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Neural Systems Affected in Developmental Dyslexia Revealed by Functional Neuroimaging

Minireview

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Reading is a uniquely human endeavor whose importance to society in this century has been heightened by steadily increasing demands for a more literate workforce. Consequently, there is great interest in uncovering the reasons that reading may fail to develop normally. During early schooling, individuals may exhibit difficulty in acquiring adequate reading skills, reading more slowly or less accurately than expected. Called developmental dyslexia, this disorder was first described over 100 years ago. It is formally defined as an unexpected reading failure that cannot be explained by low intelligence quotient (IQ) or environmental circumstances, such as teaching methods or social environment. In this decade, estimates of the incidence of reading disability vary between 5% and 15%, and its familial aggregation suggests a genetic basis.

Claims concerning the mechanisms responsible for dyslexia have been as numerous and varied as proposals for its remediation. One possibility is that the failure to fully understand the pathophysiology of dyslexia may have resulted from the complexity of its behavioral manifestations. While traditionally thought of as primarily a reading disorder, dyslexia's clinical signs are varied and may include abnormal phonological awareness (Bradley and Bryant, 1983); writing, spelling, and motor timing (Wolff et al., 1984); verbal working memory (Hulme and Roodenrys, 1995); visual processing (see Eden et al., 1996); and auditory discrimination (Tallal et al., 1993). In the face of this behavioral complexity, suggestions that the pathophysiology of this disorder may be explained with reference to dysfunction of a single sensory or cognitive process have not been widely persuasive. For example, phonological skills, requiring isolation and manipulation of the constituent word sounds, are good predictors of reading ability. Therefore, many dyslexia studies have employed phonological processing tasks and have clearly demonstrated that poor phonological skills are a hallmark of developmental dyslexia. While these failures in phonological processing are commonly invoked as causal factors in developmental reading failure, they cannot easily account for the sensory deficits in visual and auditory processing observed in other studies. Similarly, these deficits in low level auditory and visual processing do not obviously explain the equally well-documented abnormalities in verbal working memory and phonological awareness. Thus, it is possible that the language deficits in dyslexia are not causally related to low level sensory abnormalities but rather that these perceptual and cognitive abnormalities arise from dysfunction of a neural system common to both. Demonstration that disparate behavioral deficits arise from dysfunction of spatially colocalized cortical regions would be evidence favoring a common pathophysiological mechanism.

Functional neuroimaging is providing new information concerning the neuroanatomical localization of the systems affected in developmental dyslexia. Recent studies employing positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to study sensory and language processing in dyslexia have demonstrated involvement of regions including posterior temporal and inferior parietal cortical systems. Although many sensory and cognitive processes are known to be abnormal in dyslexia, this necessarily selective review will emphasize those that have been examined with functional neuroimaging.

Behavioral Evidence: Phonological Processing Deficits in Dyslexia

It has long been known that the ability to isolate and manipulate the constituent sounds of words, known as phonemic awareness, is related to reading ability. Individuals with developmental dyslexia exhibit deficits in numerous measures of phonological awareness. For example, rhyme judgement (such as, "Hat, cat, dog, mat—which is the odd one out?") can measure phonological awareness and predict reading outcome (Bradley and Bryant, 1983). Another useful task is phoneme elision,

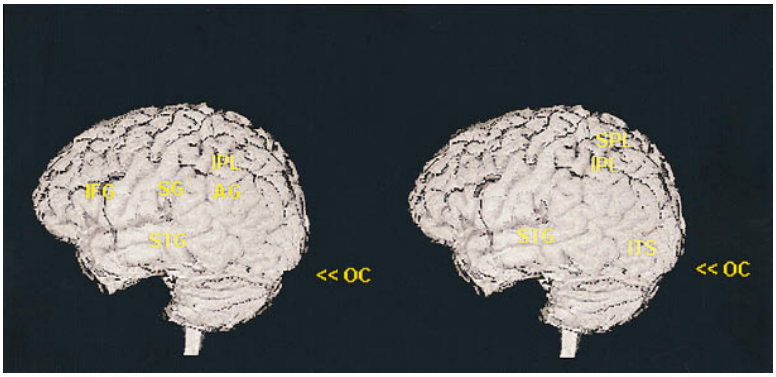

Figure 1. Cortical Location of Areas Involved in Rhyme Judgement and Visual Motion Processing

Diagrammatic representation of the cortical location of areas involved in rhyme judgement (left) and visual motion processing (right). Abbreviations, AG, angular gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITS, inferior temporal sulcus (area of MT/V5); SG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; OC, occipital cortex. These areas are present in both the left and right hemispheres. The reading pathway is more lateralized to the left hemisphere.

