Seminar

Developmental dyslexia

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Developmental dyslexia, or specific reading disability, is a disorder in which children with normal intelligence and sensory abilities show learning deficits for reading. Substantial evidence has established its biological origin and the preponderance of phonological disorders even though important phenotypic variability and comorbidity have been recorded. Diverse theories have been proposed to account for the cognitive and neurological aspects of dyslexia. Findings of genetic studies show that different loci affect specific reading disability although a direct relation has not been established between symptoms and a given genomic locus. In both children and adults with dyslexia, results of neuroimaging studies suggest defective activity and abnormal connectivity between regions crucial for language functions—eg, the left fusiform gyrus for reading—and changes in brain activity associated with performance improvement after various remedial interventions.

Unlike spoken language, reading and writing abilities only develop with explicit teaching; however, impairment of learning to read and write in seemingly healthy children is attributable to specific disorders of brain function. A century of research has established the biological origin of dyslexia despite modulation by environmental or therapeutic factors.[1] This paradox is shown by complex empirical data on the biological, cognitive, and behavioural levels of the disorder.[2] After a brief overview of the different neuropsychological conceptualisations of dyslexia, we review genetic and neuroimaging studies, ending with neural correlates of innovative remediation methods.

Definition of dyslexia

Developmental dyslexia, or specific reading disability, is defined as an unexpected, specific, and persistent failure to acquire efficient reading skills despite conventional instruction, adequate intelligence, and sociocultural opportunity. Although still a matter of debate, this exclusionary definition was adopted by the diagnostic and statistical manual of mental disorders[3] and the international classification of disorders, classification of mental and behavioural disorders.[4] Dyslexia is fairly widespread but with uncertain prevalence, ranging from 5% to 17·5%.[5] This variability is a result of the loose definition and effect of several factors. For instance, an additional diagnostic criterion frequently used in English-speaking countries is a discrepancy between verbal IQ (intelligence quotient) and performance on reading tests, correlated with verbal IQ of skilled readers; however, several researchers suggest that this discrepancy is not important.[6] Dyslexia is most typically reported in males, but Shaywitz and co-workers[7] argued that this difference was attributable to referral bias, whereas Olson[1] reported that sex ratio depended on several factors, including IQ and severity of the reading deficit. The frequency of dyslexia differs between languages, being higher in English than in Italian, for instance.[8] Diagnosis is difficult for languages with quasi-transparent orthography—eg, Italian, for which diagnosis relies only on reading speed.

Clinical features of dyslexia vary with the severity of deficits and presence of comorbidities[9] (eg, attention and hyperactivity, arithmetic, mild oral language, or visual and motor integration disorders) although reproducible epidemiological data are still scarce. Several subtypes of dyslexia have been described[10] and Castles and Coltheart[11] proposed three varieties: phonological, surface, and mixed. People with phonological dyslexia show a deficiency in development of graphophonemic reading procedure, whereas those with surface dyslexia have difficulties with development of lexical procedure, which is crucial to reading irregular words. Whether these subtypes[12–14] represent stable entities throughout development is not certain. Thomson[15] noted changes in error types (auditory *vs* visual) or cognitive profiles (phonological *vs* surface) with age. Furthermore, other dyslexia categories are proposed in line with pathophysiological hypotheses—eg, dysfunction of the magnocellular pathways.

Hypotheses about cause of dyslexia

Several theories have been proposed for the cause of dyslexia. Here, we concentrate on those that include cognitive features.[2] These hypotheses are usually opposed; however, all could be described in the framework of multiple memory systems, with links to neural and cognitive substrates of language. Although these systems

Search strategy and selection criteria

This review is based on a PubMed search (from 1980), including non-English articles and with the following keywords: "dyslexia", "specific reading disability", and "developmental"; in conjunction with "pathophysiology", "genetics", "brain imaging", "remediation", and "therapy". From more than 1500 references we selected publications mostly from the past 5 years. We searched the reference lists of the reviewed articles and considered older, classic papers, or those we judged relevant to the topics of this review.

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GLOSSARY

FREQUENCY DOMAIN
Frequencies of periodic signals in the spectrum of natural stimuli such as visual scenes or the human voice

N100m
Highly reproducible change in magnetic field recorded over the human brain using magnetoencephalography (m); occurs at a latency of 100 ms (100) following presentation of a stimulus; analogous with the negative polarity (N) event N100 recorded with electroencephalography.

MT/V5
Anatomical region of the cerebral cortex in the temporal lobe; located posteriorly and ventrally in the temporal lobe; codes for the visual perception motion; MT is for middle temporal; V5 means the 5th visual area within the hierarchical structure of the visual cortex

M100
See N100m; polarity is not necessarily negative

are separate in terms of function and neural basis, growing evidence suggests that they interact either positively or competitively during learning processes.[16]

The mainstream hypothesis implicates a deficit of direct access to, and manipulation of, phonemic language units retrieved from long-term declarative memory. Phonemes are the smallest sublexical entities that distinguish otherwise identical words—eg, bet versus pet.[17] Thus, specific neural processing results in coding /b/ or /p/ phonemes as stable representations that are of higher order than the auditory, motor-sensory, and visual counterparts of these sound units.

