Development of Neural Systems for Reading

Bradley L. Schlaggar\textsuperscript{1,*} and Bruce D. McCandliss\textsuperscript{2,*}

Departments of Neurology, Radiology, Anatomy & Neurobiology, and Pediatrics,  
\textsuperscript{1}Washington University School of Medicine, St. Louis, Missouri 63110;  
extranw@neuro.wustl.edu  
\textsuperscript{2}Sackler Institute for Developmental Psychobiology, Weill Medical College of  
Cornell University, New York, NY 10021; email: bdm2001@med.cornell.edu

Abstract

Functional and structural neuroimaging studies of adult readers have provided a deeper understanding of the neural basis of reading, yet such findings also elicit new questions about how developing neural systems come to support this learned ability. A developmental cognitive neuroscience approach provides insights into how skilled reading emerges in the developing brain, yet also raises new methodological challenges. This review focuses on functional changes that occur during reading acquisition in cortical regions associated with both the perception of visual words and spoken language, and it examines how such functional changes differ within developmental reading disabilities. We integrate these findings within an interactive specialization framework of functional development and propose that such a framework may provide insights into how individual differences at several levels of observation (genetics, white matter tract structure, functional organization of language, cultural organization of writing systems) impact the emergence of neural systems involved in reading ability and disability.

Key Words

fMRI, diffusion tensor imaging, event-related potentials, dyslexia, genetics, perceptual expertise
“One of the strong claims of developmental cognitive neuroscience is that a comprehensive understanding of mature cognition cannot be attained without understanding both normal and abnormal development of the human brain...we cannot understand how the mature system works until we understand how it is constructed in development, and we cannot fully understand that process of normal construction without understanding how development can go awry.”

– Johnson & Pennington (1999)

### INTRODUCTION

Reading ability has served as a model system within cognitive science for linking cognitive operations associated with lower-level perceptual processes and higher-level language function to specific brain systems (e.g., Posner et al. 1988). More recently, developmental cognitive neuroscience investigations have begun to examine the transformations in functional brain organization that support the emergence of reading skill. This work is beginning to address questions concerning how this evolutionarily recent human ability emerges from changes within and between brain systems associated with visual perception and language abilities, how learning experiences and maturation impact these neural changes, and how individual differences at the genetic and neural systems level influence the emergence of this skill.

### Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>476</td>
</tr>
<tr>
<td>OVERVIEW</td>
<td>478</td>
</tr>
<tr>
<td>FUNCTIONAL NEUROANATOMY OF WORD READING IN SKILLED ADULT READERS</td>
<td>478</td>
</tr>
<tr>
<td>Functional Significance of the VWFA</td>
<td>479</td>
</tr>
<tr>
<td>Studies of Letter-Sound Integration in Skilled Readers</td>
<td>480</td>
</tr>
<tr>
<td>CHALLENGES TO STUDYING THE DEVELOPMENT OF READING-RELATED TASKS</td>
<td>481</td>
</tr>
<tr>
<td>USING FUNCTIONAL NEUROIMAGING</td>
<td></td>
</tr>
<tr>
<td>SPECIALIZATION OF THE VWFA IS IMPLICATED IN THE DEVELOPMENT OF PERCEPTUAL EXPERTISE IN READING</td>
<td>483</td>
</tr>
<tr>
<td>INTEGRATION OF ORTHOGRAPHIC AND PHONOLOGICAL PROCESSING IS IMPORTANT</td>
<td></td>
</tr>
<tr>
<td>FOR READING DEVELOPMENT</td>
<td>486</td>
</tr>
<tr>
<td>NEUROSCIENCE APPROACHES TO UNDERSTANDING INDIVIDUAL DIFFERENCES IN READING</td>
<td>487</td>
</tr>
<tr>
<td>Functional Imaging of Individual Differences in Reading</td>
<td>487</td>
</tr>
<tr>
<td>Individual Differences in White Matter Tract Properties</td>
<td>489</td>
</tr>
<tr>
<td>Genetic and Cultural Contributions to Individual Differences in Reading Development</td>
<td>491</td>
</tr>
<tr>
<td>RESEARCH ON INTERVENTIONS FOR READING DISABILITY IN CHILDREN</td>
<td>493</td>
</tr>
<tr>
<td>CONCLUDING REMARKS: INTERACTIVE SPECIALIZATION AS A CONCEPTUAL FRAMEWORK FOR READING DEVELOPMENT</td>
<td>494</td>
</tr>
</tbody>
</table>
A traditional approach to understanding the neurobiology of reading ability and disability has been to investigate the consequences of focal brain lesions on the skilled adult reader (see Warrington & Shallice 1980 for review). More recently, functional neuroimaging, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), as well as event-related potentials (ERP), have been used to investigate the functional neuroanatomy of reading skills in adults. Results from these approaches have provided a foundation for understanding the neural basis of skilled reading and have been used to support theoretical distinctions between component processes of reading linked to particular cortical regions. In studying adults exclusively, however, such approaches to linking cognitive functions to particular brain systems often rely on simplifying assumptions, which becomes problematic when considering issues of how functions emerge within brain systems. For example, Johnson and coworkers (2002) note that many theories of structure/function relationships in adults either provide little insight into how such relationships emerge or rely on the “static assumption,” which presumes that functional properties of brain regions observed in adulthood necessarily reflect those observed during human development. Such assumptions may prove especially problematic in explaining the development of reading ability, in which the major component processes (i.e., visual word form recognition, letter-sound association) depend entirely on the rather recent development of writing systems and implicate learning processes that rely on explicit teaching of this cultural invention.

To understand how the brain’s organization for skilled reading emerges, one must examine the changes that the developing brain undergoes in the process of acquiring the skill. Some of the major challenges involve characterizing the nature of the progressive changes that occur over the early reading years and understanding how reading abilities emerge from preexisting visual perception and language abilities. For example, interpretation of orthography, the written form of language, places unique demands on the brain’s visual object-processing systems. Linking orthography with phonology, the sound structure of language, is the sine qua non of reading acquisition (Share 1995) and implicates the formation of functional connections between visual object processing systems and systems involved in processing spoken language.

A developmental cognitive neuroscience approach to investigating the emergence of reading ability and the associated changes in functional brain organization that accompany it provide unique perspective on these issues. Investigations of developmental changes within and between cortical regions associated with orthographic and phonological aspects of word reading help elucidate the neural basis for perceptual expertise that supports rapid word recognition. Such investigations also help delineate the neural basis for the well-established impact of individual differences in phonological skill on the development of reading ability (Share 1995). Basic research into maturational changes in the brain during the years in which reading expertise develops may provide important insights into how these changes influence learning and functional specialization in cortical regions. Finally, a comprehensive account of reading development will eventually need to incorporate molecular (such as genetic susceptibility for reading disability) and neurobiological (such as detailed information about white matter tract structure) factors that influence individual differences in the capacity to acquire reading skill. Such studies may provide a more integrated understanding of developmental disorders of reading and set forth a theoretical basis for optimizing remediation strategies. Such issues, as described below, are only now being addressed.

Over the past decade, the field of developmental cognitive neuroscience has enjoyed remarkable growth and a concomitant surge in methodological development for brain

---

**PET:** positron emission tomography  
**fMRI:** functional magnetic resonance imaging  
**ERP:** event-related potential  
**Orthography:** the graphic structure of language  
**Phonology:** the sound structure of language
mapping. Consequently, although nascent, the state of a developmental cognitive neuroscience of reading can be discussed. Although reading development implicates many forms of cognitive and neural processes that undergo changes across development and skill acquisition, the scope of this review specifically focuses on factors that may contribute to the developmental changes that occur between brain systems that support the integration of the visual and phonological aspects of deciphering written words. The development of this connection building is best explained perhaps within an interactive specialization scheme (Johnson 2001, Johnson et al. 2002) that has implications for both visual perceptual processes as well as for phonological processes, as both of these systems undergo changes in the transition from the novice child to the skilled adult reader.

OVERVIEW
This review, organized into seven sections, brings together recent insights from multiple areas of neuroscientific investigation that are germane to understanding the development of neural processes necessary to relate print to speech. We focus on this specific aspect of reading because it is both an essential subskill for reading development and also a useful vehicle to illustrate connections across multiple levels of observation in relating neural structure and function in reading development.

