Dyslexia: Advances in Cross-Level Research

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The history of dyslexia research comprises a series of successes as well as ongoing challenges. A remarkable expansion of our knowledge, spanning the fields of genetics, neurobiology, neurology, cognitive neuroscience, and education, has taken place since the first conference of the Extraordinary Brain series was inaugurated in Florence, Italy, almost 20 years ago. As the published volume from the Como Conference shows, we can say at this juncture that among those remarkable findings, there exists today for the condition known as developmental dyslexia at least one plausible known pathway between a genetic mutation and an abnormal behavior often associated with the diagnosis, including a rough description of the intervening neural structures involved. This is indeed a remarkable achievement that derives its strength mainly from cross-level approaches converging on the solution of the dyslexia problem. In the following pages I will summarize relevant findings that lead to the above optimism as well as bringing up some still unanswered questions and remaining challenges.

From Gene to Behavior: A Cross-Level and Multidisciplinary Approach

Everyone knows that complex behaviors can result from strong genetic predispositions without denying the fact that the environment helps to select among the possibilities presented by the genetic background. Thus, no complete program of research on a condition such as dyslexia could afford to ignore either the genetic background, described in the most detailed and mechanistic format permitted by current methodologies, or the cognitive and behavioral architectures that ultimately result from the interactions between genes and environment. The most laudable (but also the most challenging) goal of a dyslexia research program, which would also apply to most if not all disorders of perception, cognition, or behavior, would be to establish a clear and testable pathway between gene function and the perceptual, cognitive, and behavioral deficit. Such a research program requires a broad range of expertise amply found today, but

generally in poorly bridged laboratories of genetics (molecular and above), neurobiology (systems, cell, and molecular), cognitive psychology, cognitive neuroscience, and education and rehabilitation. Praise should be given to the National Institutes of Health, especially the National Institute of Child Health and Human Development, for risking large amounts of taxpayer funds to promote cross-level research approaches, both in human populations and in animal models. Praise is also deserved by organizations like The Research Foundation, which has been pivotal in helping bring researchers together under pleasant surroundings, to talk about their work and to foster growing numbers of cross-level collaborations. The Como Conference certainly is a case in point that will undoubtedly spawn quantities of interdisciplinary research as did the conferences that preceded it in Italy, Spain, South Africa, New Mexico and Hawaii.

The Complexity of the Problem

The Dyslexic Mind

The problem of dyslexia is complex, where complex refers to deficits and dysfunctions describable at multiple levels: behavioral and educational (e.g., Lerner, 1989; Bashir & Scavuzzo, 1992; MacArthur, 1996; Snowling, 1996; Lyon & Moats, 1997; Tallal, Merzenich, Miller, & Jenkins, 1998; Rayner, Foorman, Perfetti, Pesetsky, & Seidenberg, 2001; Foorman, Breier, & Fletcher, 2003), cognitive (Stanovich, 1982; Frith, 1998; Lundberg, 1998; Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Ramus, 2001; Rayner et al. 2001; McCandliss & Noble, 2003; Vellutino, Fletcher, Snowling, & Scanlon, 2004; and others), brain activation (e.g., Eden & Zeffiro, 1998; Connolly, D'Arcy, Lynn-Newman, & Kemps, 2000; Pugh et al., 2000; Demonet, 2002; Sarkari et al., 2002; Small & Burton, 2002), brain structure and brain development (c.f., Hynd & Semrud-Clikeman, 1989; Galaburda & Livingstone, 1993; Galaburda, 1993; Galaburda, Menard, & Rosen, 1994; Jenner, Rosen, & Galaburda, 1999; Eckert

