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Language and neurophysiological development

Ralph-Axel Müller

Erica Palmer

Brain Development Imaging Laboratory, Department of Psychology, San Diego State University, San Diego, CA 92120; Department of Cognitive Science, University of California, San Diego, CA 92093

[Abstract]

Traditional clinical approaches to the brain organization for language have in recent decades been complemented by neuroimaging techniques, most of which can be used with minimal risk in children. A growing literature mapping out developmental changes suggests that children activate grossly the same inferior frontal and temporo-parietal brain areas as adults during various types of language processing. However, there is some evidence indicating that typical left-lateralization becomes more robust with age and that frontal activity increases at the expense of posterior activation in visual cortices. While it is highly likely that genes play an important role in determining the brain organization for language, there is also ample evidence for high levels of plasticity. Early left hemisphere damage may result in reorganization of language in the right hemisphere, with often only subtle detrimental effects on language function. There is no consensus on why specific regions in perisylvian cortex are crucial for language processing, but evidence from animal and human studies suggests that Broca's area may become a 'language area' by virtue of its unique connectivity patterns, due to which several functional circuits crucial for language acquisition converge in inferior frontal cortex.

1. Introduction

Five millennia ago, the Egyptian author of the Edwin Smith papyrus (presumed to be the erudite Imhotep) noted loss of speech in a patient with a temporal wound (Critchley 1970). Although not all great minds have even considered the brain worthy of investigation – Aristotle regarded it merely as a cooling organ – the question of biological substrates for language has been with us for a very long time. Some answers to this question, as those advocated by craniologists and phrenologists around the turn of the 19th century (Gall and Spurzheim 1810), may sound rather silly to today's brain-savvy readers. How could anyone with respect for empirical evidence conclude from the observation of protruding eyes in a few eloquent subjects that language abilities were located right behind the eyes? Other answers, such as Marc Dax' observation in the early 19th century of speech loss after left hemisphere damage and Paul Broca's finding of inferior frontal damage in aphasic patient Leborgne (Broca 1861), were groundbreaking and painted the first strokes in today's rather complex picture of "language in the brain". In this chapter, we will first review some of this knowledge, which is based on a vast literature of clinical, electrophysiological and imaging evidence, and will then turn to the development of language in the brain, which is much less understood.

Since the mid-20th century, linguistics has been heavily influenced by the idea that language abilities and language processes are sharply distinct from other cognitive domains. In its strongest form, this view implies the autonomy (Chomsky 1965) and modularity (Fodor 1983) of at least some core linguistic components. This perspective on language has had important consequences for the interdisciplinary study of language. Noam Chomsky, whose groundbreaking work first formulated the idea of linguistic autonomy, considered the language ability (or 'universal grammar') as a *biological* object of study. Since the principles of universal grammar were innate, according to him, language development was to be ultimately explained by the genetic endowment of the human species (Chomsky 1976; 2002). This approach to language development had a fascinating and paradoxical effect on the field. On the one hand, it was probably mistaken in some of its basic assumptions pertaining to the autonomy of language development vis-à-vis other cognitive and sensorimotor domains (as we will discuss in Section 7). On the other hand, its nativism and biologism steered linguistics towards interdisciplinary research that has proven highly

productive and thought-provoking. Ironically, many of the interdisciplinary studies examining language with the tools of behavioral genetics, developmental cognitive neuroscience, neurolinguistics, and related fields have yielded the very evidence that forces us to revise some notions of autonomy and innateness (Bates et al. 2003a; Karmiloff-Smith 1994; Müller 1996). This evidence will be reviewed in the following sections.

Chomsky’s biological approach was paralleled and supported by Eric Lenneberg’s “Biological Foundations of Language” (Lenneberg 1967), in which Lenneberg reviewed the neurophysiological, developmental, and evolutionary correlates of language. Although Lenneberg’s review was admirably thorough and surprisingly modern for its time, the cognitive neuroscience of language acquisition has made considerable progress since then. Much of this progress derives from technological advances. For example, Lenneberg could have only dreamed of a non-invasive brain imaging technique that would map out language functions in children – a technique that is available to us today with functional MRI (see Section 3). Other advances have been conceptual, supported by a wealth of relevant data, but in some instances prompted by unreasonable theories and tales of caution, such as those of “language genes” (as discussed in Section 5 below).

2. Language in the brain

One approach to an understanding of language in the brain relies on associating components of language processing with particular brain regions. Such functional localization has been a challenge to scientists and philosophers for many centuries and continues to be so today. Part of the challenge lies in decomposing both language and the brain into meaningful units. Further, relating cognition and biology requires that the ‘grain’ (or resolution) of the units be comparable between the two fields of inquiry. In other words, an appropriate *level of analysis* must be determined.

The effort toward functional localization has benefited tremendously from advances in methods for studying the brain. Therefore, this section begins with a brief description of the methods that have made the greatest contributions to this effort. The remainder of the section discusses the progress that has been made in characterizing language in the brain.

2.1 Methods for studying language in the brain

The earliest links between brain structure and function were derived from postmortem examinations of brain lesions. Some of the most influential reports concerned patients with aphasia who exhibited different types of language impairments that appeared to be associated with lesions to different portions of the brain. For example, Paul Broca (1861; 1866) identified a portion of the left inferior frontal gyrus as being involved in speech production. Some years later, reports of patients seen by Carl Wernicke (Wernicke 1874) suggested an association between deficits in language comprehension and lesions to the left temporoparietal junction (for anatomical terms, see Figure 1).

These early reports led to the development of the first neurological models of language. Wernicke predicted that other types of aphasia could be expected based on disrupted connections between the posterior and anterior language centers. Ludwig Lichtheim (1885) fleshed out this model creating diagrams of the connections between language areas. Partly because of skepticism surrounding Broca’s and Wernicke’s reports, and partly because of a shift away from localizationist thinking, this model largely fell out of consideration until it was resurrected by Norman Geschwind (1970) almost a century later. Although many aspects of the so called “Wernicke-Geschwind” model have not withstood the test of time, it was important as a conceptual launching point for subsequent work on localization of language functions. The advent of tools for imaging the anatomy of the living brain has increased the utility of the lesion-behavior approach for relating structure and function, which remains one of the dominant approaches to research on language in the brain. Among the most advanced recent applications of this approach is ‘voxel-based lesion-symptom mapping’ (Bates et al. 2003b), which determines for each brain location in 3-dimensional space whether damage is likely to result in behavioral impairment of a particular kind. Using this technique, Bates and colleagues found that impairments of verbal fluency were associated most consistently with lesions in insular cortex of the left hemisphere (rather than, as one might expect from the Wernicke-Geschwind model, with damage to Broca’s area).

Progress in identifying brain regions important for language, particularly those related to speech, has also come from the study of patients undergoing brain surgery. In these patients, the effects of electrical stimulation of various brain regions can be observed during surgery. In addition, the consequences of removing portions of the brain can be tracked following surgery. Some of the earliest work of this type was performed by Wilder Penfield and Lamar Roberts in the 1950s (cf. Penfield and Roberts 1959). They determined that speech could be disrupted in various ways by stimulation of the language regions identified by Broca and Wernicke, and by stimulation of portions of left or right hemisphere sensorimotor and supplementary motor cortex. These findings were later supported and extended, notably by George Ojemann and colleagues (1991; see Figure 2).

Results of studies in surgical patients demonstrated that the relationships between language functions and brain regions were not as straightforward as the Wernicke-Geschwind model would suggest. For example, stimulation or removal of certain presumed language areas did not reliably produce language deficits of the type or severity that would have been predicted by the model. Furthermore, non-language functions such as short-term memory could be disrupted by stimulation of these areas, suggesting that they are not correctly classified as pure “language” areas. In short, stimulation and ablations studies provided evidence against the strictest forms of localizationism. In addition, this work lent support to an idea put forward by John Hughlings-Jackson one hundred years earlier that subcortical brain regions are important for language (cf. Kolb 1990). In particular, Penfield and Roberts, Ojemann and colleagues, and Irving Cooper and colleagues demonstrated that nuclei of the left thalamus participate in various speech and language processes (Ojemann and Mateer 1979).

