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Neuroscience, Education, and Learning Disabilities

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We are entering an age in which knowledge about the brain in general, and the mind in particular,[1] will inform policy. Genetics already informs policy, which is curious since advances in genetics are significantly more recent than advances in the brain sciences, including cognitive science, and the distance between genes and behavior is long and complex, often making poor predictions from the former to the latter. Too much has been learned about brain structure and function (including mental structure and function), their development and involution throughout the life span, and their deterioration after injury and illness, to ignore in fields such as the law, education, economics, even the humanities and others relevant to human happiness and human progress. For example, biological brain markers exist to help predict the cognitive development of children, and much is known about how children, even infants, learn (Benarós, Lipina, Segretin, Hermida, & Jorge, 2010; Berrettini, 2005; Bloom & Weisberg, 2007; Kebir, Tabbane, Sengupta, & Joober, 2009; Morley & Montgomery, 2001; Plomin & Craig, 2001; van Belzen & Heutink, 2006). Likewise, not only genetic characteristics, but also brain structural and functional markers exist that help diagnose and design treatments for developmental disorders affecting perception, cognition, and behavior, although this is still to be considered a nascent area of research (Benarós, *et al.*, 2010; Eckert, 2004; Keenan, Thangaraj, Halpern, & Schlaug, 2001; Zamarian, Ischebeck, & Delazer, 2009; Zatorre, 2003). In this brief and focused review, I will outline some of the progress made in the field of learning disabilities, particularly the biology of developmental dyslexia, which has the potential to grow into a mature neuroscience of education.

Advances in genetics and neuroscience

Advances in the neurosciences and genetics have a bearing on the future of education. Starting with genetics, just as the field of pharmacogenomics looms near (Lee & Mudaliar, 2009; Service, 2005), which means that soon

[1] Note that here I use the word 'mind' as part of the concept of brain, whereby brain also consists of structures and functions that lie outside the mind, e.g., regulation of blood pressure, temperature control, endocrine homeostasis, etc.

we will be able to know with better confidence which medications work with which people and how to minimize undesirable side effects after examining specific genetic characteristics of a given individual, we can anticipate with equal certainty that genetics will allow us to know what educational programs work better for what children. This is not pie in the sky; instead, I am referring to empirical data correlating learning styles (presentation and testing formats, speed of learning, cognitive strengths and weaknesses, etc.) with single nucleotide polymorphisms or haplotypes in genetically characterized human populations. However, the empirical research still needs to be done, which means that new resources must be allocated to this type of research, which in turn depends on the priority society gives to education. This is laborious research requiring large Ns in the samples, culturally normed psychological batteries and/or well circumscribed and highly reproducible cognitive/behavioral endophenotypes, as well as genomic analyses with high throughput and low cost. But, even assuming that this difficult to obtain knowledge can be gathered, it is still a substantial challenge to develop curricula based on it and train educators to apply them and measure their outcome, both at short and long-term follow up times.

In addition to genetics, knowledge from neuroscience also lends itself to applications to education, and I would hypothesize that the predictive value of neuroscience data to learning is apt to be, on the average, greater than that of genetic data. This is explained simply by the fact that the distance between brain and behavior is shorter than that between developmental genes and behavior, where there is much time and many possible strategies for compensation. But neuroscience is a broad subject, ranging from genetic expression in neural tissues, where predictive value is more closely shared with other aspects of genetics, to downstream pathways in cells, the formation of circuits and networks, cognitive psychology dealing with the structure of sensory-perceptual, cognitive, and behavioral representations and processes in the mind, where mental structures are much more closely paired with observed behavior. Thus, for example, the best prediction for dyslexia is not the presence of a risk allele, or even a deviant manifestation of brain asymmetry, but rather the presence of metaphonological weakness. Moreover, each of these levels has a developmental history that must be taken into consideration, as abnormal neural structures during development are possibly compatible with substantial compensation or worsening later on.

Neuroscience knowledge at low levels, involving gene expression and signaling pathways, has potential for helping develop functional chemical markers for learning style – for instance relating to ligands and receptors that are activated on PET or MRI scans during particular tasks – as well as drugs that

can enhance learning, diminish forgetting, improve attention, etc. (Eisdorfer, Nowlin, & Wilkie, 1970; Greely *et al.*, 2008; Marshall, 2004; Young & Colpaert, 2009). At the highest levels of cognitive psychology, knowledge about the structure and development of the mind can serve to devise better formats and timings for presenting educational materials (Roederer & Moody, 2008; Watson & Sanderson, 2007; Yeh, Merlo, Wickens, & Brandenburg, 2003). At the mid-levels, knowledge of structural and functional anatomy, particularly as obtained by high resolution *in vivo* imaging of the brain anatomy or by activation studies under specific cognitive and sensory-perceptual challenges, can serve not only for identifying variant anatomies associated with disability or advantage and deviant location and size of activation under specific tasks, but also to assess the effects of learning, unlearning, and the treatment of learning disorders and other disorders of cognitive function (Blair & Diamond, 2008; Draganski & May, 2008; Shaywitz & Shaywitz, 2008). However, it should be made clear that these markers are unlikely to jump up and declare themselves, as often the most obvious findings are not visible if one does not have a prediction for their existence. For instance, for decades the obvious asymmetry of the planum temporale was missed, until von Economo and Horn looked for it (Economo & Horn, 1930).