and Leonard 2000; Frenkel et al. 2000; Pennington et al. 2000; Leonard et al. 2001; Nicolson, Fawcett, & Dean, 2001; Stein, 2001; Zeffiro & Eden, 2001; Foster, Hynd, Morgan, & Hugdahl, 2002; Rae et al., 2002; Eckert et al., 2003; Sheen & Walsh, 2003), and genes (Morris et al., 2000; Nopola-Hemmi et al., 2001; Fisher & DeFries, 2002; Francks, MacPhie, & Monaco, 2002; Grigorenko et al., 2003; Kaminen et al., 2003; Londin, Meng, & Gruen, 2003; Marino et al., 2003; Richardson, Leppanen, Leiwo, & Lyytinen, 2003; Marino et al., 2004; Peyrard-Janvid et al., 2004; and others). Furthermore, it is difficult at times to know when changes first occur (the initial states, see Mehler & Bever, 1967), what changes follow, and how changes first occurring at one level spread to other levels (Galaburda, 1994; Zilles et al., 1995; Luhmann, Raabe, Qu, & Zilles, 1998; Tallal et al., 1998; Frenkel, Sherman, Bashan, Galaburda, & LoTurco, 2000; Lawn et al., 2000). Dyslexia most often is described in academic and behavioral terms, and the underlying cognitive representations and processes are less well known or even totally unknown. For example dyslexics fail at reading tests and they have difficulty playing word games that require some intimacy with the way words can be broken down into its component sounds, or phonemes (Bradley & Bryant, 1981; Snowling, 1981; Stanovich, 1982; Morais, Cluytens, & Alegria, 1984; Bertelson, 1986; Lundberg, 1998). It is assumed that these behavioral and educational problems arise from some corruption in underlying phonological representations and processes, but a clear idea of the nature of these subjacent cognitive structures does not exist. What is the fundamental nature of the phonology underlying the metaphonological and educational deficits disclosed by reading tests and word games? More research needs to be done to answer this basic question. Other behaviors are also implicated—visual perception and control of eye movements (Petri & Anderson, 1980; Pavlidis, 1985; Livingstone et al., 1991; Fischer, Biscaldi, & Otto, 1993; Lovegrove, 1993; Kubova, Kuba, Peregrin, & Novakova,1996; Slaghuis,

Twell, & Kingston, 1996; Stein & Walsh, 1997; Rayner, 1998; Christenson, Griffin, & Taylor, 2001; Facoetti & Molteni, 2001; Facoetti & Molteni, 2001; Laasonen, Service, & Virsu, 2001; Stein, 2001; Farrag, Khedr, & Abel-Naser, 2002; Williams et al., 2003; Skoyles & Skottun, 2004), motor control (Wolff, Cohen, & Drake, 1984; Nicolson et al., 1999; Lyytinen et al., 2001; Eckert et al., 2003; Mati-Zissi & Zafiropoulou, 2003; Ramus, Pidgeon, & Frith, 2003), rapid naming tasks (Denckla & Rudel, 1976; Wolf, 1986; Wolff, Michel, & Ovrut, 1990; Waber, Wolff, Forbes, & Weiler, 2000), visual neglect (Witelson, 1977; Hari, Renvall, & Tanskanen, 2001)--and again the underlying cognitive architectures, presumable corrupted, are not known.

Some researchers (Galaburda & Eidelberg, 1982; Fitch et al., 1994; Hari & Kiesila, 1996; Helenius, Uutela, & Hari, 1999; Clark et al., 2000; Benasich, 2002; Temple, 2002; , but see also Conlon, Sanders, & Zapart, 2004; Tallal, this volume), believe that the presumed problem with phonology lying underneath the deficits in phonological awareness is a sensory-perceptual distortion that arises during development and affects the processing of certain types of sounds, which in turn leads to abnormal phonological development, which in turn explains metaphonological deficits at the behavioral and educational levels. There is an interesting debate regarding this proposed anomalous pathway, which is fueled by the observation that many dyslexics do not have the expected sensory-perceptual deficits, described by Tallal (Bailey & Snowling, 2002; Heiervang, Stevenson, & Hugdahl, 2002), and that some dyslexics often have sensory-perceptual deficits of a type not predicted by Tallal's hypothesis (Farrag, Khedr, & Abel-Naser, 2002; also see Ramus, this volume). One obvious problem here, which is amenable to experimental clarification, is that the intervening level of description--the cognitive--describing the state of affairs at phonological representations and processes--is not available with nearly enough detail in the mature or developing dyslexic to permit or exclude a possible link

between sensory-perception and phonological awareness. The developmental perspective is important to stress here, whereby it is possible that initial states, effects of languages, effects of education, plasticity of and recovery from earlier deficits, all play important roles in modulating the final appearance of the dyslexic mind (for a case for developmental studies, see Thomas & Karmiloff-Smith, 2002).