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involving repetition of a heard word while omitting the first or last sound of that word. For example, "cat" without the first sound becomes "at." When employed during kindergarten, these tasks predict later reading and spelling skill at the primary school level. At most developmental stages, phonological awareness is correlated with reading, the strength of that correlation varying with the test employed. Another widely used test is Rapid Automatized Naming (RAN), in which individuals are asked to quickly name letters, numbers, colors, or line drawings from a chart. Poor naming speed is a reliable indicator of dyslexia (for references, see Bowers and Wolf, 1993). Other useful tests involve memory systems. A significant portion of reading-disabled children show deficits in verbal working memory on tasks requiring the recall of random digits, words, or letters (Hulme and Roodenrys, 1995). Although measures of elision, rapid naming, and working memory all make contributions to predicting reading outcome, these are all considered relatively independent measures of phonological awareness. Failure of any of these skills in an individual with reading difficulties is evidence of abnormal phonological processing.

Functional Neuroimaging Evidence: Phonological Processing

Both PET and fMRI studies have provided new information about the cortical areas involved in reading, object naming, and verbal working memory. Consensus concerning the localization of the phonological mechanisms responsible for the "sounding out" or decoding of words is now emerging from a controversial and seemingly inconsistent body of literature (Poeppel, 1996). Two conclusions may be drawn from these studies. First, subtle differences in task and control conditions can be associated with significant differences in the localization of task-related activity. Second, minor technical differences in spatial normalization and signal processing procedures between studies can result in apparently conflicting results. When these differences in task design and data analysis are considered, it is seen that the phonological processing system spans multiple cortical and subcortical regions, including frontal, temporal, and parietal cortex. Changes in this normal pattern of task-related activity in studies of reading-disabled adults have provided evidence bearing on existing theories of the pathophysiology of developmental dyslexia.

Current theories have variously localized the site of dysfunction to (1) the temporoparietal junction (2) the insula, and (3) the inferior frontal gyrus (see Figure 1). We argue that theories suggesting temporoparietal localization have received the strongest support (see supplemental table at http://www.neuron.org/supplemetal/21/2/279). Evidence in support of this view includes the demonstration of physiological differences between groups of adult male dyslexics and controls during performance of rhyme detection/judgement and nonword reading tasks (for references, see Rumsey et al., 1997). In these studies, the dyslexic group showed significantly less task-related signal increase in temporoparietal areas bilaterally, consistent with a role for the angular gyrus (and nearby temporal and parietal areas) in reading (Dejerine, 1892). Also consistent with this view is the recent demonstration that activity in temporal and parietal reading areas is correlated when normal readers are engaged in a pseudoword reading task and uncorrelated when dyslexics perform the same task (Horwitz et al., 1998). The second theory (insular localization) was suggested following the observation that dyslexics exhibited (1) task-related activity in frontal cortex (Broca's area) during rhyme judgement, and (2) activity in the posterior superior temporal gyrus (Wernicke's area) during a working memory task. In contrast, the controls activated both of these areas and the insula during both tasks. This absence of activation in the insula, linking the two other sites, led the authors to suggest that dyslexia is a "disconnection syndrome" (Paulesu et al., 1996). An alternative, and simpler, interpretation of the same findings is that the dyslexic group exhibited deficient activation in posterior temporal and inferior parietal cortex during rhyme judgement and short-term memory, respectively, consistent with temporoparietal localization of the disordered phonological process. The third theory (inferior frontal gyrus localization) predicts findings in frontal cortex, consistent with the motor–articulatory feedback hypothesis theory of dyslexia (Heilman et al., 1996). This theory proposes that phonetic gestures are represented as motor commands and that these codes of articulatory gestures provide the basis for phonemic categories during speech production and perception. These processes are thought to occur in the left inferior frontal gyrus. While it has recently been demonstrated that dyslexics show phonological task-related relative hyperactivity in this part of frontal cortex (Shaywitz et al., 1998), the same study documents deficient task-related activity in the posterior superior temporal gyrus, angular gyrus, and extrastriate cortex. The enhanced activity in the inferior frontal gyrus may represent a compensatory response to failure of phonological processing mechanisms in more posterior cortical areas.

Thus, it is intriguing that many of the studies employing phonological tasks in dyslexics reveal deficient task-related activation in areas surrounding the temporoparietal junction. This is not the case with regards to the insula and the inferior frontal gyrus, raising doubts that dyslexia is best viewed as a disconnection syndrome or a failure in the motor–articulatory feedback loop. Differences among the conclusions of these imaging studies employing phonological processing may therefore reflect differences in interpretation of a somewhat consistent set of experimental results.

