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Integrating Neurobiological Findings in Search of a Neurochemical "Signature" of Dyslexia

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Dyslexia is a hereditable disorder that is estimated to affect 5%–17.5% of the population (Shaywitz & Shaywitz, 2008). Researchers and clinicians characterize this developmental disorder based on a failure to read at grade level, regardless of instruction, socioeconomic status, intelligence, or motivation (Snowling, 2000). Dyslexia is primarily characterized by profound difficulties with phonological awareness (Bradley & Bryant, 1978; Liberman, Shankweiler & Liberman, 1989); remediation programs for individuals with dyslexia focus largely on phonological awareness but often only show short-term gains for 1–2 years following treatment (Peterson & Pennington, 2012). Many individuals with dyslexia also experience severe emotional repercussions—that is, these individuals view academic environments as "threatening" and often have higher rates of depression, frustration, and anxiety. Individuals with dyslexia develop avoidance behaviors and have higher rates of entry into the juvenile justice system (Sideridis, Mouzaki, Simos, & Protopapas, 2006). Despite these facts and the ability to identify dyslexia through standardized assessments, debate remains as to its underlying etiology.

In this chapter, we briefly review the core neuroimaging findings on reading development and dyslexia that indicate a replicable and robustly divergent brain activation network. We provide an introduction to the gray and white matter differences that have monopolized the attention of researchers for the last decade. Despite the enormous gains in functional and structural imaging, there is a clear gap in the neurobiology of dyslexia: the role of neurochemistry.

We give an overview of the sparse literature on the neurochemical signature of dyslexia from *in vivo* studies of magnetic resonance spectroscopy (MRS) and attempt to provide a broad understanding of genetic research and the key findings of these studies. We also briefly explain how a nonreading animal is used as a reading disorder model to investigate protein expression. Finally, we discuss studies that are bringing these diverse fields and methods together to gain a more complete understanding of the complex neurobiological systems that underlie developmental dyslexia.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

The most basic neural model of the adult reading circuit is composed of three primary regions: left occipitotemporal, left temporoparietal, and left inferior frontal regions (Pugh et al., 2010). These have been confirmed by numerous studies that show robust functional activation for reading-related tasks: the left occipitotemporal region, which includes the visual word form area (VWFA) in word-reading tasks (e.g., orthography); the left temporoparietal region in tasks focusing on the integration of oral language with reading-relevant orthographic information (e.g., phonology, morphology, and semantics); and the left inferior frontal regions, which include the *pars triangularis* and *pars opercularis* for tasks focused on naming, phonological processing, phonetic identification, and, in conjunction with temporoparietal networks, when learning to read.

Throughout development, individuals with dyslexia show differing patterns of functional activation when compared with age- and reading-matched peers. Even in infancy, for example, typically developing infants' show increased activation in the primary reading network. In infants at hereditary risk for dyslexia, this increase in activation is not seen. During childhood, typically developing children become more automatic readers; they transition to using the VWFA for fast word recognition (McCandliss, Cohen, & Dehaene, 2003). This milestone is not seen in dyslexic children (Shaywitz et al., 2007). Although it is easy to assume that dyslexic children don't use the VWFA for fast word recognition due to a failure to reach automaticity, the evidence from infant prereaders clearly emphasizes the biological nature of dyslexia.

Adults with dyslexia also consistently show aberrant functional activation (e.g., reduced or absent activation in brain regions known to be involved in reading). This reduction in activation is seen in response to phonological tasks in the left temporoparietal cortex (see Démonet, Taylor, & Chaix, 2004, for review) and orthography in the VWFA activation (Shaywitz et al., 2007). Reduction in activation is thought to reflect an immature or disconnected functional reading network. However, disruptions in the functional reading network are not simple or straightforward. Increased or dispersed activation is also often seen in dyslexic readers, particularly in the right superior temporal gyrus and the right inferior frontal gyrus. Increases in activation have been suggested to reflect a compensatory mechanism.

