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Inter-relationships among behavioral markers, genes, brain and treatment in dyslexia and dysgraphia

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Abstract

Cross-country, longitudinal twin studies provide strong evidence for both the biological and environmental basis of dyslexia, and the stability of genetic influences on reading and spelling, even when skills improve in response to instruction. Although DNA studies aimed at identifying gene candidates in dyslexia and related phenotypes (behavioral expression of underlying genotypes); and imaging studies of brain differences between individuals with and without dyslexia and the brain's response to instructional treatment are increasing, this review illustrates, with the findings of one multidisciplinary research center, an emerging trend to investigate the inter-relationships among genetic, brain and instructional treatment findings in the same sample, which are interpreted in reference to a working-memory architecture, for dyslexia (impaired decoding and spelling) and/or dysgraphia (impaired handwriting). General principles for diagnosis and treatment, based on research with children who failed to respond to the regular instructional program, are summarized for children meeting research criteria for having or being at risk for dyslexia or dysgraphia. Research documenting earlier emerging specific oral language impairment during preschool years associated with reading and writing disabilities during school years is also reviewed. Recent seminal advances and projected future trends are discussed for linking brain endophenotypes and gene candidates, identifying transchromosomal interactions, and exploring epigenetics (chemical modifications of gene expression in response to developmental or environmental changes). Rather than providing final answers, this review highlights past, current and emerging issues in dyslexia research and practice.

Keywords

brain imaging; childhood; chromosome linkage; dysgraphia; dyslexia; family genetics; gene candidates; oral and written language learning disability (OWL LD); reading and writing disorders; specific language impairment

Behavioral genetic research with twins in the USA [1,2], England [3], Australia [4] and Finland [5] has clearly demonstrated both biological and environmental influences on reading disability [6]. Comparison of twins who share the same genes versus those who share, on average, only

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half their genes has shown in these cross-country, longitudinal studies that genetic influences on reading and writing are stable from the preschool years to grade 2. Yet related instructional research has shown that children with dyslexia benefit from specialized, language-based instruction [7]. The exciting new finding in these cross-country twin studies is that new genetic influences emerge in grade 2 when curriculum requirements change relative to kindergarten, demonstrating that how genetic vulnerability expresses itself is a function of the nature of the instructional environment.

In this article we address the current understanding of the genetic and brain indicators of dyslexia and their relationship to therapy. Toward this goal, we first call attention to the initial focus of the field of dyslexia on twin studies demonstrating that dyslexia has both genetic and environmental bases [8], and brain imaging studies identifying brain differences between individuals with and without dyslexia and brain regions that changed in response to treatment. Emerging trends include an increase in the following:

- Genetic studies designed to identify the chromosome linkage or site for dyslexia gene candidates related to specific dyslexia phenotypes (behavioral expression of an underlying genotype);
- Brain imaging studies employing not only established but also many new technologies and methods.

Current evidence points to genetic heterogeneity and multiple gene candidates in dyslexia, as discussed near the end of this review. The number of reported brain imaging studies involving individuals with and without dyslexia has increased exponentially and findings depend greatly on imaging modality, acquisition parameters including use or nonuse of tasks, specific nature of task requirements when tasks are performed, and data analysis procedures. A complete review of the rapidly expanding separate literatures in genetics, brain imaging and instructional treatments is beyond the scope of this article, which will highlight currently published findings that have implications for the inter-relationships among genetics, neurology, and treatment for dyslexia.

Example of interdisciplinary genetic, neurology & treatment research

To illustrate this emerging and growing trend to examine the inter-relationships among genetic, neurological and treatment variables, this article features an interdisciplinary center that includes inter-related genetic, neurological and treatment studies. Families with multigenerational histories of written language disabilities were recruited on the basis of a child proband (grade 1–9) who met evidence-based research inclusion criteria for dyslexia (impaired oral reading of real words and pseudowords and/or spelling) [9,10] and/or dysgraphia (impaired handwriting and/or spelling without reading disability) [11]. Family history, parent interviews and test results were used to exclude those who had developmental disabilities, neurogenetic disorders or other conditions with different biological bases for their reading and writing problems. All family members were given a test battery to assess hallmark phenotypes (behavioral expression of underlying genes) in reading, writing and related neuropsychological skills, which prior developmental studies had validated for reading and writing outcomes in grades 1–9 and other researchers were reporting were impaired in reading disabilities. Children in grades 4–6 from this family genetics sample, who had not responded to school instruction, were recruited for the brain imaging and treatment studies in which changes in both behavioral and brain measures were used to assess response to intervention. Adults were also recruited from the family genetics study for brain imaging studies. All measures used in the behavioral phenotyping and genetics analyses were adapted for brain imaging tasks that had been previously validated in studies reported in the literature for dyslexia or writing. Thus, the studies reported in the first section are evidence-driven.

Recruiting from the same sample for which participants met the same inclusion criteria eliminates some sources of measurement error in investigating genetic, neurological and treatment inter-relationships. Results generalize only to samples that are carefully diagnosed as having dyslexia or dysgraphia using the same criteria as in this interdisciplinary center; replication awaits other samples so recruited and studied. Nevertheless, the results in the first section, which are organized by evidence-based phenotypes, are unique in that for the most part they are from studies in which participants were recruited from the same sample of children with dyslexia and thus offer a unique opportunity to investigate behavioral, genetic, brain and treatment inter-relationships in dyslexia. Otherwise results are developmental findings for assessment skills from cross-sectional studies (based on different samples) unless clearly labeled longitudinal (always based on the same sample). Although functional MRI (fMRI) spelling studies of students with and without dyslexia were conducted, students with and without dysgraphia were also recruited from the longitudinal study for fMRI writing studies including, but not restricted to, spelling.

Phonological decoding (oral pseudoword reading) phenotype

Developmental findings validating skills for assessment—Results supported the dominant theory that dyslexia results from a core phonological decoding disability [12,13]. Phonological decoding is assessed by oral reading of pronounceable pseudo words that have no conventional meaning and are also referred to as nonwords. This task requires application of alphabetic principle of spelling–sound correspondences to translation of a written word into speech without access to a semantic representation of a word in memory.

Pseudoword reading accuracy contributed uniquely to spelling in primary grade children [14], was significantly correlated with real-word reading, reading comprehension, handwriting, spelling, and narrative and expository composing quality in intermediate grade children [15], and differentiated superior, average, and poor spellers from grades 1–6 in a longitudinal study [16].

Behavioral phenotypes in the family genetics project—Most child probands were impaired in either accuracy or rate of phonological decoding. Even adults who had appeared to overcome their reading problems, based on real-word reading and reading comprehension achievement, had relative impairments in phonological decoding (accuracy or rate of pseudoword reading) [9,10].

Genetic studies in the family genetics project—Aggregation analyses, which employ semiparametric generalized estimating equations (GEE) to analyze correlations between parents, parents and offspring and siblings, showed a highly probable genetic basis for pseudoword reading rate and a probable genetic basis for pseudoword reading accuracy [17]. Aggregation analyses also showed genetic contribution to pseudoword reading rate independent of its shared genetic contribution with pseudoword reading accuracy [18]. Segregation analyses, which compare different models of inheritance, model the number of genes probably contributing to a phenotype, and inform DNA analyses, found evidence that 1 or 2 genes probably contribute to pseudoword reading rate through a dominant major gene mechanism; and 1 or 2 genes probably contribute to pseudoword reading accuracy through polygenic inheritance [19]. Linkage analyses which identify, based on genome scans, regions of chromosome signal associated with a specific phenotype, identified a strong signal on chromosome 2 for pseudoword reading rate but not accuracy [20]. Work in progress is focusing on gene candidates, which are variations (alleles) in DNA sequences of four chemicals in very small regions within a chromosome, reported by other research groups.