Ultimately, it is difficult and probably ill-advised to separate genetics from neuroscience, and indeed from all other branches of human biology, when thinking about the elements that contribute to learning in children and adults. A healthy mind begins with healthy genes, continues with healthy brain development, and ends with a healthy cognitive and emotional environment conducive to learning, which in turn depend on a social and political system that takes the health and education of children seriously. Healthy brain development starts with a healthy pregnancy (healthy genes and intrauterine environment) and continues with good nutrition, a culturally enriched and energetic family environment, public health measures aimed at arresting infections and toxic exposures, minimization of violence and personal loss, and the preservation of culture and the desire to pass it on and improve it through child education. Positive exposure at any of these levels propagates quickly to the other levels and augments the odds that these other levels will also be positive; injury at any of these levels also propagates quickly to the other levels. Thus toxic exposures can damage genes (Wallace, 2005; Yamashita & Matsumoto, 2007) and family stress and violence can kill hippocampal neurons, even when the affected individual has not suffered direct, visible physical injury (Eiland & McEwen, 2010). Ultimately, then, it is not possible to think of genetics, neuroscience, and education, without thinking of society as a whole.

Cultural bases of developmental dyslexia

Dyslexia has from the start been defined as a difficulty with learning to read and with reaching normal reading competency (Fletcher, 2009; Lyon & Moats, 1997), and continues to be so in the schools and in the lay literature, sometimes reduced to the inaccurate observation that it consists mainly of reading and writing in mirror (Terepocki, Kruk, & Willows, 2002). Recently, however, *endophenotypes,* such as phonological awareness or magnocellular function, increasingly have entered scientific jargon to stand for dyslexia after studies associating these features of reading disorders with genetic and/or neurobiological characteristics have been productive (Bishop, 2009; Fisher & DeFries, 2002; Fisher & Francks, 2006; Igo, *et al.*, 2006; Kebir, *et al.*, 2009; Roeske, *et al.*; C.M. Stein, *et al.*, 2006; J. Stein, 2001). 'Dyslexia', in fact, may have become an outdated term, just as 'diabetes' standing alone is an outdated term now replaced by 'diabetes mellitus, types one or two', 'gestational diabetes' and 'diabetes insipidus', with substantial biological differences among them.

Although biological differences among dyslexics, such as being identified by differences in one single nucleotide polymorphism or another, have not as yet served to differentiate among different behavioral forms of dyslexia (but see, by comparison, neurophysiological markers (Lachmann, Berti, Kujala, & Schroger, 2005)), it is possible that this differentiation will become clear in the near future, once the appropriate behavioral endophenotypes are identified. This limitation notwithstanding, efforts to understand purely environmental, cultural factors in dyslexia continue to take place and shed light onto the relationship between dyslexia and culture. Thus, for instance, the structure of the native language determines the incidence, prevalence, and behavioral characteristics of dyslexia (Huessy, 1967; Paulesu *et al.*, 2001; Ziegler & Goswami, 2005; Ziegler, Perry, MaWyatt, Ladner, & Schulte-Korne, 2003). For instance, whereas in languages with opaque orthographies, such as English, most dyslexics, particularly young ones, read slowly and make phonological errors (e.g., reading 'symphony' for 'sympathy'), in languages such as Finnish and Italian, where the orthography is transparent, only slow reading and poor spelling are seen (Angelelli, Notarnicola, Judica, Zoccolotti, & Luzzatti; Holopainen, Ahonen, & Lyytinen, 2001; Kiuru *et al.*; Serrano & Defior, 2008). On the other hand, learning a foreign language is a challenge for dyslexics anywhere (Downey, Snyder, & Hill, 2000; Sparks, Patton, Ganschow, Humbach, & Javorsky, 2006).

There is a longstanding debate as to whether dyslexia should be defined independently from intelligence, or should take intelligence into account. Although it is not possible in this brief chapter to review this complex sub-

ject, I want to make some comments that may be relevant to the subject of education, dyslexia, and neuroscience (for a more general recent review, please see (Gustafson & Samuelsson, 1999)). Intelligence, as we measure it, is influenced not only by differences in aptitude, motivation, attention, and alertness, but also by accumulated knowledge, which depends on several factors, including family and societal encouragement, opportunity, and support. In literate societies, dyslexia interferes with the acquisition of knowledge, since a large proportion of this knowledge is received *via* the written word, and dyslexics, on average, read less. This need not be true in societies where knowledge is imparted by different means, such as by imitation and story telling. Thus, it is difficult to separate intelligence, as we measure it, from a reading disorder. Even the portions of the intelligence test dealing with non-verbal skills and achievement depend in part on verbal abilities, since this is the medium through which instructions are given for skill acquisition and skill testing. In general, non-verbal abilities are found to be normal in dyslexic children (Del Giudice *et al.*, 2000, but c.f. Eden, Stein, Wood, & Wood, 1996; Eden, Wood, & Stein, 2003; Russeler, Scholz, Jordan, & Quaiser-Pohl, 2005), and, in fact, they may be underestimated during testing (Attree, Turner, & Cowell, 2009; Gotestam, 1990).

Even as dyslexia interferes with the measurement of intelligence, intelligence could interfere with the measurement of dyslexia, especially if the measures focus on reading speed and reading comprehension. Thus, a dyslexic endowed with a powerful memory will be helped with decoding text because he will be better able to guess at words he is having difficulty decoding based on prior knowledge. This type of dyslexic would read text quite well, even if he would trip when reading a word list, where he does not derive benefit from semantic, syntactic, and pragmatic cues. Similarly, a dyslexic endowed with a well-tuned attention and executive system will be able to better manage information during the original experience of acquisition and subsequent retrieval stages, such that he will be less dependent on his phonological abilities to derive meaning from text. Does this mean that his phonological abilities are stronger that those of a child who is less able? Actually, they could even be weaker, as these are independent mental faculties; but it is clear that the intelligent child with relatively mild phonological deficits will do best, and may actually defy detection and diagnosis, while the less intelligent child with severe phonological deficits will do worst. Thus, the core system mainly responsible for dyslexia, the phonological module or access to it (Ramus & Szenkovits, 2008), is independent of intelligence, in that it can be either strong or weak in intelligent and less intelligent children; thus, the influence of intelligence on the ultimate clin-

ical manifestations of a weak phonological module is difficult to ignore. What this also says is that, just as we have been able to think of and implement different enrichment programs for normally developing children according to their level of intelligence, we should likewise not treat all dyslexic children equally, and should be receptive to thinking of ways of enriching their educational experience through especially designed educational programs. Similarly, children with weaker memory and executive functions should not be expected to learn most efficiently using educational systems that have been designed without concern for the diversity of intellectual skills. This is not a matter of the influence of neuroscience on education, but rather on the importance of developmental psychology for education.