FUNCTIONAL CONNECTIVITY

Functional connectivity analysis typically describes studies in which an *a priori* region of activation is temporally associated with other regions throughout the brain; these regions, in essence, activate together in time during an in-scanner (fMRI) task. In an early study, Pugh and colleagues (2000) found that dyslexic readers showed less robust phonological representations: Disruptions were found between the left angular gyrus, the superior temporal gyrus, and the VWFA on a non-word-rhyming, phonological task. Many studies have since reported that dyslexic readers show divergent temporal connectivity—the correlations typically found among remote brain regions are irregular or absent during an in-scanner fMRI task. Findings include decreased temporal connectivity between the superior temporal gyrus and VWFA and increased temporal connectivity, bilaterally, between the left and right superior temporal gyri. Koyama et al. (2013) suggest that in children, the functional connections among the regions involved in speech production and speech perception are predictive of reading ability. Regardless of how dyslexia is studied, as a unidimensional disorder (i.e., across a spectrum of reading ability from good to very impaired) or as a multidimensional disorder (i.e., subtyping based on differences in reading-task performance), evidence seems to indicate that dyslexic readers use a divergent pathway for reading, one not as well suited to fluent, automatized reading.

STRUCTURAL DIFFERENCES

Dyslexic individuals evince cortical structural differences in both gray and white matter. Gray matter is composed of neuron cell bodies, glial cells used for support and protection, and unmyelinated axons. Dyslexic individuals have gray matter decreases bilaterally in the fusiform and temporoparietal regions, in the left occipitotemporal region, in the right lingual gyrus (Eliez et al., 2000), and throughout the cerebellum (Eckert et al., 2003). Increases in gray matter have been found in the precentral and postcentral gyri, the superior and medial frontal gyri, and the precuneus, as well as the posterior, temporal, and inferior temporal gyri (Kronbichler et al., 2008). Structural differences align very closely with functional activation differences (Linkersdörfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012).

White matter is composed of glial cells and axons myelinated by glial cells. White matter structural images are acquired through a magnetic resonance imaging (MRI) sequence called diffusion tensor imaging (DTI). White matter is typically separated into tracts—myelinated axons grouped into bundles and assessed through a measurement of fractional anisotropy. Fractional anisotropy describes the diffusion of water along the path of least resistance. In the cortex, this dispersion occurs largely in and around white matter tracts. Increased myelination causes faster signal transmission across the cortex and will result in higher levels of fractional anisotropy. Lower levels of fractional anisotropy are indicative of decreased myelination. In adults with dyslexia, fractional anisotropy has been

found to be lower in two tracts: the left arcuate fasciculus (Klingberg et al., 2000) and the longitudinal fasciculus (Steinbrink et al., 2008). This indicates that individuals with dyslexia have smaller or less tightly bundled white matter tracts.

Fractional anisotropy measures in the left arcute and longitudinal fasciculus positively correlate with increased performance on standardized reading measures (Gold, Powell, Xuan, Jiang, & Hardy, 2007; Klingberg et al., 2000; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010). Differences in fractional anisotropy have been seen between age-matched typical readers and dyslexic readers. No differences were found, however, between typical readers and dyslexic readers matched on reading ability rather than age (Krafnick, Flowers, Luetje, Napoliello, & Eden, 2014). As mentioned previously, increased myelination results in faster signal conduction; however, increased myelination also results in bigger tracts that take up more brain space. Throughout one's lifetime, pruning occurs in which some axons are left to grow and develop and other axons are eliminated. During childhood, a period of intensive neuronal pruning occurs. Yeatman, Dougherty, Ben-Shachar, and Wandell (2012) found that in an age-matched sample, above-average readers initially showed lower levels of fractional anisotropy and a longitudinal increase, whereas below-average readers showed high levels of fractional anisotropy and a longitudinal decrease. This longitudinal trajectory of fractional anisotropy suggests either that dyslexic children initially have white matter tracts that their brain is unable to support or that dyslexic children show inappropriate pruning throughout development. It is also possible that dyslexic children have both white matter tracts that cannot be supported and inappropriate developmental pruning.

PROTON MAGNETIC RESONANCE IMAGING: THE ROLE OF NEUROMETABOLITES IN READING

Magnetic resonance spectroscopy (MRS) is a noninvasive *in vivo* technique that measures biochemical concentrations in the brain using neurometabolite resonance frequencies. Proton (1H) MRS is specifically aimed at determining neurotransmitter concentrations, calculated from a composite of neurometabolite levels. MRS is generally collected for a single voxel or region, determined *a priori* to prevent signal distortion (Rothman, 1994). Neurotransmitter findings are now reported as a ratio to an internal reference to control for potential drift in the spectra during acquisition. Creatine (Cr) is currently recommended as an MRS internal reference (Li, Babb, Soher, Maudsley, & Gonen, 2002). Here we discuss known functions of neurotransmitters and examine findings from proton MRS studies of dyslexia.

