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Review article

Neurobiological systems in dyslexia

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ABSTRACT

Biological systems-level principles of the genetic landscape underlying the neurobiology of dyslexia provide a novel and heuristic theoretical framework for a new understanding of the disability. Dyslexia may result from reduced neuroplasticity and earlier peak of maturation of the posterior corpus callosum, temporoparietal region of the left hemisphere reading network, and temporoparietal region of the right hemisphere circuitry of attentional networks. This precocious abridgement of a typically prolonged maturation originates prenatally or in early childhood, driven by environmentally-guided epigenetic mechanisms as retrogressive, adaptive responses to stress. Epigenetics suggests the importance of identifying circumstances that influence reading-related maturational timing; and network control theory suggests an instructional orientation for enhancing plasticity. Thus, dyslexia may be an unexceptional genetic variation resulting from gene/environment interactions.

1. Introduction

Research demonstrating the essential influence of day-to-day environmental quality in sustaining the genetic regulatory systems subserving general maturational processes supports the adaptive significance during child development of morphological and physiological "retrogression" [112,152,177,183,210,218]. This principle can be applied more specifically to the formative roles of environmental deprivation and adversity in altering the dynamic phase of neuronal and behavioral maturation in development. Evidence suggests that suboptimal environments may accelerate and shorten the dominant evolutionary and developmental trend in our lineage. A signature feature of human maturation is a prolonged period of neuronal and network homeostatic neuroplasticity [6,29,62,96,113,115,148,157,169,196].

Lineage is a genetic heritability concept in time. Our lineage connects us to all of our ancestors reaching back to the beginning of time, and forward to our children and their children, etc. In primate brain evolution, the historic phylogenetic trend of this thread of continuity favors increasingly longer periods of neuroplasticity [125,134,203]. In theory, children born today in comparison to their parents may have the potential for a more extensive developmental phase of maximum learning capabilities. Unfortunately, such lineage potential for greater brain reserve is constrained by complex and unpredictable gene by environment interactions. In particular, risky and stressful environments, always present to some degree, are factors mitigating the dominant trend.

Attenuation or shortening of the plastic period in development appears to be mediated by homeostatic regulation of synaptic plasticity, produced by an experience-dependent disruption of an intercellular signaling cascade. This biochemical response requires ATP hydrolysis and adenosine activation of A2-type receptors [106,107]. Long term potentiation (LTP), critical for promoting synaptogenesis and increasing synaptic strength, is inhibited while promoting its opposite, long term depression (LTD). Ultimately however, brain functions of regionally-specific areas vulnerable to oxidative stress, may be shielded by the detrimental effects of highly energy-demanding metabolic and environmental processing demands [13,24,200]. In development, coactivated modules of polymorphic genes modulate neuroplasticity, and its associated high-energy requirements, through greater dependence on aerobic glycolysis (AG), or nonoxidative glucose metabolism [11,138]. AG reflects an enhanced physiological state of homeostatic or structural plasticity conducive to prolonging maturation and promoting the neuronal remodeling essential to learning [84,85]. High levels of AG are concentrated in areas of the brain that undergo prolonged maturational plasticity. Data sets vary, but two regions with consistently highest ratings are (1) the default network (DMN), primarily ventromedial prefrontal cortices and posterior cingulate/precuneus, and (2) the bilateral frontoparietal networks (FPN), primarily the ventrofrontal areas and temporoparietal junctions (TPJ) [11,241].

However, an adaptive feature of AG is that it can be down-regulated, in the absence of genetic change, in response to perturbations in environmental circumstances [138]. In supporting the course of the dominant developmental trend, AG typically maintains lineage plasticity at least into the fourth decade [85]. Early curtailment, however,

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would engage a precociously adaptive shift to the lower energy parameters of aerobic phosphorylation. This transition restricts neuronal modifiability, but avoids the potential cellular and metabolic oxidative damage associated with excessive AG activity [24,84].

Key genetic elements in this process are (1) the MEF2A mediated, activity-dependent regulatory pathway which controls the timing of synaptic development and neurite formation [134]; and (2) the PDK3 and PPM2C genes which code for the enzymes regulating the switchover from AG to aerobic phosphorylation or other less known pathways [84]. Such neuroprotective programming may be activated by the increased energy demands of aging, by early environmental adversity, or by impoverished sensory experiences. (But see Douaud et al. [52] for an alternate evolutionary interpretation of the AG aging trend). The switchover, itself, is not in debate. Its likelihood increases whenever activity exceeds or falls below a neuron's thermodynamic set-point [28]. In either event, this turnover to the greater energy efficiency of oxidative glucose metabolism offers a degree of protection against declines in general intellectual processes, memory problems, and the onset of a variety of neurodegenerative disorders [19]. The downside, however, is a regionally-targeted loss of maintaining an optimal physiological range of synaptic weight, which compromises neuronal accommodation to specific educational opportunities and ease of acquiring new knowledge. This turnover tends to safeguard more established neuronal circuitry, while the actively evolving neural modules and networks that are in an emerging state, supporting the acquisition of relatively new cognitive abilities such as literacy, become selectively vulnerable to environmental compromise [81,227].

Theoretical acknowledgement of the importance of elements of heritability interacting with the environment in orchestrating this process was first introduced over 100 years ago by Schmidt [188]. The retrogressions observed in selective phenotypic traits were portrayed as products of adaptive, Darwinian natural selection. Unfortunately, the idea received little interest, laying dormant for 50 years, until it was "rediscovered" by Dobzhansky [48,49]. In a series of a priori field experiments with plants and animals, Dobzhansky was able to document the power of ecosystem variability in adaptively shifting the duration of maturation bidirectionally. And, importantly, these studies verified that such changes could occur in response to environmental differences over the course of a single generation. Subsequently, Gould [83], in a detailed theoretical treatise, emphasized the neotenic counterpart of retrogression wherein favorable environments may promote a more extensive maturational phase of neuroplasticity and learning. There can be little doubt that environmental contingencies may affect the mode of synaptic communication by expanding or contracting dynamic periods of neuroplasticity during development.

The potential importance of retrogression to a deeper understanding of the neurobiology of dyslexia has been encouraged by recent studies of individuals with dyslexia, demonstrating wide-spread reduced neuroplasticity. The areas include synaptic functions of key posterior left hemisphere territories and their right hemisphere homologues involved in reading [3,91,104,105,167]. By compromising the brain's openness to learning, such reduced neuronal activation patterns may result in domain-specific cognitive "impairments" that are realized more accurately within an evolutionary perspective as positive "adaptations" (cf., [71]). If the current thesis proves to be correct, variability in the duration of the brain's malleable resilience to the quality of the circumstantial context of the environment will be seen as a biological wellspring for phenotypic change. Such resilience in association with adaptive neuroplastic shifts in carbohydrate metabolism may account significantly for individual differences in cognition, and more specifically, for the varying range of children's receptivity to beginning reading instruction.

Important corollaries of this approach are: (1) dyslexia represents the lower ranges of the normal distribution of an ongoing and dynamic evolution of reading skills in literate societies [164]; (2) dyslexia is independent of general intellectual performance [9,90,214]; and (3) individuals with dyslexia present a heterogeneous behavioral and cognitive profile. There can be no doubt that dyslexia involves extensive individual differences at the genetic, cellular and neurobiological levels. In attempting a coherent conception of dyslexia, numerous subtyping models have been suggested. The issue continues to be debated. However, there is substantial evidence supporting a core phonological deficit in a large number of afflicted individuals [10,122,232].

