Genetics and Neuroscience in Dyslexia: Perspectives for Education and Remediation

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ABSTRACT—Our understanding of the causes of a developmental disorder like dyslexia has received recent input from both neuroscience and genetics. The discovery of 4 candidate genes for dyslexia and the identification of neuronal networks engaged when children read and spell are the basis for introducing this knowledge into education. However, the input from educational practitioners as well as empirical knowledge from research on learning also contribute significantly to our understanding of how children acquire the basic skills for learning to read and spell. It is imperative to merge the knowledge acquired from research in the fields of neuroscience, genetics, and empirical education, as well as to understand how the learning brain and instruction interact. Doing so can be seen as a major step in attaining an optimal approach for teaching, reading, and spelling and for finding the best suited and most effective treatment concepts for dyslexic children and adolescents.

NEUROCOGNITION

Worldwide several million children and adults have a specific impairment in learning to read and spell, despite average or higher cognitive abilities, adequate instruction, and normal vision and audition. The international classification systems of diseases, the *International Statistical Classification of Diseases* (ICD-10) and the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*™), listed this disorder, commonly referred to as dyslexia, as a reading and spelling disorder (ICD-10) or a reading disorder and a disorder of written expression (*DSM-IV*), respectively. Additionally, common characteristics of this widespread developmental disorder are that it persists into adulthood, exhibits a high comorbidity with other disorders (e.g., speech and language disorders, dyscalculia, and attention-deficit/hyperactivity disorder [ADHD]), has a higher prevalence in boys, and is often characterized by a high incidence of symptoms of depression in adults, unemployment, suicide attempts, and school dropout (Daniel et al., 2006; Maughan, Rowe, Loeber, & Stouthamer-Loeber, 2003; Rutter et al., 2004; Shaywitz et al., 1999).

Due to intensive neuropsychological research, it has become clear that not only reading and spelling abilities are impaired but also processes that are strictly related to the development of these skills. The perception of single phonemes (the smallest units of sound found within a given language, e.g., *k* or *th* in English), discrimination of phonemes, the retrieval of phonemes from memory, and letter-to-phoneme mapping are all abilities that are subsumed under the construct of phonological processing. The significance of phonological processing for reading and spelling development has been strengthened by a multitude of studies (e.g., Bradley & Bryant, 1983; Torgesen, Wagnetr, & Rashotte, 1994; Wagner et al., 1997). Hereunto intervention and prevention studies show that training phonology skills before formal schooling lowers the risk of becoming dyslexic and significantly improves the command of reading and spelling in dyslexic children (Berninger et al., 2003; Schneider, Ennemoser, Roth, & Kuspert, 1999). Furthermore, teaching phonics in normal classroom settings and integrating the development of phonological skills into remediation programs for dyslexic children would be beneficial, as

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these strategies were repeatedly found to improve reading and spelling development (Rayner, Foorman, Perfetti, Pesetsky, & Seiden berg, 2001; Torgesen et al., 2001).

The acquisition of knowledge regarding the orthographic structure of language (spelling systems and rules) and morphemes (the smallest meaningful units of language) is related to the development of spelling. This knowledge and the application of this for reading and spelling are often summarized as orthographic processing. The empirical evidence is growing for the significance of disturbed orthographic processing in dyslexia and remediation studies with spelling-disordered children show that the improvement of orthographic knowledge significantly meliorates the spelling ability (Schulte-Körne, Deimel, Hülsmann, Seidler, & Remschmidt, 2001; Schulte-Körne, Deimel, & Remschmidt, 2003).

Finally, word reading requires the retrieval of lexical representations from memory. A cognitive process associated with automatic, rapid access to word representations is known as rapid automatic naming (RAN) (Wolf, 1991). The speeded naming of lists of pictures, letters, numbers, and symbols are typical tasks in RAN exercises. RAN is correlated with reading and spelling development, and in preschool, it is a predictor for developing dyslexia (Wolf, Bowers, & Biddle, 2000). It has also been found that the RAN of pictures in dyslexic adults is impaired (Wolf, Michel, & Ovrut, 1990), suggesting that problems with the retrieval from the word lexicon are stable and continuous, thus having an influence on reading and spelling throughout the life span.

Besides these neuropsychological factors, short-term auditory memory, visual spatial abilities, visual attention, motor coordination, and basic auditory and visual processes have also been found to be related to reading and spelling development (Ramus et al., 2003). However, for the purposes of education and remediation, the significance of phonological and orthographic processing for normal and impaired reading and spelling abilities are the most precisely validated factors to date.