Other theories emphasise the relevance of disorders of intervening non-declarative or implicit memory processes, such that complex linguistic information flow can be processed without error or effort. Immediate or echoic memory abilities, and learning of sensory-motor procedures, probably contribute to automatisation of complex skills. Although based on explicit memory at early stages, learning of oral or written language is subsequently facilitated since processing relies progressively on automatised stages, thus easing explicit memory load. Differentiation between the words pet and bet would not normally need conscious identification of their initial phonemes because automatised processing of acoustic features of word onset, such as voice-onset time (20–30 ms lag between laryngeal emission and burst sounds from the lips), can hasten speech recognition.

Irrespective of the cause of dyslexia, phonological problems are most evident from the perspective of learning to read.[18,19] Research suggests that dyslexia is a language-based disorder characterised by difficulties in single-word decoding[20] and phonological processing[18,21] that prevent learning of letter and phoneme associations.[22] Ramus and colleagues[19] reviewed phonological theory and presented results of cognitive assessments including phonological, auditory, visual, and motor tasks in highly selected university-educated individuals with dyslexia and controls. Those with this disorder all had phonemic deficits whereas visual difficulties were rare. The most distinctive phonological feature of participants with dyslexia was reduced short-term verbal memory and phonemic awareness—ie, the ability to manipulate sublexical units in working memory. However, the purely phonological theory of dyslexia cannot account for low-level visual, sensory, or motor coordination deficits reported in many patients.

The magnocellular theory has received much attention, and arose from observations of impaired visual processing in the magnocellular pathway. Patients with dyslexia showed poor thresholds for stimuli with low contrasts, low spatial or high temporal frequencies,[23,24] and poor sensitivity to visual motion.[25] Pure deficits for visual contrast threshold might seem to be outside the above proposed memory systems framework; however, existence of such purely visual perceptive deficiencies is much debated.[26] Stein[27] also emphasised the importance of visual and oculomotor defects in dyslexia. The magnocellular system is important for directing visual attention, control of eye movements, and visual search—three skills that have a role in reading ability.[28] Talcott and colleagues[29] suggested a link between these visual processes and reading abilities, showing a correlation between motion sensitivity and orthographic performance in an unselected sample of children. Impaired perception of hearing[30] and touch[31] has been integrated into the magnocellular hypothesis. Results of an auditory study showed that impaired perception of rapid transient events in the speech stream contributes to deficits recorded in language-impaired children.[32] These findings were extended to children with dyslexia;[33] defects of processing rapid events were described in visual and auditory modalities,[34] leading to the hypothesis of dysfunction of temporal resolution in different modality-specific magnocellular pathways.[35] This theory could account for other deficiencies, such as attention[36] or motor control, including ocular saccades.[37] However, the magnocellular hypothesis has been criticised[19] because findings are not reproducible or specific. For instance, visual deficits in dyslexia extend beyond the FREQUENCY DOMAIN that is specific to magnocellular functions;[25,38] moreover, findings of studies in visual[39] and auditory[39,40] domains suggest that people with dyslexia might have deficits in slowly evolving events.

The role of the cerebellum in the pathogenesis of dyslexia[41] stems from the conceptualisation of dyslexia as a learning disorder, in which failure to acquire and automatise reading and writing skills might be the most prominent but not a unique symptom.[42,43] Nicolson and colleagues[43] reported that children with dyslexia sometimes have balance and motor-coordination disorders in attention-demanding circumstances. This observation suggests that motor tasks in these children are undertaken at the expense of attentional resources. The cerebellum is important in higher cognitive processes, including linguistic[44] and non-limbic neural networks subserving procedural memory,[45] which ensure cost-free automatisation of sensory-motor habits. Impairment of automatisation and time-evaluation deficits in dyslexia have been linked to cerebellar dysfunction; this association could also account for disorders of handwriting and articulatory skills, the latter possibly affecting phonological awareness.[46] The conceptualisation of dyslexia as an impairment of skill automatisation accords with another important theory,[47] in which deficits affecting the speed and fluency of information processing contribute to reading impairments independent of other factors, especially phonological deficits. However, cerebellar signs are not always reported in dyslexia. Although compensatory mechanisms could account for negative findings, how important is cerebellar dysfunction to dyslexic symptoms? The architecture of the memory system subserving procedural learning is not restricted to the cerebellum, including dynamic interplay between cortical, subcortical, and some cerebellar areas during skill learning.[45] Therefore, deficits of procedural learning can result from dysfunction of an extensive neural architecture.