Brain imaging with & without treatment—When judging whether pairs of heard real words and/or pseudowords rhymed (compared with judging whether pairs of tones were the same) during fMRI, children with dyslexia had more blood oxygenation level-dependent (BOLD) activation than those without dyslexia in right than left inferior temporal gyrus and in left precentral gyrus [21]. When performing this same task during functional magnetic resonance spectroscopic (fMRS) imaging, children with and without dyslexia differed in lactate activation in left frontal regions before but not after treatment [22], thus replicating an earlier study. Children also improved significantly more on a behavioral measure of pseudoword reading rate when the training in automatic orthographic–phonological correspondences for decoding included additional morphological awareness activities rather than additional phonological awareness activities [23]. If they received additional phonological awareness activities, beyond automatic orthographic–phonological correspondences, the children did not normalize in lactate activation, whereas if they received additional morphological awareness activities, they did [23]. These findings were the first clue in the interdisciplinary center studies that decoding draws on morphological awareness as well as orthographic–phonological correspondences in English. The findings do not mean that phonological awareness is not necessary – it is but it is not sufficient. Orthographic and morphological awareness are also necessary to learn to read and spell in English, a morphophonemic language.

To assess phoneme mapping of sounds onto letters, which contributes to reading and spelling pseudowords and real words, children with and without dyslexia were asked to decide if each of the two graphemes (1- or 2-letters in pink) in pseudowords in otherwise black letters could stand for the same phoneme [24]. Before, but not after, training that included automatic orthographic–phonological correspondences and linguistic awareness (phonological or morphological), children with and without dyslexia differed in left frontal and parietal regions.

Adults with and without dyslexia differed in both functional connectivity, that is, temporal coordination of brain regions on the phoneme mapping task adapted for functional connectivity fMRI imaging [25], and structural connectivity in white fiber tracts in diffusion tensor imaging (DTI) [26]. Children who were given treatment in both naming by mouth the phonemes that correspond with viewed graphemes (one and two letter units), that is, the phonological loop of working memory, and in spelling heard phonemes with graphemes by hand, that is, the orthographic loop of working memory, close in time had normalized brain regions associated with working memory on the fMRI functional connectivity phoneme mapping task [27]. The time-sensitive phonological loop regulates cross-code mapping in one of two ways:

- Integrates an incoming visual sensation converted to an internal orthographic code (e.g., letter, written word or numeral) with an internal phonological code (word name for the orthographic code) and then outputs the spoken name via mouth; or
- Holds the output of the cross-code integration in internal working memory over time during sustained language processing (Figure 1).

The time-sensitive orthographic loop also regulates cross-code mapping from incoming auditory sensation to high-level internal phonological codes or incoming visual sensation to internal orthographic codes for letter form or written word or internal orthographic codes for letter form or written word to production of letter form or written word by hand (Figure 1). Teaching children with dyslexia to coordinate alphabet principle bidirectionally using both the phonological loop and orthographic loop may help them overcome their difficulty in tracking changing stimuli over time in working memory, which was observed in another fMRI study [28].

During the production phase of oral reading of pseudowords, children with dyslexia under-activated in Brodmann area (BA) 19/V5 compared with children without dyslexia [29].

Anomalies in the fast visual motion system in dyslexia [30] may interfere with orthographic processing [31] and compromise the orthographic-to-phonological translation process during decoding written words into spoken words [32]; decoding requires moving attentional focus across sequential orthographic units (1- or 2- letters) that correspond to phonemes in alphabetic principle or spelling units that correspond to pronounceable morphemes. However, in another study, individual children who decreased activation in right inferior frontal gyrus (IFG; possibly inhibiting orthographic processing) and increased activation in left IFG (possibly activating phonological processing) improved on phonological decoding accuracy after treatment [33]. Learning to decode may also require mastering the process of shifting, as needed, from orthographic to phonological processing.

Written spelling phenotype

Developmental findings validating skills for assessment—Of the written language factors (handwriting, spelling, composing, word reading and reading comprehension) in a longitudinal study, real-word spelling had stable paths of sizable magnitude that consistently explained unique variance in written composition across adjacent grade levels 1–7 and in word reading across adjacent grade levels 2–7 [34].

Behavioral phenotypes in the family genetics project—Spelling tended to be a more persistent impairment in dyslexia, even when reading disabilities were overcome [35], consistent with earlier work in other samples [36,37] and across languages in which alternative phonemes may correspond to the same grapheme (e.g., English) and in which a single phoneme does (e.g. German or Finnish). In fact, in Germany, dyslexia is defined on the basis of impaired spelling [38]. Gender differences related to spelling were not found in English-speaking children with dyslexia, but their fathers with dyslexia were more impaired in spelling than their mothers with dyslexia [39]. Spelling contributed uniquely to written expression (composition) in both children and adults with dyslexia [35].

Genetic studies in the family genetics project—Initial aggregation analyses showed probable genetic basis for spelling [17]. Subsequent aggregation analyses showed genetic contribution to spelling independent of its shared genetic contribution to decoding and nonword repetition [18]. Thus, impaired spelling in dyslexia may have a genetic basis that includes not only oral nonword phonological decoding or nonword repetition but also one or more other variables independent of processing spoken words alone – probably word-specific orthographic spelling for a real word [40], consistent with the brain imaging evidence reviewed next.

Brain imaging with & without treatment—Children with and without dyslexia were compared on an fMRI task contrast between judging whether two pronounceable words were both correctly spelled real words [41], an adaptation of task that could not be solved solely on the basis of phonological decoding [40], and deciding if letter strings matched (orthographic processing apart from word-specific knowledge). They differed in BOLD activation before, but not after, 2-orthographic strategies treatment (Photographic Leprechaun and Proofreaders' Trick; [42] Study 1) on this fMRI spelling contrast (word-specific spelling compared with letter string processing) only in the right inferior gyrus and right posterior parietal gyrus, which are associated with orthographic coding. Morphological strategy treatment without prior orthographic strategy treatment did not result in brain normalization [41].

In another imaging study, children with and without dysgraphia (impaired handwriting and spelling) who had completed a longitudinal study were compared on a comparable fMRI spelling task contrast [43]. Good spellers had more BOLD activation than poor spellers in the left precentral gyrus, postcentral gyrus, IFG and right superior frontal gyrus; but poor spellers

had more BOLD activation than good spellers in left primary motor and superior and middle frontal, and word form (including fusiform), and right cuneus and middle frontal regions. Of interest, although the tasks did not require writing words or letters, the good spellers activated significantly more in primary motor and sensory regions, whereas the poor spellers activated more in another part of the primary motor region, but not in the primary somato sensory region. Furthermore, good spellers activated more area than poor spellers in a superior frontal region associated with concept formation. Spelling achievement was correlated with fMRI activation in seven regions in which those with and without dysgraphia differed in BOLD activation.

Storing & processing spoken words & their parts (phonological phenotype)

Developmental findings validating skills for assessment—Categorizing sound units at a higher-level in the brain (i.e., phonemes at the phonological level) than initial auditory input transmitted to lower-level primary auditory receiving center in the brain is a significant longitudinal predictor of reading acquisition [44]. In primary grade children, syllable and phoneme segmentation of spoken words were correlated at $p < 0.001$ with handwriting, spelling and narrative and expository composition; phoneme segmentation contributed uniquely to spelling and had a canonical loading on the orthographic–linguistic dimension but not on the automaticity/fluency dimension [14]. In the intermediate grade children, phoneme localization and articulation contributed uniquely to word reading and decoding accuracy and were significantly correlated with dictated spelling, real-word reading and pseudoword reading accuracy and reading comprehension; only phoneme articulation was significantly correlated with composition quality and contributed uniquely to dictated spelling [15].