Nonetheless, it is not unusual for studies to have significant numbers of individuals with dyslexia, without an apparent phonological problem (e.g., [155]). Our approach to this conundrum is to selectively focus on phonology as a core deficit, understanding that such a framework is not all-inclusive. Consequently, the framework developed here is restricted to individuals with dyslexia with impaired phonemic and phonological processing. However, far from a single deficit orientation, such inefficiencies present a complex classroom learning profile. Their educational performance may be challenged by the high-level phonological processing requirements of: (1) initially forming and/or accessing phonological representations; (2) rapid lexical access; (3) verbal short-term or working memory; and (4) speech perception [12,150,222]. Moreover, the complexity of their cognitive difficulties does not end there. In addition to a signature domain-specific impairment in phonological processing, executive functioning deficits are also well-documented [17]. A variety of every-day behavioral management difficulties emerge, similarly affecting working memory, but also attention, general planning, and inhibitory control. Granted, while many of these executive shortfalls have been traced to more basic phonological functions [191], discoveries in network science also impute a central role in dyslexia of domain-general, cognitive control networks [187]. Indeed, the remarkable advances in modern network brain science suggest the significance for understanding neurological disorders of integrative processing bilaterally across the entire brain [69]. Hence, a broad view of the cognitive profile of the phonological form of dyslexia aligns closely to multiple deficits [165] and phonological-core variable-difference models [209]. The educational struggles of individuals with phonological-core dyslexia extend well beyond phonology [202].

The present paper presents a novel, working theoretical framework of dyslexia from a comprehensive biological orientation. The manuscript is divided into five parts. Following the Introduction, section two summarizes common properties of the neural network organization of the brain across species that have resulted from shared evolutionary pressures. The third section describes a neurobiological model of dyslexia emboldened by a broad synthesis of research efforts in the neurobiology of dyslexia (e.g., [159,236]), network neuroscience (e.g., [145]), and evolutionary developmental biology (e.g., [18]). The fourth section underscores the formative role of genetics and epigenetic mechanisms in dyslexia, and in the unique manifestation of literacy skills in human society. Both are mediated by adaptively valued patterns of brain plasticity. The last section outlines a theoretical orientation to educational intervention rooted in (1) the environmental interdependence of the disability and (2) potential of applying fundamental concepts from network and network control theory to promote optimal levels of neuroplasticity in primary and compensatory systems.

This selective review and forward looking synthesis of findings from cross-disciplinary research is intended to stimulate discussion and debate, to suggest new research directions, and to be accretive to current efforts at counseling and remediation.

2. Network neuroscience

2.1. Small world architectural design

Brain organization in our species consists of a vast phylogenetic reservoir of continuity with other organisms. Especially relevant to neurocognitive development is the striking similarity in structural and functional brain networks, defined as topologically-linked neuronal

assemblies that are co-activated by specific mental events and task demands [69,144]. Such commonalities in cytoarchitectural configuration are noteworthy for possessing “small world” properties of high clustering, high global efficiency, and a small number of densely connected, coordinating cortical regions or hubs [74,81]. As a comparative illustration, neuronal hub function is analogous to the central management of incoming and outgoing air traffic by major airport “hubs”. Few business transactions take place; their primary purpose is to coordinate the interconnecting cost-efficient flow of convergent and divergent commerce. The fundamental macroscale elements of brain network structure are nodes (neurons or cortical regions) which are parsimoniously interconnected by edges (synaptic connections and interregional pathways). Of particular importance, hominid lineage evolution has configured the topological organization of the brain to deliver a premium of high processing efficiency at low material, space, and metabolic cost: a cost/benefit trade-off between competitive selection pressures which combine in producing high modular circuitry and low average path-length [26].

Short non-Euclidian path-length enables efficient integrative communication between remote nodes, supported by provincial hubs and a few central core and rich hubs densely interconnecting multiple networks. On the other hand, the community organization of high clustering and hierarchical modularity augments regional functional segregation and specialization. Clustering is calculated by the number of edges between a node and its nearest neighbors. Indeed, the ratio of integrative path-length connectivity and segregative clustering connectivity are plausibly the twin pillars spearheading the dynamics of current evolutionary change [69]. Arguably, advances in learning ability have been the main drivers of such connectivity, dependent on the retention of high levels on interneuronal plasticity [13]. Indeed, learning depends on the dynamic neuroplastic outgrowth and retraction of synaptic connections between axonal boutons and dendritic spines, with each spine serving as an independent computational unit. But, each new connection exacts a cost in space, material, and energy. Homeostasis is evolution's answer to this quandary by serving to maintain a cost/benefit balance in the number and efficiency of connections [132]. As such, evolutionary advantage is prejudiced toward maintaining this balance while maximizing flexible variability in the emergence of adaptively beneficial circuits of locally segregated and distantly integrated neuronal assemblies [26].

The sine qua non of developmental network theory proposes a fluid course of maturation that seeks to achieve complimentarity between a decreasing dependence on segregated processing (clustering and high local connectivity), to favor greater reliance on global integration (distant connectivity) [50,61,146]. From an evolutionary perspective, the population variability of the twin processes in development of segregation and integration determines their evolvability, and evolvability, in turn, is a referendum on their potential or dispositional importance for promoting adaptive fitness [88]. This concept is basic to an appreciation of the importance of developmental evolutionary biology to cognitive development. Variability in the neural representations of processing modules within these segregated and integrated networks depends largely on neuroplasticity. In turn, neuroplasticity determines the level of resilience and flexible covariation of their patterns of functional connectivity [151]. Applications to dyslexia in this context are related to research showing: (1) that the assimilation of new knowledge depends disproportionately upon central hub and distant pathway plasticity; (2) that central hubs and distant pathway connections are relatively more energy costly to maintain; and (3) the vulnerability to abnormal development of these more costly integrative elements of brain networks [26,68,219]. Indeed, using in silico algorithmic modeling, Gollo et al. [81] demonstrated the fragility of posterior cortical hubs to disconnection resulting from energy-saving adaptations to environmental dynamics.

Recent studies of the brain's connectome have confirmed economical cost/benefit networks. These networks combine clustered regional segregation, efficient distant pathway integration, and inter-network collaboration modulated by hubs, as a common fundamental cytoarchitectural design across species, ranging from *C. elegans* with only 302 neurons, to humans with approximately 85 billion neurons [69]. Such patterns arise during development, are regulated by genetic and epigenetic mechanisms [67], are important for cognitive functions [35,208], and are disrupted in dyslexia [47,82,102,133,176,233].

2.2. Processing and control networks

Networks are distinctive in serving as either processing or control circuits, in effect, predisposing neurons and nerve pathways to proactive or reactive functions [135,174,207,238]. Processors are thought to be more modular and specialized. Controllers rely more on the integrative white matter routing of the computations that influence how processors operate. Although the distinction is not absolute, processors usually combine to recruit within-network, domain-specific computations, whereas controllers receive and relay projections through multimodal association hubs interconnecting distributed brain networks. For example, Broca's area in left inferior frontal cortex is widely believed to be recruited for processing sentences for comprehension [184] and as an important processing node in the extended reading network [159]. Homologous regions in the right hemisphere are recruited for supportive, integrative cognitive and attentional control functions [170].

Our focus in this review is on the left-processing and right-controlling, hemisphere territories of the temporoparietal junctions (TPJs) and their white matter tracts. Each region is located at the confluence of the posterior inferior parietal lobule, posterior superior temporal sulcus, lateral occipital cortex, supramarginal gyrus, and angular gyrus. Each anchors the perisylvian posterior zones of the arcuate fasciculus/superior longitudinal fasciculus of each hemisphere. Moreover, each TPJ hosts intrahemispheric cortico-cortical projections and extensive interhemispheric connections via the splenium of the corpus callosum [114]. Research quantifying the degree of local and distant functional connectivity at each vertex of brain surface, demonstrated that these left and right expansive territories qualify as multimodal associative hubs [151,193]. A few “rich club” hubs whose connections are largely to other hubs include bilateral precuneus, insular, and superior frontal/parietal cortices [37].