	Country, number of families (number of individuals)	Phenotype	Study
Principal loci			
15q21	USA, 9 (n=84)	Global	Smith et al, 1983[57]
	USA, 6 (n=94) and USA, 8 (n=171)	Single word reading	Grigorenko et al,1997[58] and 2000[59]
	Germany, 7 (n=67)	Spelling disabilities	Schulte-Korne et al, 1998[60] Nothen et al,1999[61]
	UK, 101 (n=146) and UK, 77 (n=108)	Global	Morris et al, 2000[62]
6p21.3	USA, 19 (n=358) and 46 twin pairs	Reading recognition, comprehension, and spelling	Cardon et al, 1994[63]
	USA, 6 (n=94) and USA, 8 (n=171)	Phonologic awareness	Grigorenko et al, 1997[58] and 2000[59]
	UK, 82 (n= 181)	Orthographic skill and phonologic process	Fisher et al, 1999[64]
	USA, 79 (n= 180)	Orthographic skill and phonologic process	Gayan et al, 1999[65]
	UK, 89 (n=195) and USA, 119 (n=180)	Several reading-related processes	Fisher et al, 2002[66]
2p15–p16	Norway, 1 (n=36)	Global	Fagerheim et al, 1999[67]
	UK, 89 (n=195) and USA, 119 (n=180)	Several reading-related processes	Fisher et al, 2002[66]
	Canada, 96 (n=877)	Phonologic coding	Petryshen et al, 2002[68]
3p12–q13	Finland, 1 (n=74)	Global	Nopola-Hemmi et al, 2001[69]
	UK, 89 (n=195) and USA, 119 (n=180)	Several reading-related processes	Fisher et al, 2002[66]
1p34–36	USA, 9 (n=not known)	Global	Rabin et al, 1993[70]
	USA, 8 (n=165)	Phonological decoding and rapid automatised naming	Grigorenko et al, 2001[71]
18p11.2	UK, 173 (n=338) and USA, 119 (n=180)	Several reading-related processes	Fisher et al, 2002[66]

Table 1: **Summary of linkage studies on dyslexia**

Despite the phenotypic heterogeneity of dyslexia, investigations have tried to uncover one common factor that accounts for most symptoms. Ben-Yehudah and co-workers[48] emphasised that perceptual deficits in people with dyslexia are seen only when individuals rely on perceptual memory, consistent with working memory and attention deficits noted in relation to the phonological theory. Attention difficulties are part of the cerebellar hypothesis as a result of poor automatisation. Hari and Renvall[36] proposed that people with dyslexia are slow to process perceptual tasks. The hypothesis of an attention and working memory deficit, although insufficient to account for all symptoms, is a typical finding in many studies, and is relevant in terms of neural correlates.

The genetic basis of dyslexia

In an interview-based study of 120 families, Hallgren[49] suggested that reading disability is familial and postulated that inheritance is autosomal dominant. With psychometric tests Finucci and colleagues[50] confirmed this familial nature, with genetic heterogeneity. The Colorado Family Reading study,[51] initiated in 1973, undertook longitudinal testing of reading and cognitive abilities of 125 children with dyslexia, their parents, and siblings compared with 125 matched control families. Reading performance of relatives of children with this disorder was substantially lower than in controls.[51] In comparisons of monozygotic and dizygotic twins, a higher concordance rate for reading disability was noted for monozygotic (84–100%) compared with dizygotic (20–35%) twins.[52,53] DeFries and Alercon[54] reported concordance rates for monozygotic twins (68%) exceeding those for dizygotic pairs (38%). Segregation analyses of family studies[55] and multiple regression analyses of twin data[56] confirmed that dyslexia is a genetically heterogeneous and complex trait that does not show classical mendelian inheritance.

Linkage analyses have further verified this complexity; several regions—on chromosomes 1, 2, 3, 6, 15, and 18—are reported to contain genes affecting reading disability (table 1). Links between dyslexia and markers on chromosomes 15, 6, and 2 have been confirmed by several independent studies. The first locus was identified on chromosome 15,[57] and although other studies[58,60,62] described a link or association on this chromosome, the precise locations differ substantially. Cardon and co-workers[63] reported linkage on the short arm of chromosome 6 (6p21·3), which was later replicated.[58,64,65] Linkage has also been shown on chromosome 2[67,68] and translocations have been reported on chromosome 1.[72] Most linkage studies target only specific chromosomal regions. Fisher and colleagues[66] did a complete quantitative trait loci analysis based on genome-wide scans for dyslexia in two large independent sets of families. Linkage was confirmed for chromosome 6 in both samples, although other regions were highlighted on chromosomes 2, 3, and 18. Even though no gene specific to dyslexia has been identified, several genetic loci seem to have an effect on reading. Nevertheless, subtle differences in precise chromosomal regions have been found across studies suggesting that some linkages could be false positive results.

Several factors contribute to the complexity of the genotype-phenotype correlation: genetic heterogeneity (distinct loci in different families), incomplete penetrance; phenocopies (non-hereditary variation); or oligogenicity (allelic variants at multiple loci contributing to increased risk).[73] The absence of consensus on the definition and nature of dyslexia can account for variability of inclusion criteria across studies and for contradictory results.[59] Some characteristics of people with dyslexia might affect apparent heritability. For instance, DeFries and others[74] suggested that heritability of spelling deficits seemed to increase with age whereas that of reading difficulties declined. Genetic effects are more important as a cause of reading disability in children with high IQs than in those with low IQs.[75] This difference affects use of the discrepancy definition of dyslexia, since individuals with specific reading disorders are most likely to be at-risk genetically.