Until the development of non-invasive methods for whole brain functional imaging in the late 1970s, studies of functional localization relied on examination of patients. Newer imaging methods, in addition to their important clinical applications, finally allowed for the study of healthy participants for research purposes. Among these is positron emission tomography (PET), which requires injection of radioactively labeled tracers into the blood stream. Due to increased blood flow, more active brain regions have a greater accumulation of the tracer, which is detected by the PET scanner. PET was first used in conjunction with cognitive tasks in the late 1980s, following methodological developments that allowed images to be averaged across subjects and functional activity to be related to brain anatomy (as reviewed by Raichle 2000). In addition, physiological studies have confirmed that blood flow and regional brain activity had a consistent relationship (Fox and Raichle 1984). Among the first PET studies of cognitive processing was one by Petersen et al. (Petersen et al. 1989), in which brain activity associated with input modality, spoken responses, and semantic demands during word processing was identified. The results were partly consistent with the model of left perisylvian language areas derived from clinical studies (as reviewed above), however, with some intriguing exceptions. In particular, Petersen and colleagues found very robust cerebellar activation for word generation even after subtraction of motoric and articulatory effects (i.e., subtraction of activity associated with word repetition), suggesting that the cerebellum may be involved in language processing beyond purely motoric functions.

Several years after PET became widely used in cognitive neuroscience research, developments in functional magnetic resonance imaging (fMRI) led to its use in cognitive experiments (e.g., McCarthy et al. 1993). fMRI measures the blood oxygenation level dependent (BOLD) response while subjects perform tasks in an MRI scanner. The BOLD response arises as neural activity results in local increases in blood flow and volume, and therefore increases in blood oxygenation. Oxygen metabolism also increases in these areas of the brain, but this increase is small in comparison to the increase in oxygenation (Buxton 2001). This net increase in oxygen changes the ratio of oxyhemoglobin to deoxyhemoglobin, resulting in increased BOLD contrast. While the specific neural underpinnings of the BOLD response are still under investigation (Logothetis and Pfeuffer 2004), repeated demonstrations of a reliable association between neural activity and the BOLD response have validated fMRI as a research tool. Its introduction for use in imaging cognitive tasks was facilitated by the fact that researchers using PET for similar purposes had already addressed many of the challenging analysis considerations. For example, in both PET and fMRI, functional images are registered to high-resolution images of brain anatomy acquired through structural MRI, to allow anatomical localization of functional effects. Unlike PET, however, fMRI does not require the injection of radioisotopes. Therefore, the availability of fMRI has reduced reliance on PET for many kinds of studies

and has enabled researchers to study children and to perform very large numbers scans on the same individuals in one session.

PET and fMRI are, however, not well suited for studying the temporal dynamic of language processing, since their temporal resolution is generally on the order of minutes (PET) or seconds (fMRI), whereas cognitive processes often occur within a few hundred milliseconds. Event-related potentials (ERPs) provide such temporal resolution. ERPs are recordings of the brain’s electrical activity obtained via electrodes placed on the scalp. Electrical components specific to a cognitive event can be segregated from ongoing background activity by time-locking the recordings to an event of interest (e.g., presentation of a stimulus) and by averaging across a large number of trials. This results in a canonical waveform of the brain’s electrical response to the stimulus. Precise localization of the neuronal sources of these responses is limited, but improving.

Various ERP components have been identified based on their latency and polarity, and related to specific aspects of cognitive processing. A number of these components are tied to language processing, some more specifically than others. For example, the mismatch negativity (MMN) is a negative waveform shift that occurs 100-250 msec following the presentation of a stimulus that differs in any of certain physical characteristics from a more frequently occurring standard stimulus (see Näätänen 1995 for review). While the MMN is not specific to language, it has found many uses in the study of language perception, such as determining whether infants detect a difference between two phonemes like “ba” and “ga” (Cheour et al. 2000). Two ERP components that are more specific to language are the N400 and the P600, both obtained from electrodes placed over centroparietal regions (Friederici 1997). The N400 is sensitive to semantic incongruities, as in the sentence “The box was too heavy to eat.” The P600 is observed in response to syntactic anomalies, as in the sentence “He will walked.” ERPs are valuable for characterizing the temporal dynamics of language processing in the brain, but localizing the neuronal generators underlying ERP components in the brain remains a challenge. Newer methods that combine high temporal and spatial resolution, such as magnetoencephalography (MEG) hold great promise for working toward this characterization in the future.

2.2 Functional localization of components of language processing

This section summarizes results of PET and fMRI studies identifying brain regions associated with early auditory and visual processing of words, lexico-semantic processing, language production, and postlexical processing.

Processing related specifically to spoken words primarily involves different portions of the temporal lobes, predominantly in the left hemisphere (Gernsbacher and Kaschak 2003; Hickok and Poeppel 2000). Certain posterior portions of the superior temporal gyri respond not only to auditorily presented language stimuli, but also more generally to auditory stimuli such as tones. Other bilateral posterior superior temporal regions and the right central middle temporal gyrus show greater responding to stimuli with complex acoustic properties, such as words and pseudowords (pronounceable, word-like letter strings), suggesting a possible role in linguistic processing. Portions of the left middle temporal gyrus show greater activity related to words than to pseudowords. A framework put forward by Hickok and Poeppel (2000) posits that in portions of the left middle and inferior temporal gyri, sound-based representations of words interface with their conceptual, more meaning-based representations. Another likely site important for linking sound and meaning is the inferior frontal cortex. For example, top-down information from inferior prefrontal cortex may facilitate the perception of spoken words (Marinkovic 2004).

Processing of written words, similar to other types of visual stimuli, originates from so-called early visual processing regions in the striate cortex of the occipital lobe. Processing then proceeds anteriorly to extrastriate cortex and higher-order visual association areas along the inferior surface of the occipital and temporal lobes, with representations of the written word form becoming increasingly abstract. For example, a region in the left fusiform gyrus is considered a “visual word form area”. While processing in this region is not necessarily *specific* to words and word-like stimuli, evidence from literate adults suggests that it processes visual (but not auditory) words and word-like strings, and that this processing is insensitive to physical features of the stimulus such as case, size, and font, indicating a relatively abstract representation of the word form (McCandliss et al. 2003). Studies in patients with brain damage have implicated the left angular gyrus (near the junction of the temporal, parietal, and occipital lobes) in some stage of orthographic processing as well (Cohen et al. 2003).

Lexico-semantic processing, in which meaning-based representations of words are accessed from spoken or written stimuli, appears to involve a left-lateralized network of temporal, and frontal brain regions. Data from PET and fMRI studies are consistent with the literature on patients with semantic dementia (Mummery et al. 2000), suggesting a role of left anterior and inferolateral temporal regions, as well as the left temporoparietal junction (Wernicke's area) in semantic processing. MEG studies (Halgren et al. 2002) have used source modeling to identify the left superior temporal sulcus as the generator of the semantically-sensitive N400 component of the ERP waveform, described above. These results fit with fMRI and PET studies that report activity in similar regions during tasks with semantic demands (Pugh et al. 1996). In the frontal lobe, data from functional neuroimaging studies implicate left inferior frontal regions in semantic access and lexical retrieval (Petersen et al. 1989; Warburton et al. 1996).

Spoken language production involves access to phonological representations and their corresponding articulatory programs. The left posterior inferior frontal gyrus (Broca's area) and a central portion of the superior temporal gyrus appear to participate in generation or retrieval of phonological codes. The supplementary motor area (SMA), in frontal cortex near the midline, is known to be involved in motor planning, and there is evidence that it may also play a more specific role in preparation of articulatory programs. The cerebellum is involved in fine motor control, with medial portions linked specifically to language output (Fiez 1996). Less is known about the neural mechanisms of written language production, but there is some evidence that the angular gyrus, associated with orthographic processing in reading, is also important for orthographic processing related to spelling.

Processing at the sentence level requires a variety of syntactic operations. The complexity of these operations makes the identification of associated brain activity difficult to identify in any specific manner, particularly with the limited temporal resolution of hemodynamic methods such as PET and fMRI. However, studies of patients with deficits in various aspects of syntactic processing suggest that left anterior temporal cortex (Dronkers et al. 2004) and the left inferior frontal gyrus, including Broca's area (Fiebach et al. 2005; Indefrey et al. 2001), play important roles. MEG studies (Friederici et al. 2000) have used source modeling to identify similar left temporal and inferior frontal regions as the generators of the syntactically-sensitive P600 component of the ERP waveform, described above.

3. Developmental changes in brain activity associated with language processing

A large contribution to the study of developmental changes in the neural mechanisms of language processing comes from ERP research. This technique has allowed the inclusion of even very young children, who can be seated on a parent's lap during experiments and can be studied during passive listening. A first basic question concerns lateralization: Is the left hemisphere dominance for language, as it is typically found in right-handed (and most left-handed) adults, innate and potentially predetermined by genes; or is it an outcome of language development?