NEUROSCIENCE

Research from cognitive and molecular neuroscience could build the link between behavioral and genetic findings. The characterisation of neural circuits involved in learning to read and spell and the identification of brain areas where white and gray matter are active in dyslexic subjects while reading are essential steps in understanding the complexity of brain and gene interactions in dyslexia. Clues to neural dysfunction come from postmortem studies of four dyslexic brains where several subtle cortical anomalies, all of which correspond well to the genetic model pointing toward a neuronal migration disorder, were found. Precisely, nests of neurons (ectopias) and focal microgyria were discovered primarily in left hemisphere cortical areas associated with speech perception and processing (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985).

Brain imaging studies have identified the neurobiological correlates of cognitive processes like letter perception, RAN, and phonological and orthographic processing. This research has primarily implicated three (rather large) brain regions: the left temporo-parietal, the left frontal, and the left occipito-temporal regions, based on their differential activation in dyslexic subjects.

Specifically, in terms of the left temporo-parietal region, anomalous patterns of neuronal activity, correlated with phonological processing (e.g., rhyme detection and segmentation) and word reading, were repeatedly found in the left hemisphere perisylvian cortex in dyslexia (Figure 1) (Brunswick, McCrory, Price, Frith, & Frith, 1999; Pugh et al., 2000; Rumsey et al., 1997).

The left inferior frontal area has been associated with articulatory recoding (covert pronunciation), silent reading, and naming (Pugh et al., 1996). Interestingly, when explicit demand on phonological processing, like word and pseudoword reading was required, a higher activation in the inferior frontal gyrus in dyslexics was found (Brunswick et al., 1999; Pugh et al., 2000), suggesting some compensatory functions of left frontal cortical areas (Figure 1).

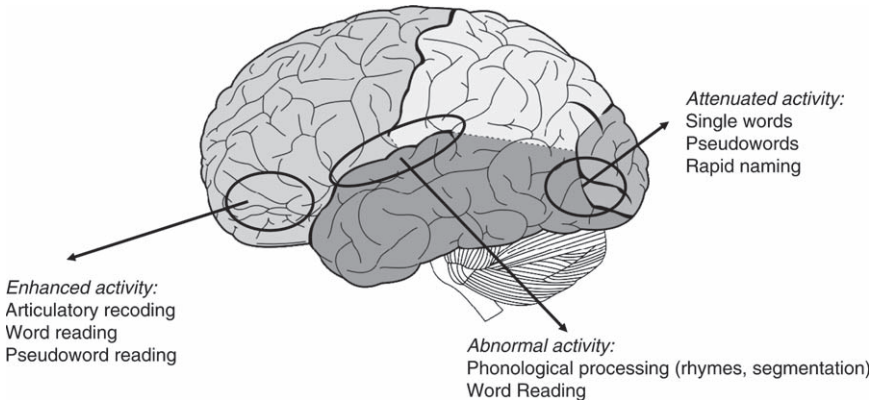

Fig. 1. Neurobiological correlates of cognitive processes in dyslexia.

Finally, robust differences between nondyslexic and dyslexic subjects were also reported in the left occipito-temporal areas (McCrory, Mechelli, Frith, & Price, 2005; Paulesu et al., 2001; Salmelin, Service, Kiesila, Uutela, & Salonen, 1996; Shaywitz et al., 2002) when processing single words and pseudowords (Figure 1). These findings may be indicative of a visual word processing correlate (McCandliss, Cohen, & Dehane, 2003). However, the left occipito-temporal region was also activated by presenting different stimuli (words, colors, pictures, and faces) and by different tasks (e.g., naming, Braille reading, and recognition) (Büchel, Price, & Friston, 1998; Chao, Weisberg, & Martin, 2002; Hasson, Levy, Behrmann, Hendler, & Malach, 2002). Due to the fact that no activation differences in this region were found when processing faces (Tarkiainen, Helenius, & Salmelin, 2003), this region was understood as a correlate of impaired phonological retrieval from visual input in dyslexia (McCrory et al., 2005).

It is important to recognize that the aforementioned brain activation differences are merely correlated with dyslexia and cannot be interpreted as proof of causality. Functional research aimed at investigating the neural changes following therapy will help bring researchers one step further in pinpointing the causal grounds of dyslexia. To this end, several studies were able to demonstrate that the training of phonological processing results in changes of neuronal activity of brain regions that are otherwise underactivated in dyslexic children and adults, for example, the left temporo-parietal region (Aylward et al., 2003; Eden et al., 2004; Richards et al., 2000; Shaywitz et al., 2004). Furthermore, Eden et al. (2004) evaluated a phonologically based treatment study in dyslexic adults and was able to demonstrate that remediation can lead to several neuronal changes, not only restricted to brain areas of the left hemisphere. The authors found that the right parietal and perisylvian regions were associated with compensatory processes in reading in addition to the left inferior parietal cortex. One explanation provided for the activation of right hemisphere areas could be a restricted availability of left hemisphere regions (Eden et al., 2004). These findings are encouraging and highlight how educational experience can influence functional anatomy. Despite this, further research is needed to precisely identify the respective brain areas involved and the respective processes underlying the therapeutic success in dyslexia.