The first section discusses the functional organization of reading in skilled adult readers as a natural end-state of development to set the stage for a review of developmental investigations.

The second section, Challenges to Studying the Development of Reading-Related Tasks Using Functional Neuroimaging, delineates some confounds inherent in interpreting developmental changes within fMRI and ERP studies and describes several approaches to differentiating the contributions of various factors that impact brain activity across development.

Next, the third and fourth sections address the developmental specialization of brain systems that occur as children develop from naive to expert readers.

The fifth section, Neuroscience Approaches to Understanding Individual Differences in Reading Development, examines several sources of individual differences that impact the development of reading ability and extends these observations to help explain the neural bases of developmental reading disabilities. A related sixth section describes recent research linking intervention efforts for children with reading disabilities with observations of changes in patterns of functional activation.

The concluding section discusses how the concept of interactive specialization and related computational models of reading may provide a framework for relating individual differences in neural systems to individual differences in the functional organization of the expert adult state.

FUNCTIONAL NEUROANATOMY OF WORD READING IN SKILLED ADULT READERS
Notions of the functional localization of component reading functions emerged in the era of classic studies of language function in the late nineteenth century. Specifically, the idea of separate neural routes to support different aspects of reading was motivated by observations of the consequences from focal brain lesions noted by Dejerine (Dejerine 1891). He described patients with different forms of acquired reading difficulty (i.e., dyslexia) due to focal lesions in the left posterior hemisphere, contrasting effects of ventral lesions (i.e., fusiform gyrus), and dorsal lesions (i.e., left angular gyrus). Clinically distinct forms of acquired dyslexia associated with different focal lesions ultimately led to the idea that there is both a direct route from print to meaning as well as an indirect route mediated by associations between letters and the

PET and fMRI investigations of such processes have contributed to numerous studies attempting to characterize the functional circuitry supporting skilled adult word reading. Convergent patterns across these studies are evident in both qualitative and quantitative meta-analyses (Fiez & Petersen 1998, Turkeltaub et al. 2002, Jobard et al. 2003, Bolger et al. 2005). In summarizing this work, we focus here on the ventral (orthographic) and the dorsal (phonological) systems because they represent the computations most directly relevant to the specialization of reading ability.

The visual orthographic regions are located ventrally in the extrastriate cortex. The bilateral regions are thought to support initial visual processing and feed into the more anterior left-lateralized region, which has been termed by some as the “visual word form area,” or VWFA (Cohen et al. 2000, 2002; McCandliss et al. 2003), and is argued to process a prelexical representation of letter patterns within visual words and pseudowords (see Functional Significance of the VWFA). The putative VWFA is among the most consistently activated regions in quantitative meta-analytic studies of adult reading. The phonological system can be functionally divided into two components: a left dorsal posterior component and a left anterior component. The left dorsal posterior component, also referred to as the perisylvian region, includes the supramarginal gyrus, angular gyrus, and superior temporal cortex (Rumsey et al. 1997). In adult imaging and ERP studies, this system tends to have greater activity while reading pseudowords than real words and is thought to function as an integrative region linking orthography to phonology (Pugh et al. 2001). The left anterior component, not emphasized in this review, includes the inferior frontal gyrus extending into the dorsal premotor cortex and has been associated with speech production as well as active analysis of phonological elements within words (Fiez & Petersen 1998, Poldrack et al. 1999).

**Functional Significance of the VWFA**

Dejerine’s pioneering work associating some specific aspects of reading function with the left mid-fusiform gyrus anticipated one of the most intriguing structure-function debates in cognitive neuroscience: the significance and specificity of the so-called visual word form area. This appellation comes from the observation across multiple studies demonstrating that contrasting visual words with other complex unfamiliar stimuli leads to increased activity within a particular brain region, typically involving a left occipitotemporal region centered on the mid-fusiform gyrus (for review see McCandliss et al. 2003). There is little controversy surrounding this principle observation and its replication across studies (McCandliss et al. 2003, Bolger et al. 2005), although current debate centers on the contribution of this area to nonreading tasks and the precise functional significance this activity contributes to reading function (for review see Price & Devlin 2003, Cohen et al. 2004).

To investigate the functional significance of the VWFA for word recognition, some studies have used higher spatial resolution techniques (intracranial electrodes, high resolution fMRI) to demonstrate increased activity for letter strings over other classes of visual stimuli presented under equivalent conditions (Allison et al. 1999, Baker et al. 2005). When such effects are reported, they are typically described in terms of relative strengths of activation, rather than demonstrating exclusivity of function for the domain of visual words. Evidence appears to support preferential, but not exclusive, processing of word form–related stimuli in the putative VWFA, which we discuss below as supporting a form of perceptual expertise for visual words.

Recent research on activation of the VWFA for visual word recognition implicates a role for this region in the bottom-up perceptual encoding of orthographic properties...
of letter strings, demonstrating a parametric relationship between activity in this region and the statistical properties by which letters are organized into word forms within a given writing system (Dehaene et al. 2004, Binder et al. 2006). However, several studies have demonstrated that although this region is not typically responsive to passive presentation of auditory words, this region’s activation level can be modulated by top-down attentional and/or linguistic processes (Booth et al. 2003, Devlin et al. 2006). Integrating these two sets of observations is the notion that word-specific activation within the extrastriate regions may reflect a “gateway” through which critical invariant information extracted from visual forms makes contact with linguistic representations (Carr & Posner 1995). Activity within the VWFA may still reflect many properties that are general to visual recognition and may also be influenced by top-down attention processes associated with increased connectivity between phonological and semantic systems outside the visual system. We propose below that a primary function of the VWFA during reading is to support a form of perceptual expertise for visual word recognition that enables rapid perception of visual words in one’s own language. However, a great deal remains to be understood regarding how this specialization develops.

Studies of Letter-Sound Integration in Skilled Readers

In addition to representing visual word forms efficiently, reading also requires the formation of highly specific mappings between visual print representations (orthography) and representations related to the sounds of language (phonology). A number of studies have begun to investigate interactions between occipital and temporal regions that may be crucially involved in the functional organization of reading ability, as such regions are implicated in letter-sound integration.

In a study of skilled adult readers, Blomert and coworkers (Van Atteveldt et al. 2004; see also Raij et al. 2000) demonstrated a role for heteromodal (i.e., responsive to both visual and auditory input) portions of the left superior temporal cortex in the integration of orthographic and phonological processing. In these experiments, visual letters and auditory letter sounds were presented simultaneously, with half the trials presenting a match between the letters in these two modalities. Responses in these heteromodal regions were enhanced when the identity of the visual and auditory letters matched. These findings suggest a form of experience-based plasticity in the response properties of these regions because associations between letters and sounds are inherent only in the subjects’ reading experience. Furthermore, these results have recently been extended to demonstrate that dyslexic adults show deficits in this experience-driven effect, suggesting that disruptions in phenomena associated with letter-sound integration may be linked to disruptions in skilled reading (Blau et al. 2007).

The link between experience and the formation of such sensitivities was further probed by Hashimoto & Sakai (2004), who investigated the cortical plasticity of skilled adult readers being trained to learn new letter-sound associates in a short-term training paradigm. In this repeated measures study, the primary sites of training-related change were in a region near the left ventral occipitotemporal cortex in the mid-fusiform gyrus and another in the left parietal/occipital cortex near the angular gyrus. The study also showed an increase in the effective connectivity (a measure of task-related correlated activity) of these two regions.

Taken together, these studies suggest a specific cortical circuitry involved in integrating orthographic and phonological information and provide initial insight into how this circuitry changes with learning in the skilled reader. The regions implicated are consistently related to orthographic and phonological processing in the functional mapping studies reviewed above. However, demonstrations of experience-dependent changes in skilled
readers might differ dramatically from beginning readers forming such connections for the first time. More direct links to development are needed, although developmental studies raise significant challenges of their own.