The left TPJ is a domain-specific processing hub, which functions in coordination with the left inferior frontal cortex, for carrying out multiple attentionally-controlled language and reading-related processes [54]. In contrast, the right TPJ, in coordination with the right medial frontal gyrus, is a domain-general hub thought to play a critical role in processing stimulus-driven, bottom-up information for goal-directed, top-down behavioral management [234]. Evolutionary studies comparing the attention networks of humans and macaques, who last had a common ancestor 25 million years ago, have found several striking differences [142,163]. Two lateralized frontoparietal networks were observed only in humans, displaying the greatest evolutionary expansion. The human dorsal network had undergone more expansive change, and macaques showed no functional evidence of either the right ventral network or a right TPJ. Left hemisphere differences have also been observed in comparisons with humans, chimpanzees, and macaques. Notably, in humans the left arcuate fasciculus (AF) was strongly modified in its perisylvian connectivity of Broca's territory in the left inferior frontal cortex, including Wernicke's area [181]. These findings support a recent evolutionary origin of the mostly right hemisphere frontoparietal ventral and dorsal attention networks, the right TPJ, and the left perisylvian region which is anchored by the left TPJ.

More specifically, the left TPJ participates as a posterior coordinating hub, primary for processing phonological information via the left arcuate fasciculus (AF) in the dorsal (temporoparietal) reading network (e.g., [224]). Furthermore, the left supramarginal gyrus has

been broken-down into four specialized functional regions supporting distinct computations for different types of phonological processes [160]. The right TPJ has been parcellated more extensively into subregions serving different cortical control networks. Ventral/dorsal and anterior/posterior subregions have been identified, with each communicating with separate bilateral areas of frontal and parietal cortex [39,98,121,141]. Each controls signaling traffic in separate but centrally integrated networks, supporting cognitive processing, attentional regulation, and social cognition. Much remains to be determined. For instance, there is a lack of clarity in defining the subregions and difficulties in tracing the non-canonical fiber connections between regions. Nonetheless, it is plausible that the right TPJ co-activates with the complex frontoparietal attention networks, and in coordination with the left TPJ and reading network, may be instrumental in modulating left hemisphere phonological processes [2,110,179].

With regard to dyslexia, the hybrid model presented by Duecker and Sack [55] is especially instructive. Their model supports a frontoparietal, ventral attention network (VAN), and a frontoparietal, dorsal attention network (DAN). In this formulation, the right hemisphere exclusively modulates the VAN and the frontal extension of the DAN. In contrast, the posterior dorsal-parietal areas of both hemispheres are characterized by competitive, interhemispheric inhibition. In common with other models (cf. [39,63]) the right TPJ plays a prominent part in managing the VAN, is pivotal in coordinating the controlling functions of the VAN and DAN, and acts to maintain interhemispheric balance. Thus, the topological organization of these processing and control systems exhibits the small world properties of modularity, global efficiency, and coordinating hubs, acting together to facilitate segregative and integrative information flow through their respective networks.

These left and right hemisphere regions were selected as our focus in this review because: (1) they demonstrate uniquely human expansive evolution and prolonged maturation in development [23,142,163,181,193]; (2) they are variable association areas, less constrained by genetics and more open to environmental factors, known to promote diversity in network connectivity [22,168]; and (3) both are associated with the impairment in dyslexia in coping with phonemic and phonological task requirements [73,110,222]. The recent hominin evolutionary origin of these territories and protracted maturation presents a fertile substrate for ongoing adaptations in development, with heightened potential for favorable and unfavorable modifiability.

3. Network aberrations in dyslexia

3.1. Modularity and white matter pathways

Modular studies examining regions of interest in the left hemisphere using age-matched controls make up the majority of imaging research in dyslexia. Without controls for group differences in reading performance and experience with reading materials, interpretations are necessarily ambiguous in pursuit of the causal factors in dyslexia. Differences may result from lower reading skill or compensatory processes. Such results have led to the identification of a wide variety of putative, but potentially mistaken primary neurobiological areas of impairment. Indeed, studies controlling for reading-level [118] and efforts at replication [178], have failed to substantiate many of these earlier findings.

In an attempt to overcome this design limitation, a recent meta-analysis of brain imaging studies was conducted with pre-reading children at familial risk for dyslexia [223]. The most frequent finding across studies demonstrated reduced functional activation and poorer structural organization, prior to reading instruction, of the left hemisphere TPJ in children at-risk for dyslexia. Several studies also identified the left fusiform gyrus, right parietal lobe, and left cerebellum. Similarly, a literature review aimed at identifying etiological neural territories in dyslexia pinpointed anomalies in left temporoparietal cortex [236]. (Also see Kraft et al. [119]). Related studies of preliterate children [120] and even 6–17 month old infants [126], have reported atypical white matter development of the left AF. Deeply interior to the cortex, the long segment of the left AF directly connects Broca's area in prefrontal cortex with Wernicke's territory in posterior temporoparietal cortex. The direct segment functionally engages a sensory-motor phonological processing loop [12,97]. However, Broca's area involvement has been questioned by an fMRI study with age and performance controls. Children with dyslexia during a phonological word rhyming task showed typical bilateral frontoparietal activation, but reduced activation in left dorsolateral prefrontal cortex (DLPFC) [116]. For non-rhyming matches, the children with dyslexia recruited greater right TPJ activation. The left DLPFC is topologically superior to Broca's area, outside of direct TPJ connectivity. If replicated, this unexpected effect implicates a wider or alternate frontal area in the phonological difficulties common to dyslexia.

What may be another dimension of impaired phonological processing in dyslexia was reported in a pilot study examining bilateral perisylvian areas [199]. Dyslexic individuals showed greater cortical myelination, especially in layer 4 of the left auditory cortex, which suggested disrupted thalamocortical feedback. Myelin is known to inhibit axonal growth and synapse formation [80]; so this would be important to replicate with reading-level controls and tests for reduced neuroplasticity. There are many unknowns and avenues to pursue for a complete picture. Nevertheless, considerable evidence suggests that atypical development of the left hemisphere TPJ and dorsal reading network predates the child's struggle to acquire beginning reading skills.

Indeed, longitudinal studies of children at familial risk for dyslexia compared to typical readers confirmed the etiological significance of the left dorsal reading network, but additionally implicated homologous regions of the right hemisphere. Prior to first grade, white matter anomalies were found in the left and right AF in children at-risk who later became dyslexic [221]. Additionally, but with a larger sample, Wang et al. [230] used a variation of diffusion tensor imaging (DTI) which allowed the assessment of specific segments of white matter tracts, but still yielding the most frequently used tensor measures: fractional anisotropy (FA) and radial diffusivity (RD). FA produced the most significant findings, thought to measure the integrity of axon microstructural properties: mainly myelination, axon caliber, and packing density [215], but also may be influenced by the density of fiber crossings [220]. Four important findings were reported: (1) at the prereading stage, lower FA was found in the at-risk children in several left posterior regions of the AF and the superior longitudinal fasciculus (SLF); (2) also at the prereading stage, children at-risk showed right lateralization of the AF compared to typical readers who showed left lateralization. This effect is consistent with Ma et al. [136] who reported increased cortical thickness of the right superior temporal gurus, extending into the planum irrespective of their reading ability; (3) lower FA was found in the left inferior longitudinal fasciculus (ILF) and visual word form area (VWFA) which followed from a lack of reading experience. This effect is consistent with the thickness reductions found in the VWFA [4], but contradicts Ma et al. [136] who showed increased thickness of the left fusiform gyrus; and (4) the at-risk children who improved in reading demonstrated faster white matter development, reducing an early atypically higher FA, in the middle region of the ventral branch of the right SLF. This suggests a right hemisphere compensatory or supportive role. However, the last finding requires a cautious interpretation in view of another study suggesting a negative correlation in dyslexic children between rightward asymmetries of the second branch of the SLF and reading accuracy [240]. Plausibly, homologous posterior zones in both hemispheres may be compromised in at-risk children prior to reading instruction, but areas of the right may retain a level of plasticity or greater scope for reorganizational compensation [100,228].

