Journal of the International Neuropsychological Society (2007), **13**, 501–504.

DOI: 10.1017/S1355617707070385

NEUROBEHAVIORAL GRAND ROUNDS—INTRODUCTION

Language localization, the developing brain and childhood epilepsy: Back to the future

MICHAEL DUCHOWNY[1,2]

[1]Comprehensive Epilepsy Program and Brain Institute, Miami Children's Hospital, Miami, Florida
[2]Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida

The defining role of language for communicating and forming social bonds has captured the imagination of scientists and scholars throughout the ages, and scientific inquiry into the neural correlates of language is now centuries old. Theories of linguistic structure and function occupy center stage in fields as diverse as neuroscience, embryology, anthropology and evolution. This should come as no surprise as the neural basis of linguistic function holds promise for understanding how the mind works and what makes us uniquely human.

Without a suitable animal model to study human language organization, clinical scientists must rely on observations of behavioral changes following ablation of language sites; hemispheric surgical ablation and vascular accidents have been particularly useful for understanding language localization and lateralization. Collectively, ablation data has yielded important insights into normal language organization, hemispheric dominance and reorganization of linguistic competence after damage.

Mapping language cortex by direct electrical stimulation in surgical epilepsy patients provides another window into linguistic processing (Ojemann, 1983). Functionality of eloquent cortical regions can be assessed in awake cooperative patients. While pathological changes in stimulated brain tissue and frequent seizures may impact findings, cortical stimulation remains decidedly advantageous in that functionality can be assessed directly rather than by inference from anatomical loss. Other noninvasive methods to investigate language cortex have emerged in recent decades including positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetic source imaging (MSI); all are powerful investigative tools into language function that utilize electromagnetic correlates and changes in regional blood flow and metabolism with active linguistic processing. Transcranial magnetic stimulation and optical imaging hold further promise for the noninvasive study of brain functionality.

Although our understanding of the neural correlates of language in health and disease has increased considerably in adults, a similar understanding of language in the developing brain remains limited. Methodological challenges to studying the childhood population abound. A limited data pool and frequent association of co-morbid developmental disorders render data acquisition difficult. Maturational changes in brain development including increased synaptic efficiency, cellular pruning, myelin deposition and the increasing complexity of neural circuits in early life may compromise the prospective validity of cross-sectional studies. Furthermore, seizures in pediatric epilepsy surgery candidates are often extremely frequent or catastrophic in their presentation. Lastly, the pathological substrate of childhood epilepsy is predominantly acquired prenatally with as much as 80% of early-onset pharmacoresistant epilepsy attributable to cortical malformation (Duchowny, 1999).

Given these methodological limitations, what have we learned about language acquisition in the normal and abnormally developing brain? There is accumulating evidence that the neural substrates for language including speech and reading are already well lateralized and regionally specific in the first decade of life (Duchowny et al., 1996; Balsamo et al., 2002; Schlaggar et al., 2002; Ahmad et al., 2003; Gaillard et al., 2003). Language cortex is identifiable in the left posterior inferior frontal gyrus and left superior temporal gyrus in children as well as adults. The left inferior frontal and superior and middle temporal gyri, angular gyrus, mesial superior frontal gyrus and contralateral cerebellum reveal reproducible patterns of activation on fMRI in normal children utilizing standardized language paradigms (Ahmad et al., 2003; Wood et al., 2004). Young readers activate the left inferior temporo-occipital junction, left fusiform gyrus, middle temporal and frontal gyri and the supplementary motor area during reading (Gaillard et al., 2003).

Correspondence and reprint requests to: Michael Duchowny, MD, Department of Neurology, Miami Children's Hospital, 3200 S.W. 60th Court, Suite 302, Miami, FL 33155. E-mail: michael.duchowny@mch.com

A remarkably dynamic picture of language consolidation is emerging from one of the few longitudinal fMRI studies of normal language development conducted over 5 years in children enrolled between ages 5–7 years (Szaflarski et al., 2006). Maturation of linguistic processing was associated with increased representation of the left inferior and middle frontal, middle temporal and angular gyri and the right lingual and inferior temporal gyri. A coincident decreased representation was observed in the left insular and peristriate cortex, left superior frontal and right angular cingulate gyri and left thalamus. The most significant age-related increases in activation occurred in frontal and parietal cortices, regions which are relatively late to mature. The diminished participation of nonclassical language regions with age implies that before adolescence language proficiency occurs through progressive consolidation of "hard-wired" language sites. This process is complex and nonlinear. Within group comparisons of age and asymmetry scores in children and adults do not show a specific age effect (Wood et al., 2004).