CHOLINE AND *N*-ACETYLASPARTATE: PROTON MAGNETIC RESONANCE IMAGING

The neurotransmitter choline (Cho) is integral to cell membrane synthesis and degradation as well as the direct precursor of acetylcholine. Choline is also

involved in metabolic pathways, cholinergic neurotransmission, and transmembrane signaling. MRS studies of developmental disorders have found atypically high concentrations of cortical choline in individuals with attention deficit-hyperactivity disorder (Perlov et al., 2009) and autism (see Baruth, Wall, Patterson, & Port, 2013). Given the number of metabolic pathways and transport mechanisms that influence choline, many theories have been suggested to explain elevated choline. These theories include increased cellular density, increased signal intensity, cell membrane synthesis, and degradation resulting in membrane turnover and changes in white matter organization.

A number of studies have investigated the role of choline in reading ability. In an early study, Rae and colleagues (1998) investigated choline differences between adults with dyslexia and age-matched typical readers (n = 29, 14 dyslexic). They found that dyslexic adults had a decreased ratio of Cho:NAA in the left temporoparietal lobe and the right cerebellum. These researchers also investigated brain laterality (right versus left) in the individuals with dyslexia (n = 14) and found a decrease in Cho:NAA in the left temporoparietal lobe and decreased Cr:NAA in the right cerebellum. A decade later, Laycock and colleagues (2008) investigated choline differences between a small sample of adults with dyslexia, controlled for brain volume–, age-, and intelligence-matched typical readers (n = 12, 6 dyslexic). They found that dyslexic adults had a decreased ratio of NAA:Cho in the right cerebellum and increased Cho:Cr in the left cerebellum. Given that we now know NAA is an unstable internal reference (Jung et al., 2005), the results of the choline and NAA ratios are difficult to parse; however, NAA is typically thought to correspond with cognitive abilities, which were only controlled for in Laycock and colleagues' work. The increase of Cho:Cr, also found in the left cerebellum (Laycock et al., 2008), suggests that dyslexics have an increase in choline concentration rather than a decrease in NAA concentration.

Bruno, Lu, and Manis (2013) further parsed the relationships between reading ability and choline and NAA. First, the more stable internal creatine reference was used for each neurotransmitter. Second, they studied adults with equated cognitive ability that ranged across a spectrum of reading ability (n = 30, 10 dyslexic). Bruno and colleagues (2013) found that although lower phonological ability was associated with increased Cho:Cr in the left angular gyrus, no association was found between NAA:Cr and reading ability. This suggests that previous results may have been indicative of an increased choline concentration.

Pugh and colleagues (2014) investigated choline and NAA in a temporoparietal-to-occipitotemporal region in children (n = 75, mean age = 7.68) whose reading skills ranged from good to very weak (i.e., dyslexic). Even in children, increased choline concentration was found to be indicative of poorer reading. A group comparison between a subsample of typical and dyslexic readers (n = 47, 10 dyslexic) found that dyslexic readers had higher concentrations of Cho:Cr. These researchers also reported a replication of their finding using a separate sample of pediatric readers from the National Institutes of

Health (NIH) MRI Study of Normal Brain Development.[1] The NIH database includes MRS data collected from a midline occipital region as well as standardized assessments of reading ability. In this sample, children (n = 85) across a wide age range (i.e., 5–18 years) had increased Cho:Cr that was correlated with poorer reading assessment scores. Again, no association was found between NAA:Cr and reading ability. Based on the combined findings from these studies, we conclude that elevated levels of choline indicate poorer reading ability in both children and adults.

GLUTAMATE AND GAMMA-AMINOBUTYRIC ACID: PROTON MAGNETIC RESONANCE IMAGING

Glutamate is an amino acid found in high concentrations throughout the brain. Glutamate is the principal excitatory neurotransmitter involved in many metabolic pathways and can be used to indicate metabolic activity—or system excitability. In MRS, glutamate (Glu) concentration is a composite of both glutamate and glutamine, reflecting tightly coupled neuroenergetics. Like choline, elevated glutamate concentrations have been reported in attention deficit-hyperactivity disorder (Perlov et al., 2009) and autism (Brown, Singel, Hepburn, & Rojas, 2013). Theories aimed at explaining elevated levels of glutamate have focused on hyperexcitability, networks involved in learning and consolidation, and neural plasticity.