Behavioral phenotypes in the family genetics project—Across the two phenotyping studies [9,10], the phonological factor, based on nonword repetition and phonological awareness (phoneme segmentation task), had a significant path to word reading and pseudoword reading accuracy. The phonological factor may have had a significant path to word reading and pseudoword reading rate in Berninger *et al.*, 2006 [10], but not in Berninger *et al.*, 2001 [9] because only prepublication norms for rate were available for the 2001 study and nationally normed ones became available for the later study [10]. Of the phonological, orthographic and morphological measures, more adults with dyslexia fell outside the normal range on the phonological one [10].

Genetic studies in the family genetics project—Aggregation analyses showed a highly probable genetic basis for nonword repetition [17,18], which has a genetic path to spelling [45], but not for phoneme awareness, which may depend, however, on the phonological memory skills assessed by nonword repetition. Evidence for chromosomal linkage of nonword repetition to chromosome 4 (4p12) and 12 (12p) in two samples and chromosome 17 (17q) in one sample was found [46]. A case–control study identified an association between a DNA variation on chromosome 15 (*DYX1C1*) and nonword repetition but not phoneme awareness [47]. The genetic basis of dyslexia may be directly related proximally to the ability to detect auditory change in heard repeated syllables of low frequency, as assessed with a passive listening task during electrophysiology [38], and to hold phonological word forms of spoken words in working memory while analyzing them for oral reproduction, as assessed with a nonword repetition task. The skills assessed by passive listening to detect auditory changes in repeating syllables and by nonword repetition may be necessary for performing phonological awareness tasks and learning to read and spell words, both of which require holding a spoken word in memory while analyzing its sounds. However, the phonological core deficit may be more directly related to the ability to store spoken words in working memory and detect change in sound units in those words and only indirectly to the ability to analyze and reflect on those sound units.

Brain imaging with & without treatment—During the phase of a nonword repetition fMRI task involving the initial processing of sounds in a word heard through ear phones, children with dyslexia overactivated compared with children without dyslexia in bilateral frontal (including IFG) and temporal regions and left parietal regions (supramarginal gyrus and somatosensory) and underactivated in right frontal and right insular regions [29]. Following phonologically based spelling and reading instruction children with dyslexia improved on behavioral measures of phonological spelling and decoding of pseudowords ([42] Study 2) and normalized in left supra marginal gyrus associated with phonological processing. However, another group of children with dyslexia improved on the same behavioral measures of spelling and decoding ([42] Study 2) and normalized in primary somatosensory regions near the supramarginal gyrus following hands-on, science problem solving using virtual reality. That hands-on learning may influence phonological learning indirectly via changes in nearby neural networks for somatosensory sensations was unexpected, but may provide support for the claim that children with dyslexia are kinesthetic learners.

Storing & processing written words & their parts (orthographic phenotypes)

Developmental findings validating skills for assessment—In primary grade children, receptive orthographic coding (holding briefly viewed written words in working memory while analyzing letter units in them to make yes/no judgments) correlated with handwriting, spelling and composing; and letter cluster coding and automatic letter writing (15 s) contributed uniquely to sustained handwriting during a copy paragraph task [14]. In intermediate grade children, expressive orthographic coding (same as receptive task except required writing the letter units – whole word, letter, or letter group), which assessed orthographic loop function, contributed uniquely to sustained handwriting during a copy paragraph task, dictated spelling of real words, and spontaneous spelling during expository composing [15]. With phonological coding as another predictor in the structural model, only the orthographic coding predictor factor had a consistently significant path to the spelling outcomes from first through sixth grade [48].

Behavioral phenotypes in the family genetics project—For children both with and without dyslexia, the orthographic coding factor, based on the receptive orthographic coding [14,15] and word-specific orthographic coding [40], had a significant path to these outcomes: reading accuracy (based on real words and pseudowords), reading rate (based on real words and pseudo words), handwriting, spelling and composing [9]. Of the children with dyslexia, 76.1% had orthographic impairment with or without phonological and/or RAN impairment [9]. A subsequent phenotyping study [10] provided three findings relevant to the orthographic word-form (storing and processing the written word) in dyslexia:

- The same orthographic coding factor as in the initial family phenotyping study had a significant path to these outcomes: word reading accuracy and rate, pseudoword decoding rate, morphological decoding rate, accuracy and rate of oral passage reading, spelling, and written expression;
- Of the phonological, orthographic, and morphological measures, orthographic was most likely to fall outside the normal range in individual children with dyslexia.
- For both children and adults with dyslexia, males were more impaired than females in orthographic coding [39].

Brain imaging with & without treatment—MRI structural measures of the right pars triangularis (part of IFG), which discriminated significantly between children with and without dyslexia, correlated significantly with a behavioral measure of orthographic coding [49]. Children with dyslexia improved on an fMRI orthographic spelling task following orthographic strategy treatment ([42] Study 1). During a receptive orthographic coding task [14,15] adapted

for fMRI, children with and without dysgraphia in a longitudinal study differed in BOLD activation in left posterior cingulate and calcarine and bilateral precuneus [43]. The cingulate activation may reflect the poor spellers' impaired executive functions for self-regulation of attentional processes while analyzing letters in written words stored temporarily in working memory, consistent with findings of a behavioral phenotyping study [31].

Storing & processing meaning/grammar word parts (morphological phenotype)

Developmental findings validating skills for assessment—From the fourth to the ninth grade, morphological measures contributed uniquely beyond shared variance with phonology to reading vocabulary, reading comprehension and spelling outcomes [50].

Behavioral phenotypes in the family genetics project—In children with dyslexia, who were not as impaired in morphological as in phonological and orthographic awareness, the morphological word-form factor (based on measures of morphological awareness that did not require reading) had a significant path to morphological decoding accuracy (oral reading of words with bases and affixes) and reading comprehension [10].

Brain imaging with & without treatment—Children with and without dyslexia differed in patterns of brain activation on an fMRI morphological task that required phonological transformations of base words when deciding whether a second word (e.g., national) could be related semantically to the first word (e.g., nation) [51]. Such coordination of morphology and phonology is necessary for reading longer, more complex English words. Children with dyslexia differed from good readers on a contrast between a morphological judgment task (deciding if a base word was or was not related to a second word that had a true suffix or a non-suffix sharing the same spelling as a true suffix) and a semantic judgment task (deciding if two words are related are synonyms) [41]. Thus, morphological word-form representations are related to but not identical with semantic meaning. Semantics is a cognitive language translation process at the word-level [52] that enables cognitive representations in implicit memory to gain access to conscious explicit memory.

Storing & processing accumulating words (syntactic phenotype)

Developmental findings validating skills for assessment—Working memory also has a syntax storage and processing unit for accumulating words, which enables children's language development from the one-word to multiword stage [53]. On a sentence combining task, most, but not all, children wrote a complete sentence, but writing a complete sentence did not correlate with or contribute uniquely to sentence combining until fourth grade; syntax production preceded syntax awareness [54]. From grades 1–7 children wrote more single independent clauses than complex clauses, but they did write more complex clauses in the upper than lower elementary grades [54].

Behavioral phenotypes in the family genetics project—More fathers than mothers with dyslexia had syntax problems, which did not show gender differences in children with dyslexia [39].