These observations collectively provide support for conceptualizing childhood language development as a process involving regional maturation and progressive organization of inter-regional interactions. Rather than being a hierarchical process with successive stages of increasing complexity, the acquisition of language competence is more likely to occur through the "fine tuning" of multiple brain regions shaped by innate and acquired factors. As stated concisely by Johnson (2001): "Human postnatal functional brain development is not just the passive unfolding of a maturational sequence, but is an activity-dependent process, albeit guided and constrained by initial biases." This model likely holds for multiple cognitive domains including language, memory and attention (Thiebaut de Schotten et al., 2005).

Even less is known about the long-term effects of compromising cortex that is not fully mature. There is general agreement that functional recovery in the immature brain is probably superior to the mature brain, but little agreement on much else. The mechanism of recovery, contribution of age and even the meaning of the term "plasticity" are imprecisely known. Why some eloquent cortical regions recover while others do not, and which regions of the brain contribute to the recovery process is poorly understood. The robust functional recovery following hemispheric ablation in some children provides compelling evidence that the nondominant hemisphere is capable of supporting language. This classical model of neural plasticity presupposes that recovery from damage to intact structures, which may or may not be fully formed, occurs through intra-hemispheric transfer to contralateral sites. For example, patients with Rasmussen's syndrome of the left hemisphere also demonstrate shift of language networks to the right hemisphere (Hertz-Pannier et al., 2002).

However, the effect of destructive lesions or surgical ablations of normal language sites are not easily extrapolated to children with focal cortical malformations and epilepsy. Language cortex in epilepsy patients with cortical malformation does not necessarily reside in classical areas (Devinsky et al., 1993), and the distribution of language networks is often atypical (Bell et al., 2002; Yuan et al., 2006). Furthermore, the increasing language lateralization observed in healthy individuals does not occur in pediatric epilepsy patients (Yuan et al., 2006). Patients with circumscribed developmental tumors may be an exception (Briellmann et al., 2006).

Because the model of hemispheric ablation is a useful tool to assess overall language recovery, complete hemispheric destruction in childhood is unusual. Language cortex is generally preserved in children with epilepsy, as cortical malformations rarely destroy eloquent cortex. Remarkably, an intimate association of cortical dysplasia and eloquent cortex has been observed repeatedly at surgical centers treating children with intractable focal epilepsy (Janszky et al., 2003). Localizing language cortex and predicting postoperative language competence are thus concerns that are more than academic for pediatric epilepsy surgery candidates with developmentally-based seizures.

Cortical malformations are a nonhomogeneous entity with complex patterns of functional specificity and reorganization. For example, motor control may either reside within dysplastic sensorimotor cortex (Jayakar & Duchowny, 1993) or relocate to contralateral sites (Maegaki et al., 1995). Dysplastic language cortex similarly may remain fixed at predetermined sites or relocate. The size of the malformation is an influential determinant as larger malformations are more often associated with inter-hemispheric transfer. Histopathological cell type and location of the malformation also figure prominently. Malformed tissue forming earlier in prenatal life are more likely to promote functional reorganization than later occurring malformations affecting cortical organization such as polymicrogyria (Burneo et al., 2004). Cortical malformations arising early in prenatal life are also less likely to activate in response to complex cognitive paradigms (Janszky et al., 2003). The importance of cell type for functionality is underscored by the observation that balloon cells do not display electrically-induced functionality (Marusic et al., 2002).

The complex functional and anatomic relationships of cortical malformations raise two important questions. First, does malformed eloquent cortex behave similarly to eloquent cortex in normal individuals? And second, if relocation occurs, which brain regions are involved? Similar questions have been asked in patients with postnatal lesions, but questions regarding cortical malformations acquired prenatally relate to future specification not reorganization of function. The consequences of cortical malformation are therefore unlikely to mimic postnatal destruction of functionally dedicated cortical sites.