In the future, we might be able to link subtypes of dyslexia with particular loci.[76] Researchers have investigated whether some loci have specific effects on distinct aspects of reading-related impairments. Grigorenko and colleagues[77] suggested that a chromosome 6 locus had a role in phonological awareness, and to a lesser extent single-word reading, whereas a locus on chromosome 15 affected single-word reading only, although these findings have not been confirmed.[64,65] Linkage analyses of univariate traits have statistical limitations, and multivariate approaches are better adapted for analysis of this complex trait. This type of analysis is the first step in genetic research to target a genomic region specific to dyslexia. Genetic association analyses are underway to identify genes within these

Study	Imaging technique	Population (age-range, years)	Tasks	Main findings in children with dyslexia compared with normal readers
Georgiewa et al, 1999[93]	fMRI	17 DYS (9–17); 17 NR (9–17)	Visual hierarchical paradigm testing orthographic, phonological and semantic processing	Less activation in left frontal and left inferior temporal areas in non-word reading and phonological transformation task
Richards et al, 1999[95]	fMRS	6 DYS (9–12); 7 NR (9–12)	Auditory rhyming	Lactate rise in left anterior region
Simos et al, 2000[96]	MEG	10 DYS (10–17); 8 NR (8–16)	Auditory and visual word recognition	Normal left basal temporal activation—reduced left and increased right temporoparietal activation during word reading
Simos et al, 2000[97]	MEG	11 DYS (10–17); 10 NR (8–16)	Visual rhyme with pseudowords	Normal left basal temporal activation—reduced left and increased right temporoparietal activation during non-word reading
Corina et al, 2000[98]	fMRI	8 DYS (10–13); 8 NR (10–13)	Phonological and lexical auditory judgment	More activity in right than left inferior temporal gyrus and left precentral gyrus during phonological judgment task Less activity in bilateral middle frontal gyrus and more activity in left orbital frontal cortex during lexical judgment task
Temple et al, 2001[99]	fMRI	24 DYS (8–12); 15 NR (8–12)	Phonologic and orthographic visual processing	Normal left frontal and reduced left temporoparietal activities during a letter rhyming task
Shaywitz et al, 2002[100]	fMRI	70 DYS (7–18); 74 NR (7–17)	Hierarchical visual paradigm testing orthographic, phonological and semantic processing	Reduced activity in parietotemporal and occipitotemporal areas during related-reading tasks. Correlation between age and right and left frontal activity (increased in older children)
Georgiewa et al, 2002[94]	fMRI and ERPs	9 DYS (mean 12·6) 8 NR (mean 12·7)	Word and pseudoword silent reading	Hyperactivation in the left frontal gyrus

fMRI= functional MRI. MEG=magnetoencephalography. fMRS=functional magnetic resonance spectroscopy. DYS=children with dyslexia. NR=normal readers.

Table 2: **Neuroimaging studies in children with dyslexia compared to normal readers**

regions, and only then will we be able to determine their contribution to specific cognitive processes.[78]

The neural basis of dyslexia

Findings of post-mortem anatomical and structural in-vivo studies have suggested distinctive architectural features of the dyslexic brain. Although acquired in few samples from a brain bank of individuals with suspected dyslexia, microscopic malformations in the perisylvian regions (cortical ectopias and dysplasias)[79] and the geniculate nuclei (size reduction of magnocellular neurons)[80] suggest abnormal neuronal migration and maturation, prompting research on the neural basis of dyslexia. Galaburda's group[81] noted abnormalities in the large-scale connectivity of ectopias in a mouse model, and structural brain abnormalities in dyslexia have been reported.[82–85] However, small samples, phenotypic heterogeneity, comorbidity, and restriction of analyses to a-priori selected regions probably account for inconsistencies in these findings. MRI has shown hypointense grey matter in most of the left temporal cortex by voxel-based morphometry[86] or anisotropy in white-matter fibres.[87] Klingberg and colleagues[87] reported a correlation between reading score and amount of anisotropy, suggesting abnormal connectivity in dyslexia.

Evidence of dysfunction in people with dyslexia in neural systems implicated in reading and related cognitive functions, has come from functional brain imaging studies. Positron emission tomography (PET) cannot be undertaken in children for non-diagnostic reasons because low-dose radiotracers are used. Neuroimaging methods are a mainstay of biological and neurological investigations; however, cautious interpretation of results is needed since they might be biased by experimental factors.

Brain correlates of language functions consist of widely distributed, weak, and transient events throughout the brain. They are affected by variables such as patient's age and handedness, exposure duration of stimuli, and rate of stimulation, which strongly bias imaging data and should be controlled in any experiment.[88] Neuroimaging studies in language disorders are especially challenging since pathology introduces complex factors related to either brain lesions (eg, aphasia) or impaired performance during experimental tasks. For dyslexia, even though brain lesions do not distort the data, some specific factors exist—eg, impairments vary in intensity and quality, and can be treatment-resistant; and reading and writing disorders are persistent and adaptive.