Neuroscience of dyslexia

There are two lines of research that characterize the neuroscience of dyslexia. First, there are imaging studies *in vivo* on dyslexics that investigate how the brain activates when performing language, reading and other cognitive tasks, which have shown differences between them and appropriate reading controls (e.g. Demonet, Taylor, & Chaix, 2004; Pugh *et al.*, 2000). Similarly, *in vivo* imaging studies have been able to show anatomical differences between dyslexic and control brains (see, for instance, Chang *et al.*, 2007; Leonard & Eckert, 2008; Pernet, Andersson, Paulesu, & Demonet, 2009). The main usefulness of knowing about these anatomical and physiological differences is their potential for (1) helping in the early diagnosis of dyslexia, before the clinical deficits are evident, so that preventive and treatment approaches can be implemented, and (2) contributing to the classification of the disorder into subtypes that may respond to different forms of prevention and treatment. For these two objectives to be reached, it appears that the most important factor is to deploy the neuroscience tools much earlier in development, at a time when the forerunners of the dyslexic cognitive and behavioral phenotypes are not well known and may look very different from the cognitive and behavioral picture at the usual time of diagnosis. However, early identification has remained a challenge, although some progress is being achieved (Benasich *et al.*, 2006; Facoetti *et al.*; Goswami *et al.*; Lyytinen *et al.*, 2004; Raschle, Chang, & Gaab; van der Lely & Marshall). Thus, for quite some time investigators have been studying younger siblings of dyslexic children, who are considered to be at an increased risk of developing dyslexia, based on early investigations demonstrating familial aggregation (DeFries, Singer, Foch, & Lewitter, 1978). More recent genetic studies using linkage and genomewide association have identified several risk alleles, some of which have gained additional strength

through replication studies in various populations and larger numbers (for recent reviews, see Fisher & Francks, 2006; Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006; Scerri & Schulte Korne; Smith, 2007). Thus, of these *KIAA0319*, *DCDC2*, and *DYX1C1* predict for increase risk of developing dyslexia, but, as with other complex traits, account for a small proportion of the dyslexic population. It is expected that additional genes will be found and associations strengthened in larger numbers as the field of genetic epidemiology continues to advance, which has been the case over the past decade. Less likely to succeed, in my view, will be our ability to link specific genetic mutations or variants to subtypes of dyslexia, since it is likely to be the case, and there is some evidence for this (Galaburda, *et al.*, 2006), that multiple genes affected participate in the same molecular pathways, thus leading ultimately to both shared brain variants and cognitive phenotypes.

The dyslexic brain

Even though dyslexia, as defined, is diagnosed during the time when a child is learning to read, usually between 5 and 7 years of age, the brain changes that seem to predispose to the learning disorder are present from a time before birth (Galaburda & Kemper, 1979; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Chang *et al.*, 2007). The first anatomical studies of dyslexia, performed on autopsy brains, disclosed evidence of neuronal migration abnormalities. These studies were limited by the fact that the number of human brains examined at autopsy was small and because additional autopsy studies were not published by others, most likely as a result of the difficulty in obtaining these brains and funding this type of research, rather than because of the finding of non confirmatory results. As a way to get around the limitations of the human autopsy studies, Galaburda and colleagues searched for and discovered mouse mutants that exhibited similar neuronal migration anomalies, and which also had learning deficits (Rosen, Sherman, & Galaburda, 1989; Rosen, Sherman, Mehler, Emsbo, & Galaburda, 1989; Sherman, Galaburda, Behan, & Rosen, 1987; Sherman, Morrison, Rosen, Behan, & Galaburda, 1990; Sherman, Stone, Press, Rosen, & Galaburda, 1990; Sherman, Stone, Rosen, & Galaburda, 1990). These early animal studies were very useful for establishing the relationship between focal neuronal migration anomalies, abnormal circuits, and abnormal learning behaviors, but lacked the ability to establish causal relationships among these findings. However, a stronger causal association between neuronal migration anomalies and learning deficits was established after these investigators learned to create neuronal migrational anomalies in otherwise normal animals. After induction of anomalies, these otherwise normal an-

imals exhibited anatomical and behavioral changes that modeled some aspects of dyslexia in humans (Herman, Galaburda, Fitch, Carter, & Rosen, 1997; Rosen, Burstein, & Galaburda, 2000; Rosen, Herman, & Galaburda, 1999; Rosen, Mesples, Hendriks, & Galaburda, 2006; Rosen, Press, Sherman, & Galaburda, 1992; Rosen, Sherman, & Galaburda, 1994, 1996; Rosen, Sigel, Sherman, & Galaburda, 1995; Rosen, Waters, Galaburda, & Denenberg, 1995; Rosen, Windzio, & Galaburda, 2001). Specifically, the rats that were thus treated showed difficulties processing certain sounds (Clark, Rosen, Tallal, & Fitch, 2000; Fitch, Breslawski, Rosen, & Chrobak, 2008; Herman, *et al.*, 1997; Peiffer, Friedman, Rosen, & Fitch, 2004; Peiffer, Rosen, & Fitch, 2002, 2004; Threlkeld *et al.*, 2007), and it was concluded that similar anatomical abnormalities in humans might also cause auditory processing deficits that could predispose to phonological deficits during and after language acquisition.