Studies of language organization in children with malformations being evaluated for epilepsy surgery reveal the complex nature of their language specification. In a recent study of children and adolescents, lateralization of language could not be inferred from the proximity of language to classical language cortex and the majority of lesions in or near Bro-

ca's area were not associated with inter-hemispheric reorganization (Liegeois et al., 2004).

In this issue of *JINS*, Kadis et al. (2007) provides additional evidence that malformations of the left hemisphere result in intra-hemispheric relocation of language sites. Utilizing co-registered MRI and extra-operative stimulation mapping, they showed that relocation of language was not random but frequently occurred anterior and superior to classical Broca's area. The reasons for this pattern of language representation are unknown but likely reflect both the potential for anterior associative zones to acquire language function as well as the inability of motor cortex lying immediately posterior to Broca's area to achieve different functional specification.

This study carries important implications with regard to two critical issues. First, it documents that pathological substrate is a critical determinant of language re-organization in the dominant cerebral hemisphere. All future investigations of linguistic competence in childhood, not only studies of children with epilepsy, must assume that underlying pathology can modify classical assumptions of language localization and networks. While an understanding of how cortical malformations affect brain organization is in its infancy, the Kadis et al. (2007) study provides compelling evidence that homologous sites within the contralateral hemisphere, traditionally assumed to be the target of language re-organization, may not become functional in individuals with developmental neuropathology.

Second, the Kadis et al. (2007) findings underscore the potential role of dominant hemisphere pre-frontal cortex for linguistic processing. Whether this is limited primarily to individuals with epilepsy and cortical malformation remains to be determined, but it appears likely that the potential anatomic contribution of prefrontal cortex to language competence has been underappreciated. It would be interesting to learn whether Broca's area is only displaced anteriorly or whether Broca's area is connected to pre-frontal cortex by normal or aberrant neural networks.

Future studies will help to sort through the complex interrelationships within malformed and mal-specified cortex. These investigations will require a greater number of subjects and likely utilize non-invasive methodologies to localize language sites and define neural networks both within the dominant hemisphere and between cerebral hemispheres. Most importantly, future solutions to these issues will need to look backwards in development to explain how aberrant cortical specification becomes established in intrauterine life.

REFERENCES

Ahmad, B.S., Balsamo, L.M., Sachs, B.C., Xu, B., & Gaillard, W.D. (2003). Auditory comprehension of language in young children. *Neurology*, *60*, 1598–1605.

Balsamo, L.M., Xu, B., Grandin, C.B., Petrella, J.R., Braniecki, S.H., Elliott, T.K., & Gaillard, W.D. (2002). A functional magnetic resonance imaging study of left hemisphere language dominance in children. *Archives of Neurology*, *59*, 1168–1174.

Bell, B., Hermann, B., Seidenberg, M., Davies, K., Cariski, D., Rosenbek, J., Woodard, A., Rutecki, P., & Bishop, M. (2002). Ipsilateral reorganization of language in early-onset left temporal lobe epilepsy. *Epilepsy & Behavior*, *3*, 158–164.

Briellmann, R.S., Labate, A., Harvey, A.S., Saling, M.M., Sveller, C., Lillywhite, W., Abbott, D.F., & Jackson, G.D. (2006). Is language lateralization in temporal lobe epilepsy patients related to the nature of the epileptogenic lesion? *Epilepsia*, *47*, 916–920.

Burneo, J.G., Kuzniecky, R.I., Bebin, M., & Knowlton, R.C. (2004). Cortical reorganization in malformations of cortical development. *Neurology*, *63*, 1818–1824.

Devinsky, O., Perrine, K., Llinas, R., Luciano, D.J., & Dogali, M. (1993). Anterior temporal language areas in patients with early onset of temporal lobe epilepsy. *Annals of Neurology*, *34*, 727–732.

Duchowny, M. (1999). Pediatric epilepsy surgery: The widening spectrum of surgical candidacy. *Epileptic Disorders*, *1*, 143–151.

Duchowny, M.S., Jayakar, P., Harvey, A.S., Resnick, T., Alvarez, L., Dean, P., & Levin, B. (1996). Language cortex representation: Effects of developmental versus acquired pathology. *Annals of Neurology*, *40*, 31–39.