Behavioral Evidence: Visual Processing Deficits in Dyslexia

The term "word blindness," once used to describe dyslexia, does not reflect current concepts of the visual system abnormalities in developmental dyslexia. The history of research into dyslexic visual skills is distinctly unlike the experience obtained from phonemic awareness studies. The visual deficit hypothesis of dyslexia, which focuses primarily on the magnocellular system (sometimes called the transient system), derives from human visual psychophysical experiments and detailed knowledge of the functional specialization of the primate visual system. The original work was a series of psychophysical visual experiments spanning 2 decades, forming the framework for what is now considered the magnocellular deficit hypothesis in dyslexia (reviewed by

Lovegrove, 1993). Using a technique in which subjects judge the orientation of a grating (horizontal black and white bars) on a computer screen, the investigators systematically varied parameters of interest, including spatial frequency, luminance contrast, and flicker rate. The subject's responses were recorded to assess contrast sensitivity or visual persistence across different parameter ranges. The results indicated that differences in response functions observed in dyslexics were attributable to stimulus conditions that are preferentially processed by the magnocellular system. For example, the contrast sensitivity of normal and reading-disabled children was different, and the largest effects were observed at low contrast (smaller difference in the grayness of the bars). These findings were explained in the framework of sustained and transient channels of the visual pathways (or parvocellular and magnocellular system, respectively). These channels can be distinguished by their preference for certain spatial frequencies, temporal properties, and contrast sensitivities. The transient or magnocellular system is associated with high temporal resolution and sensitivity to low contrast and low spatial resolution when compared to the sustained or parvocellular system. Since both contrast sensitivity and visual persistence were lower in reading-disabled children, it was concluded that these children have disturbances in the transient or magnocellular pathways. This theory is consistent with studies using electrophysiological and anatomical experimental measures (Livingstone et al., 1991). Based on these and other behavioral observations, this system has been proposed as the site of dysfunction in dyslexia (Stein and Walsh, 1997).

Studies of human visual processing, such as those described above, have enjoyed the benefit of a detailed understanding of brain anatomy and physiology gained from visual system experiments with nonhuman primates. Functional neuroimaging experiments utilizing PET and fMRI have identified analogous regional functional specialization in the human visual system. Important in the present context is the demonstration of a specific motion-sensitive area, the MT/V5 complex, located at the temporal–occipital–parietal junction (close to or on the ascending limb of the inferior temporal sulcus). This area is thought to be dominated by input from the magnocellular stream (Watson et al., 1993). The anatomical locations of areas involved in visual motion processing are summarized in Figure 1.

Because patients with vascular lesions to the MT/V5 complex can exhibit severely degraded motion perception (Zihl, 1983), dysfunction of the magnocellular pathways would be expected to cause measurable deficits in visual motion detection. As motion perception impairment is not a prominent clinical finding in developmental dyslexia, this fact would seem to present problems for any magnocellular pathophysiological account. If, on the other hand, the dysfunction of the magnocellular system results from a partially compensated developmental lesion, one might expect a subtle, but detectable, deficit in motion perception in compensated dyslexics. This is, in fact, what has been demonstrated in several studies of visual motion detection (for references, see Eden et al. 1996; Demb et al., 1998).

Functional Neuroimaging Evidence: Visual Processing

To investigate the magnocellular deficit in dyslexia, the activity in the MT/V5 complex during visual motion processing has been studied using fMRI. If dyslexics have a magnocellular deficit, then they should also have poorer visual motion discrimination due to aberrant motion processing. Presentation of moving stimuli to dyslexics failed to produce the same task-related functional activation in the MT/V5 complex as in controls. This deficit was confined to the motion processing system, as presentation of stationary patterns resulted in equivalent activation in both groups (Eden et al., 1996). It has also been possible to demonstrate a direct correlation between the amplitude of fMRI signal change in the MT/V5 complex and reading skill (Demb et al., 1998). In neuroimaging studies of dyslexia, the cortical and subcortical components of the visual motion pathway outside area MT/V5 have not yet been thoroughly investigated. The MT/V5 complex provides strong input to the inferior parietal cortex and cerebellum, areas involved in visual motion processing. Of note is the fact that both of these regions exhibit abnormal linguistic task-related activity in functional brain imaging studies of dyslexia.