In early event-related potential (ERP) studies, simple sensory tasks were mainly used and late components were measured. However, in later studies of dyslexia, more theoretically driven tasks were used and task-specific and subtype-specific deficits were recorded.[89,90] Children at risk for dyslexia can show ERP abnormalities on reading,[91] suggesting different cortical processing in this disorder,[89–92] underlining the sensitivity of this method in investigation of reading dysfunction. Georgiewa and others[93,94] first reported functional MRI results in children with dyslexia and controls (table 2), later combined with ERPs; differences between groups in visual language tasks were noted in the left inferior frontal region, at 250–600 ms.[94] With a feature or word detection task, Helenius and colleagues[101] showed that prelexical processing in left inferior occipitotemporal regions was sometimes absent in people with dyslexia, although normal N100M suggested intact early visual processing. Impairment of reading or language functions in individuals with this disorder at integrated stages of processing have been addressed with high spatial-resolution imaging methods and have had a substantial effect on our understanding of the neural substrates of reading.

In skilled adult readers the functional neuroanatomy of reading is widely distributed but dominated by a left-sided network with two posterior pathways for visual and orthographic information:[102] the ventral pathway centred in the posterior fusiform gyrus, possibly representing an automatically accessed visual word-form area;[103] the dorsal pathway, including mainly the angular and supramarginalis gyri,[104] representing slow phonology-based assembly processes; and one anterior component centred in the left inferior-frontal gyrus, connected to the two posterior pathways,[105] implicated in the output of phonological and articulatory aspects.

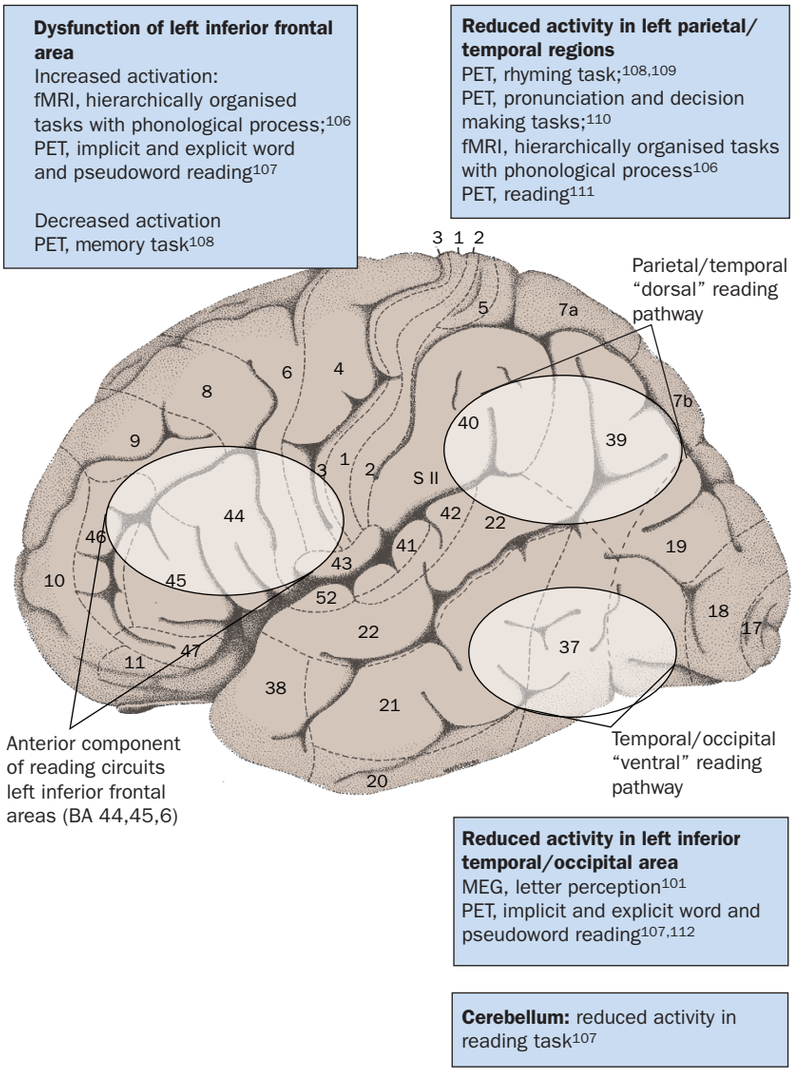

Figure 1: **Areas of the left cerebral hemisphere in which abnormal responses in neuroimaging studies were reported in adults with dyslexia compared with controls**
Modified from Duvernoy H. The human brain, surface, blood supply and three-dimensional sectional anatomy, 2nd edn. New York: Springer Verlag Wien, 1999, by permission of Professor H Duvernoy and Springer-Verlag Wien.

In adults with dyslexia compared with controls, activation in posterior pathways is reduced (figure 1). Key components of the dorsal pathway—eg, left angular gyrus—show activity positively correlated with reading scores in normal readers and negatively correlated in adults with dyslexia.[111] Findings of a PET study of homogeneous samples of well-compensated patients with this disorder and controls from three countries (Italy, France, the UK) showed a deficit in activation in the ventral pathway in those with dyslexia irrespective of language,[112] which accords with findings of magneto-encephalogram studies.[101] Although areas in the left inferior frontal and right hemispheric regions seem to be less active in people with dyslexia in some studies,[108,110] in others higher than normal activation has been described, possibly indicating compensation for the absence of activation in normal key regions for reading—eg, the left frontal[94,106,107] and right-sided[113] regions.