Neuroanatomically, leftward asymmetries of the planum temporale (a portion of Wernicke's area in the superior temporal lobe) have been observed in the fetus. This evidence is corroborated by auditory asymmetries detected in ERP and dichotic listening studies of neonates and infants (Werker and Vouloumanos 2001), consistent with limited recent evidence from fMRI studies in infants suggesting left-lateralizing temporal activation during speech stimulation (Dehaene-Lambertz et al. 2002; see Figure 3). However, there is also evidence pointing at greater right hemisphere language involvement during early stages of language acquisition. Mills et al. (1997) reported that ERPs distinguishing known from unknown words were bilateral in 13-17 month old infants, but left-lateralized in 20 month-olds. Furthermore, Neville & Mills (1997) found that a leftward asymmetry of ERPs to closed class (grammatical function) words, as observed in adults, was absent or even reversed in children under age 3 years. For children 5 years of age and older, Holcombe and colleagues (1992) reported that ERP asymmetries for semantic processing of sentence-final words were absent or inconsistent in children and became established only around age 13 years.

ERP studies have also addressed more general questions of developmental changes associated with language acquisition. For example, in a longitudinal study by Kuhl and colleagues (Rivera-Gaxiola et al. 2005),

auditory ERPs were recorded from infants at 7 months and 11 months of age during passive listening to native and non-native phonetic contrasts. Data from this and other studies (Cheour et al. 1998; Kuhl 2000) comparing peak auditory ERP responses demonstrate that over this age range, discrimination sensitivity increases to native contrasts and decreases to non-native contrasts.

While Kuhl and colleagues focused on familiar vs. unfamiliar speech sounds, Mills and coworkers have applied auditory ERPs to study brain responses to familiar vs. novel words in slightly older infants (Conboy and Mills 2006; Mills et al. 1997). Mills et al. (1997) report that during passive listening to words, 13-17 month old children show broadly distributed ERP differences between comprehended and non-comprehended words. By about 20 months of age, however, differences between known and unknown words are limited to left temporal and parietal regions. These results may reflect an increasing brain regional specialization for lexical processing.

Moving from processing of individual words to sentence-level activation, Friederici and colleagues have used ERPs to examine syntactic processing in young children. In one study (Oberecker et al. 2005), children just under 3 years of age and a group of adults listened passively to sentences that were either correct or syntactically incorrect due to phrase-structure violations. In response to these violations, children demonstrated an early negative ERP component over left anterior electrode sites, followed by a P600 component. In adults, these components have been consistently associated with detection of phrase-structure violations. While the presence of these components in children suggests that at least some neural mechanisms of syntactic processing are in place at a young age, these components had a later onset and longer duration in the children than in the adults, indicating that development was ongoing. These findings are consistent with others in the literature that have revealed generally greater latencies for ERP components in children (Courchesne 1978; Holcomb et al. 1992).

Only in the past decade has fMRI come to be used for research in children. Despite the challenges associated with having young children perform a task while lying still in a noisy and confined space, fMRI results show promise for revealing changes in functional brain organization associated with language development. To date, fMRI studies of language development have focused on children ages 5 years and older. Because of the relatively small number of published studies and the differences among these studies in tasks, methods, and designs, conclusions about specific aspects of language processing have to be drawn with caution. While overall these studies suggest that grossly similar brain regions participate in language processing in children and adults, some intriguing age-dependent changes have been identified as well.

Gaillard *et al.* (2003), for example, reported that children ages 7-14 years showed activations in brain regions similar to those activated by adults during covert semantic fluency (generation of items appropriate to an aurally presented category, such as animals). This group also examined auditory story comprehension (Ahmad et al. 2003). The simple task and selection of age-appropriate stories allowed them to include children as young as age 5. They reported that even the youngest children showed activity similar to that previously observed in adults, most notably along the left superior temporal sulcus. Booth and colleagues (2003b; 2004) reported comparisons of 9-12 year old children and adults performing lexical processing tasks including spelling judgments, rhyme judgments, and semantic judgments to visually or aurally presented words. Under various task conditions, they observed greater activation in adults than in children in the inferior frontal and angular gyri.

Studies of language development using fMRI have also demonstrated that it is possible to observe differences in activation within groups of children. For example, Holland and colleagues (Szaflarski et al. 2006) conducted a longitudinal study of verb generation (hearing a noun and silently generating an appropriate verb; e.g., “ball” ⇒ throw), testing participants once a year for five years, starting at age 5, 6, or 7 years. Over these repeated observations, they saw increases in activity in left inferior and middle frontal gyri, left middle temporal and angular gyri, and right lingual and inferior temporal gyri. Other brain regions, including portions of left extrastriate and right anterior cingulate cortex, left superior frontal gyrus and left thalamus, showed decreased activity over the five-year period (cf. Figure 4). A recent study by Chou *et al.* (Chou et al. 2006) examined semantic judgments about written words in children ages 9-15 years. They reported that increasing age was associated with increased activity in the left middle temporal gyrus and inferior parietal cortex. Younger children, however, showed greater right superior temporal gyrus activation than older children.

One difficulty in interpreting data from developmental functional neuroimaging studies is that age and performance are often confounded. Thus, differences in brain activity across different age groups that are attributed to maturation may in fact be related to the ability to perform the tasks. Careful design of task paradigms that permit the distinction of developmental changes from effects related to performance and non-specific cognitive effort is therefore important. One possibility is manipulation of task difficulty for individual subjects or subject groups, so that performance is more comparable (Balsamo et al. 2006).

Another strategy for taking performance into account is illustrated in a study by Schlaggar and colleagues (2002), who used fMRI to examine brain activity during lexical generation tasks (verb, rhyme, and opposite generation to written words). Data were compared between groups of 7–10 year old children and adults whose performance on the tasks was statistically indistinguishable, and between groups of children and adults whose performance differed. In this way, it was possible to identify age-related regions (those in which activity differed between the age groups, independent of performance), performance-related regions (those in which activity differed based on performance, regardless of age), and age/performance-independent regions (those in which activity did not differ significantly among the groups). The trajectory of change in each of the age-related regions was then characterized by Brown and colleagues (Brown et al. 2005) by including lexical generation data from participants spanning the ages of 7 to 32 years. They demonstrated age-related increases in activity primarily in left frontal and parietal regions, and age-related decreases in activity in lower-level, more peripheral processing regions such as extrastriate cortex (Figure 5).

4. Links between brain development and language acquisition

Relating changes in brain development to the acquisition of language and other higher cognitive functions is one of the greatest challenges facing developmental cognitive neuroscientists. This section provides an overview of brain development, which encompasses both maturational and experience-dependent changes in neurobiology. The distinction between maturational (primarily genetic) and experience-dependent changes (i.e., those brought about by learning and environment) is conceptual, whereas in biological reality the two constantly interact. It is thus not possible, nor is it desirable, to characterize either one in isolation. The purpose of this section is to provide an overview of a typical series of changes that roughly characterize postnatal brain development.

4.1 Progressive and regressive principles of brain development

Human postnatal brain development has been studied in part through postmortem analyses, but primarily by neuroimaging methods such as MRI, by examination of glucose metabolism using PET, and by analogy with brain development in other primates. It appears that, by birth, the basic anatomical organization of the brain is in place; neurons have completed migration to their appropriate cortical locations, and major cortical gyri and sulci are identifiable. The volume of the brain at birth is roughly a quarter of its mature volume, and increases occur with different time courses for various cortical and subcortical structures (Toga et al. 2006). Many of these changes in volume are related to the substantial developmental changes in connectivity within and between regions.

A major component of these developmental changes is synaptogenesis, which is the formation of the junctions (synapses) through which neurons send and receive electrochemical signals. Following a general increase in synaptogenesis around the time of birth, synaptogenesis proceeds in a region-specific manner. Visual cortices, for example, are among the first to show increases in synaptogenesis, starting at approximately 3 months of age and reaching its peak around 6–8 months. While prefrontal cortex also shows an increase in synaptogenesis beginning at about 3 months of age, the time course is much more protracted than in visual cortex, with a peak in synaptic density well beyond the first year (Huttenlocher and Dabholkar 1997).