CHALLENGES TO STUDYING THE DEVELOPMENT OF READING-RELATED TASKS USING FUNCTIONAL NEUROIMAGING

We now turn our attention to child studies that examine the development of functional activation within brain systems associated with the emergence of skilled visual word recognition. In doing so, we focus on several interpretational challenges inherent within developmental cognitive neuroscience research.

The ability to study typically developing children with functional neuroanatomical techniques became more available with the advent of fMRI, which uses the blood oxygenation level dependent (BOLD) signal to indirectly measure neural activity related to execution of a cognitive task such as word recognition. fMRI studies of the developmental functional neuroanatomy of reading have provided evidence related to the developmental dynamics that occur in brain circuits that support reading (Booth et al. 2001, 2004; Shaywitz et al. 2002; Schlaggar et al. 2002; Turkeltaub et al. 2003; Brown et al. 2005). A central focus of these studies is on how developmental changes in brain activity within particular cortical regions are linked to the emergence of reading skill. However, concomitant changes in brain maturation and changes in performance dynamics within the activation task also influence brain activity patterns over development, posing significant challenges to research in this area. Although no consisent solution to these challenges has emerged, a number of approaches to differentiating the contributions of these different effects have been investigated.

One common concern is that age-group imaging differences could merely be reduced to age-related changes in performance on an activation task such as time on task or number of error trials (Schlaggar et al. 2002, Murphy & Garavan 2004). The existence of age-related changes in performance on a reading-related activation task at the time of imaging does not necessarily equate with age-related changes in overall reading skill. A distinction must be made between stable measures of skill (such as psychometric tests) and in-scanner performance measures (i.e., reaction time and accuracy) within a particular session. The burden on the field is to generate schemes to differentiate these effects. This burden is not unique to developmental studies; it is germane to contrasts across the lifespan (e.g., Grossman et al. 2002) and for comparing patient to control populations (Weinberger 1998, Price & Friston 1999, Johnson et al. 2002). Multiple strategies, each with different strengths and weaknesses, exist to differentiate activation patterns that may be associated with the separable influences of age, skill, and performance effects (Palmer et al. 2004, Casey et al. 2005).

In one approach to studying developmental changes in fMRI activity to visual words, Eden and coworkers (Turkeltaub et al. 2003) attempted to minimize age-associated performance confounds that typically accompany explicit word reading tasks. They employed a strategy of studying reading as an implicit process, contrasting activation to visual words versus novel letter-like characters that served as control stimuli. To avoid developmental confounds between reading skill and execution of the activation task, subjects of all ages completed the simple task of making a physical judgment about parts of letters that appeared with equal frequency in both stimulus types. Activity attributed to implicit word reading was measured by contrasting fMRI signals for words minus letter-like stimuli. The presumption with using an implicit stimulus contrast approach is that general developmental differences for task difficulty
(including differences in error number, reaction time) will not influence the contrast between the stimulus classes. Unfortunately, such approaches are not impervious to performance effects because this very paradigm has demonstrated longer reaction times for more word-like stimuli in adults (Price et al. 1996, Binder et al. 2006). An additional complication to this approach is that differences in the difficulty of primary tasks are known to modulate the degree of implicit processing of irrelevant stimuli (Lavie & Tsal 1994). Thus, developmental differences in the ability to deal with the demands of the primary task can indirectly influence implicit word processing.

An alternative approach to segregating these influences involves contrasting subsets of the subject population according to age and performance levels and performing multiple analyses. Such approaches, called “performance-matching,” allow differentiation of activation changes associated with maturation (i.e., age) from those associated with performance dynamics. Schlaggar and coworkers demonstrated the potential of this approach within a large cross-sectional event-related fMRI study (Schlaggar et al. 2002, Brown et al. 2005) designed to examine differences between adults and school-age children in lexical processing of visually presented words. In-scanner performance differences were observed across accuracy and reaction-time profiles for adults and children, but with significant overlap between the age groups. This overlap enabled the formation of two age-group analyses, one with a performance-matched subset and another with unmatched performance subgroups. Performance matching across groups that differ (e.g., by age, diagnosis, or treatment) can introduce confounds by applying opposing selection biases. To protect against such confounds, these investigators required that the observed age-group differences in regional activation must be present in both performance-matched and non-matched group comparisons for those differences to be considered driven by subject age rather than by in-scanner performance.

Implementation of this strategy resulted in the characterization of brain regions with activity profiles common across age, regardless of performance, as age/performance independent. Regions with group differences were classified as either age related (i.e., difference present in both performance-matched and non-matched comparisons) or performance related (i.e., difference present in only the non-matched comparison). Age-related regions where activity increased with age were found in left frontal and parietal cortex. Most age-related regions, however, showed decreased activity with increased age. These regions were distributed bilaterally and were concentrated in bilateral ventral occipitotemporal cortex. Performance-related regions were also found in bilateral extrastriate cortex including a region in the right ventral extrastriate cortex—a region previously demonstrated to have a reduced involvement in reading over the course of reading development (Turkeltaub et al. 2003) and skill acquisition (Shaywitz et al. 2002). Another performance-related region in the left parietal-occipital-temporal junction has also been consistently implicated in developmental dyslexia (e.g., Temple 2002).

This analysis strategy provides a way of disentangling changes that might be linked to task performance and changes that might reflect maturational differences in the way the brain increases activity in regions related to computations in reading-related tasks. As expected, a set of regions exhibited responses that were equivalent across all age and performance groups. In addition, regions in ventral occipitotemporal extrastriate cortex typically associated with visual orthographic processing exhibited dynamic patterns of change associated with age in some regions and performance differences in other regions (see Figure 1). This pattern of strong recruitment of extrastriate regions in young readers, which gradually diminishes with age, could reflect a form of protracted development in analysis of visual words, for which top-down influences are necessary for word reading.
Figure 1

Select left extrastriate regions from a large developmental fMRI study of word generation tasks (Schlaggar et al. 2002, Brown et al. 2005) showing regions where activity differs by age but not performance (red) and where activity is present independent of age or performance (green). Left hemisphere viewed from an oblique-lateral perspective is shown in (a). The same hemisphere is viewed from a ventral (b) and posterior (c) perspective. (d) Event-related fMRI time courses for different age groups in an age-related region with activity decreasing with age. Peak BOLD activity as a function of age is shown in scatterplots with fitted curves for both the region showing decreasing activity (e) and a region (circled on the posterior view) activated in the task that did not change with age (f).

The presence of regions of the brain that show functional activation differences between adults and children, even when performance dynamics are matched, can be considered a behavioral phenocopy; the notion that identical performance is observed across groups yet is supported by different underlying neural mechanisms. In principle, these age-related differences in underlying neural mechanisms would be invisible to behavioral assessment alone, demonstrating the added value of functional imaging to revealing typical and atypical development. Age-related regions may constitute developmentally transient functional scaffolding analogous to that described for the transition from novice to expert in adults after skill learning (Raichle et al. 1994). Understanding age-related differences is crucial for revealing the developmental processes engaged during learning/skill acquisition and the interplay of maturation with learning dynamics across reading development.

SPECIALIZATION OF THE VWFA IS IMPLICATED IN THE DEVELOPMENT OF PERCEPTUAL EXPERTISE IN READING

Functional specialization of the VWFA is thought to emerge during acquisition of reading expertise (McCandliss et al. 2003, Pugh
et al. 2001). The development of a specialized ability to process letters, letter strings, and visual words could begin as a general object-recognition problem, using a large number of visual processing mechanisms. Through experience and maturation of the underlying neural substrate, and through exposure to patterned orthographic information within a specific writing system, the processing system could more efficiently utilize and tune the most appropriate mechanisms that focus on the most informative aspects of the input, while decreasing use of the less appropriate mechanisms. In this way, visual processing mechanisms can build up a neural representation of information specific to the writing system that is most relevant to the task of reading. This specialization in visual processing can be reflected across development as a change in relative activation in extrastriate regions, which could play out as a reduction of activity in some regions, with retention of a similar level of activity, or even greater activity, in other regions. This idea is consistent with reports of changes in brain activity believed to occur in adults as they acquire perceptual expertise for novel items (e.g., Gauthier 2001).