Additional work in rats with induced neuronal migration abnormalities were shown to exhibit abnormal thalamic architecture and abnormal axonal connections between the thalamus and the cortex (Herman, *et al.*, 1997; Livingstone, Rosen, Drislane, & Galaburda, 1991; Rosen, *et al.*, 2000; Rosen, *et al.*, 2006), in addition to abnormal cortical architecture and cortico-cortical connections both within and between the hemispheres. This, coupled with neurophysiological studies that showed aberrant acoustic representations in the rat's auditory cortex (Escabi, Higgins, Galaburda, Rosen, & Read, 2007; Higgins, Escabi, Rosen, Galaburda, & Read, 2008), suggested that an altered thalamocortical relationship might be behind the abnormal auditory behaviors in this rat model of dyslexia. Further details were uncovered by this research, such as male-female differences in these thalamic changes, with female thalami showing an absent response to induction of cortical neuronal migration accompanied by absent abnormalities in acoustic processing. Thus, part of the gender difference reported in dyslexia could be explained by gender-differences in the response to cortical injury, as it concerns cortico-thalamic organization.

Genes and the dyslexic brain

The earlier rodent models of abnormal auditory behaviors resulting from early damage to the cerebral cortex and secondary thalamic changes helped to understand the relationship between developmental cortical abnormalities and abnormal auditory processing, although it remained an incomplete dyslexia model for two reasons. First, abnormal auditory processing is not universally found among dyslexics, so experts argued that it is not necessary for dyslexia to occur, and, by extension, the acoustic deficits in the rat are ir-

relevant. Less clear is the answer to whether the presence of abnormal auditory processing during development is sufficient for dyslexia to occur. The fact that acoustic deficits are not found in all dyslexics may be related to the time of testing. Thus, most studies have looked at older children, and it can be argued that the hypothesized acoustic deficits improve with age and may not be diagnosable in a substantial proportion of older children. The work of April Benasich in babies (Benasich, *et al.*, 2006) and results from Holly Fitch's lab in rodents (Peiffer, Friedman, *et al.*, 2004; Threlkeld, *et al.*, 2007) would tend to support this hypothesis. Regarding the second question, whether abnormal auditory processing is sufficient for dyslexia to follow during development, the answer can be more cavalier. Recall, above, that in some languages and in certain cognitive states, e.g., high level of intelligence, and languages with transparent orthographies, the presence of even substantial precursors for dyslexia may not result in dyslexia, at least one that could easily be diagnosed during the school years. Thus, at present, these represent the best arguments for continuing to model dyslexia in rodents, by linking neuronal migration anomalies to abnormal auditory processing. However, this type of research is not a substitution for developmental research targeting infants even in the perinatal period and looking for early evidence of sound processing deficits and abnormal phonological acquisition. Despite the differences between rodents and humans, it is expected the animal research can help guide the types of questions that may be asked in clinical research searching for early markers of dyslexia risk in humans.

That said, the second reason for the rodent lesion model's remaining an incomplete animal model of dyslexia is the fact that injury to the brain has never been found to underlie developmental dyslexia (but see Downie, Frisk, & Jakobson, 2005). On the other hand, epidemiological evidence for a cause of dyslexia[2] has implicated gene mutations or gene variants, thus suggesting that appropriate genetic animal models may shed additional light linking brain and behavior in a causal manner. We have recently developed such animal models in our laboratories, taking advantage of the publication of risk dyslexia alleles in several human populations. Of these alleles, we have worked on the rodent dyslexia risk gene homologs *dyx1c1, dcdc2, and kiaa0319* (Burbridge *et al.*, 2008; Currier, Etchegaray, Haight, Galaburda, & Rosen, 2011; Peschansky *et al.*, 2010; Rosen *et al.*, 2007; Szalkowski *et al.*, 2010; Threlkeld, *et al.*, 2007). An interesting and most relevant discovery is

[2] Of course, such genetic studies do not establish causality, but make it more likely that a causal relationship exists.

the development of neuronal migration anomalies to the cerebral cortex after silencing any of the three genes by performing intrauterine electroporation of inhibiting short hairpin ribonucleic acid (shRNA) plasmids during the period of neuronal migration to the cortex. The details of these malformations need not be given in this brief review, and it suffices to state that neurons fail to migrate and remain in the subcortex, or migrate abnormally within the cortical layers. The anatomical phenotype partly resembles the migration anomalies described either in autopsy studies or in *in vivo* neuroimaging. Additional important details are still lacking in this model, such as the status of cortical connections to the thalamus and other cortical areas, and the physiological properties of the neurons and networks associated with the malformations. The establishment of abnormalities in these circuits would go a long way in helping explain the behavioral changes associated with the malformations in this model system. However, relatively little information is available on the cognitive/behavioral consequences of inducing malformations by RNA silencing, but delays in processing acoustic information and other deficits have been documented, and in cases where the hippocampus is involved, memory deficits are present, too (Fitch, *et al.*, 2008; Szalkowski, *et al.*, 2010; Threlkeld, *et al.*, 2007). Thus, we already have a model whereby manipulation of candidate genes produces anatomical abnormalities equivalent to those found in dyslexic brains, whereby auditory and memory dysfunction can occur as a result.

In summary, although much more detailed knowledge needs still to be derived in the pathways between abnormal or variant genes and the school failure that is characterized by difficulty with learning to read and achieving normal reading competency, some consistent developmental factors seem to be common. The candidate risk genes that have been published have central nervous system functions and play a role in neuronal migration to the cortex. Previous research has indicated that disorder of neuronal migration to the cortex can be associated with abnormal cortico-cortical connectivity and abnormal acoustic mapping in the cerebral cortex. Related research has shown that the abnormal cortico cortical anatomy and physiology may be the crucial factor underlying deficits in sound and phonological processing in dyslexia.