Genetic studies in the family genetics project—Of 73 probands with dyslexia in a sample of multigenerational extended family members selected for genome-wide scanning, 24.7% had syntactic awareness problems and 9.6% also had dysgraphia [47]. Thus, children with dyslexia are less likely to have syntactic problems than those with selective language impairment (SLI); and their syntactic awareness problems may be the result of less experience in reading text, due to unremediated word decoding problems, or written expression, due to spelling problems – that is the result rather than the cause of their reading and writing problems.

By contrast, impaired syntactic skills may be a causal factor for reading and writing problems of children with SLI.

Brain imaging without treatment—In a study that included other samples in addition to the one from the interdisciplinary center, individuals with dyslexia and SLI were compared with individuals with milder reading problems associated only with phonological problems [55]. SLI is characterized by impaired syntax and reading comprehension problems beyond only phonological decoding [56]. Individuals with dyslexia and SLI were differentiated on a quantitative anatomical risk index based on posterior temporal/parietal anomalies [55] from those with milder reading problems associated with only phonological problems [55]. Future research might explore the phenotypes and genotypes predicted from this anatomical risk factor and what is common and/or unique to dyslexia and to SLI.

Phonological loop of working memory phenotype

Only sensory and motor systems have direct contact with the external world and thus are end organs. Language, which does not have direct contact with the external world, teams up with various sensory and motor systems to create functional systems that receive from or send to the external world indirectly through those end organs [32]. The phonological loop, which is teamed with the mouth overtly or covertly is involved in language learning [57], for example, in learning to repeat heard words, name visual objects, and name written letters or words. Rapid automatic naming (RAN) total time [58] assesses phonological loop function for cross-code integration for cross-code integration of orthographic/visual symbols and spoken name codes. In all the family genetics studies we used a prepublication version of RAN and rapid automatic switching (RAS) [58] given to us by Maryanne Wolf to use for the research purposes of the interdisciplinary center.

RAS total time [58] assesses the executive function for regulating phonological loop function while switching attention across different stimulus categories, as one has to do when parsing a written word from left to right into graphemes for phonological decoding. Flexibility is as important as automaticity in self-regulating reading [59]. Thus, the RAS phenotype reflects the coordination of two working memory components – phonological loop and executive functions.

Behavioral phenotypes in the family genetics project—Of children with dyslexia, 73.3% had a RAN and/or RAS impairment with or without phonological and orthographic word-form impairments [10]. Paths from RAN or RAS to word reading and word decoding rates were significant in the children and parents with dyslexia [9].

Behavioral phenotypes in the family genetics project & longitudinal findings validating skills for assessment—Growth mixture modeling of trajectories across each of five rows during RAN or RAS (instead of total time) identified two latent classes (steady slow across the rows and slow and slower across the rows) [60]. The steady slow class occurred in children and adults with dyslexia and third and fifth graders without dyslexia; the slow and slower class occurred only in children with dyslexia [60]. Both latent classes may explain the invisible disability of dyslexia – difficulty in maintaining over time the cross-code integration involved in language learning and sustained language processing.

Brain imaging study without treatment—In a structural imaging study (MRI), three neuroanatomical structures differentiated children with and without dyslexia with high reliability: left pars triangularis (associated with phonological coding), right pars triangularis (associated with orthographic coding), and right anterior cerebellum (associated with precise timing). The first two frontal regions and the latter subcortical regions were significantly

correlated with RAN [49]. These regions may be part of the neural network that supports the phonological loop function for time-sensitive cross-code integration or sustained covert language processing [10,33,47].

Orthographic loop phenotype of working memory

Likewise, an orthographic loop may serve to integrate incoming sensations with internal codes (e.g., aural stimuli transformed into higher level, internal phonological codes for heard words and their sound parts or visual stimuli transformed into higher-level, internal orthographic codes for written words and their letters). The internal codes are then expressed via the finger movements of hand during handwriting (sequential strokes in letter formation), spelling while composing (sequential letters in spelling), and composing (sequential words in text). This time-sensitive, cross-code integration of the orthographic loop in working memory is assessed by rapid automatic letter writing from memory on an alphabet writing task (first 15 s) [9,10]; this task assesses letter finding, retrieving, planning and producing of letter forms in the serial order of the alphabetic sequence [35,43,61,62].

Developmental findings validating skills for assessment—In structural equation modeling, automatic legible letter writing on an alphabet task (first 15 s) uniquely predicted length and quality of composing in grades 1–6 [63]. The same measure used as a covariate eliminated gender differences in compositional fluency of junior high writers [64].

Behavioral phenotypes in the family genetics project—Both boys and fathers with dyslexia were more impaired than girls and mothers with dyslexia on automatic alphabet letter writing (15 s) [39].

Brain imaging without treatment—Individual children with and without dysgraphia in a longitudinal study differed during fMRI automatic letter writing in left fusiform [62]. Fusiform is a brain region associated with orthographic coding – translating visual stimuli into visible language at the subword or word level (for a review of brain and behavioral evidence see [32,43,65]).

Executive function: inhibition & rapid automatic switching phenotypes

Developmental findings validating skills for assessment—A longitudinal study by Altemeier *et al.* found that [66] :

- Hierarchical linear modeling of growth trajectories showed steady growth in inhibition, as assessed by the color-inconsistent naming on a Stroop task, from first to fourth grade;
- Inhibition contributed unique variance to many reading and writing skills at fourth grade;
- RAS, entered after inhibition, contributed uniquely to word reading accuracy and rate, pseudoword reading accuracy and rate, and spelling in grades 1–5, reading comprehension (grades 2, 3 and 5, marginally in grade 4), and written expression (grades 2–4);
- Growth in RAS from grades 1–4 predicted all reading and writing outcomes at grade 4.

Behavioral phenotypes in the family genetics project—Executive functions, based on RAS, were impaired in both children and adults with dyslexia [10,67]. Of three components of working memory architecture (word forms, phonological loop and executive functions), more individual children fell outside the normal range on executive functions than the other components [10]. For children with dyslexia, inhibition uniquely predicted outcomes for real-word reading rate and pseudoword reading rate, oral passage reading accuracy and rate, and spelling and written expression. Inhibition also predicted RAN slope within the slow and slower latent class, and RAS, after inhibition was entered into the model, uniquely predicted outcomes

for real-word and pseudoword reading accuracy and rate, oral passage reading accuracy and rate, reading comprehension, spelling and written expression. In addition, phonological working memory predicted RAS slope for both the steady slow and slow and slower latent classes [66]. For children, the inattention ratings factor also had a significant path to the orthographic word-form factor [31]. For adults with dyslexia, inhibition and phonological working memory differentiated both latent classes on RAN intercept and RAS slope [60], and RAS was a persisting impairment [67]. For adults, not children, with dyslexia, both phonological loop of working memory (RAN) and supervisory executive function for regulating switching attention (RAS) jointly explained outcomes in structural models; thus, they may work collaboratively in working memory [10].

Genetic studies in the family genetics project—Aggregation analyses showed that inattention ratings had shared and unique genetic contribution to RAS [18]. A comparison of children with dyslexia and two kinds of controls showed that a DNA variation on chromosome 6 (DCDC2 allele) was associated with impairment in RAS (and to some extent with impaired inattention ratings) [47].

Finger sequencing phenotype for orthographic loop of working memory—

Orthographic loop, which regulates processing that proceeds from ear to mind's eye (internal orthographic codes for letters and written words) or eye to mind's eye, or directly from the mind's eye to the hand for writing letters, words and text, draws on the ability to plan and execute sequential finger movements [43,53,61,68,69].