Indeed, developmental fMRI studies (reviewed in detail below) have examined changes in neural responses in children studied across several ages during the acquisition of reading skill. Studying both reading-disabled (RD) and nonimpaired (NI) readers, Shaywitz and coworkers investigated the relationship of BOLD signals to reading skill and age. They describe increased activity in a left ventral occipitotemporal region (likely including the VWFA), which correlated more robustly with reading skill than with age (Sandak et al. 2004). In a two-year longitudinal component of RD children who had received intensive intervention leading to improved skill, the putative VWFA showed increased activity over the interval, which suggested the change in regional activity is related to change in skill level as well as impacted by educational activities (Shaywitz et al. 2004). Future research will be required to isolate whether the observed changes are systematically linked to improvements in general reading skill, improvements in in-scanner task performance, or maturational changes that might modulate how the task elicits activity in a given region.

Developmental functional imaging results from several groups are beginning to converge on a central conclusion regarding developmental changes in extrastriate regions involved in reading. During the ages when reading skill is acquired, a transition occurs from bilateral extrastriate region involvement for reading to a predominance of left (relative to right) ventral occipitotemporal cortex involvement. This finding was evident in several large cross-sectional developmental fMRI studies of reading-related tasks (Schlaggar et al. 2002, Shaywitz et al. 2002, Brown et al. 2005) described above. Additionally, as described previously, Eden and coworkers (Turkeltaub et al. 2003) reported a similar pattern in their large cross-sectional developmental fMRI study that related age and various measures of linguistic skill to activation elicited by an implicit reading task. They showed an age-related decline in right extrastriate activity, whereas homologous left cortical regions maintained their level of activity across age groups.

Another critical aspect of understanding the development of function in the VWFA involves distinguishing between activity reflecting early perceptual processes and later post-perceptual processes, as well as characterizing changes that occur as the perception of visual words emerges from a slow effortful process to the rapid automatic process that occurs in the mind of a skilled reader within the span of several hundred milliseconds. Because the fMRI signal is based on changes in deoxygenated hemoglobin that slowly accumulate in seconds after changes in neural activity, this measure has an inherent temporal sluggishness that limits one’s ability to differentiate activations associated with early perceptual processes versus later post-perceptual processes.
and limits one’s ability to trace changes in fluency during development.

Thus investigators must supplement fMRI investigations with event-related potential (ERP) measures that are more sensitive to the temporal dynamics of brain activity at the ms scale. ERP studies in adults have shown that within 200 ms of viewing a visual word, electrical activity recorded over left posterior inferior regions of skilled readers respond differently to visual words versus control stimuli (i.e., strings of novel letter-like characters). This sensitivity, present in the negative deflection over posterior-occipito-temporal channels at 170 ms (i.e. the N170 component), is thought to reflect fast perceptual specialization for processing visual word forms in adults (Rossion et al. 2003, Simon et al. 2004, Maurer et al. 2005a). Researchers have found similar N170 effects in several other forms of visual expertise that result from extensive training experiences with a particular class of stimuli (Tanaka & Curran 2001), although such effects tend to be bilateral. Thus the left lateralization of the N170 response to visual words has been proposed as a phenomena that differentiates visual word expertise from other forms of visual expertise effects (Maurer & McCandliss 2007).

The left-lateralized N170 ERP response has been linked to neural activity within the left ventral occipitotemporal region, which includes the VWFA. A recent joint fMRI/ERP study (Brem et al. 2006) showed systematic correlations between individual differences in the magnitude of the N170 for words and the magnitude of the BOLD response to words in the VWFA. Furthermore, source estimation for word effects localized maximal activity during the N170 to the left ventral temporal area (Maurer et al. 2005b). Thus, part of the observed fMRI BOLD response to visual words may reflect early perceptual analysis procedures characteristic of the expert reader.

Developmental reading studies have used ERP recordings to examine more directly the experience-dependent nature of the N170 response to visual word forms and the relationship between these signals and the rise of fast perceptual specializations for reading (Posner & McCandliss 1999; Maurer et al. 2005b, 2006). Brandeis and coworkers (Maurer et al. 2005b) used this method to contrast responses to words and visual control stimuli (e.g. novel characters that resembled letters) in children just before the onset of reading instruction in school. Before the onset of formal schooling in reading, children produced a delayed N170-like component (peaking at 220 ms) in response to both visual words and control visual stimuli. Unlike adults and older children, however, this ERP response in preschool children showed no sensitivity to visual words or letters. Mere familiarity with letters by many of the kindergarten children was insufficient to produce this N170-like response. In fact, the subset of children most familiar with letters produced some modulation of the N170, but with a right lateralized pattern. Presumably, experiences taking place between kindergarten and adulthood progressively lead to functional tuning of the N170, which becomes somewhat specific to the writing system in which an individual is trained.

These same children were followed longitudinally to examine the impact of ~1.5 years of formal schooling on the sensitivity of the N170 to visual word form processing (Maurer et al. 2006). Across these years, an N170-like response demonstrated strong amplitude differences between the same visual words and control stimuli they had seen 18 months previously, directly demonstrating the impact of development and experience on the response properties of the N170. As discussed above, this design does not directly differentiate maturation and learning-related effects, yet the contrast effect between visual words and control stimuli suggests that experiences with visual words drive changes in N170 responses that are not observed in the control stimuli. In addition, individual differences in reading skill (i.e., fluency) were systematically correlated with the degree to which N170 responses came to resemble the...
adult-like pattern. Another critical issue in considering the development of visual word recognition skills and the underlying changes in neural processing concerns developments that occur between adolescence and adulthood, as such systems continue to improve in fluency. When the same N170 paradigm described above was used to contrast adolescents (i.e., ~16 years of age) and adults, the adolescent N170 response showed adult-like topographies in general. However, the latency of the N170 was shorter for adults than for adolescents when visual words were presented, but not when the control stimuli were presented. These findings provide further support for a role for specific experience with visual words driving changes even late in development as fluency in word recognition is progressively refined (Brem et al. 2006). Furthermore, Brem and coworkers demonstrated correlations across individuals in this adolescent age group between word-related N170 responses and word-related fMRI responses in the VWFA, suggesting further links between late developments in this cortical region and functional changes in fast perceptual processes applied to visual words.

These findings converge to support the notion that the development of fluent word recognition is systematically related to functional refinements in early perceptual processes. These novel perceptual abilities, which are triggered during the first few hundred ms of processing a visual word, undergo considerable experience-dependent refinement manifest as more focal, left-lateralized patterns as reading experience develops. This process continues through adolescence and into early adulthood and is linked to the development of efficiency of visual word recognition.

**INTEGRATION OF ORTHOGRAPHIC AND PHONOLOGICAL PROCESSING IS IMPORTANT FOR READING DEVELOPMENT**

Reading ultimately requires expertise in linking phonological and orthographical aspects of language. The developmental changes described above in ventral occipitotemporal regions associated with visual word form processing may be accompanied over the course of reading development by changes in the dorsal phonological (i.e. perisylvian) regions consistently implicated as critical to accessing speech sounds associated with letters (Raij et al. 2000, Van Atteveldt et al. 2004). Pugh and coworkers (2001) have proposed a model of skilled reading acquisition that highlights the importance of phonological systems in the functional development of orthographic regions such as the left VWFA. In this scheme, the novice/child reader implements the dorsal phonological system to sound out novel or irregular words. With increasing reading experience, however, the dorsal system, via an interactive process, eventually serves to train the ventral visual word form system to recognize orthographic patterns related to high frequency and irregular words so that they can be processed rapidly.

Investigators have also described a similar developmental progression within connectionist models of reading development. This approach instantiates explicit computer models that “learn” to relate print to speech and meaning. Early in the learning process the predominance of changes within connection weights (analogous to the strength and reliability of neural connections) capitalize on statistical patterns that systematically relate orthography to phonology. Later in the learning process, however, when such regularities are well learned, the predominant changes in connection weights occur between orthography and semantic units (Seidenberg 2005). Such models are explanatory such that they explicitly relate the observed changes in learning dynamics to differences in the statistical consistencies between mapping print to speech versus mapping print to meaning.