Synaptogenesis during the first two years of life is accompanied and followed by increasing myelination. Myelination is the process by which axons, the signal-transmitting projections from neuronal cell bodies, become insulated by a fatty sheath (myelin) that enhances conduction velocity. Increases in white matter (myelinated axons) contribute to the overall increase in brain volume that occurs through childhood. Myelination continues into the second decade of life, with prefrontal regions being among the last to attain mature levels (Giedd 2004). Myelination

of fibers in lower cortical layers is also thought to underlie an apparent cortical thinning in children between the ages of 5 and 11 years (Sowell et al. 2004). Intriguingly, anterior and posterior language areas (Broca's and Wernicke's) show inverse age-dependent changes, suggesting very robust increases in cortical thickness that outweigh deep-layer myelination. Furthermore, age-dependent increases in the thickness of left inferior frontal cortex correlated with phonological abilities in the same sample of children. Improvements in motor skills, on the other hand, were associated with *decreases* in thickness of primary motor cortex (Lu et al. 2006).

These findings reflect that progressive events in brain development, such as synaptogenesis and myelination, are accompanied by regressive events. For example, there is extensive synaptic pruning, a process by which weaker or less active connections are eliminated (Kandel et al. 2000). Such pruning follows the extensive period of synaptogenesis described above, during which there is overgrowth, with synaptic density reaching approximately 150% of adult levels in 1 year old children (Huttenlocher 1994). The majority of synaptic pruning appears to occur in late childhood and early adolescence (cf. Figure 6).

4.2 Relating functional and structural changes

The maturation of particular brain regions does not appear to be straightforwardly associated with the emergence of new skills or functions (cf. Bates et al. 2003a). Simply looking at changes in individual brain regions may only provide part of the picture. The relationship is likely more complex in that new functions are supported by changes in functional brain organization affecting both activity within a brain region and connections between brain regions, i.e., the emerging organization of distributed functional networks. An example of a framework for thinking about functional brain development in this manner is provided by the interactive specialization approach put forward by Johnson (2000; 2002; 2003), which takes into account both *inter*-regional and *intra*-regional changes.

In the interactive specialization framework, brain regions whose functional roles are initially not well defined compete with each other to perform certain kinds of processing, thereby altering connections among regions. At the same time, individual brain regions undergo functional fine-tuning, becoming most efficient at processing a particular class of stimuli or performing certain kinds of computations. These processes of inter-regional and intra-regional specialization influence each other to enhance tuning within selected brain regions and to shape a network of regions whose functional roles are more precisely defined. The process of interactive specialization may be related not only to maturational changes that support more efficient processing, but also to environmental factors. For example, there is evidence for changes in functional brain organization for word processing that are very closely tied to the size of a child's vocabulary, indicating the importance of language exposure in interactive specialization (Neville et al. 1992).

In considering how the interactive specialization framework might be applied more specifically to language development, some questions come immediately to mind: Which regions become specialized for language? Why these regions? How specialized are they? Is their specialization predetermined by genes or the outcome of experience and development? While these questions will remain under debate for years to come, some preliminary answers are provided by evidence from behavior genetics and the study of brain plasticity, which will be reviewed in the next two sections.

5. Language and genes

As already alluded to at the outset of this chapter, it was the groundbreaking work of Noam Chomsky that led linguists to consider their object of study as ultimately biological and determined by genes. Although psycholinguists may occasionally have been tempted by overly simple ideas of "language genes", the question is valid and important and a neurophysiological account of language development cannot ignore genetics. At the same time, the reader should be warned that the corpus of solid and relevant data remains extremely small and that no comprehensive and accepted theory of the link between genes and language acquisition is available today.

5.1 Genetic bases of language impairment

One approach to the genetic bases of language lies in the study of children with specific language impairment (SLI; i.e., language deficits in the context of otherwise normal development) that may be genetically based. For the population of children with specific language impairment at large, several quantitative trait loci (i.e., regions with genes suspected to contribute to SLI) have been identified on chromosomes 3p, 13q, 16q, and 19q (p and q indicating short and long arms, respectively; Newbury et al. 2005). An interesting familial aggregation of language impairment was described by Gopnik and colleagues (1990; 1991) in family KE. Initial studies in this family seemed to support a selective linguistic deficit relating to specific aspects of morphosyntax (such as past tense formation). This discovery was greeted with great enthusiasm in part of the linguistic community (e.g., Pinker 1991) because it appeared compatible with a gene-based modular architecture of linguistic subsystems, as proposed by Chomsky (1981). Even more intriguingly, the speech disorder in family KE was identified in subsequent studies as an autosomal-dominant trait involving a single gene on chromosome 7 (Fisher et al. 1998; Lai et al. 2001). These findings in family KE are consistent with independent evidence for strong genetic factors in the general SLI population (Bishop 2002; Tomblin and Buckwalter 1998). Indeed, recent studies indicate potentially distinct genetic factors underlying grammatical functions versus auditory working memory (Bishop et al. 2006).

Returning to family KE, it should be noted, however, that comprehensive examination of affected members does not support the initial impression of an exclusive or specific morphosyntactic deficit (Vargha-Khadem et al. 1995; Watkins et al. 2002a). Instead, affected (compared to unaffected family members) showed significantly lower nonverbal IQ scores as well as evidence of orofacial apraxia and impaired phonological working memory. Furthermore, anatomical MRI studies analyzed by means of voxel-based morphometry demonstrate gray matter reduction primarily in perirolandic sensorimotor cortex and the caudate nuclei in affected members compared to normal control participants (Watkins et al. 2002b), which appears to be more suggestive of neural defects in motor (rather than morphosyntactic) systems.

Nonetheless, family KE and the gene identified on chromosome 7 may serve as the best available example for a better understanding of potential links between genes, developing brains, and impairments of language acquisition. Before examining the role of this gene, it is important to review very briefly what is known more generally about the genetic impact on the regional functional differentiation of the developing brain. There is overwhelming consensus regarding regional functional specificity, both with regard to the mature and the developing brain. This implies that a neurobiological approach to developmental disorders of language should specifically target brain regions known for their role in language acquisition, despite the obvious added complexity of developmental links between lesion site and behavioral impairment (Thomas and Karmiloff-Smith 2002).

5.2 Genes and functional brain specialization

Some recent neuroanatomical studies have suggested very strong genetic factors affecting morphological variability (Bartley et al. 1997; Geschwind et al. 2002; Thompson et al. 2001). Following a review by Pallas (2001), one can distinguish between early *regionalization*, which is determined largely intrinsically and is thus under tight genetic control, and subsequent *arealization*, which is strongly affected by extrinsic and activity-driven factors. Knockout studies of regulatory genes, such as *Emx2* and *Pax6*, illustrate the impact of intrinsic factors on regionalization. In embryonic mice, these two genes are expressed in gradients along the antero-posterior and lateral-medial axes. In knockout models (i.e., in mice missing one of these genes), corresponding distortions of regionalization can be found. For example, *Pax6* knockout mice will have very small anterolateral cerebral regions, but disproportionately large posterior-medial regions (including very large visual cortex; O'Leary and Nakagawa 2002). Roughly the opposite pattern is found in *Emx2* knockout mice (Cecchi 2002).

Neocortical differentiation into fully specialized functional areas is, however, not strictly predetermined intrinsically (genetically), but instead largely driven by input information (i.e., afferent connections) and thus characterized by high levels of plasticity (O'Leary et al. 1994). Some compelling evidence for such epigenetic effects on arealization comes from transplantation and rewiring studies. Schlaggar and colleagues (1991) transplanted embryonic occipital cortex into the postcentral region in neonatal rats and found that "barrel fields" (separate

representations for sensory hairs or whiskers normally found in primary somatosensory cortex) developed almost normally in this transplanted cortex. This implies that cortical tissue that would normally develop visual specialization in occipital cortex has the potential to develop somatosensory functions if transplanted into a brain region where it receives somatosensory information through fibers from the thalamus (Schlaggar et al. 1993). This type of functional malleability of developing cortex is called *crossmodal plasticity* and has also been documented in rewiring experiments by Sur and colleagues (1990), who experimentally connected retinal afferents in newborn ferrets to the medial geniculate nucleus (MGN) in the thalamus. MGN is normally an auditory structure connecting, in turn, to auditory cortex. Sur *et al.* (1988) found that following such rewiring both MGN and primary auditory cortex responded to visual stimulation. Indeed, such electrophysiological responses are functionally relevant and contribute to stimulus-appropriate behavior (von Melchner et al. 2000).