Developmental findings validating skills for assessment—Finger succession [70, 71], which assesses sequential finger movements and has excellent interrater reliability and validity [72], contributed uniquely to handwriting and to narrative length in the primary grades [14] and narrative length and expository length in the intermediate grades [15].

Behavioral phenotypes in the family genetics project—Gene alleles for sequential finger movements and for sequential mouth movements are different but in close proximity [73]. However, impaired sequencing of motor acts appears to be task-specific for written language at the phenotype level: sequential finger movements were correlated with the word-form factor, which in turn explained unique variance in written composition in children and adults with dyslexia. Sequential mouth movements explained the unique variance in oral reading of passages-rate in children with dyslexia and accuracy in adults with dyslexia [35].

Brain imaging without treatment—During an fMRI finger sequencing contrast, which controlled for motor production alone, children with and without dysgraphia in a longitudinal study differed in a brain region associated with orthographic word-form processing; and even though the task did not involve producing written words by hand, brain activation related to this task was significantly correlated with handwriting and spelling measures [69]. Thus, this task may assess part of the orthographic loop circuit. Handwriting, spelling and composing measures were significantly correlated with significant BOLD activation in the same five brain regions during fMRI finger sequencing contrast [74]: bilateral inferior temporal, right precuneus and inferior frontal orbital and left superior parietal. These regions may comprise a writing center served or regulated by the orthographic loop. One of these regions during the fMRI sequencing contrast – left superior parietal – was the only brain region during any task contrast showing gender differences [69] in a series of fMRI writing studies of children with and without dysgraphia in the longitudinal study [43,62,69,74,75]. Thus, gender differences occurred in orthographic coding at the behavioral levels and in finger sequencing at the brain level; collectively they suggest gender differences in the orthographic loop.

Theoretical framework for integrating past and current phenotype findings

In contrast to the findings in the first section based on evidence-driven research, the results discussed below are organized around a theoretical model based on an integration of the brain, genetics and treatment findings [10,33,47]. This model also integrates the most widely supported theories in the research literature of causes for dyslexia (phonological core, double deficit, executive functions and working memory), language learning disability or SLI (impaired morphology and syntax) and dysgraphia (impaired handwriting and sometimes spelling even though reading is not disabled).

All phenotypes are components of a working-memory architecture consisting of three word-form storage and processing units, two loops for integrating internal codes with end organs, and a panel of executive functions including inhibition and rapid automatic switching. The phonological word form unit stores and processes heard/spoken words and their sound parts; the orthographic-word form units stores and processes written words and their letter parts; and the morphological word form unit stores and processes bases, suffixes and prefixes in spoken and written words. Not all phonological word-unit impairments are the same: some occur with aural/oral language and/or speech sound disorders (SSDs) early in preschool development; others, such as problems in phonological awareness (metalinguistic analysis), emerge during the transition to schooling and formal literacy instruction, even in children with no evidence of preschool language or speech problems who have dyslexia during the school years [9,10]. Although both phonological awareness and phonological loop share the common word phonological in their names, they are not identical – the former involves an analytic processing of only the spoken word and its parts and the latter the automatic integration of orthographic stimuli/codes (written word parts or letters) and phonological stimuli/codes (spoken words). Whereas phonological loop is assessed by rapid automatic naming of written stimuli, orthographic loop is assessed by rapid automatic writing of the alphabet.

Consistent with the dominant single-variable, phonological core deficit theory of dyslexia [33,47], each of the three working memory components involves a phonological core for processing spoken words and their parts: phonological word-form unit, phonological loop and executive functions for inhibition and rapid switching while processing phonological information during cross-code orthographic and phonological integration. Consistent with the double-deficit theory that individuals with dyslexia may be impaired in both phonological awareness of sound units in spoken words and rapid automatic naming [58], a task requiring rapid cross-code integration regulated by the phonological loop [33], many children and adults with dyslexia showed both of these deficits in the family genetics phenotyping studies [9,10]. Consistent with the view that dyslexia may present as a problem in either accuracy or fluency of word reading and decoding or both, this working-memory model also explains impaired accuracy (related to specific underdeveloped working memory components) and fluency (related to inefficient temporal coordination of working memory components) [10]. Consistent with the evidence that individuals with dyslexia have working memory problems involving executive function [10], they require more teacher-directed, explicit instruction than peers to develop strategies for self-regulated learning. Not all individuals with dyslexia are impaired in the same behavioral marker of the underlying gene and brain differences, but the number of these behavioral markers of underlying biological risk predicts severity of overall academic learning problems [9].

This working-memory architecture model also explains the learning disabilities that are not dyslexia: in SLI/oral and written language learning disability (OWL LD), impaired morphological and syntactic processing interferes with listening and reading comprehension and oral and written expression. In dysgraphia, impaired legible automatic letter writing interferes with spelling and written expression, but working memory anomalies also are related

to idea expression in dysgraphia [75]. However, dysgraphia, dyslexia and SLI/OWL LD share the strong probability of impaired executive functions, especially inhibition, RAS and inattention, which are not differentiating features among them.

Dealing with heterogeneous phenotypes & genotypes

Both at the genetic [76,77] and behavioral [78] levels phenotypes appear to be heterogeneous and may also, in some cases, reflect atypical neurodevelopmental variation during neural migration [79,80] rather than normal genetic variation [4]. The Human Gene Nomenclature Committee defined nine genomic loci for dyslexia, *DYX1-9* [76]. Four loci for dyslexia gene candidates have been hypothesized to be involved in regulating neural migration [77]:

- *DYX1C1* (also *EKNI*) on chromosome 15
- *ROBO1* on chromosome 3
- *KIAA0319* on chromosome 6
- *DCDC2*, also on chromosome 6

Per Hoffman's group found genetic variation on chromosome 12 (*GRIN2B*) in dyslexia [76]. Other gene candidate loci have been recently proposed and more are likely to be proposed in the future.

However, structure may be discernible within the heterogeneous biological and behavioral markers, just as the double helix structure underlies the complex human genome. In the combined brain imaging and treatment studies in the featured interdisciplinary center, on only one fMRI contrast – between n-back and 0-back, which assesses temporal tracking of events over time (two stimulus trials back vs the current trial) in working memory – was no evidence of treatment responding observed [28], suggesting that another core deficit in dyslexia may be working memory. Recent research developments in the study of working memory show that a single measure is unlikely to fully capture the functional working memory system [10,53,67, 68,81]. Rather, multiple measures are required to assess whether each of the component processes in a working memory architecture is developed to an age-appropriate level – three word forms, two loops and a panel of executive functions – and synchronized with the other components in real time. Evidence for this organizing structure is summarized next. Collectively, these components may serve as a language learning mechanism that supports both oral and written language development [82]. Also see Figure 1 for a graphical portrayal of the model that depicts the two end organs that work with the internal components – the mouth and the hand.

Three word-form phenotypes for storing & processing words in working memory

According to Triple Word Form Theory, awareness of phonological, orthographic and morphological word-forms and their parts and their coordination through cross-word form mapping are necessary for reading and writing acquisition in English [10,23,32,47]. Morphological word-forms (bases, suffixes and prefixes), which are coded in both oral and written words (e.g., the derivational suffix '-er' transforms a verb 'work' into a noun 'worker'), serve as bridges between spoken and written words during decoding and spelling, and also bridge the word- and syntax-level in creating functional language systems that comprehend and construct text.