EDUCATION

What is the most effective way that we can teach children to learn and spell? How can we optimize therapy programs aimed at the remediation of reading and spelling disorders in children? These are two of the most exciting research questions that are gaining interest in cognitive neurosciences (Tallal, 2004) and genetics (Grigorenko, 2007) today. Integrating knowledge from neuroscience into classroom practice is one strategic goal that has been recently proposed (Tallal, 2004) but also critically reviewed as a "bridge too far" (Bruer, 1997). To date, the majority of criticism revolves around the argument that cognitive neuroscience cannot elucidate the teachers' problem of how to teach their pupils to read and spell. In turn, following an overly optimistic promise of the success of "brain-based-learning" would disregard the importance of empirical research in educational and instructional science (Stern, 2005).

The significance of classroom instruction and intervention for learning, reading, and spelling has been found in several studies (Torgesen, Rose, Lindamood, Conway, & Garvan, 1999; Vellutino, Fletcher, Snowling, & Scanlon, 2004). In general, integrating methods that facilitate the acquisition of phonological awareness, learning the letter–sound correspondence and vice versa, and word reading skills are suited to ameliorate reading levels of poor readers. The classroom instructions for teaching spelling are different and depend on, for example, the child's level of spelling achievement, the individual cognitive factors of the child (working memory resources, self-regulating abilities of the child), and the goals of teaching (e.g., pure spelling, composition of text) (Berninger et al., 2002). Evaluation of classroom instruction recommends the explicit instruction of writing skills and spelling training that outclasses mere spelling practice alone (Berninger et al., 2003).

The differences between languages and orthographies also interact with teaching and instruction (see Ziegler & Goswami, 2005). For example, in the English writing system, phonemes correspond to sets of alternative one- or two-letter functional spelling units (Venezky, 1995). As an example, the phoneme /a/ can be spelled as the letter *a* in cat, as *ei* in eight, as *ey* in they, as *ai* in aim, or as *ea* in team (Berninger et al., 2002). In contrast, in regular orthographies like Italian, the phoneme /a/ always corresponds to the letter *a*. Thus, the instruction to apply phonics in order to transform the phonemes into spelling is confusing in English and relatively straightforward in Italian.

Currently, empirically validated knowledge from neuroscience, which could be implemented in the instructional setting, for example, that which would give insight into how phoneme mapping across diverse languages is accrued, is not available. Nevertheless, there are initial reports available illustrating that knowledge from neuroscience could be effectively applied to instructional settings (Kujala et al., 2001; Simos et al., 2007).

Tallal et al. (1996) developed a complex intensive training program based on findings that dyslexic individuals suffer from a basic auditory perception disorder characterized by deficient neural processing of rapidly presented or rapidly changing dynamic sensory stimuli. Indeed, during training a significant improvement in language tasks (word reading, passage comprehension) was observed in dyslexic children (Merzenich et al., 1996; Temple et al., 2003). In conjunction

with these behavioral improvements, it was found that a left-hemisphere temporo-parietal underactivation approached "normal" in the respective brain areas posttraining (Temple et al., 2003). Based on this research, the authors have recommended an adequate implementation of the basic elements of their training into school education in order to base remediation and education on proven scientific methods (Tallal, 2004).

GENETICS

What is known about the causes of dyslexia so far? It is widely accepted that dyslexia is caused by several factors originating from the environment and genetics, as well as their interaction. Although the specific nature of these factors remains to be identified, a large portion is considered to be of neurobiological and genetic origin. The existence of genetic effects in the development of dyslexia was recognized only a few years after the first description of the disorder by Hinshelwood in 1895, when several authors observed hereditary effects. Specifically, they noted that dyslexia appeared more frequently within families than in the normal population (Hinshelwood, 1895; Stephenson, 1907; Thomas, 1905). The risk for a child to develop dyslexia today is estimated between 40% and 60% if one parent is affected. The risk is further increased in the case that other family members are also affected. Furthermore, a sibling's relative risk of being affected is increased three- to ten-fold (Hallgren, 1950; Olson, Forsberg, & Wise, 1994; Schulte-Körne, Deimel, Müller, Gutenbrunner, & Remschmidt, 1996; Stephenson, 1907; Stevenson, 1991; Ziegler et al., 2005).