The mind of a dyslexic contains other structures besides auditory and linguistic processes and representations, which include visual, motor, somesthetic, memory, attentional, motivations and other executive functions, the roles of which are not known in dyslexia. Lip service is given to plausible roles of these functions in the behavioral expression of dyslexia, but lip service is also given to the implausibility of their roles. The fact is that reaching reading competence is a task complex enough to be likely to involve bottom-up and top-down processes that piggyback squarely on executive functions controlling motivation and planning, attention, motor control, mental imagery, and various forms of memory function affecting multiple modalities. It is difficult to believe that a single lesion at any focus of any of the many pathways involved could produce a devastating reading disorder, and the possibility that injury at multiple levels and in multiple pathways is to be found remains alive. That said, there is no other way but the empirical one to find out to what extent dysfunction in any combination of these mental functions contributes to the dyslexia behavioral phenotype. Moreover, the research has to be intrusive enough to take knowledge beyond mere associations and correlations into the realm of causality. Thus, for instance, if blind people cannot read regular print and adults with attention deficit disorders have poor reading comprehension (Loge, Staton, & Beatty, 1990; Johnson, 1995), it is not only possible but likely that disturbances in visual and attentional domains, and in the other above-mentioned domains, could be playing a role in the dyslexic reading deficits. Moreover,

there is the pesky issue of co-morbidity. For instance, conditions such as Attention Deficit Disorder are often difficult to diagnose, especially when mild, leading to the possibility that there may be significant numbers of undiagnosed co-morbidities in our dyslexic populations that can explain the variability seen among dyslexic samples, which often leads to so much acrimonious debate about one cause or another (Semrud-Clikeman et al., 1992; Light & DeFries, 1995; Maughan et al., 1996; Purvis & Tannock, 1997; Richardson & Ross, 2000; King et al., 2003; Toplak, Rucklidge, Hetherington, John, & Tannock, 2003).

The Dyslexic Brain

Any attempt to examine the brain in order to explain behavior is fraught with serious complications, from the philosophical (Fodor, 1981) to the methodological (Poeppel, 1996). Given the fact that we have no idea about how the brain produces or supports cognitive phenomena and, indirectly through them, behaviors, the problem is at present made easier and we can focus simply on the parts of the brain that seem to participate and the level of description that is most useful for building cross-level bridges. This phrenological approach has not changed in principle for 200 years where it concerns the types of cognitively based behaviors that interest u--language, high-level vision, memory, attention, planning, motivation and emotions. But, even if we are better able to determine the parts of the brain involved, and even the useful level at which description should be carried out, we need to worry about time, because cognition and behavior have initial states and subsequent developmental courses. Plasticity changes after early injury could wreak havoc on the functional localization maps, for instance (Ojemann, 1979). Development, furthermore, may be accompanied by acquired injury at some point between childhood and senescence (because of stroke, head trauma, infection, trauma) and later still there can be added degenerative or involutional changes, which begin to take an insurmountable toll

on structural and functional integrity. In other words, whatever brain structure is associated with a given behavior, and whatever anomaly in brain structure is associated with a given behavioral deficit, there is likely to come along co-morbidities piggy-backing along to make interpretation more difficult.

In the case of developmental disorders such as dyslexia we assume that the initial state of brain structure is already altered, an assumption based on some supportive evidence (Galaburda, 1994; Galaburda & Cestnick, 2003). On top of that initial anomaly, there is also likely to occur additional developmental, acquired, involutional and degenerative changes, likely to be similar to that occurring among good readers, but not necessarily so if plasticity differs between dyslexic and non-dyslexic populations.