Pugh and colleagues (2014) also investigated glutamate and gamma-aminobutyric acid (GABA) in a temporoparietal-to-occipitotemporal region in children (n = 75, mean age = 7.68), whose reading skills ranged from good to very weak (i.e., dyslexic). Increased Glu:Cr was indicative of poorer reading ability and vocabulary scores. In the subsample the group, comparison of typically developing readers and dyslexic readers (n = 47, 10 dyslexic) resulted in dyslexic readers with higher Glu:Cr. No significant relationship was found between GABA and reading ability. The association between reading ability and Glu:Cr concentration was robust enough to indicate reading ability at a follow-up assessment 24 months later (n =45, mean age = 10.1). Although further studies and replications are needed, given the resilience of this association, we suggest that adult dyslexics may also show elevated levels of Glutamate.

LACTATE: PROTON MAGNETIC RESONANCE SPECTROSCOPY

Many early MRS studies focused on the relation of lactate to reading ability (Richards et al., 2002, 2000, 1999). Lactate, in addition to glutamate oxidation and glycolysis, contributes to the energy demands of excitatory neurotransmission. Low lactate levels are typically coupled with low glutamine. Although clearly relevant, early MRS studies of lactate are often overlooked because of potential

1. http://pediatricmri.nih.gov, release 5.

confounds, such as the inability to stabilize lactate concentration, given that lactate crosses the blood–brain barrier (Dienel & Cruz, 2009). Although results should therefore be interpreted with caution, we can clearly gain direction from some of the findings.

Richards and colleagues (1999) found increased lactate:NAA along the Sylvian fissure in dyslexic children (n = 6) compared to age-matched, typically developing readers (n = 7). In a replication with an added phonological intervention, Richards and colleagues (2000) found that prior to intervention, there was an increase in lactate:NAA in dyslexic readers (n = 8) compared with age-matched, typically developing readers (n = 7) in a very large region encompassing frontal and parietal lobe regions. Following intervention, dyslexic readers (n = 6) were found to have either elevated or typical levels of lactate:NAA. Richards and colleagues (2002) investigated a large area that encompassed the frontal operculum and the posterior portion of the superior temporal gyrus in dyslexic children and age-matched, typically developing readers (n = 8). Between scans, dyslexic readers were randomly assigned to either a morphological or phonological intervention. Prior to intervention, dyslexic readers had significantly elevated levels of lactate:NAA. Following the morphological intervention, five of the six dyslexic readers showed decreased but still elevated levels of lactate:NAA (compared with typical readers). All four dyslexic readers who had received the phonological intervention continued to show elevated lactate:NAA. Richards and colleagues' work suggests that lactate:NAA levels in dyslexic readers tend to be elevated when compared with typically developing peers. We caution that the small sample and the inability to stabilize lactate concentration during MRS acquisition make these results very hard to interpret. They appear to demonstrate, however, that a link between reading and lactate in MRS is relevant and worthy of further investigation.

PHOSPHORUS MAGNETIC RESONANCE SPECTROSCOPY: THE NEUROMETABOLIC SIGNATURE

Phosphorus magnetic resonance spectroscopy (MRS) is clinically used to determine metabolic abnormalities, primarily in chronic cerebrovascular disease but also in schizophrenia, depression, chronic fatigue syndrome, and dyslexia (see Puri, 2006, for review). Although methodologically similar, the phosphorus MRS reflects a composite of metabolic energy sources, primarily adenosine triphosphate (ATP), phosphocreatine (PCr), and several other low-weighted molecules that contain phosphate (Qiao, Zhang, Zhu, Du, & Chen, 2006). Results of phosphorus MRS studies are also reported as a ratio (e.g., PCr:ATP) to control for inhomogeneity during image acquisition. To prevent signal distortion, the phosphorus MRS is also collected for a single voxel or region determined *a priori.*

A limited amount of research using phosphorus MRS has focused on the link between cortical metabolic levels and reading ability. Rae and colleagues (1998) further hypothesized that differences in the phosphorus MR spectra

would be coupled with changes in Choline, as Choline was known to be indicative of cellular density. This pilot study investigated a region in the frontal lobe that extended onto both sides of the intrahemispheric fissure as well as into the parietal lobe. No significant differences between dyslexic and typical adult readers were found, although the reported ratios of PCr:ATP are interesting; however, Rae and colleagues admittedly state that the results are inconclusive due to limited statistical power.