Another approach to estimate the influences of heritability and the impact of environmental factors is the analysis of twins: although, on the genetic level, monozygotic twins are 100% identical, dizygotic twins only share 50% of their genetic information. Thus, the comparison of monozygotic and dizygotic twins with respect to a disorder such as dyslexia allows estimations of genetic and environmental influences. Based on twin studies, it could be confirmed that genetic factors substantially contribute to the familial clustering of dyslexia (Olson, 2002; Plomin & Kovas, 2005). The proportion of inherited factors is estimated to be about 40%–80% for the development of dyslexia, with highest estimates being reported for the subdimensions word reading and spelling (58% and 70%, respectively) (Gayán & Olson, 2001; Olson, 2002; Plomin & Kovas, 2005). On the environmental level, it has been shown that the impact of factors that are shared between twins is low for word reading but substantially higher (at about 14%) for reading- and spelling-correlated traits, for example, phonological awareness (Gayán & Olson, 2001).

Molecular Genetics

When hereditary influences for the development of a disease are assumed, the molecular identification of the responsible genes offers the chance for a profound understanding of underlying biological factors. In contrast to monogenic disorders (e.g., Chorea Huntington), in which a variation in one single gene is responsible for the majority of the cases, complex disorders like dyslexia are caused by several genes. Thereby, every single gene has only a limited contribution to the development of those disorders, which makes the identification of the genetic pattern very challenging.

As with most complex disorders, an important step toward the identification of the genetic basis underlying dyslexia is the analysis of a large number of DNA samples. Throughout the last few years, researchers (especially in the United States, United Kingdom, Canada, the Netherlands, and Germany) have collected DNA samples from a large number of families with at least one child suffering from dyslexia. Using those DNA samples, a variety of studies were conducted in order to explore genetic patterns in dyslexia and to identify particular chromosomal regions ("loci") that confer susceptibility for dyslexia. As the human genome comprises 23 pairs of chromosomes and about 3.2 billion base pairs, the identification of loci is a crucial step in order to narrow down the region in which one looks for specific candidate genes.

Using an approach known as "linkage analysis," nine chromosomal regions that are most probably harboring genes linked to the development of dyslexia have been found so far. They are listed as DYX1 to DYX9 by the HUGO Gene Nomenclature Committee (Figure 2; for a detailed review please refer to Schumacher et al., 2006). From these nine loci, the evidence for regions on chromosomes 1, 3, 6, 15, and 18 is the most convincing, as positive results have been found in at least two of the large family samples, which means that the first findings have been replicated independently. There were also attempts to correlate these findings not only to dyslexia itself but also to particular phenotypic measurements (e.g., phonological decoding, phoneme awareness, orthographic processing, RAN, working memory) but so far, initial findings in this direction are still waiting for confirmation from independent groups. Nevertheless, the linkage findings for dyslexia are relatively consistent when compared to other neuropsychiatric disorders such as schizophrenia or bipolar disorder.

According to the evidence for the chromosomal loci, the hope that several of these regions would harbor true susceptibility (candidate) genes was great. It was thus not surprising that the first candidate gene findings were presented shortly thereafter (Cope, Harold, et al., 2005; Deffenbacher et al., 2004; Hannula-Jouppi et al., 2005; Meng, Smith, et al., 2005; Paracchini et al., 2006; Schumacher et al., 2006; Taipale et al., 2003). To date, four candidate genes for dyslexia have been identified: *DCDC2* and *KIAA0319* (both Chromosome