Developmental findings validating skills for assessment—Orthographic, phonological and morphological coding skills show considerable longitudinal growth during the first four grades [83] when word-level working memory processes contribute the most to reading and writing acquisition in English, which is a morphophonemic orthography [82]. All

second order word-form paths underlying the three word-form factors and the total second order word form paths contributed uniquely to word reading and decoding accuracy, oral passage reading accuracy and rate, reading comprehension, spelling, and written expression in normally developing children in grades 3 and 5 [47]. These findings from a longitudinal study show that the integration of phonological, orthographic and morphological word-form units rather than a single word-form unit alone underlies normal reading and writing development in English.

Behavioral phenotypes in the family genetics project—In children with dyslexia, all second order word form paths and the total second order word form paths contributed uniquely to real-word reading and pseudoword decoding accuracy, oral passage reading accuracy and rate, reading comprehension, spelling and written expression in children with dyslexia [47]. These outcomes were better modeled by second order factors underlying the phonological, orthographic and morphological word forms than by first order factors underlying them. Thus, in a morphophonemic language such as English, the integration of phonological, orthographic and morphological word-form units is relevant for treatment, even if morphological awareness does not tend to be impaired in dyslexia.

Genetic studies in the family genetics project—Aggregation studies have shown the probable genetic basis of Wechsler Digit Span, which is a subtest on the Working Memory Index [17]. Segregation analyses showed that nonword repetition and digit span, both phonological memory measures, share common and unique genetic mechanisms [45].

Brain imaging with & without treatment—Common and unique brain fMRI BOLD activation on tasks involving phonological, orthographic and morphological word-forms and their parts were identified for groups of good and poor spellers and individuals [33,51]. However, a phonological core appeared to underlie the cross-word form mapping illustrated with overlapping circles in Figure 1 (phonological–orthographic, phonological–morphological, orthographic–morphological) in response to treatment [51]. Children with dyslexia given phonological treatment normalized on the fMRI morphological contrast task and children with dyslexia given morphological treatment normalized on the fMRI phonological contrast task [33], consistent with Triple Word Form theory predictions that cross-word form mapping underlies learning to read and spell words [23].

Diagnosis & treatment

Moreover, the model can be used, as explained below, to make differential diagnoses and treatment plans based on which storage and processing units and loops are impaired. However, in applying this model, bear in mind that different aspects of processing speech sounds receptively or producing them overtly, may be involved in each of the specific learning disabilities and SSD. For language, which has word/morphological, syntax and discorsal levels, syntax is the hallmark feature. Phonological awareness (metalinguistic awareness of sound segments that correspond to letters) does not necessarily reflect difficulty with either the same aspects of the sound systems as SSD does or with vocabulary meaning, syntax or discourse skills.

Evidence-based differential diagnosis

Progress in science involving humans requires careful and precise definitions so that other scientists and the consuming public understand whom was studied and to whom the results can be generalized (external validity). The field of learning disability is plagued by a lack of evidence-based definitions for which there is consensus. Three definable, contrasting constellations or profiles of phenotypes were repeatedly discerned in the interdisciplinary

research: dysgraphia, dyslexia and SLI, which is the same as OWL LD [53,67,68,84]. Identifying these requires administering normreferenced measures of handwriting (letter legibility and automaticity), spelling, composing, pseudoword and real-word reading accuracy and rate, and reading comprehension and each hallmark phenotype in the working memory architecture (three word forms, two loops and a panel of executive functions). In addition, it will also require parent and teacher interviews to gather developmental, educational and medical histories from birth to school entry and beyond.

These three specific learning disabilities differ in predictable ways in which word-form and/or loop skills are impaired: dysgraphia involves orthographic word-form coding and/or orthographic loop; dyslexia is characterized by phonological and orthographic word forms and loops; and SLI/OWL LD involves morphological and syntactic awareness plus or minus any other word-form unit or loop [47]. As a result, individuals with dysgraphia are impaired in letter writing and sometimes spelling via its relationship to handwriting [85], and their impaired handwriting and/or spelling may interfere with written expression of ideas. Individuals with dyslexia are impaired in word-level reading accuracy and rate especially decoding and spelling. Individuals with SLI/OWL LD are impaired in word-, syntax- and/or text-level skills that affect their real-word reading, reading comprehension and written expression. At the same time, all three specific learning disabilities share a likelihood that executive functions, especially inhibition, RAS and inattention, may be impaired.

Despite shared nonword repetition deficits in dyslexia and SLI, these are distinct disorders [67,84,86,87] in the timing of onset and nature of their behavioral expression and instructional needs. Clinical assessment studies of children with OWL LD who did not meet research inclusion criteria for the family genetics dyslexia study revealed the following. Their language problems, which first affect their language acquisition during the preschool years (aural through the ear and/or oral through the mouth), also affect their acquisition of written language (reading and writing) and their using language to learn across the curriculum during the school age years. They often respond to early intervention for aural/oral language problems in the preschool years, but if not identified and provided with appropriate instruction during the school years, may be the slow responders or nonresponders to early intervention that emphasizes only phonological awareness and phonological decoding; they often have relatively greater impairment in reading comprehension than word reading [53,88]. Children with SLI/OWL LD can become treatment responders when morphological and syntactic awareness treatment is introduced [89].

By contrast, the problems of those with dyslexia were generally first observable by parents and teachers in kindergarten when children could not learn to name letters or associate sounds with letters (cross-code integration by phonological loop) or first grade when they struggled with phonological awareness. Their problems were mainly in cross-code integration of orthographic and phonological codes and phonological skills at a metalinguistic level. Their listening comprehension and verbal reasoning were remarkably spared.

For evidence-based differential diagnosis, cognitive measures are also administered to evaluate whether the individual's verbal IQ is in the top 75% of the population (a score of 90, or -2/3 standard deviation or above) because the frequency of developmental disabilities and other neurogenetic disorders that have other biological etiologies for their reading and writing problems, is considerably higher in the bottom 25% of the distribution of cognitive abilities. Inclusion criteria for dyslexia also require that at least one of the hallmark reading or writing phenotypes is below the population mean, and at least a standard deviation below the verbal IQ. Impaired phonological awareness does not interfere with comprehension the way impaired morphology and syntax do. Some individuals are much more discrepant than one standard

deviation – but the exact size of discrepancy may be influenced by how much appropriate instructional treatment they have received.

For dysgraphia, low achievement below the population mean on a standardized measure of legible and automatic letter writing is sufficient for diagnosis because handwriting is not correlated with verbal IQ [14]. However, in diagnosing dysgraphia, handwriting in daily classwork and written assignments should be examined for legibility and an assessment should be conducted of how many written assignments are not completed (because child cannot write legibly) or completed on time (because writing is slow and labored). For impaired spelling, which is correlated with verbal IQ and vocabulary knowledge [14], verbal IQ should be taken into account in diagnosing spelling disability without reading disability (spelling below population mean and at least 1 standard deviation below verbal IQ).

For the SLI/OWL LD diagnosis, nonverbal reasoning measures are given to evaluate whether cognition falls at least within the lower limits of the normal range. Because oral language impairments may lower scores on Verbal IQ measures and underestimate cognition, measures of nonverbal cognition, which are less dependent on language, are more appropriate for this diagnosis. The children with OWL LD were less likely than those with dyslexia to show an IQ-achievement discrepancy in written language skills, but nevertheless showed evidence of a specific learning disability characterized by very low reading achievement and impaired phenotypes in the working memory architecture.