A year prior, Richardson, Cox, Sargentoni, and Puri (1997) investigated an area centered in the basal ganglia in dyslexic (n = 12) and age- and intelligence-matched, typically reading adults (n =10) and found an increase in dyslexic readers' phosphomonoesters as compared with typically developing readers. This phosphomonoester peak included phosphocholine, phospoethanolamine, and L-phosphoserine as well as smaller sugar phosphates. The internal references, nucleotide triphosphates, contain spectral contributions from ATP, PCr, and inorganic phosphate and may therefore result in an increase in phosphomonoesters; however, because the majority of the phosphorus MR signal is the result of ATP and PCr, the results are more likely a reflection of decreases in ATP, PCr, and/or inorganic phosphate. The results of these initial studies, though they require additional confirmation, suggest that there may be a deviant metabolic signature in individuals with dyslexia.

THE GENETICS OF READING DISABILITY

Early genetic research on dyslexia relied primarily on heritability due to the anecdotal evidence of dyslexia in family lines. Heritability studies investigate the proportion of disorder, disease, or trait that can be assigned to genetic influences. The results of these initial genetic studies found that a large portion of reading performance is accounted for by genetic influences. Although these studies were highly replicable and confirmed dyslexia heritability, to date there remains no answer as to the biological loci of dyslexia.

Linkage and association studies are used to determine susceptibility genes—genes with possible causal variants resulting in a disorder. To begin to localize genetic effects within a family, linkage studies trace the segregation of a trait and the segregation of one or more chromosomes, allowing a comparison between segregated traits (e.g., reading difficulty) and the selected chromosomes. Linkage studies often use single-nucleotide polymorphisms (SNPs) for better genetic resolution. Although association studies follow the same pattern of analysis, they focus on a sample across families. These techniques were used to identify the first chromosomes associated with reading difficulty: chromosomes 1, 2, 3, 6, 15, and 18.

In dyslexia, the links between genes and reading ability (genotype) and among genes, environment, and reading ability (phenotype) do not result from a direct correspondence. Candidate gene studies begin with the selection of proposed genes based on chromosomal regions from linkage and association studies or mechanisms relevant to the disorder. The first series of

candidate dyslexia genes, *DYX1C1, ROBO1, KIAA0319,* and *DCDC2,* resulted from proposed genes based on findings from linkage studies. It is of note that at least 10 additional candidate genes have been purported. Gialluisi and colleagues (2014) reported the results of a genome-wide association study (GWAS) focused on reading ability. A GWAS is a partial survey that results from genotyping large numbers of common single-nucleotide polymorphisms (SNPs). Novel associations were found for the *RBFOX2* gene (chromosome 22) as well as *CCDC136* and *FLNC* (chromosome 7). Each of these candidate genes and association genes plays a complex role in the development of the nervous system. These genetic associations have been found in both neurons and glial cells. Glial cells contribute to cell migration, plasticity, organization, structure, and widespread protein synthesis. In short, dyslexia is the result of extremely complex neurobiology that is interacting and changing throughout development.

ANIMAL MODELS OF DYSLEXIA

The *dyslexic rodent* is a candidate gene rodent model of dyslexia and underlies much of what researchers know about protein expression in dyslexia. Although there was initially much conjecture regarding a "reading" rodent, the increased, cross-disciplinary knowledge of genetics has resulted in a slow acceptance across the fields of psychology and education. There are four primary types of rodent models of dyslexia. The first two rodent models focus on stopping candidate gene expression. In these models, the candidate gene is stopped from directing the assembly of a protein (see Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006, for review). Rodent knockout models are genetically engineered never to express a particular gene. No part of the knockout rodent's development occurs with typical gene expression. The third rodent model consists of rodents with ribonucleic acid interference, commonly called RNAi rodents. RNAi rodents begin gestation normally. Following typical neural tube and brainstem development, ribonucleic acid inference stops gene expression. Both of these rodent models of dyslexia reported behavioral deficits in nonspatial and spatial discrimination learning, auditory processing, and memory.