However, plasticity issues notwithstanding, the data thus far supports the presence of an abnormal initial state preceding reading acquisition, even language acquisition. The anomalies of cortical development seen in the dyslexic brain are traceable to fetal life (Galaburda & Kemper, 1979; Galaburda et al., 1985; Humphreys, Kaufmann, & Galaburda, 1990). Thus, we see nests of neurons and glia in the molecular layer of neocortex (called ectopias), representing errors of neuronal migration, which are located predominantly in perisylvian cortex and are found in greater numbers in the left hemisphere. Primary visual cortex is not affected by these malformations, although cortices known to be involved in high-level visual functions along the middle and inferior temporal lobes (e. g., area 37 of Brodmann) often show malformations. There are also frequent clusters in the superior temporal gyrus, on the planum temporale, in the inferior premotor and prefrontal cortex, and in the supramarginal and angular gyri (See Figure 1). These areas have been found to be implicated in dyslexics with the use of functional imaging techniques, including the letter string, or word-form, area that overlaps with area 37 (Frith &

Frith, 1996; Paulesu et al., 2001; Pugh et al., 2001; Shaywitz et al., 2002; Cohen & Dehaene, 2004). We have reason to suspect that the cortical lesions are related to the cognitive and metacognitive deficits demonstrable in many dyslexics in language and visual functions, but there is no way at present to prove this causality short of carrying out detailed transcranial magnetic stimulations experiments (see Théoret, this volume). Although one such study was performed by Branch Coslett in a patient with acquired alexia (Coslett & Monsul, 1994), I am not aware that the method has been applied to the study of developmental dyslexia. Experimental work in rodents would suggest that the anomalies can indeed cause disturbances in working memory and spatial maze functions (Schrott et al., 1993; Boehm, Sherman, Hoplight et al., 1996; Boehm, Sherman, Rosen et al., 1996; Balogh et al., 1998; Hyde, Sherman, Stavnezer, & Denenberg, 2000; Hyde et al., 2001; Hyde, Stavnezer, , Bimonte, Sherman, & Denenberg, 2002).

Insert Figure 1 about here

In addition to the cortical anomalies, there are abnormalities in the thalamus in the dyslexic brain, which consist of changes in the size of neurons in the medial and lateral geniculate nuclei. Such changes cannot be accurately dated, since they may reflect functional events taking place later in life (Greenough, Larson, & Withers, 1985; Grossman et al., 2003). We have reason to believe that these changes cause auditory and visual temporal processing deficits, which are found in some dyslexics. This statement about causality represents an extrapolation from experiments carried out in animals (see below under ”Help from animal studies”).

Experimental work in rodents has helped establish a causal relationship between brain changes and behavior, which can be used to hypothesize about the situation in the human dyslexic. It is possible to induce cortical anomalies similar to those found in the dyslexic cortex

(Rosen & Galaburda, 2000). Neuronal ectopias in the molecular layer and microgyria (both of which can be seen in the dyslexic brain) can be induced using a freezing probe near the end of neuronal migration to the cortex. Induction of these anomalies is associated with behavioral changes in the animal (Rosen, Waters, Galaburda, & Denenberg, 1995), but they also lead to secondary changes in the thalamus that mimic those found in the dyslexic brains (Herman et al., 1997). This has lead us to postulate without direct evidence in the human that the cortical anomaly occurs first in the dyslexic brain, some time during mid gestation, which in turn causes secondary changes in the thalamus. The secondary changes in the thalamus, either directly or indirectly, cause the deficits in temporal processing in the animal. Thus, we have proposed that in the dyslexic brain some factor, or perhaps several factors, can result in disordered neuronal migration. The latter then causes secondary changes in the thalamus, or alternatively the same factors that cause neuronal migration anomalies also cause changes in the thalamus (Galaburda & Duchaine, 2003). The changes in the cortex then lead to cognitive and metacognitive deficits, while the changes in the thalamus produce deficits in sensory-perceptual processing. But, what causes the initial cortical anomaly in dyslexics? I will outline one plausible pathway from brain back to gene in the following section, but first I want to review some outstanding anatomical issues.

