects (hemimegalencephaly - HM, cortical dysplasia/multilobar involvement - ML, and prenatal infarct); acquired pathology - 15 subjects (Rasmussen's encephalitis - RE and postnatal infarct). Postoperative spoken language outcome was rated based on spontaneous speech samples from 0 = no language to 6 = fluent mature grammar. Language scores were defined on the basis of stages in normal language development. The complete information regarding the breakdown of our population is shown in Table 3.

Discussion

Based on the animal studies we suggest that the Critical Maturation Period in humans is limited by the following thresholds: the lower threshold that is characterized by the completion of neuro/morthogenesis and establishment of experience independent connectivity; and the upper threshold of the completion of the period of neuronal/synaptic adjustment. Next, following Greenough et al. (1999) we assume that the following components underlie functional and neurological maturation of language: (1) developmental processes that are insensitive to experience, i.e. the genetic envelope of *predetermined plasticity*; (2) an *experience-expectant* period of neuronal plasticity also known as the Critical Maturation Period; and (3) an *experience-dependent* period of neuronal plasticity which underlies the ability to encode new experiences throughout the lifespan (Table 2). We thus hypothesized that superimposing effects of specific etiologies on these developmental stages would allow for more accurate prediction of language outcomes following hemispherectomy, since in our model functional reorganization reflects underlying neurobiological reorganization.

Our results confirmed our hypothesis in that postoperative language outcomes correlated with etiology. This would be expected since as shown in Table 2 different etiologies result in different potential for recovery (due to timing and extent). Developmental plasticity, i.e. reinnervation and neuronal sparing, seem to be more efficient in etiologies with later onset. In addition, when pathology disrupts genetically determined processes (as in hemimegalencephaly and cortical dysplasia) functional development seems to be particularly compromised. Thus the best language scores were found in Rasmussen's encephalitis and the poorest in hemimegalencephaly. Moreover, etiology

(developmental or acquired) consistently emerged as a significant variable distinguishing linguistic outcomes in all statistical analyses. In all cases it was possible to predict postsurgery language outcomes by considering the effect of specific etiologies within the framework of the categories of neural plasticity. It should be noted that we have deliberately chosen to relate functional outcomes and the broad categories/stages of neuronal plasticity instead of providing direct correlations with age at insult. It is our belief that in such correlations the confound between etiology and age at insult is unavoidable (Curtiss, de Bode and Mathern, submitted).

The rate and quality of neuronal reorganization reflected in language outcome also confirmed the left hemisphere's predisposition to support language, since children with an isolated right hemisphere had significantly more problems acquiring/restoring their language. Importantly, however, though age at surgery for two of our RE children was as old as 12, neither of them has remained mute after left hemispherectomy, suggesting that language specialization had not yet reached its peak, and reorganization was still possible. Our preliminary research also indicates that even in the most severely compromised cases, language development follows the normal course of language acquisition albeit on a prolonged scale. These findings lead us to suggest that innate language universals are resilient to brain damage, although language representation in the brain does not seems to be anatomically-bound to the left hemisphere only.

Table 2. The impact of specific etiologies on the categories of neural plasticity

Stages/Etiology	**Genetic Envelope** (innate constraints specifying cortex differentiation including ensembles that would support language-related properties)	**Experience-Expectant Period** (=Critical Maturation Period, input-dependent period of maximum plasticity)	**Experience-Dependent Period** (plasticity underlying the ability to incorporate new experiences throughout the lifespan)
Normals	normal	birth – 12 years, reduced vulnerability to injury	normal, life-long
Hemimegalencephaly	affected	increased vulnerability	Limited in most cases, thus lowered FSIQ
Cortical Dysplasia	affected-to-normal	variable	
Infarct prenatal	affected-to-normal	variable	
Infarct postnatal	normal	reduced vulnerability to injury similar to normals	
Rasmussen's Encephalitis	normal	reduced vulnerability to injury similar to normals	

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Table 3. Subjects

No/Sex	Side 1-L, 2-R	Post-op (years)	Age/onset (years)	Age/surgery (years)	Sz control 1yes 2no	SLR 1to 6
			Hemimegalencephaly			
1M	1	5.2	0.05	2.8	1	4
2M	1	10.1	0.08	3.3	2	0
3M	1	7.8	0.01	0.25	1	0
4F	2	3.3	0.5	2.6	2	1
5F	2	4.3	0.02	2.1	2	0
6F	2	6.7	0.01	0.41	2	1
7M	2	6.2	0.01	1.5	2	0
			Cortical Dysplasia/Multilobar Involvement			
8M	1	3.1	0.5	1.6	1	3
9F	1	5.1	0.01	1.4	2	6
10M	1	8.0	0.01	0.7	1	6
11M	1	9.3	0.01	1.4	2	2
12M	1	5.8	0.01	1	1	4
13M	1	7.2	0.5	1.5	1	6
14F	1	7.4	0.05	0.4	2	5
15M	1	8.1	0.1	0.75	1	3
16F	2	5.6	0.01	0.3	2	3
17F	2	5.3	0.4	0.75	1	5
18F	2	6.1	0.01	1.1	2	2.5
19M	2	8.6	0.75	3.8	2	1
			Rasmussen's Encephalitis			
20M	1	4.7	3.3	4.58	2	4
21M	1	4.3	2.25	3.5	1	4
22M	1	4.2	2.9	5.95	2	3
23M	1	4.11	10.3	12.75	1	5
24F	1	2.0	5	1 0	1	5
25F	1	3.1	5.5	6.91	2	5
26F	2	8.7	4.75	5.7	1	6
27F	2	12.1	4.18	14	2	6
28F	2	5.9	11	17.3	2	6
29M	2	5.1	2.05	3.41	1	5.5
			Infarct			
30F	1pre-natal	0.6	0.01	6.9	1	4
31M	1post	5.1	3	9.5	2	4
32M	1post	10.2	0.8	6.2	1	5
33M	1pre	4.11	0.25	2.6	1	3
34F	1pre	3.1	0.02	1.3	2	0
35M	1pre	7.8	0.6	8.6	2	0
36F	1pre	8.9	0.01	4	1	5
37M	1pre	5.2	0.5	9.75	1	6
38F	1post	8.8	1.5	6.75	1	5
39F	2pre	8.1	0.3	0.8	2	0
40M	2post	4.9	4	7.75	2	5
41M	2post	11.2	0.6	2.2	1	6
42F	2pre	7.9	1.2	4.25	1	4
43F	2pre	8.1	0.16	5.1	2	5