Neuroscience and education

A neuroscience of learning disorders can contribute to the development of a complete neuroscience of education. For a successful education of children to take place, it is important to know how the mind and brain work, how they achieve mature functioning after a period of developmental

change, and how genes and environments modulate this growth, on-line functioning, and ultimate achievement. As with any biological process, we expect variation in the developmental trajectories and in ultimate achievement, but we do not know as yet what the normal ranges of variation are. We are slightly familiar with the fact that there is variation far outside the normal range, causing cases of genius, cases of learning disability, and occasionally combinations of both. We have very little knowledge about how this happens, and what are the interactions among genes, brains, behaviors, and environments in these situations. However, this type of knowledge is tractable, if enough resources are thrown in the direction of developmental neuroscience and cognitive science, as well as for a scientifically based educational research program. Such an effort is not only expected to shed light on better ways to educate children, with or without learning disabilities, but also are likely to uncover wonderful mysteries about the development of the human mind, the sources of genius and creativity, and the range of human potential.

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References

Angelelli, P., Notarnicola, A., Judica, A., Zoccolotti, P., & Luzzatti, C. (2010). Spelling impairments in Italian dyslexic children: phenomenological changes in primary school. *Cortex, 46*(10), 1299-1311.

Attree, E.A., Turner, M.J., & Cowell, N. (2009). A virtual reality test identifies the visuospatial strengths of adolescents with dyslexia. *Cyberpsychol Behav, 12*(2), 163-168.

Benarós, S., Lipina, S.J., Segretin, M.S., Hermida, M.J., & Jorge, J.A. (2010). Neuroscience and education: towards the construction of interactive bridges. *Revista de Neurología, 50*(3), 179-186.

Benasich, A.A., Choudhury, N., Friedman, J.T., Realpe Bonilla, T., Chojnowska, C., & Gou, Z. (2006). The infant as a prelinguistic model for language learning impairments: predicting from event related potentials to behavior. *Neuropsychologia, 44*(3), 396-411.

Berrettini, W.H. (2005). Genetic bases for endophenotypes in psychiatric disorders. *Dialogues Clin Neurosci, 7*(2), 95-101.

Bishop, D.V. (2009). Genes, cognition, and communication: insights from neurodevelopmental disorders. *Ann NY Acad Sci, 1156*, 1-18.

Blair, C., & Diamond, A. (2008). Biological processes in prevention and intervention: the promotion of self-regulation as a means of preventing school failure. *Dev Psychopathol, 20*(3), 899-911.

Bloom, P., & Weisberg, D.S. (2007). Childhood origins of adult resistance to science. *Science, 316*(5827), 996-997.

Burbridge, T.J., Wang, Y., Volz, A.J., Peschansky, V.J., Lisann, L., Galaburda, A.M., *et*

al. (2008). Postnatal analysis of the effect of embryonic knockdown and overexpression of candidate dyslexia susceptibility gene homolog Dcdc2 in the rat. *Neuroscience, 152*(3), 723-733.

Chang, B.S., Katzir, T., Liu, T., Corriveau, K., Barzillai, M., Apse, K.A., *et al.* (2007). A structural basis for reading fluency: white matter defects in a genetic brain malformation. *Neurology, 69*(23), 2146-2154.

Clark, M.G., Rosen, G.D., Tallal, P., & Fitch, R.H. (2000). Impaired processing of complex auditory stimuli in rats with induced cerebrocortical microgyria: An animal model of developmental language disabilities. *J Cogn Neurosci, 12*(5), 828-839.

Currier, T.A., Etchegaray, M.A., Haight, J.L., Galaburda, A.M., & Rosen, G.D. (2011). The effects of embryonic knockdown of the candidate dyslexia susceptibility gene homologue Dyx1c1 on the distribution of GABAergic neurons in the cerebral cortex. *Neuroscience, 172*, 535-546.

DeFries, J.C., Singer, S.M., Foch, T.T., & Lewitter, F.I. (1978). Familial nature of reading disability. *Br J Psychiatry, 132*, 361-367.

Del Giudice, E., Trojano, L., Fragassi, N.A., Posteraro, S., Crisanti, A.F., Tanzarella, P., *et al.* (2000). Spatial cognition in children. II. Visuospatial and constructional skills in developmental reading disability. *Brain Dev, 22*(6), 368-372.

Demonet, J.F., Taylor, M.J., & Chaix, Y. (2004). Developmental dyslexia. *Lancet, 363*(9419), 1451-1460.

Downey, D.M., Snyder, L.E., & Hill, B. (2000). College students with dyslexia: persistent linguistic deficits and foreign language learning. *Dyslexia, 6*(2), 101-111.

Downie, A.L., Frisk, V., & Jakobson, L.S. (2005). The impact of periventricular brain injury on reading and spelling abilities in the late elementary and adolescent years. *Child Neuropsychol, 11*(6), 479-495.

Draganski, B., & May, A. (2008). Training induced structural changes in the adult human brain. *Behav Brain Res, 192*(1), 137-142.

Eckert, M. (2004). Neuroanatomical markers for dyslexia: a review of dyslexia structural imaging studies. *Neuroscientist, 10*(4), 362-371.

von Economo, C., & Horn, L. (1930). Ueber windungsrelief, masse und rindenarchitektonik der supratemporalflaeche, ihre individuellen und ihre seitenunterschiede. *Zeitschrift fuer die Gesamte Neurologie und Psychiatrie, 130*, 678-757.

Eden, G.F., Stein, J.F., Wood, H.M., & Wood, F.B. (1996). Differences in visuospatial judgement in reading-disabled and normal children. *Percept Mot Skills, 82*(1), 155-177.

Eden, G.F., Wood, F.B., & Stein, J.F. (2003). Clock drawing in developmental dyslexia. *J Learn Disabil, 36*(3), 216-228.

Eiland, L., & McEwen, B.S. (2010). Early life stress followed by subsequent adult chronic stress potentiates anxiety and blunts hippocampal structural remodeling. *Hippocampus*, Sept. 16 [Epub ahead of print].