One of the persisting problems in dyslexia research is that because investigators are not using evidence-based, precise inclusion criteria or definitions, some samples, which are identified only on basis of nonverbal intelligence measures and very low reading achievement, may have OWL LD over-represented, whereas other samples based on full-scale or verbal IQ-achievement discrepancy may have dyslexia over-represented. This confounding of children with different profiles of hallmark phenotypes linked to genetic and brain research seriously limits the external validity of all the research in the field of dyslexia and reading disability – valid generalization from research findings to individuals in the general population with reading and writing problems. Neither the definition nor treatment-relevant features are exactly the same for dyslexia and SLD/OWL LD.

Comorbidities—Some individuals had clear cases of dyslexia or SLI/OWL LD, but others had comorbid dyslexia plus dysgraphia or SLI/OWL LD plus dysgraphia. More research is needed on the instructional implications for those with and without comorbid written language learning disabilities.

Some children with dyslexia or SLI/OWL LD may also have SSD, for which the diagnosis also has to be made on basis of history and clinical observation as well as test results. Importantly, SSD [90], dyslexia [38,76,77] and SLI [91] may share some common as well as unique gene candidates, but when the whole configuration of an individual's profile of evidence-based phenotypes and developmental history is considered, it often becomes clear that etiology, current instructional needs and prognosis are not identical for each of these disorders. SSD shows its initial signs in the early developmental years. Speech and language clinicians are trained to differentiate whether speech or receptive or expressive language impairments contribute to problems in learning to talk. Each of these disorders requires a different kind of therapy, for example, speech therapy for SSD, but therapies linked to specific receptive or expressive language skills such as word-retrieval or syntactic awareness and production for SLI/OWL LD. In addition, some children with intelligible speech have oral motor planning problems and are at risk for dysfluent oral reading of passages; they tend to dread having to read aloud in front of others, and may benefit from accommodations in how oral reading is taught and practiced [35].

The definition of dyslexia and related inclusion criteria used in the featured interdisciplinary research – unexpectedly impaired oral word reading and decoding and spelling – is consistent with that used by the International Dyslexia Association [92] and resulted in few individuals meeting criteria for a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR diagnosis of attention-deficit hyperactivity disorder (ADHD) or its subtypes. However, individuals did vary along a continuum on inhibition, RAS, and inattention ratings and values on these were related to their reading and writing achievement [9,10,31]. ADHD probably has a higher comorbidity in dysgraphia involving impaired handwriting, and also in SLI/OWL LD, but more research is needed on these frequent clinical observations for both specific learning disabilities.

Instructional treatment—Evidence-based diagnosis is treatment-relevant: treatment nonresponders are transformed into treatment responders when the specific impaired phenotypes are identified and treated [89]. The randomized, controlled treatment studies with children who met inclusion criteria for being at risk in specific reading or writing skills or for having dysgraphia or dyslexia have been translated into lesson plans, organized by developmental stepping stones for learning to read and write in grades 1–6 [93] and for older students with dyslexia with or without dysgraphia in grades 4–9 ([94] Unit I readers' workshop, Unit II writers' workshop, Unit III writing readers workshop, Unit IV reading writers workshop). In contrast to other approaches to teaching students with specific learning disabilities that involve intensive therapy on one or a small set of skills in isolation, in the interdisciplinary studies a systems approach was adopted with multiple, varying instructional components integrated close in time during a lesson to avoid habituation (brain nonresponding when instruction does not vary), maximize attention and engagement and create functional reading and writing systems and self-regulated learners.

The general principles underlying the interventions validated in the interdisciplinary research can be implemented in general education as well as special education classrooms [95]. Lessons teach:

- Phonological, orthographic, and/or morphological awareness and the interrelationships of the word forms and their parts;
- Automatic correspondences between orthographic and phonological units of alphabetic principle in the reading direction (phonological loop) and/or spelling direction (orthographic loop);
- Transfer of the first two general principles to reading or spelling real words or Jabberwocky words out of context;
- Transfer to reading or spelling real words in sentence or passage context to comprehend or express ideas within a social context that also uses oral language to facilitate the learning process;
- Integration of reading and writing for academic learning;
- Teaching all levels of language (subword, word, syntax/text) close in time to overcome inefficiencies in temporally coordinating working-memory components that contribute to dysfluency;
- Executive function strategies for self-regulation of learning to read and write.

Emerging issues & future perspective

The recent ground-breaking studies by Schulte-Körne's group in Germany identified a brain endophenotype for dyslexia [38]: mismatch negativity during brain detection of auditory change in repeating syllables is associated with a marker on chromosome 4 (*4q32.1*), which

regulates mRNA gene expression on chromosome 12 (*SLC2A3*) that is related to glucose transporters of neurons. Thus, they provided the first evidence that not only is gene expression linked to a brain endophenotype in dyslexia but also that an interaction occurs across chromosomes in dyslexia ('chromosome kissing' [96]). Linkage to chromosomes 4 (4p) and 12 (12p) has also replicated across samples on a nonword repetition task [46], which also resulted in fMRI BOLD differences in children with and without dyslexia [29]; thus chromosome linkage may replicate across phonological tasks that share some but not all processing requirements.

Future research should use, when possible, both brain and behavioral phenotypes and their associations and interactions to investigate the genetic influences on reading and spelling disabilities. For example, are different gene candidates linked to different phenotypes or components of a system model (e.g., working memory architecture)? Do transchromosome effects [96] related to glucose regulation [38] influence the efficiency of a functional system that orchestrates the temporal coordination of all the components relevant to a language task at hand?

On the one hand, many individuals with a biologically based reading or writing disability can learn to read and/or write with some proficiency. On the other hand, just because short-term instructional treatment normalizes specific brain regions during specific tasks performed during brain imaging, it does not follow that only instructional research is needed in the future. These brain and behavioral changes may be due to epigenetic changes (e.g., methyl groups attached to cytosine following an environmental intervention) but whether instructional interventions result in modification of gene expression affecting brain function and behavior [97,201] is not known. Although evidence-based treatment may help children with dysgraphia, dyslexia or SLI/OWL LD overcome reading and writing problems at one phase of schooling through epigenetic modification of gene expression by chemically altering DNA's protein products, such treatment probably does not alter gene sequences thus totally eliminating genetic vulnerability [201]. Further research is needed on these issues because the underlying genetic vulnerability may remain as the curriculum requirements change in nature and complexity [4,89]. For example, one of the most common concerns of parents in the family genetics study whose children had overcome their reading problems was inability to convince schools to continue helping their children overcome their persisting writing problems in the upper grades [84].

Dyslexia is not just a reading disorder. It is also a writing disorder – impaired spelling interferes with written composition [35]. Dysgraphia is a handwriting disorder, but handwriting can interfere with spelling [85] and written composition [14,15,63]. In fact, evidence is growing that one of the most effective ways for overcoming both the reading and writing problems is to provide evidence-based writing instruction (handwriting, spelling and composing) and integrated reading–writing instruction beginning in kindergarten and throughout the elementary grades [98].

Evidence-based treatment that included many of the components described above brought all at-risk readers [88] and spellers [53,99] whose development is at least within the lower limits of the normal range up to grade level; but some needed one and others two treatment doses. Genetics variables should be studied not only to explain dyslexia or dysgraphia but also as predictors in research on evaluating response to intervention. Do genetic variables (e.g., gene candidates or epigenetic changes) predict who does and does not respond to evidence-based instruction? Does a treatment result in epigenetic changes, which are known to be brought about with changes in development and environment [201]? Are epigenetic changes sufficient to eliminate future genetic vulnerability in academic learning? Such genetic criteria should be

considered in evaluating effectiveness of treatment and response to instruction in future research.