In the 8 dyslexic brains examined we found a comparable distribution of cortical anomalies, namely the left perisylvian cortex more so than the right and more so than non-perisylvian cortex (Humphreys, Kaufmann, & Galaburda, 1990, Figure 1). Why that distribution of lesions? One possibility that has been raised in discussion before is that the location of the lesions is such because we selected our cases for being dyslexic. Were we to have chosen cases with non-verbal learning disabilities, autism, mathematical learning disability, etc., we would have found the

same lesions somewhere else—a good phrenological hypothesis. However, although cortical ectopias are indeed described in other neurodevelopmental syndromes (Wisniewski, Dambska, Sher, & Qazi, 1983; Kotkoskie & Norton, 1988; Kuzniecky, 1994; Konovalov, Kovetsky, Bobryshev, & Ashwell 1997; Barkovich, Kuzniecky, Jackson, Guerrini, & Dobyns 2001; Komatsu, Sakata-Haga, Sawada, Hisano, & Fukui, 2001), they have not been found in specific learning disorders of the types listed above. It may indeed be the case that dyslexia is the only consequence of focally clustered ectopias in perisylvian cortex and that this is the only known distribution. We have no idea to date for this distribution, once we exclude a selection bias. There are other genetic disorders that produced uneven cortical pathology (Pilz et al., 1998), and several genes have been identified that act regionally in the brain to pattern cortical development (Bishop, Goudreau, & O'Leary, 2000; Grove & Fukuchi-Shimogori, 2003). The possibility exists that the fundamental causes of dyslexia interact in this way with other genes that are expressed regionally.

A second problem with our current knowledge about the anatomy of dyslexia relates to the planum temporale. This structure, which is an arbitrarily defined region on the superior temporal plane, contains bits and pieces of a variety of auditory regions, including those spilling out of Heschl's gyrus (BA 41 and 42), and caudal and lateral auditory associations cortices. This region is known to show a leftward bias in human populations and has been thought to be a marker for language lateralization to the left hemisphere (reviewed in (Hugdahl, 2000). Deviations from this pattern have been described in dyslexia (Galaburda et al., 1985; Hugdahl et al., 1998; Eckert & Leonard, 2000) and other developmental disorders (Frangou et al., 1997; Sommer, Ramsey, Kahn, Aleman, & Bouma, 2001; Rojas et al., 2002), as well as in non-righthanders (Foundas, Leonard, & Hanna-Pladdy, 2002). However, there is something more to the lack of asymmetry in

the dyslexic planum temporale. We carried out experimental studies in rats that showed that there should be an inverse relationship between areal asymmetry and total size (Galaburda et al., 1986; Rosen, Sherman, Mehler, Emsbo, & Galaburda, 1989), i.e., the sum of the two sides is greater the more symmetric an area is. Asymmetry, therefore, appears to be the curtailment of one side, rather than the enlargement of one side or a storage issue, whereby the left and right sides add up to a constant with population variation. However, in the presence of cortical malformations, this relationship breaks down and there is no longer a prediction about total size from degree of asymmetry (Rosen et al., 1989). There have been reports, for instance, that the plana are small in dyslexics even though they are more symmetric (Humphreys, Kaufmann, & Galaburda, 1990; Eckert & Leonard, 2000; Leonard et al., 2001). At present we do not know the mechanism of interaction between asymmetry and brain malformation. We also do not know whether this abnormal symmetry in dyslexics (as opposed to a 'normal' symmetry in left-handers and other normal individuals) plays a causative role in the behavioral profile of dyslexia.