Eisdorfer, C., Nowlin, J., & Wilkie, F. (1970). Improvement of learning in the aged by modification of autonomic nervous system activity. *Science, 170*(964), 1327-1329.

Escabi, M.A., Higgins, N.C., Galaburda, A.M., Rosen, G.D., & Read, H.L. (2007). Early cortical damage in rat somatosensory cortex alters acoustic feature representation in primary auditory cortex. *Neuroscience, 150*(4), 970-983.

Facoetti, A., Trussardi, A.N., Ruffino, M., Lorusso, M.L., Cattaneo, C., Galli, R., *et al.* (2010). Multisensory spatial attention deficits are predictive of phonological decoding skills in developmental dyslexia. *J Cogn Neurosci, 22*(5), 1011-1025.

Fisher, S.E., & DeFries, J.C. (2002). Developmental dyslexia: genetic dissection of a complex cognitive trait. *Nat Rev Neurosci, 3*(10), 767-780.

Fisher, S.E., & Francks, C. (2006). Genes, cognition and dyslexia: learning to read the genome. *Trends Cogn Sci, 10*(6), 250-257.

Fitch, R.H., Breslawski, H., Rosen, G.D., & Chrobak, J.J. (2008). Persistent spatial working memory deficits in rats with bilateral cortical microgyria. *Behav Brain Funct, 4*, 45.

Fletcher, J.M. (2009). Dyslexia: The evolution of a scientific concept. *J Int Neuropsychol Soc, 15*(4), 501-508.

Galaburda, A.M., & Kemper, T.L. (1979). Cytoarchitectonic abnormalities in developmental dyslexia: a case study. *Ann Neurol, 6*(2), 94-100.

Galaburda, A.M., LoTurco, J., Ramus, F., Fitch, R.H., & Rosen, G.D. (2006). From genes to behavior in developmental dyslexia. *Nat Neurosci, 9*(10), 1213-1217.

Galaburda, A.M., Sherman, G.F., Rosen, G.D., Aboitiz, F., & Geschwind, N. (1985). Developmental dyslexia: four consecutive patients with cortical anomalies. *Ann Neurol, 18*(2), 222-233.

Goswami, U., Wang, H.L., Cruz, A., Fosker, T., Mead, N., & Huss, M. (2011). Language universal sensory deficits in developmental dyslexia: English, Spanish, and Chinese. *J Cogn Neurosci, 23*(2), 325-337.

Gotestam, K.O. (1990). Lefthandedness among students of architecture and music. *Percept Mot Skills, 70*(3 Pt 2), 1323-1327; discussion 1345-1326.

Greely, H., Sahakian, B., Harris, J., Kessler, R.C., Gazzaniga, M., Campbell, P., *et al.* (2008). Towards responsible use of cognitive-enhancing drugs by the healthy. *Nature, 456*(7223), 702-705.

Gustafson, S., & Samuelsson, S. (1999). Intelligence and dyslexia: implications for diagnosis and intervention. *Scand J Psychol, 40*(2), 127-134.

Herman, A.E., Galaburda, A.M., Fitch, R.H., Carter, A.R., & Rosen, G.D. (1997). Cerebral microgyria, thalamic cell size and auditory temporal processing in male and female rats. *Cereb Cortex, 7*(5), 453-464.

Higgins, N.C., Escabi, M.A., Rosen, G.D., Galaburda, A.M., & Read, H.L. (2008). Spectral processing deficits in belt auditory cortex following early postnatal lesions of somatosensory cortex. *Neuroscience, 153*(2), 535-549.

Holopainen, L., Ahonen, T., & Lyytinen, H. (2001). Predicting delay in reading achievement in a highly transparent language. *J Learn Disabil, 34*(5), 401-413.

Huessy, H.R. (1967). The comparative epidemiology of reading disability in German and English speaking countries. *Acta Paedopsychiatr, 34*(9), 273-277.

Igo, R.P., Jr., Chapman, N.H., Berninger, V.W., Matsushita, M., Brkanac, Z., Rothstein, J.H., *et al.* (2006). Genomewide scan for real-word reading subphenotypes of dyslexia: novel chromosome 13 locus and genetic complexity. *Am J Med Genet B Neuropsychiatr Genet, 141B*(1), 15-27.

Kebir, O., Tabbane, K., Sengupta, S., & Joober, R. (2009). Candidate genes and neuropsychological phenotypes in children with ADHD: review of association studies. *J Psychiatry Neurosci, 34*(2), 88-101.

Keenan, J.P., Thangaraj, V., Halpern, A.R., & Schlaug, G. (2001). Absolute pitch and planum temporale. *Neuroimage, 14*(6), 1402-1408.

Kiuru, N., Haverinen, K., Salmela Aro, K., Nurmi, J.E., Savolainen, H., & Holopainen, L. (2011). Students With Reading and Spelling Disabilities: Peer Groups and Educational Attainment in Secondary Education. *J Learn Disabil,* 44(6), 556-569.

Lachmann, T., Berti, S., Kujala, T., & Schroger, E. (2005). Diagnostic subgroups of developmental dyslexia have different deficits in neural processing of tones and phonemes. *Int J Psychophysiol, 56*(2), 105-120.

Lee, S.S., & Mudaliar, A. (2009). Medicine. Racing forward: the Genomics and Per-

sonalized Medicine Act. *Science, 323*(5912), 342.

Leonard, C.M., & Eckert, M.A. (2008). Asymmetry and dyslexia. *Dev Neuropsychol, 33*(6), 663-681.

Livingstone, M.S., Rosen, G.D., Drislane, F.W., & Galaburda, A.M. (1991). Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. *Proc Natl Acad Sci U S A, 88*(18), 7943-7947.