5.3 Language genes?

The evidence sketched above suggests that both intrinsic and extrinsic (or genetic and epigenetic) mechanisms are at work in determining a region's function in the mature brain. This implies that genes may play an important very basic role in creating brain substrates necessary for typical language acquisition, but that much of the regional functional fine-tuning is driven by connectivity and activity (i.e., ultimately by experience). Within this general framework, it is not surprising that the gene on chromosome 7, identified as the critical locus in language impaired members of family KE (as discussed above) is not a 'language gene' that would specifically code for grammatical abilities or narrowly specialized brain substrates. The gene involved – at first suggestively labeled “SPCH1” (Fisher et al. 1998) – was subsequently classified as a gene encoding forkhead transcription factors, therefore called *FOXP2* (Lai et al. 2001). Forkhead proteins are transcription factors that play important roles in various basic developmental processes, such as cell differentiation and proliferation (Marcus and Fisher 2003). Indeed, during embryonic development *FOXP2* is expressed far beyond the brain, for example, in the lungs and in the heart. From this perspective, the apparently more specific role of this gene in language impairment in family KE remains puzzling. More recent studies have shown a cosegregation of one coding change of *FOXP2* with verbal apraxia that could reflect a more specific link (MacDermot et al. 2005). Nonetheless, it must be noted that defects in this gene account for only a very small fraction of developmental language impairments. It is therefore likely that the *FOXP2* gene sheds light only on a small fraction of the links between genes and language development. These links are far from being completely understood, but the current evidence suggests that (a) the typically developing brain's capacity for language acquisition relies on the presence and interaction of a multitude of genes; and (b) these genes are shared, i.e., they also play other roles in the development of other brain systems and bodily systems outside the brain (for discussion, see Fisher 2005; Müller 2005).

The example of *FOXP2* may also be enlightening with regard to the phylogenetic emergence of language. While this gene is evolutionarily very old and highly conserved in vertebrate evolution, two amino-acid substitutions that distinguish humans from chimpanzees have been identified in the *FOXP2* sequence, suggesting the impact of selectional pressures within the last 200,000 years, which may be at least indirectly linked to language emergence (Fisher and Marcus 2006). The current knowledge of the role of *FOXP2* can thus help to modify the search for “language genes” that would correspond to the traditional Chomskian notion of evolutionarily discontinuous emergence of universal grammar due to specific mutations. In the last two sections, we will address the question of genetically anchored specific biological substrates for language, first reviewing evidence for plasticity in brain networks subserving language. Finally, we will reformulate the Chomskian quest, arguing that his overly exclusive view of language vis-à-vis other sensorimotor and cognitive domains needs to be broadened.

6. Damage and plasticity

In previous sections, we have discussed neurofunctional plasticity in the context of typical development (Section 3) and specifically with regard to the impact of afferent connectivity (Section 5.2). As described in Section 2.1, the study of adults with aphasia subsequent to localized brain damage served as the main knowledge source for neurolinguistics until the emergence of functional neuroimaging techniques. Conclusions for healthy brain organization can be

drawn from adult lesion studies on the assumption of limited plasticity in the mature brain. For example, the symptoms of non-fluent Broca's aphasia can be attributed to damage in the left inferior frontal lobe, assuming that there is only limited postlesional reorganization and that brain function in the patient can be equated to normal systems minus the function of a damaged anterior language area. While such assumptions are probably too simple even with regard to the mature brain, they are clearly wrong for the developing brain (Thomas and Karmiloff-Smith 2002).

Behavioral studies show that early-onset left hemisphere damage is often associated with delayed language milestones (Chilosi et al. 2005), but ultimately normal or near-normal language outcome, unless such damage is associated with seizure disorder (MacWhinney et al. 2000; Max 2004; Muter et al. 1997). In children with localized left hemisphere damage, it remains possible that intact parts of the left hemisphere may assume language functions. However, similarly good language outcomes are also seen in patients with left hemispherectomy (i.e., the removal or complete disconnection of an entire hemisphere), on condition that the right hemisphere remains intact (Boatman et al. 1999; Curtiss et al. 2001; Vargha-Khadem and Mishkin 1997; Vargha-Khadem et al. 1997). The behavioral literature would therefore suggest a potential for the right hemisphere to assume language functions in the face of massive left hemisphere damage early in life.

This indirect conclusion has been corroborated by functional neuroimaging studies. In a series of PET studies (Müller et al. 1997; 1998a; 1998b; 1998c), right hemisphere reorganization was observed in most children with early left hemisphere damage (Figure 7). In these subjects, right hemisphere activation was typically found in regions homotopic to left perisylvian language cortices. These studies also showed an enhanced potential for interhemispheric reorganization in the developing child brain, compared to the adult brain (Müller et al. 1999a; 1999b). A few functional MRI studies have more recently corroborated these findings. Staudt and colleagues (2002) found right-hemisphere activations in regions homotopic with left perisylvian language areas for silent word generation in adults with a history of congenital left periventricular lesions (Figure 8) – a finding corroborated more recently by Liegeois and coworkers (2004), who observed right-hemisphere dominance for language in five of ten adolescent patients with early onset damage due to diverse conditions. In a single-case study, language reorganization was examined in a child with Rasmussen's encephalitis before and after left hemispherotomy (extrathalamic white matter disconnection and callosotomy; (Hertz-Pannier et al. 2002). Whereas word generation was associated with left frontal and inferior parietal activation before surgery, extensive right hemisphere activation was found after the resection.

The brief review in this section underlines that the brain organization for language is not fully determined at birth. While the ERP and imaging evidence on typically developing children suggest early biases of portions of the left hemisphere to assume a pivotal role in language acquisition (as reviewed in Section 3), the right hemisphere also has a similar potential early in life. Overall, the evidence is thus consistent neither with genetically driven predetermination nor with "equipotentiality" and exclusively epigenetic causes of functional specialization.

7. "Language areas": A developmental account

Current knowledge about the brain organization for language, as described in Section 2.2, is almost entirely based on evidence from healthy and brain damaged adults. This is related to scientific and conceptual pragmatism, since it is easier to acquire relevant data from adults and to draw conclusions about brain-behavior relationships at what is considered a 'steady-state' (compared to the dynamic changes of the maturing brain). However, this adultocentric approach that considers children as not quite finished adults can be deeply misleading. The perspective taken in this section is informed by the constructivism of Swiss psychologist Jean Piaget (Piaget 1979), according to whom the cognitive system at any stage is erected on the building blocks of previous stages. With regard to brain-behavior links in the language system, this approach implies that it is preposterous (in the literal sense of putting the cart before the horse) to inspect the child brain in the search for language areas as defined by adult brain organization. Instead, we can study the maturing brain in search for explanations of why certain brain regions have come to assume language specialization in the adult brain.

7.1 Broca's area and the mirror neuron system

An exemplary case can be made with regard to Broca's area in left inferior frontal cortex. Despite some claims for highly specialized syntactic functions (Grodzinsky 2000), neuroimaging evidence shows overlapping cortex within this area involved in phonology and semantics as well (cf. Hagoort 2005). Indeed, a more comprehensive review of the literature suggests participation of the left inferior frontal gyrus in a large array of functions that are not even considered linguistic (Cabeza and Nyberg 2000). Among the examples are functions related to motor planning and action, such as imitation (Buccino et al. 2004; Iacoboni et al. 1999), motor preparation (Krams et al. 1998) and complex motor planning (Fincham et al. 2002), sequence learning (Haslinger et al. 2002), action imagery (Binkofski et al. 2000) and observation (Buccino et al. 2001), but also functions considered of executive nature, such as rule shifting (Konishi et al. 1998), response selection (Thompson-Schill et al. 1997), response inhibition (Kemmons et al. 2005; Rubia et al. 2001), perceptual fusion and resolution of audiovisual stimulus conflict (Dale and Buckner 1997; Miller and D'Esposito 2005), as well as working memory (Chen and Desmond 2005). Some of these findings can be considered reflections of inferior frontal participation in the mirror neuron system (Rizzolatti and Arbib 1998).

Mirror neurons were first observed in primate area F5, which is a likely homologue to human area 44 in inferior frontal cortex (Grèzes et al. 2003; Petrides and Pandya 1994) and thus to the core portion of Broca's area. Mirror neurons show increased firing rates for internally generated action as well as for corresponding externally observed actions (Fadiga et al. 2000), including actions performed with tools (Ferrari et al. 2005). While mirror neurons have been mostly studied using visuomotor conditions, the existence of multimodal auditory-visual-motor mirror neurons has also been demonstrated in monkey area F5 (Kohler et al. 2002). The mirror neuron system, which additionally incorporates parietal cortex and the superior temporal sulcus, can thus be considered crucial to action understanding (Rizzolatti and Craighero 2004). More importantly, since this system affords a matching of self-generated actions to those observed in others, it is likely to provide a crucial component in the development of theory of mind, i.e., the ability to attribute intentions to other people's actions according to intentions underlying our own actions. The mirror neuron system is thus vital, not only for sensorimotor integration involved in language acquisition (e.g., the child's ability to imitate phonemes based on adult models), but in a deeper sense because it contributes to the understanding that verbal actions are *meaningful*, i.e., reflect the speaker's state of mind, intentions etc. (cf. Gallese 2003; Nishitani et al. 2005; Rizzolatti and Arbib 1998).