Help from animal studies

From brain to behavior

Examination of autopsied brains in humans cannot address the issue of causality, and functional imaging studies in living dyslexics do not answer questions of etiology, i.e., the reason for which the brain activates in the particular way that it does. Experimental work on rodents has been helpful in disclosing possible pathways between brain changes and behavior, with the limitation that modeling human behaviors in rodents entails. Initially the research in our laboratories focused on behaviors related to the cortical malformations. The first models, those of immune-defective mice with spontaneously occurring cortical ectopias (Sherman, Galaburda, & Geschwind, 1985; Sherman, Galaburda, Behan, & Rosen, 1987), showed a range of behavioral

anomalies, including many areas where affected animals were weaker than controls and some where they were more adept (Schrott et al., 1993; Boehm, Sherman, Hoplight et al., 1996; Boehm, Sherman, Rosen et al., 1996; Balogh et al., 1998; Hyde et al., 2000; Hyde et al., 2002). Those findings were interesting in that they linked up nicely to the human data on dyslexics, which has from time to time mentioned cognitive deficits but also special skills (Rack, 1981; McNamara et al., 1994; Wolff & Lundberg, 2002; von Karolyi ,Winner, Gray, & Sherman, 2003).

Some of the deficits associated with the presence of cortical malformations could be assuaged if young animals were raised in enriched environments (cages with ramps, balls of yarn, etc.; (Schrott et al., 1992; Boehm, Sherman, Hoplight et al., 1996; Hoplight et al., 2001). This, too, suggested a link to the situation in human dyslexics where it appeared that an enriched environment minimized the impact of risk (Foorman, Breier, & Fletcher, 2003). Such an effect had also begun to appear in the Alzheimer's literature, whereby individuals with more years of education were demonstrated to stave off the onset of Alzheimer symptoms for up to 10 years in some cases (Stern et al., 1994).

One problem with the cortical ectopias/behavioral correlations in the rodents was the absence of sex differences. Most studies on the prevalence of dyslexia indicated a sex bias, whereby boys were affected more often than girls (see recent study by Rutter et al., 2004). A selection bias was cited to explain this difference (Shaywitz et al., 1990), but control for this factor still showed a male predominance, although perhaps not as high as previously thought (Rutter et al., 2004). Leaving aside a selection bias, how else to explain a sex difference such as this? One possibility is that the trait is Y-chromosome related; another is that it is X-linked and recessive; a third is the uneven effect of sex steroids in the causation of the disorder or its manifestations (Geschwind &

Galaburda, 1985a; 1985b), acting directly or indirectly on the malformations. A fourth possibility is that the brains of males and females are fundamentally different at the initial state (Geschwind & Galaburda, 1985a; 1985b; Aboitiz et al., 1995; Wisniewski, 1998) so that any perturbation--congenital, acquired, degenerative--will have a different impact on the two sexes.

A Y-linked trait would never be expected to occur in females, so this possibility is easily excluded. An X-linked recessive trait would be expected to occur in females only rarely, which is not the case for dyslexia. The effects of hormones remain the most likely explanation for the observed sex difference. The possibility of lesions occurring with comparable frequency between the sexes but falling upon a different brain substrate and thus leading to different effects is also an attractive one, but difficult to support by what we know about gender based sex differences in the brain. In general, brain differences between the sexes have been demonstrated mainly in those parts of the brain that regulate reproductive behavior and not in regards to perceptual or cognitive behaviors, with rare exceptions (Wisniewski, 1998).

One more contrast to consider is whether lesions themselves occur at different rates between males and females (by any of the above-mentioned explanations), or whether differences in brain plasticity after the lesion account for the observed sex differences (Teskey, Hutchinson, & Kolb, 1999; Trentani et al., 2003). Soon after we started to introduce cortical malformations in newborn rat brains Holly Fitch discovered that the males and females in the sample were not responding equally to the lesions when tested on one specific behavior—auditory temporal processing (Fitch et al., 1997; Herman et al., 1997; Peiffer, Rosen, & Fitch, 2002b; 2004). Glenn Rosen, in our laboratory, went back and carefully analyzed the size and location of the lesions with the idea that perhaps the explanation lay in unplanned differences in the original lesions. However, no such differences were found. We had to conclude that the effect of the lesions on

some auditory behaviors was different between the sexes. Following these early experiments, we have consistently found that the cortical lesions produce different effects in males and females in a range of auditory behaviors (also, see Fitch, this volume), and that this can be explained by changes that do not occur in the cerebral cortex, but rather in the rat thalamus (Herman et al., 1997).