Another approach to studying brain activity associated with the integration of orthographic and phonological processing involves contrasting explicit task demands across
visual and auditory words. In a study of skilled adult readers, Booth and coworkers (2002) presented auditory and visual words within a rhyming task to focus attention on phonology versus within a spelling task to focus on orthography. Consistent with previous findings, the auditory-rhyming task activated left superior temporal gyrus, and the visual-spelling task activated left fusiform. When conditions required integrating orthography and phonology, as in the visual-rhyming or the auditory-spelling condition, performance on both of these tasks was associated with activation levels in supramarginal/angular gyrus regions in a manner suggesting that these regions were associated with the integration of phonological and orthographic codes. When this work was extended to children (aged 9–12 years), Booth and coworkers (2004) found that children demonstrated many of the same effects, although tasks that required orthographic and phonological integration produced stronger activation in the angular gyrus in the adults than in the children. These results suggest that this form of integration continues to develop well after late childhood. Although this interpretation may appear to contradict the prediction of age/skill-related decreased activity in the dorsal system (i.e., Pugh et al. 2001), this work sets the stage for investigation of the relationship between changes in the phonological system, changes in the orthographic system, and integration across these two systems as it relates to development and skill acquisition for reading.

Additional empirical work within this domain needs to examine such hypotheses directly in terms of developmental changes in cortical activation associated with phonology, orthography, and the integration across these two forms of information. A developmental cognitive neuroscience account of how these systems change and come to interact over the course of typical development may prove crucial in constructing frameworks for understanding atypical development of reading abilities.

NEUROSCIENCE APPROACHES TO UNDERSTANDING INDIVIDUAL DIFFERENCES IN READING DEVELOPMENT

Recent work investigating brain mechanisms of reading difficulties may provide an explanatory framework for the wide range of individual differences evident in the reading acquisition process and the etiology of developmental reading disabilities estimated to impact ~5%–15% of the U.S. population (Rutter 1978, Stanovich 1986).

The prevailing theory of reading disability, the core phonological deficit hypothesis, holds that subtle language deficits introduce difficulties in accessing and manipulating sounds within speech at the phoneme (i.e., sound elements roughly corresponding to letters) level, which result in atypical processing of visual words forms. This view has substantial empirical support from cognitive studies, and the most commonly observed cognitive disruption associated with RD in the English language is the presence of phonological processing difficulties such as rhyming skills and other tasks that require accessing and manipulating sounds within words (Shankweiler et al. 1999, NRP 2000). (For alternate theories, see Ramus et al. 2003.) These phonological processing deficits may be sufficiently subtle to allow apparently typical development of aural/oral aspects of language, but may be substantial enough to prevent adequate mapping of orthography onto phonology, leading to reading disability.

Functional Imaging of Individual Differences in Reading

An extensive literature of adult functional neuroimaging studies examining the activation correlates of RD has emerged (Habib 2000, McCandliss & Noble 2003). Converging findings support two central insights into individual differences related to phonological processing of linguistic information and processing of visual word forms. First, studies

Phoneme: the smallest contrastive sound unit of spoken language
that target phonological processing skills demonstrate atypically small or absent modulation of functional activation in left perisylvian regions in RD adults (e.g., Temple 2002).

Second, in studies that isolate activity associated with visual words versus lower-level control conditions, RD adults produce less robust activation in left ventral occipitotemporal cortex (e.g., Brunswick 1999, Paulesu et al. 2001).

Progress has been made in extending functional neuroimaging studies of developmental dyslexia earlier into development, demonstrating some continuity of findings across adults, adolescents, and children. The largest cross-sectional developmental fMRI study of reading development reported to date examined 70 RD and 74 NI children ranging in age from 7 to 17 years (Shaywitz et al. 2002).

RD children showed reduced reading-related activity in left ventral occipitotemporal and left perisylvian regions including the mid-temporal and angular gyrus. This pattern of group effects was restricted primarily to these regions when the activation task involved actively reading words to make semantic decisions versus a control condition, yet similar regions were implicated in a pseudoword-rhyming task. Across all subjects and both reading tasks, correlation analyses that first regressed out age effects revealed a positive relationship between reading skill and activation in left ventral occipitotemporal regions. Furthermore, for the semantic task, negative correlations were evident between reading skill and activity in right ventral occipitotemporal regions, such that the poorest readers showed an increased tendency to recruit right hemisphere regions during this task.

The finding that skill level and brain activity correlate, even when age is regressed out, suggests that much of the observed individual differences in brain activity may be related to the emergence of reading skill across this population. Group differences between RD and NI children in these regions may be more influenced by the relationship between cognitive skills and activation patterns than by age-related effects.

Several other developmental fMRI studies on reading disability have been conducted. Although such studies generally rely on RD versus NI group comparisons using substantially smaller samples of children, they provide some support for the previously reported findings of NI > RD activation for left perisylvian (Temple 2001, Backes et al. 2002) and left ventral occipitotemporal regions (Temple et al. 2001, but see Backes et al. 2002). An additional study (n = 17 per group) failed to demonstrate group differences in any region except for left frontal regions, and such differences were specific to reading-related tasks (Georgiewa et al. 1999).

Parallel findings regarding group comparisons between RD and NI groups have been reported in MEG investigations, providing insights into the time course of these atypical activations. MEG is closely related to ERP methods and shares the same high temporal resolution, while providing some advantages for localizing neural activity. In NI adults, the contrast between visual words and low-level visual control stimuli produces activation localized to left ventral occipitotemporal regions within ~150–200 ms. RD adults, however, fail to show such differentiation within this timeframe (Helenius et al. 1999), suggesting that RD affects even the early perceptual analysis of visual words forms. Later in the timeline, ~200–400 ms after stimulus presentation, group differences emerge over left posterior superior temporal regions (Salmelin et al. 1996), demonstrating reduced signal strength in RD adults.

MEG studies in typically developing children demonstrate similar responses in left perisylvian regions when reading words (Simos et al. 2000a) or pseudowords (Simos et al. 2000b). However, children fail to demonstrate the left-lateralized ventral occipitotemporal response demonstrated by adults during the first several hundred ms of viewing a visual word or pseudoword, suggesting that the adult phenomenon emerges during development of reading skill acquisition. Contrasts between NI and RD children...
generally demonstrate patterns in left perisylvian regions similar to those seen in adults. However, RD children demonstrate strong right perisylvian activity that is not observed in NI children. In an additional experiment that involved listening to words, RD and NI children showed equivalent responses in left and right superior temporal gyrus regions, suggesting that the observed group differences are somewhat specific to reading but could be attributable to performance differences.

As reviewed above (see Challenges to Studying the Development of Reading-Related Tasks Using Functional Neuroimaging), investigations of brain activation patterns that differentiate typically developing readers from dyslexic children necessarily face a multitude of confounding factors related to the intrinsic relationship between task performance, reading skill, and brain activity. By definition, RD readers cannot be equated on reading skill with same-age, typically developing children. Furthermore, any reading-related task performed as an activation paradigm is likely to show some performance differences. One recent set of studies has attempted to address these issues in the investigation of RD by employing two groups of controls: one group that is matched on chronological age and a second control group comprised of younger, typically developing children. Furthermore, any reading-related task performed as an activation paradigm is likely to show some performance differences. One recent set of studies has attempted to address these issues in the investigation of RD by employing two groups of controls: one group that is matched on chronological age and a second control group comprised of younger, typically developing children. Furthermore, any reading-related task performed as an activation paradigm is likely to show some performance differences.

Individual Differences in White Matter Tract Properties

Properties of long axonal connections between regions may systematically account for individual differences in cognitive skill and the development of skills such as reading. Diffusion tensor imaging (DTI) employs 3D tensors to provide a measure of the degree to which diffusion is constrained by white matter tracts, resulting in anisotropic patterns of diffusion. High fractional anisotropy (FA) values correspond to voxels dominated by dense large, well-myelinated axon fibers oriented in a coherent direction, and variations in these properties lead to reductions in FA (Basser et al. 1994). Correlations between FA values in left temporal white matter tracts and reading ability quantified by standardized measures were first reported in adults ranging from skilled readers to poor readers with a history of developmental dyslexia (Klingberg et al. 2000). Three developmental studies have since examined relationships between FA values and standardized reading scores in children at ages.
when persistent reading disabilities are typically first diagnosed. Two of these studies included children predominantly in the average to above-average range (Beaulieu et al. 2005, Deutsch et al. 2005), and one study recruited children predominantly in the average to impaired range (Niogi & McCandliss 2006). All three studies converged on the central finding of a strong positive correlation between standardized reading scores and FA in a left hemisphere region centered on the superior corona radiata (SCR) at the level of the corpus callosum. These effects were robust, accounting for 29%–42% of variance in reading skills across studies. The same relationship that held between FA and reading ability demonstrated in the normal range was also present in the more extreme range of scores, both impaired and above average. This structural anatomical contribution to reading skill is more consistent with the view that reading disability is not a discrete syndrome but is on a continuum with typical reading.