Lyon, G.R., & Moats, L.C. (1997). Critical conceptual and methodological considerations in reading intervention research. *J Learn Disabil, 30*(6), 578-588.

Lyytinen, H., Aro, M., Eklund, K., Erskine, J., Guttorm, T., Laakso, M.L., *et al.* (2004). The development of children at familial risk for dyslexia: birth to early school age. *Ann Dyslexia, 54*(2), 184-220.

Marshall, E. (2004). Forgetting and remembering. A star-studded search for memory enhancing drugs. *Science, 304*(5667), 36-38.

Morley, K.I., & Montgomery, G.W. (2001). The genetics of cognitive processes: candidate genes in humans and animals. *Behav Genet, 31*(6), 511-531.

Paulesu, E., Demonet, J.F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., *et al.* (2001). Dyslexia: cultural diversity and biological unity. *Science, 291*(5511), 2165-2167.

Peiffer, A.M., Friedman, J.T., Rosen, G.D., & Fitch, R.H. (2004). Impaired gap detection in juvenile microgyric rats. *Brain Res Dev Brain Res, 152*(2), 93-98.

Peiffer, A.M., Rosen, G.D., & Fitch, R.H. (2002). Rapid auditory processing and MGN morphology in microgyric rats reared in varied acoustic environments. *Brain Res Dev Brain Res, 138*(2), 187-193.

Peiffer, A.M., Rosen, G.D., & Fitch, R.H. (2004). Sex differences in rapid auditory processing deficits in microgyric rats. *Brain Res Dev Brain Res, 148*(1), 53-57.

Pernet, C., Andersson, J., Paulesu, E., & Demonet, J.F. (2009). When all hypotheses are right: a multifocal account of dyslexia. *Hum Brain Mapp, 30*(7), 2278-2292.

Peschansky, V.J., Burbridge, T.J., Volz, A.J., Fiondella, C., Wissner Gross, Z., Galaburda, A.M., *et al.* (2010). The effect of variation in expression of the candidate dyslexia susceptibility gene homolog Kiaa0319 on neuronal migration and dendritic morphology in the rat. *Cereb Cortex, 20*(4), 884-897.

Plomin, R., & Craig, I. (2001). Genetics, environment and cognitive abilities: review and work in progress towards a genome scan for quantitative trait locus associations using DNA pooling. *British Journal of Psychiatry Suppl., 40*(s41-48).

Pugh, K.R., Mencl, W.E., Jenner, A.R., Katz, L., Frost, S.J., Lee, J.R., *et al.* (2000). Functional neuroimaging studies of reading and reading disability (developmental dyslexia). *Ment Retard Dev Disabil Res Rev, 6*(3), 207-213.

Ramus, F., & Szenkovits, G. (2008). What phonological deficit? *Q J Exp Psychol (Colchester), 61*(1), 129-141.

Raschle, N.M., Chang, M., & Gaab, N. (2011). Structural brain alterations associated with dyslexia predate reading onset. *Neuroimage*, 57(3), 742-749.

Roederer, M., & Moody, M.A. (2008). Polychromatic plots: graphical display of multidimensional data. *Cytometry A, 73*(9), 868-874.

Roeske, D., Ludwig, K.U., Neuhoff, N., Becker, J., Bartling, J., Bruder, J., *et al.* (2011). First genome wide association scan on neurophysiological endophenotypes points to trans-regulation effects on SLC2A3 in dyslexic children. *Mol Psychiatry, 16*(1), 97-107.

Rosen, G.D., Bai, J., Wang, Y., Fiondella, C.G., Threlkeld, S.W., LoTurco, J.J., *et al.* (2007). Disruption of neuronal migration by RNAi of Dyx1c1 results in neocortical and hippocampal malformations. *Cereb Cortex, 17*(11), 2562-2572.

Rosen, G.D., Burstein, D., & Galaburda, A.M. (2000). Changes in efferent and afferent connectivity in rats with induced cerebrocortical microgyria. *J Comp Neurol, 418*(4), 423-440.

Rosen, G.D., Herman, A.E., & Galaburda, A.M. (1999). Sex differences in the effects of early neocortical injury on neuronal size distribution of the medial geniculate nucleus in the rat are mediated by perinatal gonadal steroids. *Cereb Cortex, 9*(1), 27-34.

Rosen, G.D., Mesples, B., Hendriks, M., & Galaburda, A.M. (2006). Histometric changes and cell death in the thalamus after neonatal neocortical injury in the rat. *Neuroscience, 141*(2), 875-888.

Rosen, G.D., Press, D.M., Sherman, G.F., & Galaburda, A.M. (1992). The development of induced cerebrocortical microgyria in the rat. *J Neuropathol Exp Neurol, 51*(6), 601-611.

Rosen, G.D., Sherman, G.F., & Galaburda, A.M. (1989). Interhemispheric connections differ between symmetrical and asymmetrical brain regions. *Neuroscience, 33*(3), 525-533.

Rosen, G.D., Sherman, G.F., & Galaburda, A.M. (1994). Radial glia in the neocortex of adult rats: effects of neonatal brain injury. *Brain Res Dev Brain Res, 82*(1-2), 127-135.

Rosen, G.D., Sherman, G.F., & Galaburda, A.M. (1996). Birthdates of neurons in induced microgyria. *Brain Res, 727*(1-2), 71-78.

Rosen, G.D., Sherman, G.F., Mehler, C., Emsbo, K., & Galaburda, A.M. (1989). The effect of developmental neuropathology on neocortical asymmetry in New Zealand black mice. *Int J Neurosci, 45*(3-4), 247-254.

Rosen, G.D., Sigel, E.A., Sherman, G.F., & Galaburda, A.M. (1995). The neuroprotective effects of MK-801 on the induction of microgyria by freezing injury to the newborn rat neocortex. *Neuroscience, 69*(1), 107-114.