Rodent models of dyslexia reported anatomical abnormalities—focal microgyria and molecular layer ectopias (small structural malformations in the brain) that are associated with failures in neuronal migration. These abnormalities closely resemble early postmortem evidence found in humans with dyslexia (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). Based on these findings, a fourth rodent model of dyslexia was created with experimentally induced neuronal microgyria but with no underlying genetic manipulation (Fitch, Tallal, Brown, Galaburda, & Rosen, 1994). In rodents with induced microgyria that have normal gene expression, deficits were still seen in auditory processing, learning, and memory. This suggests that some of the deficits commonly seen in dyslexia may be associated with, rather than dependent on, neuronal migration failures.

THE NEUROBIOLOGY OF DYSLEXIA: STUDIES LINKING GENES, ANIMAL MODELS, AND NEUROIMAGING

As mentioned previously, studies investigating white matter in dyslexic adults have reported lower levels of fractional anisotropy (i.e., decreased strength of water diffusion in and around axonal fibers). White matter density is tightly linked to a number of neurotransmitters, including Glutamate and GABA in the corpus callosum and cerebellum and Choline and NAA in the cortex. Decreased white matter has been found to correspond to decreased levels of both NAA and Choline in individuals with multiple sclerosis and traumatic brain injury (Gustafsson, Dahlqvist, Jaworski, Lundberg, & Landtblom, 2007). Darki, Peyrard-Janvid, Matsson, Kere, and Klingberg (2012) and Marino and colleagues (2014) found *KIAA0319* and *DCDC2* to be associated with regions in the superior longitudinal fasciculus and corpus callosum, tracts that connect the middle temporal gyrus to the angular gyrus and supramarginal gyri. The middle temporal gyrus and the angular gyrus are involved in lexical–semantic processing, whereas the supramarginal gyrus is involved in speech-sound processing. Darki and colleagues (2012) also reported that *DYX1C1* was associated bilaterally with the cingulum, a white matter bundle that connects temporoparietal regions. The left temporoparietal regions integrate many levels of auditory language with orthographic information. This finding emphasizes the need for the investigation of white matter tract formation, particularly at the level of gene expression.

DCDC2 expression in gray matter has been found to be widespread and robust across lobes and throughout the reading network, composed of the inferior temporal cortex, superior temporal cortex, superior parietal cortex, frontal cortex, and prefrontal cortex. Meda and colleagues (2008) investigated gray matter structure in typically developing individuals who showed variants of the *DCDC2* genotype. They found that for the *DCDC2* dyslexia variant, there was an increase in gray matter in the superior temporal, medial temporal, and inferior temporal cortex; the fusiform; the hippocampal gyrus; the inferior occipitoparietal, inferior, and middle frontal gyri; and the parahippocampal gyrus. As mentioned previously, increased and decreased gray matter have now been reported in dyslexic readers. Given the small sample size (n = 56), replication on a larger scale is needed, but these results are intriguing. It is worth considering the source of differences in gray matter structural imaging.

Typically, voxel-based morphometry (VBM) is used in neuroimaging to identify differences in gray matter concentration. These VBM changes have a complex relation with neuronal density. Animal work suggests that changes seen in VBM may be largely due to neuron rebuilding through processes such as the growth of dendritic spines (see Thomas & Baker, 2013, for review). Szalkowski and colleagues (2013) reported that RNAi *DYX1C1* rodents had a gray matter volume increase in the medial geniculate nucleus. Galaburda, Menard, and Rosen (1994) reported postmortem reductions in the number of "large cells" in the medial geniculate nucleus of dyslexic readers. Szalkowski

and colleagues (2013) reported RNAi *DYX1C1* rodents with an increased number of "small cells" and a smaller number of "large cells"−−specifically in the medial geniculate nucleus. This suggests that there is much more to gray matter differences than simply a measure of more or less gray matter.

CONCLUSION

Dyslexia presents as a failure to achieve adequate reading ability. There are other behavioral difficulties seen in dyslexia, yet only reading failure has been robustly shown to have severe emotional and educational repercussions. The day-to-day repercussions of dyslexia may seem far removed from the complex neurobiology underlying dyslexia. There is currently no direct, noninvasive way to detect and assess the expression, transfer, and therapeutic changes of genes in living humans. This makes it difficult to create and monitor pharmacological interventions and reinforces the need for rodent models of dyslexia. Linking research to practice and practice to research is not easy, but there are large repercussions of nontargeted practice and research. Future dyslexia practice focused on identification and intervention must be grounded in genetic and animal model research, in neurochemistry, and in neuroimaging studies. Future dyslexia research must not lose sight of identification, intervention, and clinical practice.

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