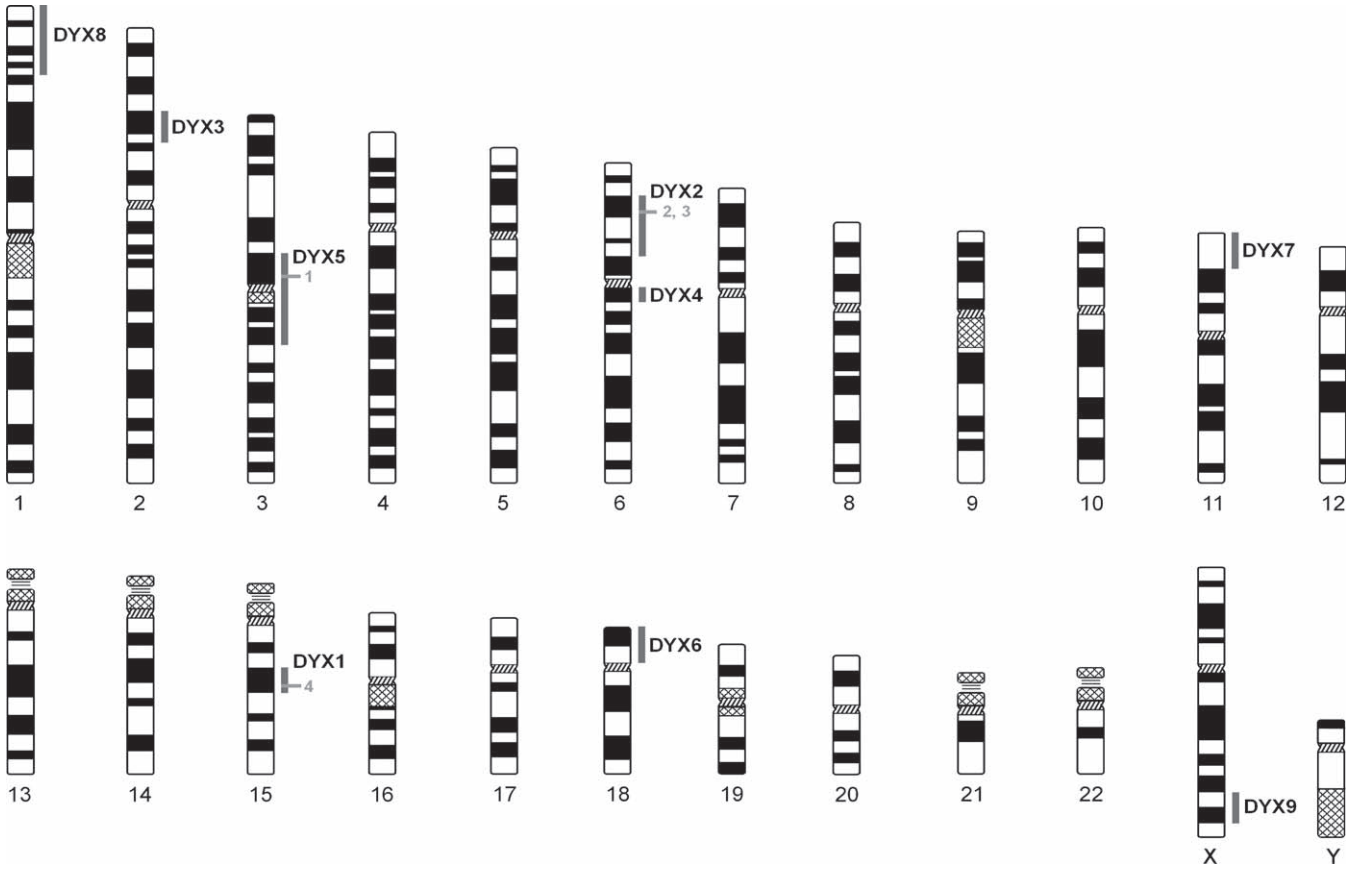

Fig. 2. Dyslexia susceptibility loci. The chromosomal regions which have been reported in linkage studies are shown in vertical lines. Horizontal lines represent dyslexia candidate genes: 1, ROBO1; 2, DCDC2; 3, KIAA0319; 4, DYX1C1.

6), *DYX1C1* (Chromosome 15), and *ROBO1* (Chromosome 3) (Figure 2).

DCDC2 and *KIAA0319* are located on the short arm of Chromosome 6, only 500kb apart from each other (to be more precise, the region is named "6p22," with "6" indicating the chromosome, "p" the small arm, and 22 the specific band of the chromosome). For both genes, findings linking them to dyslexia have been reported and replicated, with the strongest effect being observed in the most severely affected subjects (Cope, Harold, et al., 2005; Francks et al., 2004; Meng, Smith, et al., 2005; Schumacher et al., 2006). Although Harold et al. (2006) have recently reported evidence for some interaction between both genes in two UK samples, it is very likely that there is an independent contribution from both genes to the development of dyslexia because strong association for either of the two genes has been found in independent samples. So far, specific variations (mutations) having an effect on either the protein function or the expression of the genes have not been found, indicating that more research needs to be done on those genes in order to find causal variation in the DNA sequence that is responsible for the gene's contribution to the development of dyslexia.

DYX1C1 on chromosome 15q21 and *ROBO1* on chromosome 3p12 have both been found by breakpoint mapping in Finnish families (Hannula-Jouppi et al., 2005; Taipale et al., 2003). Different than in family studies with large numbers of families, this approach uses only single families, in which dyslexia is inherited together ("cosegregates") with a chromosomal aberration (translocation). The initial positive findings for *DYX1C1* were not replicated (Bellini et al., 2005; Cope, Hill, et al., 2005; Marino et al., 2005; Meng, Hager, et al., 2005; Scerri et al., 2004; Wigg et al., 2004) and only recently some weak evidence for this gene was reported (Brkanac et al., 2007; Marino et al., 2007). Currently, it might be questionable whether *DYX1C1* makes a significant contribution to the development of dyslexia in non-Finnish European populations.