Developmental neurofunctional studies (table 2) have helped to interpret and reconcile discrepant findings. Shaywitz and co-workers[100] studied 144 children with dyslexia and controls and noted that fMRI activity rose with age in those with the disorder in left and right inferior frontal regions during a rhyming task. These results lend support to the compensatory hypothesis: raised activation in frontal or right-sided regions, or both, indicating attempts to overcome failure to engage automatic processes of the left posterior areas. These researchers[100] also suggested that a decline in activity in the ventral reading pathway in adults with dyslexia does not show longstanding poor reading ability because activity in this area correlated positively with that task in children. However, Simos and colleagues[96,114] reported that neural activity in this region was not reduced in children with dyslexia. The difference between those with the disorder and controls was in aberrant dynamic connectivity: neural activity 250–1200 ms after stimulation shifted towards right temporal regions in people with the disorder,[97] whereas the normal dynamics spread towards the left temporal or parietal junction in controls. Overall, these results suggest a disruption of connections between dorsal and ventral routes for reading, which accords with other studies.[87,115]

Since a prominent factor in dyslexia is a phonological deficit, neurofunctional indices have been investigated in a similar way to reading experiments that included judgments of phonology,[97,110] verbal working memory tasks,[108] or auditory presentation of verbal stimuli.[96,109] Most studies show reduced activity in the left, rather than bilateral,[109] perisylvian regions. Paulesu and colleagues[108] suggested that the activation pattern in people with dyslexia might relate to a disconnection within the left perisylvian network, which has a role in phonological processes.[116] We have studied auditory categorical perception of phonemes that seem abnormal in individuals with this disorder by looking at neural counterparts of implicit perception of phonemic contrast.[17] Those with dyslexia showed a pronounced decline in fMRI activation in the left supra-marginal gyrus,[117] a region important for phonological processing.[116] Compared with people with the disorder, normal readers showed activation in the auditory association cortex bilaterally (figure 2). In normal readers, no-change stimuli induced a decline of activation, suggesting habituation to repetitive input, whereas phonemic changes elicited a specific rise. No habituation or speech-related responses were noted in those with the disorder since activation fell for both types of change. However, behavioural performance for these stimuli was normal in individuals with dyslexia, suggesting compensatory mechanisms existed.

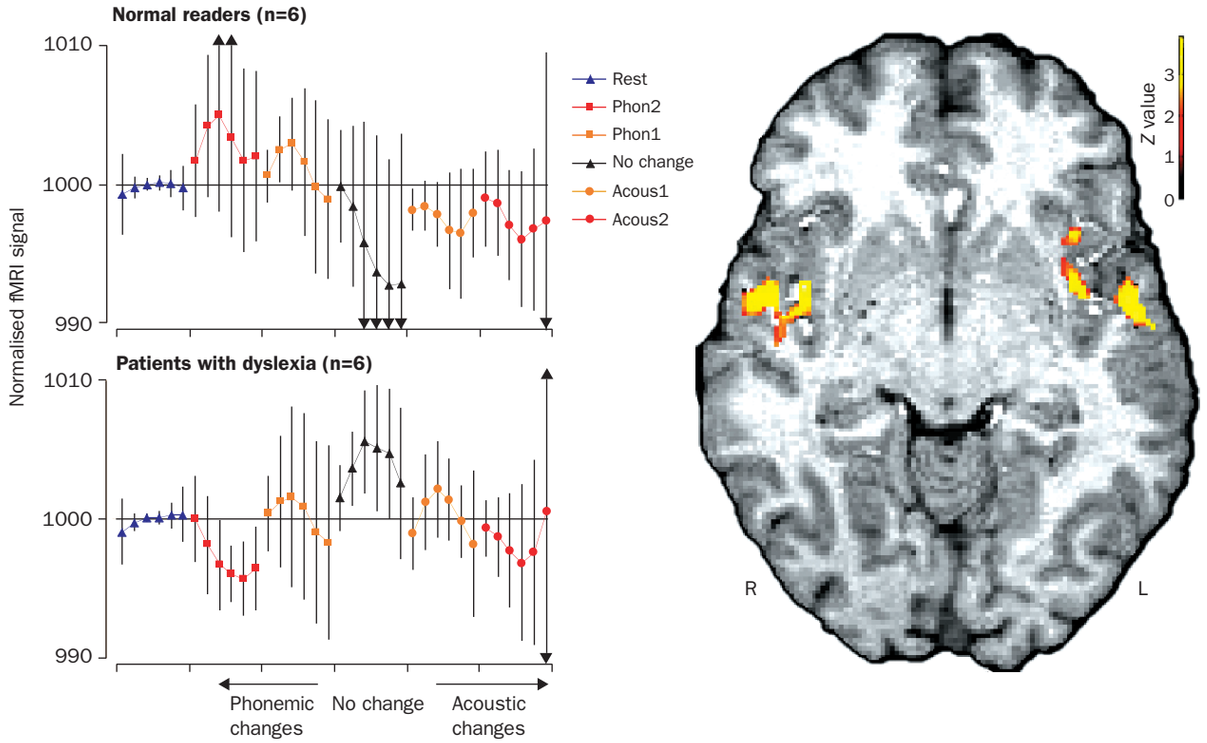

Figure 2: **Changes in functional MRI signal indicating categorical perception (A) and signal increase to phonemes in normal readers versus people with dyslexia localised in Brodmann's areas 22 (B)[118]**