Rosen, G.D., Waters, N.S., Galaburda, A.M., & Denenberg, V.H. (1995). Behavioral consequences of neonatal injury of the neocortex. *Brain Res, 681*(1 2), 177-189.

Rosen, G.D., Windzio, H., & Galaburda, A.M. (2001). Unilateral induced neocortical malformation and the formation of ipsilateral and contralateral barrel fields. *Neuroscience, 103*(4), 931-939.

Russeler, J., Scholz, J., Jordan, K., & Quaiser Pohl, C. (2005). Mental rotation of letters, pictures, and three dimensional objects in German dyslexic children. *Child Neuropsychol, 11*(6), 497-512.

Scerri, T.S., & Schulte Korne, G. (2010). Genetics of developmental dyslexia. *Eur Child Adolesc Psychiatry, 19*(3), 179-197.

Serrano, F., & Defior, S. (2008). Dyslexia speed problems in a transparent orthography. *Ann Dyslexia, 58*(1), 81-95.

Service, R.F. (2005). Pharmacogenomics. Going from genome to pill. *Science, 308*(5730), 1858 1860. Shaywitz, S.E., & Shaywitz, B.A. (2008). Paying attention to reading: the neurobiology of reading and dyslexia. *Dev Psychopathol, 20*(4), 1329-1349.

Sherman, G.F., Galaburda, A.M., Behan, P.O., & Rosen, G.D. (1987). Neuroanatomical anomalies in autoimmune mice. *Acta Neuropathol, 74*(3), 239-242.

Sherman, G.F., Morrison, L., Rosen, G.D., Behan, P.O., & Galaburda, A.M. (1990). Brain abnormalities in immune defective mice. *Brain Res, 532*(1 2), 25-33.

Sherman, G.F., Stone, J.S., Press, D.M., Rosen, G.D., & Galaburda, A.M. (1990). Abnormal architecture and connections disclosed by neurofilament staining in the cerebral cortex of autoimmune mice. *Brain Res, 529*(1 2), 202-207.

Sherman, G.F., Stone, J.S., Rosen, G.D., & Galaburda, A.M. (1990). Neocortical VIP neurons are increased in the hemisphere containing focal cerebrocortical microdysgenesis in New Zealand Black mice. *Brain Res, 532*(1 2), 232-236.

Smith, S.D. (2007). Genes, language development, and language disorders. *Ment Retard Dev Disabil Res Rev, 13*(1), 96-105.

Sparks, R.L., Patton, J., Ganschow, L., Humbach, N., & Javorsky, J. (2006). Native language predictors of foreign language proficiency and foreign language aptitude. *Ann Dyslexia, 56*(1), 129-160.

Stein, C.M., Millard, C., Kluge, A., Miscimarra, L.E., Cartier, K.C., Freebairn, L.A., *et al.* (2006). Speech sound disorder influenced by a locus in 15q14 region. *Behav Genet, 36*(6), 858-868.

Stein, J. (2001). The magnocellular theory of developmental dyslexia. *Dyslexia, 7*(1), 12-36.

Szalkowski, C.E., Hinman, J.R., Threlkeld, S.W., Wang, Y., Lepack, A., Rosen, G.D., *et al.* (2010). Persistent spatial working memory deficits in rats following in utero RNAi of Dyx1c1. *Genes Brain Behav*, 10(2), 244-252.

Terepocki, M., Kruk, R.S., & Willows, D.M. (2002). The incidence and nature of letter orientation errors in reading disability. *J Learn Disabil, 35*(3), 214-233.

Threlkeld, S.W., McClure, M.M., Bai, J., Wang, Y., LoTurco, J.J., Rosen, G.D., *et al.* (2007). Developmental disruptions and behavioral impairments in rats following in utero RNAi of Dyx1c1. *Brain Res Bull, 71*(5), 508-514.

van Belzen, M.J., & Heutink, P. (2006). Genetic analysis of psychiatric disorders in humans. *Genes Brain Behav, 5 Suppl 2*, 25-33.

van der Lely, H.K., & Marshall, C.R. (2010). Assessing component language deficits in the early detection of reading difficulty risk. *J Learn Disabil, 43*(4), 357-368.

Wallace, D.R. (2005). Overview of molecular, cellular, and genetic neurotoxicology. *Neurol Clin, 23*(2), 307-320.

Watson, M.O., & Sanderson, P. (2007). Designing for attention with sound: challenges and extensions to ecological interface design. *Hum Factors, 49*(2), 331-346.

Yamashita, H., & Matsumoto, M. (2007). Molecular pathogenesis, experimental models and new therapeutic strategies for Parkinson's disease. *Regen Med, 2*(4), 447-455.

Yeh, M., Merlo, J.L., Wickens, C.D., & Brandenburg, D.L. (2003). Head up versus head down: the costs of imprecision, unreliability, and visual clutter on cue effectiveness for display signaling. *Hum Factors, 45*(3), 390-407.

Young, A.M., & Colpaert, F.C. (2009). Recall of learned information may rely on taking drug again. *Nature, 457*(7229), 533.

Zamarian, L., Ischebeck, A., & Delazer, M. (2009). Neuroscience of learning arithmetic evidence from brain imaging studies. *Neuroscience and Biobehavioral Reviews, 33*(6), 909-925.

Zatorre, R.J. (2003). Absolute pitch: a model for understanding the influence of genes and development on neural and cognitive function. *Nat Neurosci, 6*(7), 692-695.

Ziegler, J.C., & Goswami, U. (2005). Reading acquisition, developmental dyslexia, and skilled reading across languages: a psycholinguistic grain size theory. *Psychol Bull, 131*(1), 3-29.

Ziegler, J.C., Perry, C., Ma Wyatt, A., Ladner, D., & Schulte Korne, G. (2003). Developmental dyslexia in different languages: language specific or universal? *J Exp Child Psychol, 86*(3), 169-193.