Whether or not *ROBO1* actually contributes to the development of dyslexia is at present unclear. A critical point is that the correlation between the translocation and the dyslexia phenotype in the original translocation patient was not imperative; a sibling of the translocation carrier also had dyslexia without carrying the translocation (Taipale et al., 2003).

In addition to the described dyslexia susceptibility loci, linkage with dyslexia has also been reported for other chromosomal regions, although without replication in independent samples. For example, Igo et al. (2006) were able to link word reading to chromosome 13q12 and Raskind et al. (2005) found evidence for linkage with phonemic decoding efficiency, a measure for phonological decoding efficiency on chromosome 2q22.

As mentioned, comorbidity plays an important role in dyslexia. Most markedly is the comorbidity between ADHD and dyslexia, with a prevalence significantly higher than would be expected by chance (25%–40%; Dykman & Ackerman, 1991; McGee & Share, 1988; Semrud-Clikeman et al., 1992). In order to assess the potential genetic aspects of the comorbidity observed between dyslexia and ADHD, two genome-wide linkage studies have been published (Gayán et al., 2005; Loo et al., 2004). Both studies aimed at identifying chromosomal loci with "pleiotropic" effects on ADHD and dyslexia: they looked for regions harboring genes, which are responsible for the development of either of the two disorders. One study (Gayán et al., 2005) was conducted in dyslexia families with ADHD and evidence for linkage was shown in regions 14q32, 13q32, and 20q11 (Gayán et al., 2005), whereas a study in ADHD families identified linkage regions on chromosomes 10q11, 16p12, and 17q22 (Loo et al., 2004). None of those genome-wide studies identified regions that were already known for dyslexia susceptibility. A third study, carried out on Dutch sib pairs with ADHD, showed strong evidence for linkage to ADHD in region 15q21, which is identical to the dyslexia susceptibility locus DYX1 (Bakker et al., 2003). Although the corresponding risk conferring genes in ADHD have not been identified yet, it might be possible that, once identified, they will contribute to the observed comorbidity between the two disorders.

Functional Analysis

All four currently identified dyslexia candidate genes (*DCDC2*, *KIAA0319*, *DYX1C1*, and *ROBO1*) have already been investigated regarding their functional relevance for the development of dyslexia. As with most of the neuropsychiatric disorders, a direct assessment of protein functions in human brains is difficult as they can only be analyzed postmortem. Thus, in order to gain insights into the morphological and functional processes in dyslexic brains, the use of animal models is crucial.

In recent publications by Meng, Smith, et al. (2005) and Paracchini et al. (2006), the rodent homologues of *DCDC2* and *KIAA0319* have been targeted *in utero* in rats using the method of RNA interference. Specifically, the concentration of the specific gene was decreased artificially by inserting small molecules that explicitly inhibit the gene's mediator on the way from gene to the gene product, the messenger RNA. For each of the two genes, this down regulation of its expression resulted in a significant reduction of cortical neuronal migration in the brain. What is more, further functional evidence for *KIAA0319* was found via studies on human lymphoblastoid cell lines (Paracchini et al., 2006). The authors were able to show that the expression of *KIAA0319* is reduced by 40% in carriers of a specific dyslexia risk haplotype for *KIAA0319* when compared to other genes in the region.

DYX1C1, which is expressed in many tissues, is also found in the central nervous system where it is particularly localized in cortical neurons and white matter glial cells (Taipale et al., 2003). Animal studies in embryonic rats demonstrated that *DYX1C1*, similar to *DCDC2* and *KIAA0319*, decreased the migration of neurons in the developing neocortex (Wang et al., 2006).

Finally, the fourth candidate gene, *ROBO1*, has been mainly targeted via its orthologous genes in drosophila flies and mice (Andrews et al., 2006; Kidd, Bland, & Goodman, 1999; Seeger, Tear, Ferres-Marco, & Goodman, 1993). It was shown that this gene is involved in neuronal axon guidance in brain development and, when knocked out, increases the number of interneurons entering the cerebral cortex at specific developmental time points.