Two distinct anatomical findings were made in the dyslexic brains--cortical malformations and changes in cell distribution and size in the medial and lateral geniculate nuclei. After finding sex differences in auditory temporal processing in the rats with induced malformations we went back and examined the geniculate nuclei of affected and control animals. The possibility existed that even though cortical malformations and cortical behaviors did not differentiate males and females, thalamic changes and auditory processing behaviors might, which turned out to be the case (Herman et al., 1997; Rosen, Burstein, & Galaburda, 2000; Peiffer, Rosen, & Fitch, 2002a). Numerous studies showed that the induction of cortical malformations in the rat lead to changes in the medial geniculate nucleus of male rats only, whereby there was a redistribution of neuronal sizes from larger to smaller, similar to the findings in the dyslexic brains. Female brains did not show these neuronal size changes, and female rats did not show temporal processing deficits, thus suggesting that the two were linked.

Are the sex differences seen in the dyslexia population related to thalamic cell changes and temporal processing deficits? The answer to this question is not as yet known and would be difficult to obtain. We can postulate that once a female is found to be dyslexic, she will be found to have the thalamic changes, if the above suppositions are valid. The population of interest in this case would be the group of girls or women from dyslexic families who have cortical malformations, absence of thalamic changes, and absence of dyslexic symptoms and another

with both cortical malformations and thalamic changes, this group with dyslexia. We may expect to discover these individuals once structural MRI imaging technology is sufficiently developed to image cortical ectopias in living subjects. If the hypothesis is correct, we should expect to find girls or women from dyslexic families who have cortical malformations and no dyslexia, presumably due to a lack of thalamic change in response to the cortical malformations. To image in living human subject the cell changes in the thalamus directly would require a technology not as yet available, even in its infancy.

To summarize, we find ourselves in a situation whereby the only sex difference we can demonstrate anatomically and behaviorally in animal models is one that links auditory temporal processing to changes in the thalamus, which in turn are secondary to induced cortical malformations. The cortical changes themselves, or the behaviors linked to them, do not show a sex bias. This can be taken to mean that fundamental to the sex differences seen in dyslexia is an underlying problem in auditory temporal processing defect, a statement that would be met with a great deal of resistance by some experts (see Ramus, this volume). However, another possibility is that we have not found the right level at which to analyze the cortical anatomy and cortically based behaviors and that sex differences are indeed to be found at those levels. Recently in our laboratory, Bettina Meples carried out two experiments (unpublished) that seem to indicate that subtle differences in the cortical lesions may exist between males and females. Relying on information from the field of cerebral palsy (Patkai et al., 2001; also see Gressens, this volume)), she exposed pregnant females to the cytokine Interleukin-9. This substance was implicated in changing the size of the lesion in models of periventricular leukomalacia. Intraperitoneal injection of 60 µg/kg of IL-9 produced an enlargement of the area of microgyria induced by the usual method of cortical freezing, but this effect was found only in male rats. Experiments such

as this demonstrate that there could be circulating factors such as IL-9 that can modify the severity of cortical a malformation in utero in dyslexic families so that females will end up with smaller lesions and possibly smaller behavioral effects.

Another finding made by Mesples in a second experiment (unpublished) designed to investigate the possibility that plasticity effects from induced cortical malformations that affected cell sizes in the thalamus involved sexually dimorphic differential cell death. Both decreased and increased survival has been reported in males versus female neurons (Nunez, Lauschke, & Juraska, 2001; Zhang et al., 2003). Mesples found that markers of cell death by Fluoro-Jade B staining after induction of a microgyrus in the barrel fields, characterized as small and large degenerating profiles in the ventrobasal complex, were qualitatively and quantitatively different in male and female rats, with males showing evidence of more cell death than females from presumably the same initial cortical freezing injury.

In summary these findings do suggest that male-female differences may exist both in the cortex and in the thalamus in relation to cortical malformations and thalamic cell changes, which would help to explain sex differences in the prevalence of dyslexia between men and women. Despite the possibility that cortical sex differences play a role in this sex difference, most of the current evidence still points to differences in plasticity affecting the thalamus and resulting auditory processing deficits, which keeps the idea of this anatomical-behavioral complex alive as an important ingredient of the behavioral trait we call dyslexia.