As it is difficult to selectively activate specialized visual areas, careful control of stimulus parameters is necessary to demonstrate dysfunction of a particular portion of the visual system. Specifically, demonstration of the motion processing deficit in dyslexia depends upon utilization of stimuli with low luminance and contrast, stimulus characteristics that will selectively activate the magnocellular pathways (Eden et al., 1996; Demb et al., 1998). This raises the question of how such a subtle and delicately elicited deficit could impair reading, which usually occurs under a range of luminance conditions and involves high contrast visual input. Stated somewhat differently, although there is now substantial evidence for visual behavioral deficits in dyslexics during the processing of magnocellular/transient stimuli, it has been difficult to establish a causal relationship between the demonstrable visual processing deficits and reading abnormalities.

A Temporoparietal Localization for Developmental Dyslexia?

While the studies reviewed above do not permit any definitive conclusions concerning the etiology or precise mechanism of the behavioral deficits characteristic of developmental dyslexia, they may be consistent with a common neuroanatomical localization for the disordered processes. Combining the experimental results from neuroimaging studies of reading and reading-related processing with those demonstrating a magnocellular visual system deficit, the cortical regions surrounding the temporoparietal junction emerge as possible candidates for the principal loci of cerebral dysfunction in dyslexia. The argument supporting this presumptive localization may be presented in four parts. First, visual input to posterior temporal and inferior parietal areas originates predominantly from the magnocellular system. These pathways originate in the magnocellular layers of the lateral geniculate nucleus (LGN) and project to the MT/V5 complex and inferior parietal cortex as depicted in Figure 1. Functional neuroimaging studies

have demonstrated localization of visual motion processing to extrastriate (MT/V5 complex) and inferior parietal cortex in the human visual system. Second, this magnocellular system has been demonstrated to be abnormal in developmental dyslexia using behavioral, electrophysiological, and functional neuroimaging techniques. These abnormalities, although subtle, are reproducible when care is taken to match subject selection criteria and stimulus conditions. Third, neuroimaging studies examining localization of different reading tasks have regularly identified task-related activity in the posterior superior temporal gyrus and inferior parietal lobule. In addition, it has long been known that lesions confined to the angular gyrus are known to disrupt processing of written material. Lastly, four recent neuroimaging studies employing phonological tasks in dyslexics have found deficient task-related activation in the posterior superior temporal gyrus or inferior parietal lobule. Taken together, these independent lines of inquiry provide strong circumstantial evidence for localization of the principal function lesion in developmental dyslexia to a set of regions surrounding the temporoparietal junction.

Caveats and Implications for Future Studies

What, if any, are be the mechanistic implications of this suggested temporoparietal localization for dyslexia? If the primary lesion in developmental dyslexia is confined to posterior temporal and inferior parietal cortex, a number of predictions follow.

First, the demonstrated overlap of visual and phonological processing mechanisms in posterior temporal and inferior parietal cortex has been somewhat approximate and could be improved with single subject analysis using recent advances in spatial normalization and image registration. A particularly compelling finding would be the demonstration of colocalization of visual motion and phonological processing to the same cortical area(s). Correlation analysis of phonological task data have demonstrated that normal readers show functional connectivity between the left angular gyrus and MT/V5; this functional correlation is absent in dyslexics, suggesting a relationship between these linguistic and visual areas (Horwitz et al., 1998). Even if the visual and linguistic processing regions are not found to be completely coextensive, it is possible that they are close neighbors, both subject to the same abnormal developmental processes.

Second, if cortical areas surrounding the temporoparietal junction are selectively affected, it should be possible to detect these abnormalities in young children, before the effects of compensatory processing mechanisms manifest. In examining older, mostly compensated, dyslexics, we may be imaging the results of neural plasticity as much as the results of the developmental lesion itself. Functional imaging studies employing a wider age range and longitudinal studies of single subjects will be essential to achieve a deeper understanding of these complex issues.

Third, demonstration of spatial colocalization of functions does not imply causal relationships among the functions. Demonstrated spatial contiguity may only provide a simple mechanism for unrelated functions to be affected by common pathological processes. Thus, discussion of the inability to account for reading deficits with reference to abnormal low level perceptual functions may not be particularly relevant to the search for pathophysiological mechanisms of dyslexia. A more productive avenue for future research might focus on common causes. Demonstration that disparate behavioral deficits arise from dysfunction of spatially colocalized cortical regions would be evidence in favor of common pathophysiological mechanisms.

In summary, better neuroanatomical localization of the abnormal developmental processes in dyslexia is the first step in understanding how interaction of genetic and environmental factors results in the complex constellation of sensory and cognitive disorders that characterizes developmental dyslexia. While many researchers believe that the core deficit in dyslexia involves linguistic dysfunction, others emphasize the role of abnormal sensory processing. Functional neuroimaging now provides a way to identify the regional specialization and spatial congruence of the cortical areas engaged in visual, auditory, and linguistic processing. These new techniques may allow reconciliation of apparently disparate views concerning the causes of this disorder.

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