The functional evidence for the candidate genes in animal models may support their respective role in the development of dyslexia. This is particularly true for *DCDC2*, *KIAA0139*, and *DYX1C1—all of which were implicated in neuronal migration*–because the concept of disturbed neuronal migration and axon growth is also supported from anatomical findings in postmortem brain studies (Galaburda, 1994; Galaburda & Kemper, 1979; Galaburda et al., 1985). Together with the altered activation of reading- and spelling-related brain areas found in brain imaging studies, the discovery of specific molecular mechanisms is most interesting as it could provide a chance to see some of the phenotype-relevant processes directly.

PERSPECTIVES FOR RESEARCH AND EDUCATION

Molecular Genetics

While nine chromosomal loci have been identified by linkage studies so far, only four of them have been attributed to specific candidate genes. It is thus necessary to further analyze those loci in order to obtain a comprehensive picture of the genes responsible for the positive linkage findings. Recent advances in genotyping technology (e.g., Illumina and Affymetrix whole genome association chips) could also help to identify the genes and, equally interesting, new loci.

Because dyslexia is a complex disorder, it is expected that the genetic background of dyslexia, as with many other phenotypes, is in fact due to rather common polymorphisms with only moderate increases in risk, instead of rare mutations with strong effects on risk. This hypothesis of common

disease–common polymorphism has been the basis for the basic design of genome-wide association studies building on the seminal paper of Risch and Merikangas (1996) and a series of efforts to build the technology (mostly by Biotech companies) and knowledge base (the HAPMAP project) to correctly perform these studies. Recently, this approach has seen some great success, such as the discovery of polymorphisms in the IL23 receptor gene as a risk factor for inflammatory bowel diseases (Duerr et al., 2006) and very recently (Easton et al., 2007) in breast cancer. In dyslexia research, such a breakthrough is yet to be achieved. Here it is important to note that findings of one or more common polymorphisms associated with dyslexia do not invalidate prior findings based on linkage in single families. However, the relative contribution of the findings based on family studies to the overall prevalence of the phenotype might be rather limited.

Furthermore, it is not immediately evident that the findings in linkage and association studies need to overlap. As an example, one can take a hypothetical locus with a risk disease allele frequency of 0.5 and a genotypic relative risk of 1.5 under a multiplicative risk model. In this case, the risk fraction attributed to the population would be 36%, or put into other words, more than a third of the cases would be attributed to this polymorphism, whereas the risk increase to sibs of a proband would be only 4%. Thus, if the baseline risk in the population were 10.0%, the risk to the sib of an affected individual due to such a locus would be increased to 10.4%. Clearly, this type of risk increase would be difficult to interpret in counseling situations in families. It should be noted that this type of polymorphism would be virtually undetectable by linkage analysis (at least requiring several thousands of nuclear families to be tested).

Apart from the obvious consequences for the design of genetic studies in dyslexia, the consequences of such very moderate risk alterations in families cast severe doubts on the importance of such findings for the individual diagnostics of dyslexia. However, it is evident that these results may indeed shed light on important biological pathways in the elucidation of the etiology or (patho)genesis of dyslexia. Possibly their relative magnitudes of effects, both for the risk increases inferred or the population attributable risks may provide further guidance here.

To overcome the limitations of family studies and to address the issue of having only moderate genetic effects of single genes, it is necessary to collect new large collectives. In order to do just this, a recent project funded by the European Union (EU) in the Sixth Framework (http://www.NeuroDys.com) addresses this problem and has started to build the largest sample of children with dyslexia worldwide.

Neuroscience

Looking at the candidate genes known to date, the evidence for *DCDC2* and *KIAA0319* is the most convincing. Their identification represents an important step that will greatly improve our understanding of the molecular bases of dyslexia. Their involvement in cortical neuronal migration, as shown in fetal rats by specific siRNA experiments (Meng, Smith, et al., 2005; Paracchini et al., 2006), enables first insights into the molecular processes leading to dyslexia. However, neither the evidence for *DCDC2* nor that for *KIAA0319* has been replicated in all samples, and contradictive findings have also been reported for both genes. Thus, future investigations of the two genes will have to address the questions of whether those discrepancies are due to population-specific effects or whether they represent specific phenotypic patterns that were introduced into the samples by different ascertainment criteria. Furthermore, the lack of functional mutations in the candidate genes requires in-depth analysis of noncoding gene areas such as introns and up- and downstream regulatory regions. Mutations in those areas might result in over- or underexpression of target genes, thus setting the well-regulated molecular processes in the brain off balance. The hypothesis that the causal variants in the genes are of regulatory origin may be supported by the expression patterns of the two genes. Being widely expressed in the brain, none of the corresponding gene products is restricted to one specific brain area. Thus, the identification of the specific regulatory partners such as transcription factors or structural components would be the next area of interest and, furthermore, help to understand the complex interactions of molecules and structures in the brain.