Finally, atypical right hemisphere oscillatory entrainment to speech

in dyslexia appears to be precursory to their phonological deficits [40,44, 173]. Oscillations occur rapidly over fractions of a second in normal conversational speech, carrying information which must be phase locked for assimilation with endogenous auditory rhythms across the frequency rates of delta (1–3 Hz), theta (4–8 Hz), beta (15–30 Hz), and low gamma (30–40 Hz). They appear to be modulated by attentional networks [41,124], largely engaging regions in the right TPJ: Heschl's gyrus, superior temporal gyrus and sulcus, planum temporale and inferior parietal lobe, and inferior frontal gyrus [171,173]. Oscillatory synchronization segregates, and organizes Hebbian neuroplastic spike timing, via phase and amplitude coupling [30,79]. Oscillatory synchronization segregates information, and organizes Hebbian neuroplastic spike timing, via phase and amplitude coupling [79]. The recent reading-level controls in this line of research suggest strongly that dyslexic individuals "over sample" the right hemisphere low frequency delta/theta syllabic and phonemic oscillations, important for establishing a phonological lexicon. The mechanism linking this dysfunction to the typical processing of the left reading circuitry is unclear. A possibility was discovered by Molinaro et al. [150], who reported an impairment in feed-forward oscillatory coupling between right and left hemispheres in children and adults with dyslexia. The energy trade-off of such oversampling would reduce the hightened metabolic load of lower frequencies, but at the expense of computational efficiency. Faster speeds are also thought to overload working memory and reduce the time for semantic processing [79].

In summary, there are many issues to work out, and many dimensions to explore. Nevertheless, it is reasonably clear that dyslexia involves early developmental aberrations affecting key modular and white matter components of the bilateral reading network organization of both hemispheres and their interactions.

3.2. Network connectivity

Connectivity studies in dyslexia demonstrate a variety of widespread differences in network organization, especially affecting path-length and hubs (e.g., [82]). Although important in their own right, a number of studies have not controlled for the differential effects of reading-level. Nonetheless, atypical patterns of left and right hemisphere activation and connectivity have been frequent findings, which align well with the performance-controlled modular and white matter research [46,65,239]. Two studies with performance controls stand out to more firmly substantiate dyslexia as an impairment in interhemispheric network connectivity ([197,198]). Magnetic source images were recorded while children performed visually presented letter or word identification tasks. The results with nine year-old children who were dyslexic and with at-risk kindergarten children, showed a lack of activation in the left TPJ, coupled with predominantly higher activation by the right TPJ.

Greater specificity was achieved in a causal neuroimaging study with young adults who were dyslexic [73]. The strength and direction of connectivity changes between nodes were examined by identifying the source of incoming and outgoing activity, just prior to performing a visual nonverbal naming task. Individuals with dyslexia were compared to age-matched controls. The main findings of interest revealed that poorer performance by the disabled readers (1) was correlated with relatively greater outward connectivity (vs inward) of the right TPJ in the low beta frequency range to the rest of the brain bilaterally, and (2) the right rather than left TPJ acted as the controlling hub in phonological processing. It is important to point out that these results are contradictory to an exclusive compensatory role by the right TPJ. Faster and stronger outward connectivity of the right TPJ in this experiment with adults correlated with inferior phonological coding, possibly reflecting an early developmental failure, or an aftermath of years of recruiting unsuccessful strategies in attempting to improve their reading skills.

Finally, three studies in dyslexia examined network integrity by measuring regional topological properties of nodes. Two studies with age-matched controls were conducted with Chinese children, using MRI derived graph-theory analyses of pair-wise gray matter volume [133,176]. Both reported left and right hemisphere aberrations in ``betweenness" and ``degree", but meaningful interpretation of the results is obscured by group differences in reading-level. A better study, controlling for performance, also calculated betweenness and degree in a group of children at-risk for dyslexia who were just beginning kindergarten [102]. Betweenness is the fraction of shortest-paths that pass through a node, useful in identifying hubs with distal integrative functions. In contrast, degree considers the number of connections of a node with the rest of the network, reflecting the density of within-network interactions.

Networks constructed from measurements of surface area found that the children at-risk had lower betweenness and degree in left hemisphere reading areas, supporting disconnections not only within the perisylvian network, but also with more distant centralized hub linkage. Hub calculations generally demonstrated less left hemisphere hub definition, coupled with greater right hemisphere hub definition in the children at-risk. And, of particular interest to our focus, evidence of surface area hub connectivity in the superior temporal and supramarginal regions bilaterally was only found in the typical children. This finding indicates the possibility of early maldevelopment and reduced connectivity bilaterally of the TPJ hubs in the children at-risk for dyslexia.

Together, these data suggest that a right lateralized cognitive control system may be a core component, interacting with the left hemisphere reading network, in the domain-specific phonological processing deficit in dyslexia. However, such attentional dysregulation undoubtedly has broader effects on domain-general executive functions (e.g., [98]). Principally, the area of this dysfunction appears to have its nucleus in a miswiring of the right temporoparietal region of the brain, the TPJ.

To summarize, individuals struggling with dyslexia demonstrate developmental anomalies before reading instruction in the hub and topologically associated networks of the TPJs of both hemispheres. Such differences may have their origin in patterns of development that are well-established in evolutionary principals and in area-specific disadvantaged variability in the small world architectural organization of the brain. These areas have evolved relatively recently. A recent origin presents a fluid neurobiological substrate for literacy acquisition, plausibly accounting for the distributed ability range and large numbers of individuals failing to read at grade-level [153].

3.3. Corpus callosum

No neurological structure is more essential in development to the integrative network functions of the brain than the corpus callosum (CC). The CC evolved in our recent past, first appearing in the brains of placental mammals [1], and stands out as the main commissure coordinating facilitative and inhibitory processing between the left and right cerebral hemispheres [77]. Moreover, the integrity of the bundle of CC axons is a referendum on the maturational status of topologically and secondarily connected cortico-cortical regions [59]. Callosal development begins in utero and continues throughout the first three decades of life [114], suggesting a high unmyelinated/myelinated ratio in childhood. In vitro studies with mice have shown that at three months of age 72% of CC axons are unmyelinated [129]. Even in adult mice, the majority of CC axons remain unmyelinated [229]. Evolutionary principals would expect such prolonged immaturity to be progressively exaggerated in the hominin lineage, providing a resilient scaffolding to support an extended period of developmental plasticity in interhemispheric processes.