Gaillard, W.D., Balsamo, M.A., Ibrahim, B.A., Sachs, B.C., & Xu, B. (2003). fMRI identifies regional specialization of neural networks for reading in young children. *Neurology*, *60*, 94–100.

Hertz-Pannier, L., Chiron, C., Jambaque, I., Renaux-Kieffer, V., Van de Moortele, P.F., Delalande, O., Fohlen, M., Brunelle, F., & Le Bihan, D. (2002). Late plasticity for language in a child's nondominant hemisphere: A pre- and post-surgery fMRI study. *Brain*, *125*, 361–372.

Janszky, J., Ebner, A., Kruse, B., Mertens, M., Jokeit, H., Seitz, R.J., Witte, O.W., Tuxhorn, I., & Woermann, F.G. (2003). Functional organization of the brain with malformations of cortical development. *Annals of Neurology*, *53*, 759–767.

Jayakar, P. & Duchowny, M. (1993). Functional cortical mapping in children. In O. Devinsky, A. Beric, & M. Dogali (Eds.), *Electrical and Magnetic Stimulation of the Brain and Spinal Cord* (pp. 149–154). New York: Raven Press.

Johnson, M.H. (2001). Functional brain development in humans. *Nature Reviews Neuroscience*, *2*, 475–483.

Kadis, D.S., Iida, K., Kerr, E.N., Logan, W.J., McAndrews, M.P., Ochi, A., Otsubo, H., Rutka, J.T., Snead III, O.C., Weiss, S.K., & Smith, M.L. (2007, this issue). Intrahemispheric reorganization of language in children with medically intractable epilepsy of the left hemisphere. *Journal of the International Neuropsychological Society*, *13*, 505–516.

Liegeois, F., Connelly, A., Cross, J.H., Boyd, S.G., Gadian, D.G., Vargha-Khadem, F., & Baldeweg, T. (2004). Language reorganization in children with early-onset lesions of the left hemisphere: An fMRI study. *Brain*, *127*, 1229–1236.

Maegaki, Y., Yamamoto, T., & Takeshita, K. (1995). Plasticity of central motor and sensory pathways in a case of unilateral extensive cortical dysplasia. *Neurology*, *45*, 2255–2261.

Marusic, P., Najm, I.M., Ying, Z., Prayson, R., Rona, S., Nair, D., Hadar, E., Kotagal, P., Bej, M.D., Wyllie, E., Bingaman, W., & Luders, H. (2002). Focal cortical dysplasias in eloquent cortex: Functional characteristics and correlation with MRI and histopathologic changes. *Epilepsia*, *43*, 27–32.

Ojemann, G.A. (1983). Brain organization for language from the

perspective of electrical stimulation mapping. *The Behavioral and Brain Sciences*, *2*, 189–230.

Schlaggar, B.L., Brown, T.T., Lugar, H.M., Visscher, K.M., Miezin, F.M., & Petersen, S.E. (2002). Functional neuroanatomical differences between adults and school-age children in the processing of single words. *Science*, *296*, 1476–1479.

Szaflarski, J.P., Schmithorst, V.J., Altaye, M., Byars, A.W., Ret, J., Plante, E., & Holland, S.K. (2006). A longitudinal functional magnetic resonance imaging study of language development in children 5 to 11 years old. *Annals of Neurology*, *59*, 796–807.

Thiebaut de Schotten, M., Urbanski, M., Duffau, H., Volle, E., Levy, R., Dubois, B., & Bartolomeo, P. (2005). Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. *Science*, *309*, 2226–2228.

Wood, A.G., Harvey, A.S., Wellard, R.M., Abbott, D.F., Anderson, V., Kean, M., Saling, M.M., & Jackson, G.D. (2004). Language cortex activation in normal children. *Neurology*, *63*, 1035–1044.

Yuan, W., Szaflarski, J.P., Schmithorst, V.J., Schapiro, M., Byars, A.W., Strawsburg, R.H., & Holland, S.K. (2006). fMRI shows atypical language lateralization in pediatric epilepsy patients. *Epilepsia*, *47*, 593–600.