A large number of recent functional neuroimaging studies have documented that inferior frontal cortex participates in the described functions of the mirror neuron system in similar ways in adult humans as in monkeys. For example, activation in area 44 has been reported for action observation and imagery (Binkofski et al. 2000; Buccino et al. 2001), processing of action-related (compared to abstract) sentences (Tettamanti et al. 2005), as well as imitation (Grèzes et al. 2003; Heiser et al. 2003; Leslie et al. 2004), including imitation of lip forms (Nishitani and Hari 2002). Indeed, consistent with the idea that the mirror neuron system provides the basis of mentalizing abilities mentioned above, Iacoboni and colleagues (2005) showed inferior frontal activity related to the processing of intentions (as compared to simple action observation).

While the important role of Broca's area in the mirror neuron system is well documented, inferior frontal cortex also receives afferents from the ventral visual stream (Di Virgilio and Clarke 1997; Petrides and Pandya 2002) – a processing stream extending from visual cortex in the occipital lobe into inferior portion of the temporal lobe, which is crucial for the meaningful interpretation of perceived objects. Broca's area can thus be considered pivotal for language learning – not because it contains cortical tissue specifically predestined for morphosyntactic or other language functions (cf. Amunts et al. 2003) – but because a number of functional pathways providing crucial components for language learning converge in this brain area. The most important components are the mirror neuron system and dorsal stream (action understanding), the ventral stream (semantics), and executive components (working memory, response inhibition). The limited spatial resolution of functional neuroimaging techniques such as fMRI makes it hard to determine to what extent each of these components may be distinctly organized within inferior frontal cortex. In a recent review, Molnar-Szakacs and colleagues (2005) conclude that mirror neurons may themselves have working memory capacity, suggesting potential overlap of tissue involved in action understanding and executive components. Activity related to the mirror neuron system, such as action recognition, was also found

to occur in close proximity to language-related activity (verb generation), with a distance of peaks below 10mm in many individuals (Hamzei et al. 2003).

Although the above example relates specifically to Broca's area, the approach to functional characterization will likely also apply to other presumed "language areas", such as Wernicke's area in posterior perisylvian cortex. The discussion of Broca's area suggests that its importance in language processing may be developmentally explained by this region's anatomical connectivity patterns and its participation in multiple functional networks that are important "ingredients" of language acquisition (see Müller, in press, for more extensive discussion).

8. Conclusion

The human ability to acquire languages ultimately rests on genetic endowment. Although there are a few intriguing genetic findings of changes in hominid evolution that may be related to language emergence, it is likely that many genes are involved in the phylogenetic emergence and ontogenetic acquisition of language. It remains open whether any genes may specifically code for language-related abilities. However, evidence for activity-driven (and thus not entirely intrinsic) specialization from developmental neuroscience suggests that the brain substrates for language functionally differentiate in part due to epigenetic processes. This is consistent with evidence for plasticity following damage to typical language regions in children. Further evidence was discussed regarding the precise functional characterization of Broca's area, the most universally accepted brain substrate for language processing, suggesting that this area's readiness for language acquisition relates to converging precursor functions (such as imitation, action understanding, attribution of intention, meaningful interpretation, working memory, and response inhibition). While a comprehensive explanatory model of the links between brain maturation and language remains unavailable, advances in functional imaging and neurophysiological techniques in the past decades promise to provide ever deeper insights into the nature and bases of language acquisition.

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Figures

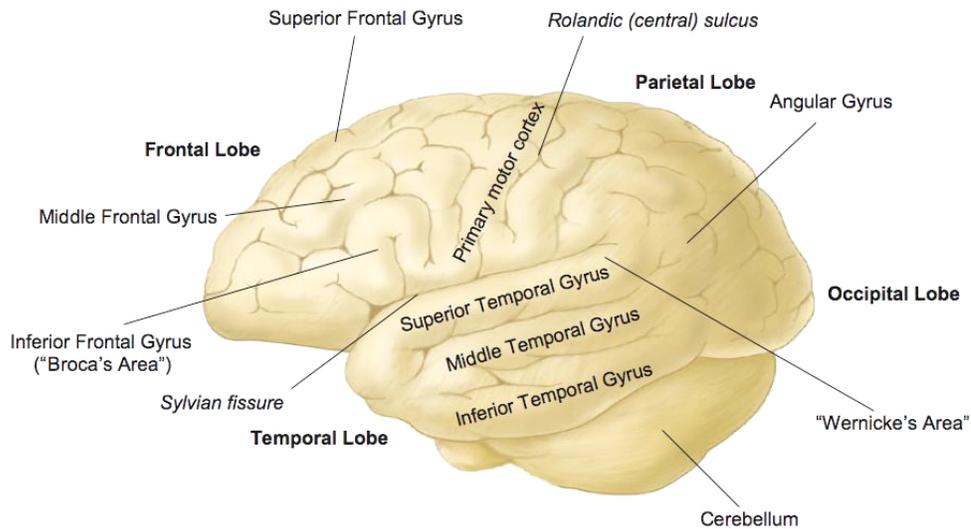


Figure 1. Main anatomical terms used in this chapter, indicated on the left hemisphere. Names of larger lobar subdivisions are shown in boldface, sulci are indicated in italics. Subcortical structures are not shown.

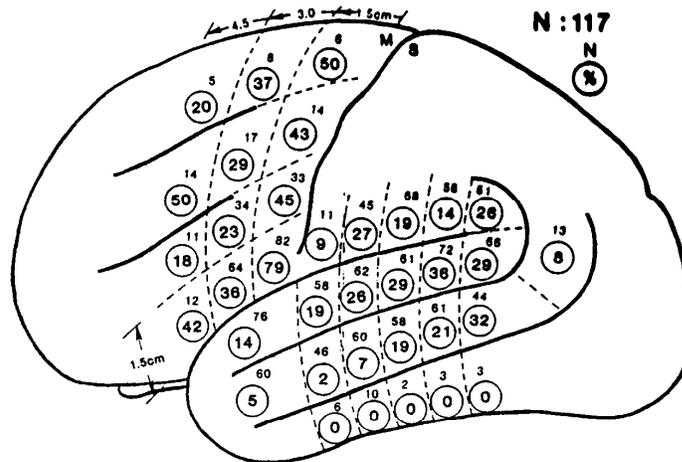


Figure 2. Results from electrical stimulation mapping by Ojemann and colleagues. The numbers in circles indicate the percentage of patients, in whom stimulation at the given site caused naming errors. The small numbers above each circle represent the total number of patients stimulated at the particular site. Results suggest that large regions of the left hemisphere are involved in processes that support naming. From Ojemann et al. (1991).

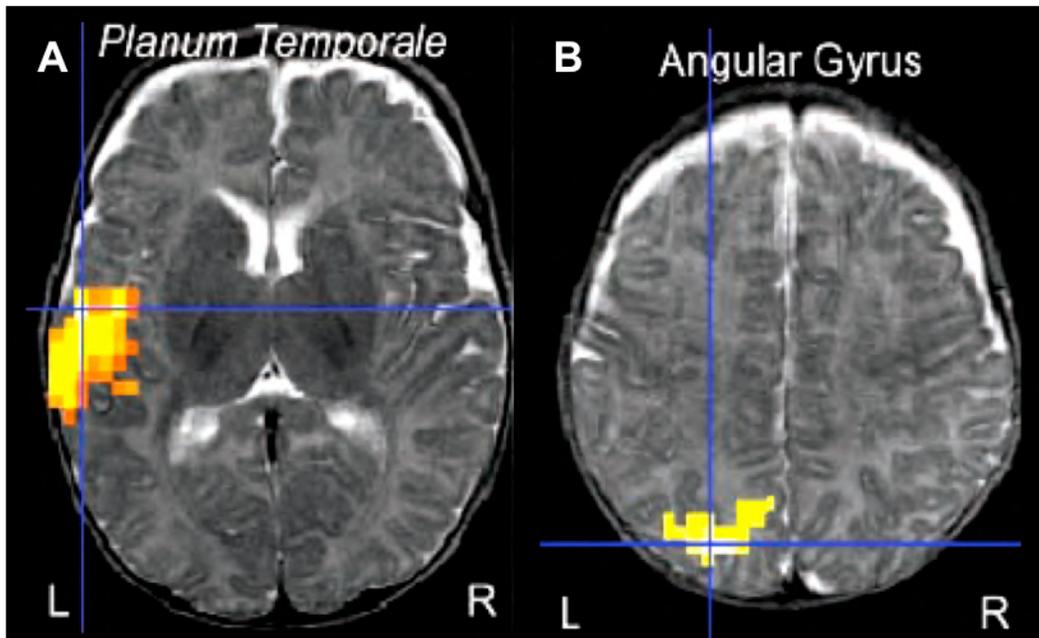


Figure 3. (A) Activation during sound stimulation (forward and backward speech) in 20 infants ages 2-3 months. Sites of significant activation in the left temporal lobe (indicated by the crosshairs) are overlaid in white onto structural MRI. (B) Direct comparison between conditions shows greater activity for forward (compared to backward) speech in the left angular gyrus. From an fMRI study by Dehaene-Lambertz et al. (2002).