Nicolson and co-workers[46] used PET and a motor learning paradigm to address the hypothesis of skill learning. They recorded less activation in the right cerebellum and the left inferior frontal cortex in people with dyslexia than in controls. These findings accord with reported metabolic abnormalities in the right cerebellum.[119] In functional imaging studies of reading, cerebellar activations are sometimes presented, although not always interpreted, with signal reduction in these regions in individuals with dyslexia.[107]

In several studies, evidence concordant with dysfunction of the visual magnocellular system in dyslexia has been presented[120] such as failure of activation in MT/V5 during a motion-detection task, with a correlation between this MT activity and reading speed for patients with dyslexia and controls patients. However, findings of other studies have not confirmed these results;[39,121,122] magnocellular effects seem subtle, arising only under constrained conditions.[123]

Auditory mismatch negativity is important for investigations of perceptual deficits since this component is elicited by any discriminable change in a repetitive auditory stimulus, irrespective of attention,[124] indicating automatic processing. Initial studies in children with learning-impairment showed lower amplitude auditory mismatch negativity with speech stimuli.[125] Subsequently, these values were reduced only for some stimuli—eg, pitch changes, speech stimuli—in individuals with dyslexia.[126] Since auditory mismatch negativity amplitude indicates ease of detecting differences, these studies showed that for specific sounds, differences were less perceptible in individuals with dyslexia than in controls. Similar paradigms have been used with infants, with or without a family history of dyslexia,[127] and suggested that at-risk infants process stimuli differently, starting at 6 months of age.

Temple and others[128] studied neural responses to rapid acoustic changes and showed that normal adult readers had increased fMRI activity of the left prefrontal cortex and right cerebellum during rapidly—relative to slowly—changing stimuli. In readers who had dyslexia the investigators noted enhanced responses in these regions for slowly changing stimuli. Similarly, Nagarajan and colleagues[129] reported small magnetoencephalogram M100 responses to rapidly changing auditory stimuli in people with this disorder, although they had larger M100s than did controls for slow stimuli.

These effects were also investigated with natural syllables (ma/na), that were either untransformed or stretched out, slowing down the consonant features.[117] Regions sensitive to the rate of acoustic change were identified by fMRI in left frontal areas,[128] and slowed speech elicited signal increase in those with dyslexia. However, neural responses in the left supramarginal gyrus were insensitive to the rate of speech changes; this region showed defective activation in adults with this disorder. Two effects relevant to the underpinnings of dyslexia were identified: neural activity was enhanced by slowing down acoustic changes in speech in some cortical areas; and poor neural responses in the left supramarginal gyrus indicated the fundamental phonological deficit in dyslexia. Such topographic variability of neural responses could account for diverse, seemingly discrepant, results of various experiments, and is an example of when empirical findings suggest that accounts of dyslexia can be both verified and complementary to each other.

Remediation and its neurological basis

Together with appropriate teaching conditions, remediation relies on interventions for language, phonology, reading, and speech adapted to a child's disability. Although some compensation can occur over

Study	Imaging technique	Population (age-range, years)	Training method	Post-training results
Richards et al, 2000[141]	fMRS	8 DYS (10·6) 7 NR (10·3)	Phonological, 3 weeks, 15×2 h sessions	Improved phonological performances; changes in brain lactate metabolism in left anterior quadrant
Kujala et al, 2001[142]	ERPs (MMN)	24 DYS (7) 24 NR (7) 11 DYS (7) 11 NR (7)	Non-verbal audiovisual, 7 weeks, 2×10 min sessions per week	Improved reading ability; increased amplitude of MMN; correlation with change in reading performance
Simos et al, 2002[113]	MEG	8 DYS (11·4) 8 NR (10·3)	Phonological, 8 weeks, 1–2 h/day	Improved reading ability; increase activation in left STGp and inferior parietal areas
Temple et al, 2003[143]	fMRI	20 DYS (9·9) 12 NR (10·7)	Non-linguistic items and acoustically modified speech	Improved reading and oral language; activation in left parietal/temporal and left inferior frontal areas

MEG=magnetoencephalography. fMRS=functional magnetic resonance spectroscopy. fMRI=functional MRI. MMN=mismatch negativity. DYS=children with dyslexia. NR=normal readers.