Of great importance, the thorny issue of epistasis (interactions among genes and chromosomal sites) needs to be addressed, even though statistical methods may assume no epistasis. Transchromosomal regulation effects have been documented [38,96]. One way to uncover some other interaction effects for dyslexia and dysgraphia is to compare brain–gene associations across clear cases of a single, evidence-based diagnosis and cases with definable comorbidities. Considering that clear cases of dysgraphia only, dyslexia only, or OWL LD (SLI) only do exist, they could be identified, based on their profiles of reading, writing and related skills derived from the structural components of a working-memory architecture, and those with and without comorbidities could be compared. Because profiles have common and unique phenotypes, both generalist and specific gene candidates [77] and their interactions [38,96] may be identified and investigated.

Longitudinal research designs that follow individuals with and without dyslexia or related learning disabilities developmentally from birth may be very fruitful. For example, an overview of the findings of the pioneering Jyväskylä longitudinal study of dyslexia in Finland [100, 101,202] supports multiple phenotypes that emerge at different developmental times: early compromised categorical speech perception in infancy, regression in development of phonological skills in the preschool years, rapid automatic naming of serially presented familiar stimuli (RAN), and delays in attending to and storing letter names (cross-code orthographic–phonological integration) beginning at age 5 years and thereafter. These findings for children aged 5 years and over in Finland with single grapheme–phoneme correspondences are consistent with those at school entrance in a US family genetics study with alternative grapheme–phoneme correspondences [9,10]. Even though the Finnish sample probably has more children with SLI than the English-speaking US sample, which used inclusion criteria to exclude SLI and focus on dyslexia that emerges early in schooling, findings in both languages may be explained in reference to inefficient working memory architecture. This architecture has phonological, orthographic and morphological and phonological loop phenotypes, any one or a combination of which might be impaired in an affected individual [101]. Replication of linkage to chromosome 2 in both the Finnish [102] and US [20] samples may be related to the working memory architecture underlying the temporal coordination phonological, orthographic and morphological codes for words and their parts during fluent, timed phonological decoding.

Future research might address whether an underlying working memory architecture with a phonological core, which fails to develop during neural migration due to a major gene (perhaps related to a neuroanatomical risk factor [55]), may account for the cascading emergence of phenotypes across development observed in the Finnish sample: initial difficulty in storing and processing receptive speech at a phonetic level (see [102] for review) and in supervisory attention regulation for inhibiting competing phonetic neighbors and switching attention across sequential stimuli that change over time, subsequent problems at a phonological level resulting from those earlier problems, and then at time of school entrance temporal inefficiencies in the phonological loop for integrating phonological codes and orthographic codes that are needed to learn to read [100]. Alternatively, multiple gene variations may underlie each of these cascading phenotypes across development; or both a common major gene and a number of minor ones related to specific phenotypes that vary across affected individuals may be involved.

Another example of a fruitful longitudinal study design is the pioneering work of Molfese and colleagues who recorded newborns' auditory evoked potentials (EPs) of speech-like stimuli at birth. Quantitative parameters of EPs differentiated oral language development at age 3 years [103] and verbal IQ and normal reading, dyslexia and low reading achievement within the

normal range at age 8 years [104]. These findings are consistent with the strong possibility that different kinds of specific learning disabilities emerge at different stages of development – oral language (SLI) during the preschool years and written language due to difficulties in making connections between oral and written language (classic dyslexia) early in formal schooling.

The jury is still out on whether individuals with dyslexia may be impaired in the same way on these gene–brain variables across languages, which differ in how dimensions of language are orchestrated for translating written words into spoken words. On the one hand, cross-language differences in dyslexia may be related to differences in the relationships between the spoken and the written language in specific orthographies. On the other hand, no matter what language individuals with dyslexia speak or read, they may share common working memory deficits associated with anomalies in middle frontal and parietal regions (e.g., [105,106]).

Alternatively, how dyslexia expresses in a specific language and culture may be affected by:

- Differences specific to written orthographies of different languages;
- Differences in the nature and timing of formal school instruction;
- Impairment in phonological and other components of working memory and their temporal coordination, which not only have genetic–brain bases but also respond to treatment.

Clearly more research is needed on the interactions among phenotypes, genotypes, brain and treatment for dysgraphia, dyslexia and SLI/OWL LD, as well as SSD and normal reading and writing development, in order to resolve current research controversies regarding etiology, diagnosis and treatment, apply research, on which there is a consensus, into practice, and achieve optimal educational achievement of all human beings who exhibit normal and atypical variation in their genes, brains and home and school environments.

Executive summary

Twin studies

- Although considerable evidence has demonstrated both heritable (genetic) and environmental influences on reading and spelling disability, recent cross-country research has shown that the genetic risk factors during the preschool years are stable through the beginning elementary years, even when children respond to instruction.
- The nature of genetic risk factors may change across the grades as the nature of the curriculum changes.

Studies of the biological basis of dyslexia

- Initial genetic studies focused on chromosome linkage for phenotypes shown in twin or family aggregation studies to be heritable. More recent research has focused on at least 10 proposed gene candidates (very precise regions on chromosomes).
- Initial brain imaging studies focused on showing that individuals with and without dyslexia differed in structural or functional imaging and then on identifying how functional imaging results may or may not change in response to instruction.
- More recent research has focused on identifying endophenotypes (brain–gene relationships).

Emerging trend to study phenotype–gene–brain–treatment relationships

- The most promising phenotypes identified in an interdisciplinary research center included: storing and processing spoken words in working memory (phonology); phonological decoding (translating written words into spoken words); written spelling;

storing and processing written words in working memory (orthography); storing and processing word parts in working memory (morphology); and storing and processing accumulating words organized by order and other grammar features in working memory (syntax); phonological and orthographic loops for time-sensitive integration of internal word codes with end organs for interacting with the environment (mouth and hand); and executive functions for supervising working memory operations (e.g., inhibition and flexible attention switching).

- All the findings can be organized within a working memory architecture that accounts for the four leading theories of causal mechanisms in dyslexia: phonological core, rapid automatic naming, executive functions and working memory.
- The working memory model can be used to generate evidence-based differential diagnosis of dysgraphia, dyslexia, and specific language impairment (SLI), also referred to as oral and written language learning disability (OWL LD). The importance of using evidence-based definitions of specific learning disabilities involving reading and writing is emphasized as current research samples vary greatly in criteria used for ascertaining the sample and, thus, in external validity for generalizing findings to only individuals who are similar to those studied. For example, samples differ greatly in whether research inclusion criteria tend to identify SLI/OWL LD (typically when nonverbal IQ is used for inclusion criteria and IQ-achievement discrepancy is not used) or classic dyslexia (typically when Verbal IQ or Full Scale IQ-achievement discrepancy is used).

Instructional treatment

- There are evidence-based general principles for teaching students with dyslexia and/or dysgraphia who have not responded to the regular instructional program.

Emerging issues & future perspective

- Section IV reviews recent ground-breaking evidence for an interaction between genes on different chromosomes (epistasis) associated with a well-documented brain endophenotype (brain–genotype relationship) in dyslexia. Future research should investigate other possible gene interactions within and across chromosomal sites.
- Section IV also calls attention to the need for more research on whether gene candidates predict response to intervention.
- Section IV also highlights the need for more research on epigenetics – how development or environmental interventions such as teaching change gene expression in individuals with dyslexia (probably not their underlying gene sequences but rather the epigenetic modification of gene expression through chemical alterations of DNA's protein or glucose products). The contributions of longitudinal research to identifying cascading changes in endophenotype expression are highlighted.

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Figure 1.
Working memory architecture supporting language learning within which dysgraphia, dyslexia, and oral and written language learning disability can be defined and differentiated. For evidence and/or applications see [53,67,68,82].
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