In dyslexia, structural neuroimaging studies of the CC suggest an accelerated or shortened period of plasticity. An abnormally high FA in the splenium area of the CC has been a frequent finding in poor readers,

often associated with inferior phonological skills [51,58,72,93,161].The splenium, which is the caudal segment lying adjacent posteriorly to the isthmus, interconnects its foremost axons to bilateral areas of the TPJ; hindmost fibers are connected to primary and secondary visual areas [114]. High FA is most likely driven by reduced radial diffusivity (RD) due to an abnormally thick myelination or greater density of axons [204]. Thus it may reflect an earlier onset of myelination in dyslexia. Of course, confirming an earlier onset will require longitudinal data. However, the protracted ontogeny of the CC in humans biases development toward a preponderance of unmyelinated axons in childhood and adolescence. Hence, an earlier onset of myelination in dyslexia is a plausible hypothesis. A larger and abnormally shaped callosum in individuals with dyslexia has also been reported in association with poor phonological ability [182,226]. In development, increased myelination is paralleled by axon pruning which results in a continuous reduction in the number of axons [103]. Therefore, increased FA and a larger CC in dyslexia may reflect prematurely advanced myelination and/or precocious cessation of pruning. In either event, maturational plasticity has been compromised.

Such micro-and macro-structural callosal “overdevelopment”, clearly has negative implications for the course of maturation in both hemispheres and for learning to read. For instance, atypical maturation of the callosum is known to reduce the drive for left hemisphere lateralization of the reading network [99]. Indeed, from four to ten years-of-age, the splenium undergoes rapid development during a phase of enhanced plasticity, which coincides with the time most children learn to read [231]. Early development, however, would offset the speed, fidelity, and timing of signal transmission and curtail neuroplasticity [78].

The detrimental effects of such overdevelopment cannot be overestimated. The realities are significant. Consider that an increase in CC transduction times between hemispheres is estimated at ten times faster (300 vs 30 ms) through a myelinated axon compared to an unmyelinated axon [66]. The magnitude of such a timing disruption would seriously impact the essential counterbalance between Hebbian and homeostatic plasticity in learning [237]. Hebbian plasticity-dependent increases in synaptic strength requires the precise and sequential millisecond-by-millisecond synchronization of spike-time excitatory presynaptic and postsynaptic action potentials. This plasticity-dependent interaction is embodied in the concept of cell assembly proposed by Hebb [94], where precisely timed signals synchronize oscillatory phase coupling between neurons and act to coordinate fluctuations in excitability [30]. Hebbian plasticity facilitates functional change in synaptic strength via a positive feedback loop between activity and connectivity [64]. At the same time, network integration requiring hundreds of milliseconds requires homeostatic plasticity to maintain the global stability of processing across networks [107]. Homeostatic plasticity serves two functions: (1) a negative feedback function, maintaining the net strength of all of the cells incoming signals to stabilize the range of activity around some set-point value; and (2) drives morphological change in the expansion or shrinkage of axonal/dendritic arbors, and change in the addition/deletion of synapses and network rewiring [28]. Hebbian rules can only function after morphological modifications have been accomplished through new neuronal connectivity. Thus, the joint engagement of Hebbian distributed neuronal connectivity, concurrent with the maintenance of global stability is essential for the clocklike synchronization of synaptic conduction [66,201]. Both forms of plasticity are activity-dependent cellular processes which are essential to learning by modulating the efficiency of neural transmission. As the processing dynamics of learning to read require reorganizational neuronal capabilities [223], compromised neuroplasticity, alone, presents a formidable educational hurdle for beginning readers to overcome.

Furthermore, the hemispheres are thought to compete in development by mutual inhibition controlled transcallosally [162]. Hence, one would expect a dysfunctional CC not only to constrain the phase of active maturation of the left reading network, but also to disinhibit and accelerate maturation of homologous regions of the right hemisphere. Such detrimental reciprocity was confirmed recently in a magnetoencephalographic study of subjects with partial or full agenesis of the CC compared to typical individuals with intact commissures [99]. An absent or maldeveloped CC were both associated with (1) failure to establish left language lateralization and (2) hyperdevelopment of the right hemisphere. Rumsey et al. [186] were first to suggest that the apparently “advanced” development in dyslexia of axons traversing the posterior CC may be due to a shortened period of callosal plasticity, and early cessation of synaptic pruning of the right angular gyrus. Thus, a larger CC with less diffusivity may result from an earlier peak and abbreviated phase of maturation compromising the interhemispheric network functions of both hemispheres.

It is important to point out, unlike the hypertrophied CC in dyslexia, a broad spectrum of other developmental disorders, i.e., schizophrenia, bipolar disorder, autism, alien hand syndrome, and ADHD, have all demonstrated a smaller than normal CC with sparser connectivity [225].

In summary, our current understanding of the underlying neurobiology of dyslexia is consistent in very general terms with the theory of experience-dependent adaptive retrogression. In addition, based on indirect evidence, we have hypothesized that the splenium of the CC, a high traffic conduit between hemispheres, may play a central role in bihemispheric neuronal plasticity and phonological processing. In dyslexia, excessive connectivity of the CC in early development may desynchronize the integrative network functions of the key hubs embedded in the posterior temporoparietal territories (TPJs) of both hemispheres. As a result, posterior regions of the left lateralized reading network and the system of right lateralized control networks may fail to reach peak levels of maturity through typically extended periods of plasticity. From this perspective, the logical avenue to an intervention strategy is dependent upon an elucidation of the G X E interactions that may be at the etiological core of the disability.

4. Evolutionary genetics and literacy

4.1. Epigenetic gene regulation

Unlike the deep phylogenetic roots of general intelligence and spoken language, literacy has evolved relatively recently. Written language as a socially advantageous human skill is evolving by the selective coadaptation and embellishment of ancient, antecedent, domain-general neurological substrates [14]. As an ongoing transformational process, neo-Darwinian evolution can promote transgenerational innovative alterations in complex phenotypes over a few hundred years [15]. However, research in cognitive epigenetics suggests that mitotically heritable molecular change outside of the DNA sequence can occur in response to environmental circumstances over the course of a single generation [43,123,190]. Neuroepigenetic change in development is commonly defined as heritable and potentially reversible phenotypic variation, produced by environmentally-sensitive modifications of gene expression without altering DNA sequence (e.g., [32,53,143]).

Epigenetic, nonsequence-coding genetic mechanisms drive much of the variation in complex biological systems [177], and are essential in regulating the pace of maturation [112,115,134,152,183,210]. The primary elements of these algorithmic mechanisms are thought to be chromatic remodeling, DNA methylation, histone modification, and noncoding RNAs [137]. Unlike the highly conservative DNA code, they are dynamic over the life-span, bridging an environmental link between genes and their output. Such transactional causal mechanisms provide the biological substrate for life's experiences to act upon, as children construct individualized developmental trajectories.

Moreover, epigenetic mechanisms officiate the post-mitotic transcription and translation processes essential to fine-tuning the quantitative gene expression associated with functional and structural

dendritic and synaptic plasticity, interneuronal connectivity, and learning [20,24,27,131]. Homeostatic plasticity primarily involves: (1) the formation of new synapses and/or loss of pre-existing synapses; (2) increased proliferation of oligodendrocyte myelination progenitor cells and/or myelin remodeling; (3) rearrangements of network connectivity; and (4) neurogenic replacement of nonfunctioning neurons [25,60,66,101,107,229]. In any event, the common outcome of each is to modify the Hebbian strength of interneuronal synaptic connections [108].

Of particular significance is that such epigenetically guided changes occur largely in interaction with current events [20,149]. From this dynamic perspective, a range of socio-cultural opportunities and challenges would be expected to have a meaningful shaping influence on the neural architecture of the evolving computational systems underlying literacy [16,26,168]. Indeed, mounting evidence from studies in dyslexia suggests that most etiologically-linked genetic variants may encode transcription regulatory proteins, in a common biological process as opposed to rare alterations of protein-sequence [31].