The specificity of this structure-function relationship was also investigated, both in terms of the degree to which the implicated white matter tracts were region-specific versus systemic throughout the brain, as well as the degree to which the cognitive differences were specific to the reading domain. Each of the published studies demonstrated a similar region in the left hemisphere but showed weaker or nonsignificant relationships in the right homologue. When factors such as IQ were controlled for, the results remained significant. Finally, Niogi & McCandliss (2006) demonstrated a “statistical double dissociation” between the left SCR reading relationship and another structure-function relationship between short-term memory and a frontal white matter tract structure (see Figure 2). These findings strongly suggest that reading ability has a specific association

Figure 2

Variability in children’s white matter tract microstructure demonstrates a “statistical double dissociation” in the patterns of correlation with two cognitive domains. Red sections indicate regions of interest used for both data selection and seed volumes for fiber tracking for (a) left SCR (blue) and (b) bilateral ACR (green). Bivariate scatterplots demonstrate standardized scores on X-axes for reading (left) and short-term memory (right). Y-axes indicate fractional anisotropy (FA) values for SCR (blue) and bilateral ACR (green). Trend lines indicating significant correlations are presented as solid lines.
with SCR structure that is independent of at least one other high-level linguistic cognitive ability and is not found in other white matter regions.

Although the same general region is implicated across multiple studies, researchers have reported some discrepancies regarding the nature of the associated fiber tract. Two studies that performed fiber-tracking analyses (Beaulieu et al. 2005, Niogi & McCandliss 2006) converged on the conclusion that the dominant tract represents a superior-inferior tract connecting the left internal capsule with left motor and premotor regions. This conclusion contrasts earlier speculations that this region implicates the superior longitudinal fasciculus (Klingberg et al. 2000). Such findings present the new challenge of understanding the way in which this left-lateralized white matter tract is systematically related to reading ability. One possible mechanism is that subtle motor disruption early in life could alter the development of language and reading skills emerging later in life, as suggested by recent findings in children genetically at risk for reading disability (Viholainen et al. 2006).

Genetic and Cultural Contributions to Individual Differences in Reading Development

Genetic susceptibility provides another source of individual variation in properties of the neural systems for reading and has a profound impact on the emergence of reading ability. Evidence for a genetic role in developmental dyslexia has been available for more than 50 years (Halgren 1950). The identification of multiple dyslexia susceptibility loci strongly supports the heritable basis of dyslexia with estimates of heritability ranging from ~45% to 70%. Recent progress has identified multiple susceptibility loci with additional ones quite likely to follow (McGrath et al. 2006).

Across studies, the dyslexia susceptibility locus most reliably identified at present appears to be DYX2 on 6p22, which is associated with reading-related skill variance independent from general intelligence (Schumacher et al. 2006). Multiple genes likely conspire to modulate susceptibility to dyslexia, and multiple candidate genes are under investigation. Two candidate genes found at 6p22 are linked to susceptibility to dyslexia. The pattern of expression of both genes in the mature system is not restricted to reading-related brain regions. Recent work suggests that disruption of normal function of either gene during cortical development interferes with migration of cortical neurons (Meng et al. 2005, McGrath et al. 2006).

Although all the susceptibility loci identified to date likely contribute to the dyslexic phenotype, the identification of functional candidate genes, whose products can potentially be linked to specific influences on the wiring of the brain, leads to a consideration of how directly these genes may be linked to reading development. Evidence supports the contention that the component processes of reading (e.g., orthographic skill, phonological skill, phonemic awareness, word recognition) are heritable (Gayan & Olson 2001, Grigorenko 2001). For example, Knopik et al. (2002), using a twin study approach, employed linkage analysis at the dyslexia susceptibility locus on 6p to quantify the heritability of the above component processes. They found clear evidence for the role of a locus on 6p that influences orthographic and phonological skills, as well as phonemic awareness. In addition, the influence on phonemic awareness appeared stronger for individuals with higher IQs. These results suggest that a single susceptibility locus is unlikely to independently influence a single component process of reading.

Examining the development of differential phenotypic expression in genetically at-risk groups provides further support for the prevailing view that the influence of genetics on reading ability is mediated via subtle deficits in language development. Scarborough (1990) examined the early development of children at familial risk for dyslexia who did
or did not go on to demonstrate school-age reading difficulties and found that affected children demonstrated differences in speech accuracy as early as 2.5 years of age and showed deficits in phonemic awareness and letter sound knowledge by age 5.

The Jyvaskyla Longitudinal Study (Lyytinen et al. 2004) has been following genetically at-risk children from birth to school age to track the development of the phenotypic expression of heritable reading disability. Currently available data suggest that although many early developmental language assays correlate with early reading development, deficiencies in receptive language ability at age 3.5 years are strongly associated with early reading difficulties at age 7 years for the at-risk group, yet are uncorrelated in the control group. Such studies may provide early phenotypic markers for the expression of genetic risk for reading disability.

The Jyvaskyla study also investigated ERP responses for at-risk and control infants. Presentation of repeated simple speech sounds with an occasional deviant stimulus that shortened the vowel duration resulted in ERP responses to the mismatched stimuli that differentiated the two groups. Control infants demonstrated responses predominantly over the left hemisphere, and at-risk infants over the right hemisphere, suggesting early hemispheric differences in auditory speech processing. Furthermore, right hemisphere ERP responses to a more complex speech sound pattern (i.e., /ga/) correlated with deficits of receptive language skills at 2.5 years of age for both groups of infants (Guttorm et al. 2005), yet in a larger sample, these responses were more pronounced in the at-risk group (Guttorm et al. 2003). As this at-risk sample is now old enough to start formal instruction in reading, their success in reading development can be retrospectively linked to their ERP responses collected near birth, providing a new opportunity to investigate whether infant ERP signals contain predictive information regarding the expression of reading difficulties in at-risk populations.

Although researchers are directing much attention toward identifying genetic risks for reading disability, an often overlooked aspect of reading development that must be considered when constructing theories relating brain activity to reading function is the fact that writing systems and languages differ from one culture to the next. Accordingly, the degree to which one might generalize findings across cultures remains a crucial empirical issue. Investigators recently identified a cultural effect in a functional neuroimaging study of reading pseudowords, which demonstrated differential activation across a network of reading-related regions dependent on whether the subject’s native language for reading was Italian (a shallow orthography with predictable spelling-to-sound patterns) or English (a deep orthography containing less consistent mappings between letters and sound) (Paulesu et al. 2001). Extending the concept of cultural differences in writing systems to nonalphabetic writing systems, the meta-analysis of reading-related studies performed by Bolger and colleagues (2005) showed that one of the most consistent regions of activation across writing systems is in the left VWFA, and the greatest variability among activations is in the left phonological system. Considering that these results reflect language-dependent phonological demands, these findings fit with a substantial literature implicating phonological ability in reading skill acquisition and as a remediation target (NRP 2000).