Besides the functional analysis of identified genes, the interaction between genotypes and the underlying cognitive and neurophysiological processes must be further analyzed. To date, only some specific cognitive processes, for example, phonological processing and rapid naming, are known to be influenced by the already identified candidate genes (Fisher et al., 2002; Grigorenko et al., 1997; Raskind et al., 2005). However, this understanding is an important prerequisite for the identification of the processes, which are closest to the known genes and their biological functions.

It is obvious that a gene is not an island. It has been already shown for dyslexia as well as other disorders that the action of genes (or rather the products of genes) is partially regulated by the environment. These regulations need not necessarily be of a very simple manner, thus maintaining relative advantages of certain genotypes over others across all possible environmental conditions. In the simplest terms, this means that what is advantageous in one environment may well be detrimental in another. However, this may also provide a useful entry point for genetic results into the therapy of dyslexia. Studies relating success of therapies to genotypes and/or genotype/environment combinations may provide useful results with importance for dyslectic individuals, which should be the ultimate goal. It is interesting to see from other phenotypes, for example, from affective disorder (Binder et al., 2004), that the effect sizes relating to genetic studies of

therapy success tend to be considerably larger than the effect sizes for studies on susceptibility. This renders these studies much more powerful, and at the same time, the results could be potentially more important on the individual level.

Education

Overall, one strategy that would target the conjoining of brain science and educational practice could be the integration of findings from molecular genetics, neuroscience, and pedagogy. As stated by Bruer (2002), there is no empirical evidence that encourages or facilitates the integration of neuroscientific research results into educational practice. Having said this, what are the needs and also the perspectives for dyslexic individuals from neuroscience and genetic research?

Currently, there are no causative models of dyslexia. Therefore, the discovery of causative mutations in dyslexia will be unparalleled and will facilitate the understanding of the etiology for, at the very least, a subgroup of dyslexic individuals. Further, it could facilitate a very early diagnosis of dyslexia or identify the risk of becoming dyslexic at an early age. This, in turn, would offer the possibility of early prevention. Most children suffering from dyslexia are diagnosed in the third grade. Depending on the schooling in the different countries, the children are between 7 and 9 years old. Although controversially debated, there are critical (or highly sensitive) periods in cortical development (Huttenlocher, 2003) and in language learning specifically (Kuhl, Williams, Lacerda, Stevens, & Lindblom, 1992). There is clear empirical evidence that speech perception is altered in dyslexia (e.g., Kraus et al., 1996; Schulte-Körne, Deimel, Bartling, & Remschmidt, 1998). Adapting the concept of critical periods for dyslexia could mean that there is a phase of brain development where environmental speech signals alter neural circuits responsible for speech perception. If we can ascertain that a particular child is at risk for developing dyslexia and that the child has a mutation that influences cortical areas responsible for speech perception, early speech perception training could be justified with good reason.

Besides language-related issues, the burden of dyslexia for the affected children and their families is known to be high. Thus, there is an urgent need to intervene as early as possible in order to avoid the psychosocial consequences of this disorder. Therefore combining the knowledge from the different disciplines discussed, neuroscience, education, and genetics in order to develop specific and effective prevention and remediation strategies will be an important challenge for the coming years.

In conclusion, we have attempted to highlight the intricacies of what are considered to be the most plausible causes of dyslexia as discussed within a neurobiological and genetic framework. Furthermore, the environment, such as educational settings, is known to play a pertinent role in the subsequent expression of dyslexia and must therefore also be taken into consideration when discussing causal models of dyslexia.

Both educators and researchers could benefit from actively integrating knowledge from each others' disciplines. Well-informed educators, profiting from knowledge about the diverse and complex nature of dyslexia from empirical science, would be assets to classroom settings and schools. Furthermore, their knowledge would aid them in their interaction with dyslexic children and their parents on a daily basis. Reciprocally, dyslexia researchers would benefit from an increased awareness about educational practices revolving around reading and spelling instruction. This information gives important insight into the environmental factors influencing the acquisition of reading and spelling and can be used to effectively expand etiological models of dyslexia.

Unfortunately, the available knowledge about dyslexia from neuroscience and genetics is currently too basic to draw specific and applicable conclusions for teaching and educational practice. Thus, current practices are based on behavioral findings, such as treatment of impaired skills (e.g., phonics). What is positive is that there is legitimate hope that future results from actual collaborative interdisciplinary studies, like the EU-funded NeuroDys study, will improve our understanding of the complex interaction of neuroscience and genetics in dyslexia. Such findings will consequently bring us closer to the point where, together with educators, specific plans (beyond treating phenotypes) for remedial education in dyslexia can be developed and implemented.

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