4.2. Epigenetics in dyslexia

An epigenetic origin of the cellular and genetic basis of dyslexia was encouraged by the seminal identification of four candidate dyslexia genes– DYXIC1, K1AA0319, DCDC2, and ROBO1 [75]. For instance, support has been found for single nucleotide polymorphisms of the DYX1C1, K1AA0319 and DCDC2 genes in sustaining a gene/brain/literacy correlation. In average readers, all three genes previously associated with dyslexia and neuronal migration, were shown to affect white matter volume regionally in the left TPJ [42].This morphological effect was positively correlated with reading after controlling for gender, age, and handedness. None of these genetic effects, however, result from coding-sequence allelic mutations. Rather, it appears that the gene/behavioral deficits associated with dyslexia result from neurodevelopmental changes in the spatial or temporal patterns of gene expression. Complex and little understood environmental interactions are implicated. Additionally, the reported effects themselves should be interpreted with caution. A meta-analysis of 46 studies published between 2005–2016 found little agreement and few replications [8]. Nonetheless, there are interesting trends worth considering from the present framework.

Human, mouse, and rat studies have given priority to variants of the K1AA0319 and DCDC2 genes, confirming that degraded neuronal processes linked with dyslexia often follow when their regulatory expression is disrupted Both have been linked to excessive glutamatergic activity and to aberrant patterns of in utero neuronal migration [33,91]. Candidate chromosome locations and DNA variants have been suggested for K1AA0319 and DCDC2 effects. A promoter region for DNA methylated, reduced activation of the K1AA039 risk gene, has been localized to a region 2kbs extending upstream and downstream of start sites [70]. In addition, K1AA0139 and DCDC2 gene expression affecting reading speed and accuracy has been traced to non-additive, synergistic effects of (1) a regulatory element located in intron 2 of DCDC2, and (2) a nucleotide polymorphism spanning K1AA0319 [217]. Such anomalies appear to have a direct influence on cortical connectivity, which targets specific networks in the left hemisphere perisylvian region and axons interconnecting the two hemispheres of the human brain (e.g., [75]). DNA methylation in the K1AA0139 promoter region has also been associated with cognitive control processes in dichotic listening [189], suggesting a component genetic precursor of the impaired dichotic performance of dyslexic individuals [111]. Adding to the weight of evidence, a knockdown study with rats of the K1AA039 gene found a significant reduction in the midsagittal area of the CC [212]. Also showing effects outside of the CC and TPJ, markers in K1AA031, DYX2, AND FAM65B genes were associated with cortical thickness in the left orbitofrontal region [57]. Other studies support the involvement of the DCDC2 gene in myelination and pre-synaptic function, both important precursors of neuroplasticity. In a longitudinal study using resonance spectroscopy with a sample of emergent readers, excitatory metabolites of DCDC2 were related to abnormal myelination and to poor performance on measures of phonology and vocabulary [175]. In individuals with reading disability, variants of DCDC2 have been shown to exacerbate activation patterns during reading in the left inferior parietal lobe, impugning pre-synaptic function and plasticity [38]. The importance of environmental interaction with risk genes has been documented [56]. Self-perceived, antenatal maternal stress was measured at birth, followed by reading measures at age seven and 16. DNA samples were collected at age 11. Individuals carrying polymorphisms of the K1AA0319 gene who were exposed to high stress were poorer in reading during adolescence.

Finally, ongoing genetic studies are beginning to identify variants of DCDC2 which are protective as well as deleterious [34]. In a diffusion tensor imaging study of four groups of 16–21 year-old subjects (dyslexia with/without the DCDC2 variant, and normal readers with/without the variant), Marino et al. [140] found that irrespective of dyslexia, individuals with the DCDC2 gene had reduced FA in the left arcuate fasciculus and left hemisphere region of the splenium of the corpus callosum. Moreover, the individuals with dyslexia who also possessed the DCDC2 variant had reduced splenium FA which favored better reading ability. In addition, a K1AA0319 variant was found surprisingly to have a protective effect among Asians, but was a risk allele in a European sample [194]. Obviously, environmental differences are at play. These provocative findings suggest that such dyslexia “susceptibility genes” may play a protective or liability role.

There are several salient points to make in this formative stage in genetic studies in dyslexia. First, such mixed results caution against firm conclusions. Second, genes do not act in isolation. And thirdly, genetic lines of inheritance do not invariably cause polygenetic disorders like dyslexia. Heritability estimates range from 0.4 to 0.8 [192], but the heritability range, itself, is more accurately conceptualized as a G X E interactional factor. A genomic study in autism illustrates these cautionary points [166]. Entering well-established autism risk genes into a machine learning algorithm culled another 2500 genes likely to be involved; and the behavior of the original genes was shaped by epigenetic interactions involving millions of noncoding, regulatory genetic variants. Thus, finding the environmentally-sensitive regulatory variants in dyslexia is an even more daunting challenge than identifying the risk genes themselves. Without question, the genetic regulatory landscape (and by inference the neurobiological basis) of literacy is an adaptively evolving work-in-progress. The genetic constraints underlying literacy are changing in dynamic and combinatorially complex, regulatory gene/environment interactions.

In summary, genetic research in pursuing the underlying heritable architecture in dyslexia has demonstrated the tentative nature of our knowledge base and immensity of the challenge. However, this line of research does have clear implications for intervention. For instance, environmentally-sensitive epigenetic mechanisms are associated with: (1) the expression of dyslexia risk genes; (2) normative variability in maturational timing; and (3) cellular and molecular neuroplasticity. Finally, and most importantly from an intervention standpoint, in theory neuroepigenetic changes are reversible (e.g., [211]). Hence, to ameliorate the high incidence of reading failure in literate societies, the research together advocates focused efforts aimed at early identification and educational modifications.

5. Prevention and treatment

5.1. Environmental quality

Reading is an evolving trait that greatly increases adaptive fitness in literate societies, leading to enhanced emotional stability, and greater vocational and socio-cultural success. It follows, that individuals who can recruit neuronal and networking plasticity to learn to read early

and easily are aligned with the dominant trend, and such plasticity will continue to be favored by evolution [235]. Thus, natural selection, given agency by epigenetic mechanisms, will typically act to engender this environmentally-sensitive developmental opportunity by prolonging the timing of maturation and neuroplasticity to match the quality of the environment. However, competitive selection for near-term advantage can accelerate and shorten such trends by a protective neurophysiological and bioenergetic response to environmental adversity and/or deprivation [29,84,96,148,169,196]. Behavioral and brain plasticity for the trait in question will be favored in some environments and discouraged in other environments [127]. However, irrespective of the circumstances of specific environments, increases or decreases in plasticity are both seen as positive adaptations ultimately enhancing reproductive success. For uniquely human, adaptive cultural inventions requiring an extended period of learning, the expected cross-generational trend is for a decreasing dependence on the environment as the task becomes easier and more automatic for a greater percentage of children [183].

In a teaching environment, the population trend in evolution favors earlier and increasingly less effort for children to acquire fluent reading skills. Nature has no master plan for the developing brain, but our unique potential for extended neuroplasticity suggests that the ease of acquiring spoken language may be a precursor for similar future automaticity in becoming literate (cf. [128]). However, individuals who are at familial or environmental risk for dyslexia or struggling with dyslexia, may remain heavily interdependent on plasticity-linked environmental and educational quality (e.g., [21,185]).