However, Tan et al. (2005) note that this emphasis on phonology is based largely on Western/alphabetic languages, which engage letter-sound processing. In contrast, logographic characters in Chinese are associated with elementary aspects of word meaning and place little emphasis on phonology. They investigated the relative contributions of phonological and orthographic abilities to Chinese reading development. In contrast to English, they found a stronger relationship between a child’s reading and character writing abilities and a weaker relationship between
their phonological skills and reading abilities. Such results emphasize the importance of orthographic awareness over phonological awareness as a critical individual difference impacting the development of reading in Chinese. A recent fMRI study of Chinese reading development contrasting activity between RD and NI in children (Siok et al. 2004) demonstrated that reading disabilities were associated not with decreased activity in left posterior dorsal or ventral regions as typically seen in alphabetic writing systems, but rather with decreased activity in a left middle frontal region, which the authors attributed to the demands of coordinating spatial and verbal information with logographic characters. These studies provide insights into the interaction of cultural-specific features of writing systems on the neural systems involved. Furthermore, they highlight the notion that as different writing systems place different computational demands on reading development, different brain systems will likely be engaged.

**RESEARCH ON INTERVENTIONS FOR READING DISABILITY IN CHILDREN**

Numerous reading intervention studies have been reported in the educational and cognitive science literature. These studies range from contrasts between entire programs based on different theoretical approaches to attempts at isolating particular critical elements of effectiveness (Bus et al. 1999). Recently, several studies have examined the impact of reading intervention programs on RD children and the changes in brain activity before and after intervention, typically spanning several months. These studies include an fMRI investigation of a computer-based auditory-linguistic intervention program (Fast ForWord Language) spanning 2 months (Temple et al. 2003), an ERP study of a 7-week nonlinguistic auditory training program (Kujala et al. 2001), an fMRI study of a classroom-based intervention spanning 14 days (Aylward et al. 2003) or spanning the school year (Shaywitz et al. 2004), and a MEG study spanning 2 months of intensive phonological skill intervention (Simos et al. 2002). Such studies combine the pragmatic challenges and attrition rates of two difficult research enterprises: child neuroimaging and educational intervention. Thus, these initial studies have been marked by small sample sizes, inconsistent outcome measures, and lack of randomized assignment or skill-matched controls. Nonetheless, most of the reported studies demonstrate an important first-order principle: Current imaging protocols for children are sensitive to changes that occur on the order of weeks to months. Consequently, this initial wave of studies provides a form of proof-of-concept, validating the potential use of neuroimaging to study the neural basis of educationally based changes (McCandliss & Wolmetz 2004).

Critical assessment of these initial studies also raises several concerns regarding interpretation of observed dynamic changes in brain activity and its association with a particular learning activity. First, many of the activation tasks used to elicit neural responses are fundamentally related to reading ability. The associated dynamic changes in brain activity may be highly sensitive to changes in both task performance and reading skill, making the result difficult to interpret. For example, Simos et al. (2002) demonstrated that for a particular task, training significantly improved the performance of RD children from their initial pretest level of chance. This scenario is relevant to the performance-matching issue discussed above, highlighting difficulties for making inferences about the functional significance of the observed changes in neural responses and the added value neuroimaging might provide beyond the observation of skill and performance gains following intervention.

Second, direct comparison of changes in brain activity before and after intervention can result in widespread patterns of activity differences throughout multiple brain regions. For example, Temple et al. (2003) reported
significant changes in 17 regions, some of which incorporated more than 8500 voxels. Interpretation of the relevance of observing change within a single region of interest must therefore be made in the context of large-scale changes in activity.

Future intervention studies will need to introduce additional procedures for establishing the connection between changes in activation patterns and changes in skill and performance dynamics to allow inferences about processing to be made. They will also need to contrast alternate intervention protocols to provide the basis for examining the connection between an intervention procedure and changes in cognitive skills, and the neurological changes that support these skills. Contrasts between interventions not only provide a control for general effects of participating in an intervention, but also provide a means for designing contrasting interventions to contribute to specific hypothesis testing and theory building. Such contrasts may take the form of modified versions of interventions in which the theory-driven active ingredient is withheld (e.g., Friel-Patti et al. 2001) or may contrast the impact of two interventions using different theoretical perspectives (e.g., Pokorni et al. 2004).

CONCLUDING REMARKS: INTERACTIVE SPECIALIZATION AS A CONCEPTUAL FRAMEWORK FOR READING DEVELOPMENT

A conceptual framework for human brain development termed interactive specialization (IS) is useful for thinking about how cortical circuits associated with visual and linguistic processes change and form specific links in the child's brain during the course of learning to read. This emergentist approach to the development of functional specialization may help explain the development of the rich functional specialization observed in adults given the relatively limited information present in genetic information for coding-specific brain pathways (Johnson 2001, Johnson et al. 2002). IS posits that the emergence of functional development (i.e., the relationship between the neuroanatomical and perceptual/cognitive development) of the brain is driven largely by “changes in the interactions between several brain regions that were already partially active.” (Johnson 2001, p. 479). The adjustments of interactivity within and between regions provide the basis for a form of systems-level plasticity allowing novel computations that support emerging behavioral abilities.

Applied to reading, IS provides a framework for considering how a relatively new cultural invention of reading can lead to shaping a novel pattern of integration across extant perceptual/cognitive mechanisms to result in a new behavioral ability. When a child comes to the task of reading he/she already has well-established visual processes and linguistic processes, yet these systems are not integrated in a way that supports reading; that is, there are no specific mappings from particular visual inputs to particular elementary speech sounds. The demands of learning to read, played out by an interactive process, place stress on extant circuits for visual object processing and phonology, leading them to change in interesting ways. Novel functional connections also form between extant circuits to form a new functional circuit, as seen in the case of the multisensory integration studies of letters and letter-sounds (Van Atteveldt et al. 2004). Furthermore, the observation of progressive lateralization and focalization of visual regions may also reflect a process of interactive specialization. The development of a specialized ability to process orthography could begin as a general object recognition problem, utilizing a large array of processing mechanisms, and integration with left-lateralized phonological systems could increase processing demands on specific forms of visual information, leading to both the left lateralization of the VWFA as well as an increased sensitivity to commonly recurring letter patterns in this system noted above. Thus,
through reading experience and maturation of the underlying neural substrate, the processing system could more efficiently utilize and tune the most appropriate mechanisms (i.e., VWFA), eventually decreasing the demands on regions that were initially critical (i.e., the dorsal phonological system). The wide range of evidence for functional changes in cortical regions that occur across the years of reading development reviewed above is generally consistent with this account of changes that occur in functional circuitry over the course of development.

Another aspect of IS provides a plausible framework for considering how the child’s brain can take advantage of “primitive biases” or mechanisms for perception to attend to salient environmental stimuli and, in the context of experience, to sculpt interregional relationships. A relevant example of a primitive bias is the left hemispheric lateralization of preverbal infant speech perception (Dehaene-Lambertz et al. 2002). If reading builds on extant language structures, the tendency for language processing to be left lateralized could represent an important primitive bias for left hemisphere reading mechanisms to emerge and could explain why a left-lateralized subcortical white matter measure of structure (such as DTI) is linked to individual differences in reading ability. The presence of evidence of hemispheric biases in typically developing infants, however, does not necessarily imply the presence of specified circuitry for carrying out language function in early infancy. For example, infants with perinatal brain injury demonstrate that other brain regions have the capacity to implement the necessary operations for language and eventually implement novel pathways for reading (Cohen et al. 2004, Fair et al. 2007).

One limitation of the IS framework is that it fails to provide explicit, quantifiable predictions regarding behavior or changes in function associated with particular neural systems. This framework, however, is highly consistent with connectionist modeling efforts, which do provide explicit, quantifiable computer learning models of systems-level changes in functional processes associated with reading development. Such models have been used to study how learning to read changes representations within neural systems dedicated to representing phonology, orthography, and the mappings between them. For example, Harm & Seidenberg (1999) presented a model of reading development that allowed learning interactions to take place between neuronal populations associated with visual print representations and regions associated with phonological representations. Probing the model at different points in the learning process allowed these researchers to examine the rise of functional specializations within these systems, as well the development of association patterns between the spelling and sound systems. This model also provided an explicit computational account of an interactive specialization process in which learning to read improved the precision of phonological representations.