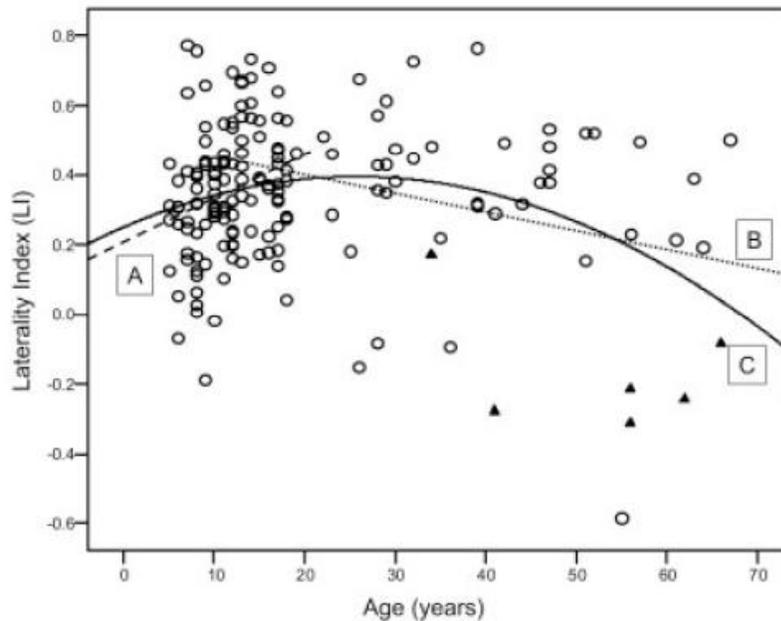


Figure 4. Hemispheric dominance for language as a function of age, based on fMRI activation findings in 170 healthy children and adults. Positive numbers in the upper half of the y-axis indicate leftward asymmetry of activation in Broca's and Wernicke's areas; negative numbers indicate rightward asymmetry. Circles and triangles indicate two different scanners used for data acquisition. Separate regressions were performed for children (A, dashed line), adults (B, dotted line), and all subjects together (C). The task was covert verb generation for aurally presented nouns. The results suggest that left lateralization increases throughout childhood and up to late adolescence, but slowly diminishes in adulthood. From Szaflarski et al. (2006).

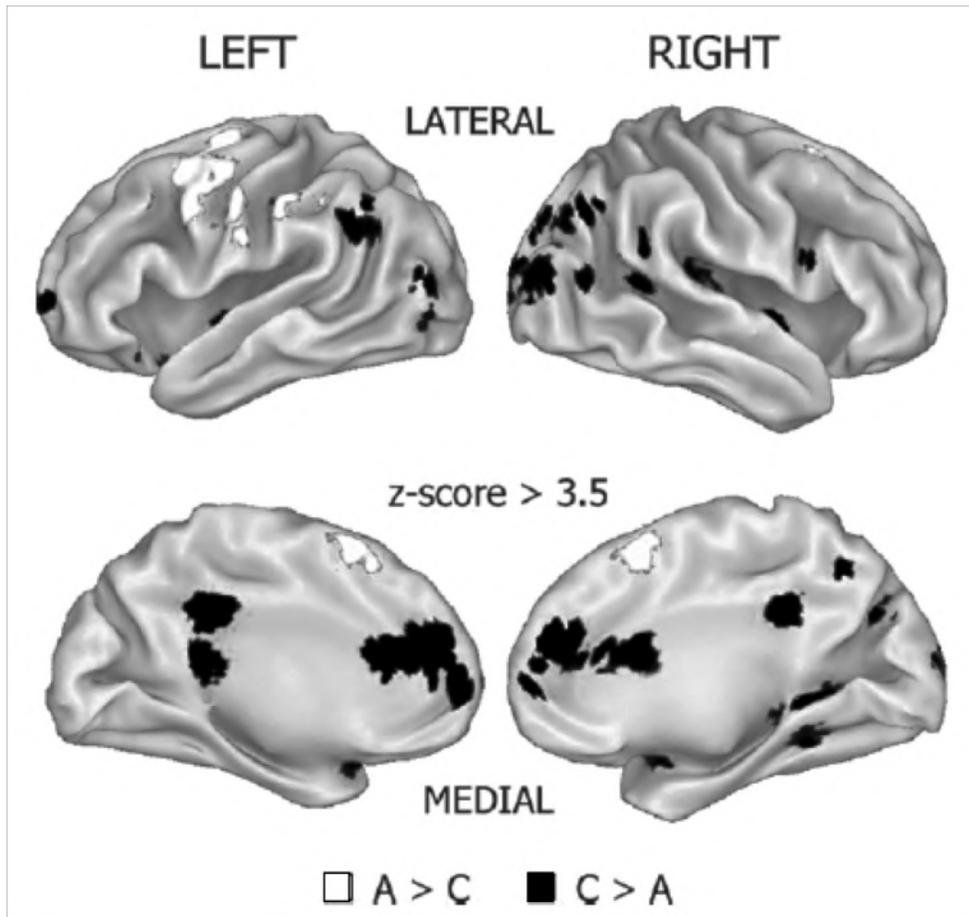


Figure 5. Age-dependent differences in activation for overt word production from an fMRI study in 95 children and adults, ages 7-32 years. White regions overlaid onto lateral and medial brain surfaces indicate greater activity in adults than in children ($A > C$), which is found mainly in frontal regions, such as premotor and supplementary motor cortex. Black overlays indicate regions with greater activity in children. These effects are extensive in posterior cortex, mostly in the occipital and parietal lobes, and in medial frontal and anterior cingulate regions. From Brown et al. (2005).