Direct evidence of environmentally facilitated change in gene expression affecting plasticity has been demonstrated in rat studies [115]. Varying levels of stress, parent-child interaction, and peer relations were shown to strongly influence myelination which, in turn, negatively affected synaptic organization at pre-conceptual, prenatal, infant, and juvenile periods of growth. Prenatal stress altered global myelination, upregulating 45 genes and down-regulating 404 genes in frontal cortex. Research in humans has shown that the plasticity of developing neural structure is particularly vulnerable to environmental factors. Such effects on brain development have been associated with the quality of parental care, cognitive enrichment, an atmosphere of violence and threat, prenatal life stress and trauma, prenatal maternal stress, exposure to nicotine, and alcohol and drug use [29,34,169,196]. More generally, a series of large-sample, cross-sectional studies reported associations of socio-economic status (SES) with the regional brain structures supporting language, reading, executive, and spatial skills [21,156,158,169]. Studies focused on dyslexia have identified home literacy environment and, more specifically, early storybook exposure as a predictor of reading readiness and phonemic awareness [45,89].

Unfortunately for our purposes, while SES is an acceptable measure of a family's financial resources, it is not a reliable predictor of reading achievement. Good and poor readers can be found at all levels of the normal distribution of SES (e.g., [76]). For example, family, neighborhood, and school stressors are more than likely to occur across SES levels. The same is probably true of many favorable home circumstances like storybook reading, which can also be stressful. SES corresponds to a complex mishmash of social circumstances [62], and has little chance of holding the key to unravelling the mysteries of dyslexia. However, it appears that SES can interact statistically with reading level, and the specificity of neurological effects. Gullick et al. [87], studied 10-year-old children from typical two-parent families representing a middle to upper-middle range of SES. They found that higher SES good readers displayed greater white matter coherence in left hemisphere tracts, whereas lower SES readers demonstrated greater development of right hemisphere homologues. SES per se did not correlate with reading. The importance of the study was finding an interaction between SES, reading achievement, and lateralized white matter development. Greater dependence of the low SES students on the right hemisphere may reflect compensatory mechanisms, different reading strategies, or the greater engagement of attentional controls. This study of interaction effects raises the bar for future SES research. From our perspective, however, the use of a broad measure of parental education to gage environmental quality is uninformative. We need research suited to identify specific stressful circumstances, regardless of SES, with developmental impacts on neuroplasticity, brain regions, and phonological processing. In the short term, this may not be a realistic priority.

Moreover, evolution contextualizes poor reading as a blameless gene/epigenetic and environmental mismatch, with a direct influence on the timing of neuroplasticity in evolving brain networks. Risky and stressful environments are ubiquitous over the course of development. Thus, dyslexia is not the fault of parents or teachers and not invariably associated with a particular social class. It is safe to say that equally across social class, there will always be unforeseen individual variations in rates of maturation. Thus, the search for universal circumstances that may trigger the onset of dyslexia is bound to be at least as elusive as detailing the causative genetic landscape.

With due caution, these studies, nonetheless, have identified putative features of the environment to consider in future research. However, our immediate concern needs be intervention. The retrogression model of dyslexia presents a variable neurobiological substrate for applications to educational programming based on neuro-network control theory.

5.2. Neuro-network control theory

5.2.1. Basic parameters

The core principle of neuro-network control theory is the operational identification of mechanisms of network resilience to promote changes in brain structure and dynamics [145]. Network controllability through mechanisms of plasticity is the foremost teaching concept in control theory. Such an approach necessitates the identification of the flexible brain systems or cognitive control networks that enable the achievement of desired behaviors. As an important first step in realizing this goal, the brain's major large-scale cognitive control networks have been extracted from systems-based clustering approaches of hundreds of neuronal regions [36,172]. Five distinct control networks have been identified: (1) a frontoparietal network (FPN), with primary connections between the right dorsolateral prefrontal cortex and the right posterior parietal region; (2) a dorsal attention network (DAN), connecting the right frontal eye-field with the right posterior parietal region; (3) a ventral attention network (VAN), connecting the right inferior frontal cortex with the right TPJ; (4) a cingular-opercular network (C-0), primarily connecting right frontal insular cortex with the anterior cingulate; and (5) a default network (DMN), connecting ventromedial prefrontal cortices with the posterior cingulate and precuneus.

Subsequent research into the control features of these networks used a mathematical tool to measure the degree and global controllability of hubs corresponding to each system [86]. This establishes a teaching platform for the design of network-compatible teaching modules with maximum learning potential. The results showed that hub connectivity of each regional network could be assigned to one of three metrics of diagnostic control, creating networks of average, modal, and boundary hub controllability. Average control hubs, which were densely connected and concentrated in the DMN, were suited to guide the brain to easily reached states with little effort. Modal control hubs were found in the FPN and C−O regions, thought to be important in switching between functions requiring considerable effort. Most importantly for our thesis, boundary hubs were found predominantly imbedded in the VAN and DAN, with responsibility for maintaining variability in flexibly controlling the segregative and integrative functions of the “small world” architectural organization of the brain, capabilities that are crucial to learning and memory [5,18].

Therefore, network connectivity and network control studies converge in suggesting dense organizational cohesion between the posterior articulations of the attention networks and the right TPJ [36,39,121,141,234]. Together, this research supports the right TPJ as a boundary hub in the circuitry of modulatory networks. In effect, the VAN and DAN, mediated by the right TPJ, appear to be of fundamental importance in controlling the network dynamics implicated in phonological processing and dyslexia [73,173,197,198], and, more generally in executive functions [98,121].

5.2.2. Dyslexia interventions

In network control theory, the neurobiological impairment in dyslexia can be conceptualized broadly in terms of a system malfunction in the engineering sciences. Unlike engineering, however, breakdown of the complex circuitry of networks in dyslexia is unique in possessing inbuilt evolutionary adaptive mechanisms of self-correction [145]. Genetic research in dyslexia has identified these mechanisms as internal epigenetic signaling devices, nourished by environmental opportunities in a binary, non-stationary dynamic process. Neuroplasticity can be curtailed under suboptimal conditions and extended under more favorable conditions. Thus, the key to successful intervention will be the identification and operational management of the educational drivers of the G X E neuroepigenetic mechanisms at the nucleus of such adaptive biological reprogramming.

As desired outcomes, the overriding neurobiological objectives are for educational interventions to promote greater response variability and neuroplasticity in the extended bilateral reading circuitry of processing and control networks. Confirmation of experience-dependent homeostatic plasticity requires metrics of change in brain structure [206]. Homeostatic structural plasticity triggers the formation of neuronal network and compensatory change [28]. Moreover, structural changes are fueled by AG in a neuroplastic transaction, whereas functional change can reflect a Hebbian increase in synaptic strength linked to oxidative glucose metabolism [84].

Three studies in dyslexia have reported neuroanatomical changes following intervention. A voxel-based morphology study by Krafnick et al. [117], with a small sample of eleven dyslexic children, aged 9–12, examined changes in gray matter volume (GMV). Using a within-subject design, bilateral increases in brain volume were reported after eight weeks of training. Unfortunately, GMV is a composite measure combining cortical thickness and surface area, which have different evolutionary and genetic origins and very different timing trajectories in development [147]. Indeed, thickness and surface area also show complex regional and topological patterns of association with some regions showing positive correlations and other regions negative correlations over the course of development [213]. Consequently, the reported results are theoretically uninterpretable. On the other hand, a more informative study by Keller and Just [109] found an increase in FA and a decrease in RD in the white matter tract of the left anterior centrum semiovale, accompanied by gains in phonological processing and reading, after 100 hours of remedial training over six months. The study compared 35 experimental group children with dyslexia, aged 8–10, to dyslexia controls and typical readers. Although the area of modification is positioned medially and anteriorly to the left arcuate, that region may have been affected indirectly by fibers of the adjoining corona radiata and arcuate [7]. A likely explanation is that training in word decoding may have induced a plasticity-dependent, favorable increase in myelination of a left hemisphere area with connectivity to the reading network.