From Genes to Brain

So far I have reviewed with a broad brush the evidence linking brain changes, in the cortex and thalamus, to behaviors seen among individuals with developmental dyslexia. But, how do the changes originate in the dyslexic brain? In the experimental animal model we induce them with a

freezing probe, but this is hardly the mechanism active in dyslexics. In a group a mutant mice, which includes spontaneous mutations as well as recombinant inbred strains and congenic animals, the cortical malformations arise without additional cortical manipulation at birth. There are potential chromosomal sites linked to the malformations, but not genes so far identified. On the other hand, progress has been made in the discovery of genes related to dyslexia in humans (see review by Cecilia Marino, this volume). Here I focus on a gene on Chromosome 15 recently proposed to be a dyslexia candidate gene, the so-called DYX1C1 gene (Taipale et al., 2003). As Joe LoTurco reports in this volume, Dyx1c1 is essential for neurons in the developing cerebral neocortex to migrate. Interference of Dyx1c1 in the fetal brain disrupts neuronal migration and creates malformations similar to those observed in the brains of dyslexics. The immediate malformation is neuronal migration arrest near the ventricular zone, followed later by evidence of cortical dysplasias. The region of Dyx1c1 previously associated with dyslexia susceptibility by mutation or deletion is necessary and sufficient to rescue disrupted migration. These results establish Dyx1c1 as a novel neuronal migration gene, and link a probable genetic cause of dyslexia with alterations in neuronal migration.

Even though Cecilia Marino and colleagues (this volume) did not find a link between DYX1C1 and dyslexia in her Italian cohorts, such a link was established in the Finish population published by Taippale and by others (Grigorenko et al., 1997; Schulte-Korne et al., 1998; Morris et al., 2000; Wigg et al., 2004), and one must entertain the possibility that different genes act in different ethnic groups. Several neuronal migration genes have been reported and it is likely that many others are still to be discovered. The finding that DYX1C1 is indeed a neuronal migration gene, would serve to indicate that a plausible pathway exists between a specific gene mutation and the brain changes seen in dyslexia. There are likely to be others yet unspecified.

Conclusions

A plausible pathway now available to explain how a genetic mutation produces an abnormal behavior often, if not always, associated with dyslexia. The pathway is the following: a gene mutation affecting a neuronal migration gene produces a cortical migration anomaly. This migration anomaly is associated secondary changes in the thalamus and perhaps other subcortical structures. The data do not exclude the possibility that the genetic mutation also has a direct effect on the development of subcortical structures (although there are no present data for or against this possibility), and that the plasticity interactions between cortical and thalamic developments are additional to the underlying direct effects. As the abnormal genes and subsequent plasticity effects cause the brain changes, the latter are responsible for sensory-perceptual-motor low level and cognitive and metacognitive deficits, attributable respectively to plasticity related thalamic and other subcortical changes as well as direct effects of the cortical malformation and secondary cortical changes. The direct pathway is, then, from gene to brain to behavior, although important details need to be worked out and other pathways, active in other subgroups of dyslexics, arising in different genes perhaps, need to be discovered.

The program of research on the fundamental causes of dyslexia has been successful so far to the extent that a pathway such as that outlined above has been possible to emerge from a broad collaboration of expertise on brain development, genetics, and behavioral science with healthy bridges among them. It is to my knowledge the first time a rough pathway has been presented for a complex abnormal trait in a complex species. But more work is needed to fully understand dyslexia and to make progress in other developmental disorders of behavior and cognition.

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Figure Legends

Figure 1: Examples of anomalous activation (arrows) of the letter string/word form area (Brunswick et al. 1999) and left perisylvian cortex (Georgiewa et al. 2002) (A and B, respectively) in dyslexics. A composite map of the location of ectopias over 8 brains studied is shown in C and D. The distribution of the anomalies is comparable to that of the activation studies; note arrow.