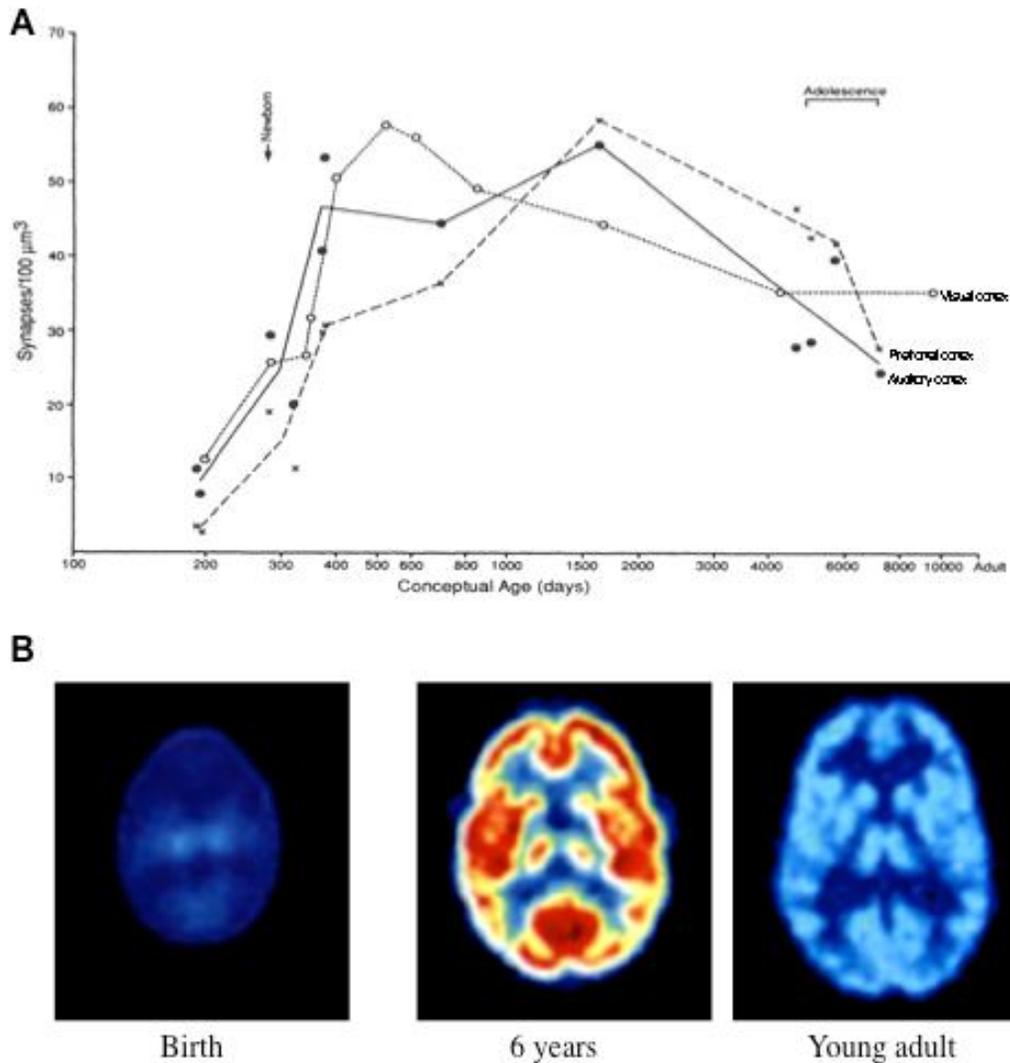


Figure 6. (A) Changes in synaptic density in primary auditory cortex (filled circles), primary visual cortex (open circles), and prefrontal cortex (middle frontal gyrus; x symbols) during development. The findings from Huttenlocher and Dabholkar (1997) show steep increases in synaptic density in the third gestational trimester and in the first postnatal year. High levels are maintained for several years, until synaptic density slowly declines to adult levels. Related age-dependent changes in glucose metabolism can be seen in (B). PET studies by Chugani et al. (1986) show much higher glucose metabolic rate in 6-year old children, compared to neonates and young adults. Adapted from Huttenlocher and Dabholkar (1997) and Chugani et al. (1991).

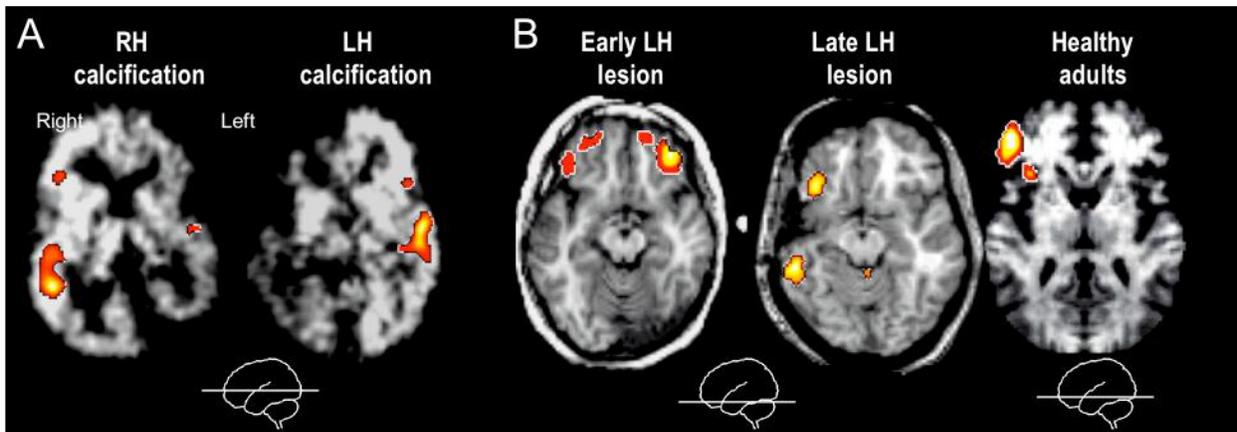


Figure 7. (A) PET activation studies in two subjects with progressive calcification of one hemisphere due to congenital Sturge-Weber syndrome. This disease is usually limited to a single hemisphere. During listening to sentences, the patient with right hemisphere damage shows a normal pattern of activation in left superior and middle temporal gyri, with slight additional activity in Broca's areas and in the temporal lobe of the affected right hemisphere. The patient with left hemisphere calcification shows almost a mirror image of activity in right temporal and inferior frontal regions. Activations are overlaid on resting blood flow images. Based on data from Müller et al. (1997; 1998b). (B) Activations for sentence generation (compared to sentence repetition) in a patient with congenital onset left hemisphere damage, a patient with left hemisphere damage in the second decade of life, and in a group of healthy young adults. Early lesion is associated with extensive right frontal activation, whereas the late lesion patient shows left-lateralizing activity in inferior frontal and superior temporal lobes. Healthy adults show robust activity in left inferior frontal cortex. Note that images are shown in radiological convention, with sides inverted, as indicated in (A). Approximate slice locations are indicated on the small brain icons at the bottom. Based on data from Müller et al. (1999a; 1999b).

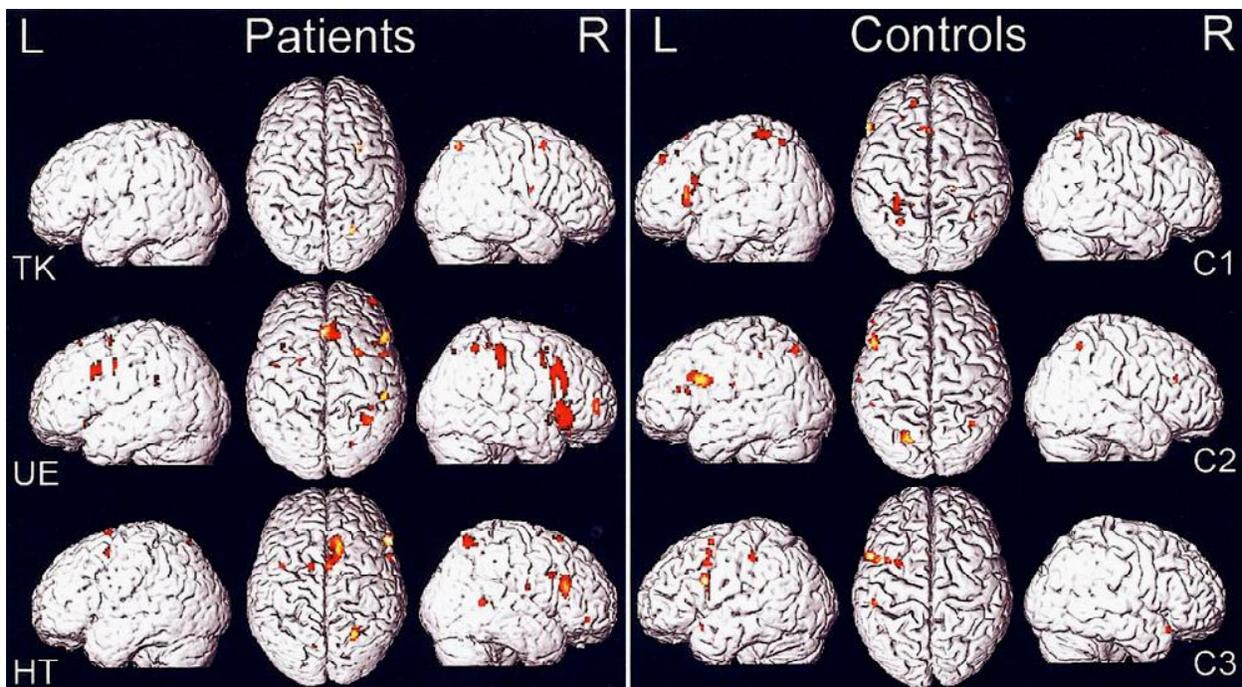


Figure 8. Examples of brain activation during covert word generation in three adult patients with a history of pre- and perinatal left hemisphere damage. All three subjects show activation in the right hemisphere that is not seen in control subjects. This activation, which is considered to reflect interhemispheric reorganization, varies strongly between individual patients, however. From an fMRI study by Staudt et al. (2002).