The third study of plasticity in response to intervention in dyslexia investigated the combined interactional effects of SES and educational intervention on cortical thickness changes in multiple bilateral regions associated with the processing and control functions of language and reading [185]. Thirty-nine children, aged 6–9, with a history of reading difficulty spanning a range of SES were assigned to a 6-week reading program, and compared to 25 waiting-list controls. At baseline, higher SES correlated with greater vocabulary and cortical thickness in bilateral perisylvian and supramarginal regions in both groups of children. Significantly, half of the children receiving the educational program improved in reading, and their improvement occurred in parallel with increased thickness bilaterally in occipitotemporal and temporoparietal (TPJs) regions, which was most pronounced in children from low SES families. Two results are important to consider from our perspective. With low SES defined by less maternal education and lower economic prestige, the training effect suggests that children from such homes may be more plastic in response to treatment. This finding should encourage follow-up with more nuanced measures of SES and tests for neuroplasticity. Secondly, the training effect on brain structure fits the maturational expectations of the current framework.

The developmental relation of cortical thickness to myelination and pruning is not well understood as it is covaries with age and regional diversity [180]. However, in general, cortical thickness is known to decrease rapidly in early childhood, followed by a leveling-off into early adulthood [205]. And, thinning generally is thought to be associated with increased pruning and stronger myelination, consequently reducing plasticity [78,147,154]. Thus, a plausible account is that short-term intensive instruction with young children with dyslexia may have promoted improved reading via a neuroplastic-mediated deceleration of cortical thickening and delayed thinning. Without intervention, the results suggest that maturation may be accelerated by advanced thinning with a loss of neuroplasticity. Such an interpretation is consistent with other cross-sectional data with a large nondisabled sample [169].

In summary, this study demonstrates that thickness measures taken at one point in time can easily be misinterpreted. The cautious significance of early measures of morphological integrity is that they are a time-restricted window into an unfolding developmental process, in this case likely reflecting a delay in maturation and consequently prolonged period of neuroplasticity. Only longitudinal data can confirm this inference. The Romeo et al. [185] study needs to be replicated for confirmation, but the results as they stand offer tentative support for the maturational plasticity prediction of the retrogressive model of dyslexia. Moreover, although the remedial program was relatively successful in improving reading, application of control theory to dyslexia will favor teaching strategies that expand their traditional emphasis on orthographic and phonological training to include equal time for activities aimed more directly at strengthening the broader network control functions of the right hemisphere.

5.2.3. Right hemisphere network controls

The frontoparietal VAN and DAN boundary control networks, functionally coordinated by the right TPJ, are implicated etiologically in dyslexia. Their boundary status suggests a receptivity to classroom interventions. These networks are fundamental in parsing intrahemispheric low-frequency oscillatory entrainment to speech, and interhemispheric cross-frequency phase coupling. It follows that remediation emphasizing speech prosody, rhyming, and syllable segmention may help in establishing a phonological lexicon by strengthening these networks. Exercises using frequency modified speech and modified voice feedback may also strengthen the auditory feedback loop between auditory inputs and the articulatory encodings of speech.

In addition, the boundary network functions extend beyond phonology to include a variety of executive control functions. Consequently, as an overriding instructional strategy, the control framework highlights the importance of improving attentional and higher-order organizational skills with the twin objectives of improving phonological processing and behavioral management. There is no doubt that the nature of the training program will determine which brain systems are activated [95]. Therefore, control theory in dyslexia provides the rationale for a focus in teaching on challenging the environmental constraints on the typically prolonged maturation of the circuitry of right hemisphere boundary networks.

Finally, an educational focus on the functions of the right hemisphere control networks has the theoretical potential to activate compensatory mechanisms [92,100,130,195,228]. In principle, homologous but structurally different modules have the secondary dual capacity to perform outputs similar to their homologues, while retaining their primary independent functions [216]. Thus, in theory the VAN and DAN networks, with primary neural modulatory functions, may be recruited for both control and compensatory information processing. Such putative versatility provides a systems-level explanation for a long-standing issue in cognitive neuroscience. Right hemisphere hyperactivation is typically interpreted as compensation, but research also supports a role in the etiology of the disability [92]. Dual capacity, control and processing functions of the attentional networks suggest that both interpretations are correct. It is important, however, to point out that such versatility differs from redundancy, where interconnected identical modules perform the same functions [216]. Redundancy is rare in neurobiological systems, and in any event would contravene selection for the cost/benefit economic organization of network architecture.

6. Summary

Pretermitted neuroplasticty of the brain's phonological and control networks in dyslexia suggests that individuals with dyslexia are struggling with reading because they are functioning in a narrower and reduced range of intra-individual, task-specific neuroplasticity (cf. [139]). Such compromised structural, neuronal and network homeostatic plasticity may have its origin prenatally or in early postnatal development in alterations of gene expression, linked to the high-energy requirements of AG metabolism and keyed by suboptimal environmental conditions. This offset in timing primarily involves the interactional integrity of the left hemisphere dorsal reading network and the right hemisphere system of cognitive control networks, coordinated by the CC and by multi-modal associative hubs embedded in the temporoparietal regions of both hemispheres. Fundamental biological systems-level principles applied to dyslexia present (1) a more comprehensive theoretical platform for a deeper understanding of the neurobiology of dyslexia and (2) a theoretically motivated orientation for educational programming.

This review suggests that the neurobiology of dyslexia is coterminous with the small world architecture underlying the emergent and ongoing evolution of literacy in society. Reading must be taught, but children's ease in acquiring beginning reading skills is expected to range widely in interdependence with the nurturing quality of the environment. Epigenetics dispels any notion of genetic determinism. Only approximately 40–60% of children at familial-risk become dyslexic. Furthermore, after statistically controlling for environmental adversity, home literacy environment, and health issues, genetic risk alone loses predictive significance [45]. Environmentally-responsive epigenetic mechanisms are essential to initiating, maintaining, and modulating the timing of maturation and brain plasticity, congruent with canalized slower patterns of growth. As a result, neuroepigenetic changes under unfavorable environmental circumstances may predispose individuals to dyslexia by conferring a short-term selection advantage, i.e., retrogressive adaptation, but at the expense of a loss of neuroplasticity in the ease of learning to read.

Considerable evidence reviewed demonstrates reduced neuroplasticity affecting the extended reading circuitry, and the quality controls of much of this research suggests that the resulting loss of learning capacity may be the proximal cause of reading problems in society. However, this is not a new revelation. The novelty of the present model is (1) forging a systems-level integration of these disparate findings into an evolutionary developmental framework, which normalizes the disability, and (2) identification of the biological evolutionary principles and epigenetic mechanisms regulating maturational timing and neuroplasticity.

Network control theory presents a rationale for potentially increasing the success rate of educational interventions. Control theory suggests a programming focus on the frontoparietal, right hemisphere boundary control networks. They are thought to modulate the early oscillatory encoding of the speech envelope, coactivate with the left hemisphere reading network, exercise control over broader executive functions, and may be instrumental in non-redundant compensatory processing. Future research is needed to test the validity of the model's more conjectural parameters, and to refine the model so that more specific practical recommendations can be suggested for intervention. For instance, current structural imaging methods can be used longitudinally to test for periods of peak maturation, which could also help in early identification. Finally, methodologies new to dyslexia are called for to test the two key features of the present model: (1) measurements of the timing of the expression of the genes regulating the duration of neuro-maturation in regions of interest can be undertaken by mRNA microanalysis; and (2) PET studies with adults can test regional brain areas for glucose and oxygen metabolism, and use AG/aerobic glucose metabolism ratios to study the longitudinal development of plasticity in nodes and network organization.

Conflicts of interest

None.

Ethical statement

This is original and has not been submitted elsewhere.

Financial disclosure statement

None.

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