The IS framework, combined with connectionist models of reading development, may prove to be relevant to understanding the development of the neural basis of reading disability. Perhaps one of the fundamental challenges to understanding this disability involves creating an integrated neuroscientific account of how specific individual differences in properties of the nervous system observed at the molecular or anatomical level (e.g., differences in specific genetic loadings or differences in white matter microstructure) give rise to the wide range of individual differences observed at the cognitive level, from skilled reading to reading disability. Harm and coworkers (Harm et al. 2003, Harm & Seidenberg 1999) provided a quantitative connectionist model that allowed them to investigate how parametric manipulations of the neural properties of the phonological system could lead to differences in the emergence of reading performance, which could be quantified in terms of standardized reading tests used to assess reading development in children. As they parametrically increased the level of neural deficits in
the phonological system prior to learning to read, the model began to exhibit several symptoms of developmental dyslexia, as assessed by quantitative measures. Their analysis of the model over the course of reading development demonstrated how differences in phonological properties of the model led to systematic changes in the association pathways between orthography and phonology. Such models are beginning to provide quantifiable predictions regarding pathways by which individual differences at the level of neural circuitry can impact the emergence of reading ability (or disability). Another promising aspect of this approach is that connectionist models provide a means of testing the impact of particular reading intervention strategies for reading disability, promising novel insights into the mechanisms of change associated with effective intervention (Harm et al. 2003).

An important future direction for this research will involve building more explicit links between quantifiable aspects of these models and empirical observations from developmental neuroimaging studies, such as developmental changes and individual differences in specific white matter tracts potentially related to functional connectivity (i.e., inter-regional correlated activity measured at rest) between cortical regions, as well as patterns of cortical activity related to cognitive processing within particular regions. Such developments may eventually help create an integrative theory of reading development and disability capable of relating observations at these different neural and cognitive levels, helping to inform remediation efforts.

These are early days in the study of the development of neural systems for reading. Nonetheless, investigators have successfully employed several cutting-edge imaging tools to provide initial insights into the nature of changes that occur in typically developing readers as well as the nature of individual differences that help account for reading disabilities. We argue that a deep understanding of how the developing child acquires reading skill requires a convergence of psychological and neuroscientific approaches. Attaining this level of understanding poses challenging issues regarding the development of functional specialization, as well as challenging interpretational issues regarding how to relate changes in regional brain activity to changes in reading ability. Separating contributions of maturation, overall skill, and in-scanner performance on an activation task presents significant challenges to the field, although substantial progress has been made in approaching these challenges. Furthermore, combining observations across the relative strengths of imaging methods such as fMRI, MEG, DTI, and ERP provides the basis for more complete theories of online processing dynamics, developmental change, and individual differences. Eventually, the field must develop explicit theories to explain how experience in reading leads to changes in functional organization. Such theories must span multiple levels of observation, including genetic, anatomical, physiological, and psychological, to explain how individual variation at any level can lead to differences in the emergence of reading ability. Conceptual frameworks such as IS and computational accounts such as connectionist models of reading provide some progress toward these goals, but additional developments that constrain such frameworks/models with neurobiological observations are needed.

FUTURE ISSUES

1. Future studies of visual word form processes will elucidate both the development of perceptual expertise for letter identities and statistical patterns by which letters are associated with pronunciations and grouped together into visual words.
2. Cognitive and neural function models need to account for multiple dimensions of individual differences (e.g., genetic, sociocultural, cognitive) and their interactions in the development of reading to drive more specific connections between theory and intervention practice.

3. As training and intervention studies emerge beyond the proof-of-concept phase, such studies will provide constraints on theories by directly testing intervention principles in randomized controlled trials that isolate particular variables of interest.

4. Critical data are needed from pre-literate children to separate the influence of individual differences on reading from the influence of reading development on individual differences. This may require methodological advances in functional neuroimaging approaches to infant and preschool populations.

5. Psychological models and hypotheses concerning the mental computations in reading need to make more direct contact with investigations of functional significance of activation in particular brain regions. Specifically, connectionist models of brain activity may be well poised to provide insight into the dynamic relationship between brain development and skill learning.

6. Functional connectivity MRI (based on very low frequency interregional correlated activity at rest) may help reveal the development of reading circuits without confounds of task-related performance differences.

ACKNOWLEDGMENTS

The authors thank Steve Petersen, Jason Zevin, Urs Maurer, Fumiko Hoeft, Vera Blau, Alecia Vogel, Rebecca Coalson, Jessica Church, and Cathy Yun for helpful discussions and comments on the manuscript. Both authors are recipients of the John Merck Scholars Fund Award. Support for this work was also provided by NSF-REC-0337715 (B.D.M.), R01 DC007694 (B.D.M.), NIH NSADA (B.L.S.), R21 NS41255 (B.L.S.), and the Burroughs Wellcome Fund (B.L.S).

LITERATURE CITED


Dejerine J. 1891. Sur un cas de cécité verbale avec agraphie, suivi d’autopsie. *C. R. Soc. Biol.* 4:61–90


Natl. Read. Panel. 2000. *Teaching Children to Read: An Evidence-Based Assessment of the Scientific Research Literature on Reading and its Implications for Reading Instruction*. Washington, DC: NICHD

Niogi SN, McCandliss BD. 2006. Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. *Neuropsychologia* 44:2178–88


Contents

Information Processing in the Primate Retina: Circuitry and Coding
G.D. Field and E.J. Chichilnisky ................................................................. 1

Orbitofrontal Cortex and Its Contribution to Decision-Making
Jonathan D. Wallis .................................................................................. 31

Fundamental Components of Attention
Eric I. Knudsen ....................................................................................... 57

Anatomical and Physiological Plasticity of Dendritic Spines
Veronica A. Alvarez and Bernardo L. Sabatini ........................................ 79

Visual Perception and Memory: A New View of Medial Temporal
Lobe Function in Primates and Rodents
Elisabeth A. Murray, Timothy J. Busey, and Lisa M. Saksida ..................... 99

The Medial Temporal Lobe and Recognition Memory
H. Eichenbaum, A.P. Yonelinas, and C. Ranganath ................................. 123

Why Is Wallerian Degeneration in the CNS So Slow?
Mauricio E. Vargas and Ben A. Barres .................................................. 153

The Head Direction Signal: Origins and Sensory-Motor Integration
Jeffrey S. Taube ....................................................................................... 181

Peripheral Regeneration
Zu-Lin Chen, Wei-Ming Yu, and Sidney Strickland ................................. 209

Neuron-Glial Interactions in Blood-Brain Barrier Formation
Swati Banerjee and Manzoor A. Bhat ................................................... 235

Multiple Dopamine Functions at Different Time Courses
Wolfram Schultz ....................................................................................... 259

Ventral Tegmental Area Neurons in Learned Appetitive Behavior and
Positive Reinforcement
Howard L. Fields, Gregory O. Hjelmstad, Elyssa B. Margolis,
and Saleem M. Nicola ............................................................................. 289
Copper and Iron Disorders of the Brain
Erik Madsen and Jonathan D. Gitlin ..............................................317

The Micromachinery of Mechanotransduction in Hair Cells
Melissa A. Vollrath, Kelvin Y. Kwan, and David P. Corey ..................339

Neurobiology of Feeding and Energy Expenditure
Qian Gao and Tamas L. Horvath ..................................................367

Mechanisms that Regulate Establishment, Maintenance, and Remodeling of Dendritic Fields
Jay Z. Parrish, Kazuo Emoto, Michael D. Kim, and Yuh Nung Jan ........399

Dynamic Aspects of CNS Synapse Formation
A. Kimberley McAllister ...........................................................425

Adhesion Molecules in the Nervous System: Structural Insights into Function and Diversity
Lawrence Shapiro, James Love, and David R. Colman .....................451

Development of Neural Systems for Reading
Bradley L. Schlaggar and Bruce D. McCandliss .............................475

Molecular Architecture of Smell and Taste in Drosophila
Leslie B. Vosshall and Reinhard F. Stocker ..................................505

The Neural Basis of Decision Making
Joshua I. Gold and Michael N. Shadlen ........................................535

Trinucleotide Repeat Disorders
Harry T. Orr and Huda Y. Zoghbi .............................................575

Indexes
Cumulative Index of Contributing Authors, Volumes 21–30 ..................623
Cumulative Index of Chapter Titles, Volumes 21–30 ........................627

Errata
An online log of corrections to Annual Review of Neuroscience chapters (if any, 1997 to the present) may be found at http://neuro.annualreviews.org/