Table 3: **Brain correlates of training methods in children with dyslexia and normal readers**

time, dyslexia is usually persistent[130] and could have a severe effect on academic achievement. Treatments entail phonology-based training and, soon after the first stage of remediation, other dimensions of language—eg, morphology, grammar, and discourse processing. Few commercially available and clinically used methods have been assessed for their relevance. Despite differing modalities and duration of training, studies of phonology-based methods show improvement in phonological capacities after intensive training.[131–133] Nevertheless, generalisations of remedial effects to reading are inconsistent; success varies depending on individual differences and predictive factors are still to be elucidated. These pathophysiological hypotheses—based on implicit perceptual or motor deficits, or both—have led investigators to propose new remedial strategies. Tallal and others[134] assessed the rapid temporal processing model by slowed speech in language learning-impaired children, and suggested a long-lasting efficacy of intensive training on phonological processing and oral comprehension; these results were replicated in a sample of 500 children.[135] However, deficits in temporal processing of non-verbal auditory stimuli were frequent in these children. In another study,[136] improvement of phonological capacities was seen after intensive training with slowed speech—without, unfortunately, generalisation to lexical processes. Moreover, some children did not respond to this remediation.

In the context of the magnocellular hypothesis, Stein and colleagues[137] studied binocular vision in children with unstable binocular fixation; half underwent monocular occlusion with a yellow lens. During repeated assessments those with occlusion showed substantial progress in the stability of binocular fixation and especially in reading performances. However, use of the binocular fixation (Dunlop) test, a poorly reproducible measure, has been criticised.[138]

Pertinent to the cerebellar hypothesis, abnormal persistence of primitive reflexes—eg, the tonic neck reflex—has been reported in dyslexia. McPhillips and co-workers[139] compared three groups of children with dyslexia: one received re-education specific for reduction of this persistent reflex; the second received non-specific motor re-education; and the third was not re-educated. The specific re-education was effective for both the motor difficulties and reading abilities. The specific effects of these methods on different linguistic deficits, and the ideal age and duration of beneficial effects for these training programmes, should be determined. At a population level, could highly specific and costly interventions given to every child prove more efficient than appropriate educational interventions?

Functional imaging (fMRI or magnetoencephalogram) not only allows investigation of deficits of neuronal networks implicated in language functions but also assesses neural plasticity as a function of either compensation[140] or re-educative training. In four studies done in children with dyslexia (table 3), cerebral correlates of improved linguistic performance were shown with various re-education protocols. In another study,[99] before training, children with dyslexia failed to activate the left temporoparietal junction, which was activated by normal readers during a rhyming task; both groups activated the left frontal territories, but in distinct areas. After training,[143] those with the disorder showed increased activation in the left temporal or parietal junction that did not overlap with hypoactivation, and in the same frontal area as that seen in controls. Increased activities were also noted post-training in right temporal and frontal areas. Positive correlations between changes in fMRI signal in these left temporal or parietal and right frontal areas, and changes in language or phonological scores, were recorded, but no correlation was noted with reading scores.

Although sensitive enough to show brain changes after remediation, neuroimaging studies should also address specificity of the cognitive and neuronal mechanisms implicated for the reported effects. Although to find evidence of cerebral plasticity seems easy, that such effects are found behaviourally and cortically for both non-language[142] and phonological[113] training is perplexing. Many factors, both non-specific and language-specific, seem to have an influence on symptoms and their neurological basis during remediation. How do the functional neuroimaging techniques improve our understanding of the dynamics and remediation of dyslexia? Kujala and co-workers[142] did not show a direct link between audiovisual training and a reading test, whereas other researchers[113,143] focused on a link between the phonological deficit tested, the re-education method, and the imaging paradigm.

A potential contribution of neuroimaging studies relates to preclinical diagnosis and prognosis to allow commencement of early treatment. Improved detection of young children at risk for dyslexia could allow implementation of early re-educational training to achieve greater efficiency in neural reorganisation underlying reading dysfunction.[144,145] Behavioural testing in preschool children[146] will probably remain the most effective way of screening for economical reasons. However, neuroimaging could contribute to early diagnosis in family studies in which genetic and neuropsychological data define at-risk individuals. Simos and others[147] showed an unusual pattern of activity in 5–6-year-old children with a

scarcity of activity in the left temporoparietal region and early activation in the homologous region. These results accord with findings in young children deemed at risk for dyslexia owing to their familial antecedents, in whom abnormal ERPs were predictive of the occurrence of dyslexia. [127]

Future prospects

Although controversies about pathophysiology and therapy of dyslexia continue, the various hypotheses might be complementary rather than mutually exclusive. Findings in genetics and neuroimaging should encourage specific hypothesis testing. Although genotype/phenotype relations are complex,[73] future progress in genetics could allow identification of genetic markers for risk of dyslexia. In addition to results suggesting abnormal activation and connectivity in posterior and perisylvian systems, functional neuroimaging studies show evidence of plasticity after diverse interventions. The cognitive and neural specificity of longitudinal changes—eg, compensatory mechanisms occurring spontaneously or after therapies—is still unknown.

Further studies of pathophysiology of dyslexia should include behavioural and neuroimaging studies in large developmental series from different linguistic communities, with investigations of multiple cognitive domains—eg, addressing not only single-word reading but also text processing. Finally, therapeutic research should develop customised interventions to fit with data from behavioural and neuroimaging investigations in every individual.

Conflict of interest statement
None declared

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