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The neurological basis of developmental dyslexia
An overview and working hypothesis

Michel Habib

Cognitive Neurology Laboratory, Department of Neurology, CHU Timone, 13385 Marseille, France

Correspondence to: Dr Michel Habib, Centre de recherche, Institut Universitaire de Gériatrie, 4565 Ch. Queen Mary, Montréal (QUE), Canada H3W 1W5
E-mail: rnp@romarin.univ-aix.fr

Summary
Five to ten per cent of school-age children fail to learn to read in spite of normal intelligence, adequate environment and educational opportunities. Thus defined, developmental dyslexia (hereafter referred to as dyslexia) is usually considered of constitutional origin, but its actual mechanisms are still mysterious and currently remain the subject of intense research endeavour in various neuroscientific areas and along several theoretical frameworks. This article reviews evidence accumulated to date that favours a dysfunction of neural systems known to participate in the normal acquisition and achievement of reading and other related cognitive functions. Historically, the first arguments for a neurological basis of dyslexia came from neuropathological studies of brains from dyslexic individuals. These early studies, although open to criticism, for the first time drew attention towards a possible abnormality in specific stages of prenatal maturation of the cerebral cortex and suggested a role of atypical development of brain asymmetries. This has prompted a large amount of subsequent work using *in vivo* imaging methods in the same vein. These latter studies, however, have yielded less clear-cut results than expected, but have globally confirmed some subtle differences in brain anatomy whose exact significance is still under investigation. Neuropsychological studies have provided considerable evidence that the main mechanism leading to these children's learning difficulties is phonological in nature, namely a basic defect in segmenting and manipulating the phoneme constituents of speech. A case has also been made for impairment in brain visual mechanisms of reading as a possible contributing factor. This approach has led to an important conceptual advance with the suggestion of a specific involvement of one subsystem of vision pathways (the so-called magnosystem hypothesis). Both phonological and visual hypotheses have received valuable contribution from modern functional imaging techniques. Results of recent PET and functional MRI studies are reported here in some detail. Finally, one attractive interpretation of available evidence points to dyslexia as a multi-system deficit possibly based on a fundamental incapacity of the brain in performing tasks requiring processing of brief stimuli in rapid temporal succession. It is proposed that this so-called 'temporal processing impairment' theory of dyslexia could also account for at least some of the perceptual, motor and cognitive symptoms very often associated with the learning disorder, a coincidence that has remained unexplained so far.

Keywords: dyslexia; brain imaging; phonology; temporal processing; reading

Abbreviations: BA = Brodmann area; CVC = consonant–vowel–consonant; ERP = event related potential; fMRI = functional MRI; LLI = language learning impairment; MMN = mismatch negativity

Introduction
During the past few years, dyslexia has been the focus of considerable interest from researchers in different scientific areas, for both theoretical and practical reasons. First, public awareness that this condition, which affects ~10% of the population (or up to 20% depending on a more or less conservative definition), has a neurobiological basis, gave rise to the hope of rational and effective therapy, which stimulated research in quite different areas such as neurophysiology, neuropathology, neuropsychology, linguistics and the educational sciences. As a consequence, dyslexia

has become a fertile ground for transdisciplinary studies and a model for elucidating biological, educational and socio-cultural factors of brain/cognition interactions and development. Finally, the recent explosion of brain imaging methods has found a unique experimental setting for studying the brain mechanisms of reading in general and those of impaired reading in particular.

The notion that dyslexia may have a neurological origin was initially and independently mentioned at the turn of the last century by the Scottish ophthalmologist James Hinshelwood and the British physician Pringle Morgan who both emphasized the similarity of certain symptoms in dyslexic children or teenagers with the neurological syndrome of 'visual word blindness' (Hinshelwood, 1895; Morgan, 1896). Indeed, as first reported by the French neurologist Jules Dejerine, damage to the left inferior parieto-occipital region (in adults) results in a specific, more or less severe, impairment in reading and writing, suggesting that this region, namely the left angular gyrus, may play a special role in processing the 'optic images of letters' (Dejerine, 1891). These early authors thus reasoned that impaired reading and writing in their young dyslexic patients could be due to defective development of the same parietal region which was damaged in adult alexic patients (Hinshelwood, 1917).

However, these speculations remained unconfirmed until the first description of the brain of a dyslexic boy who died from brain haemorrhage due to a vascular malformation (Drake, 1968). Besides evidence of difficulties learning to read, this patient also had a family history of migraine and learning disorders and this was especially the case in his only brother. Pathological examination showed a series of brain malformations principally in the cortical gyri of the left inferior parietal region, including ectopias in the outer (molecular) cortical layer. As will be developed below, this pattern of cortical abnormalities, suggesting defective brain maturation, is central to the description given in more recent studies and to pathophysiological hypotheses which have been proposed since then.

Another line of neurological speculation has followed the initial observations that dyslexic children have poor or inadequate brain lateralization, especially for language. It is customary to cite the American neurologist Samuel Orton (Orton, 1925, 1937) as the 'founding father' of the now famous atypical lateralization theory of dyslexia. In particular, one idea proposed by Orton and later appropriated by Geschwind, was that the lateralization of language functions to the left hemisphere was delayed in dyslexics, so that the language prerequisites for learning to read could not develop normally. (For instance, the high incidence of left-handers and the mirror-writing phenomenon were taken as evidence for abnormal lateralization in these children.) This theory has been at the origin of a large number of experimental studies, especially those using lateralized brain stimulation such as dichotic listening (see, for instance, Obrzut, 1988; Harel and Nachson, 1997). With his colleague Albert Galaburda, the late Norman Geschwind was, undeniably, the originator of a current of thought (and thereby of the vast research effort which followed) turning brain asymmetry in general, and cortical asymmetry in dyslexia in particular, into one of the key issues in neurological science for the second half of the twentieth century (see, for instance, Geschwind and Behan, 1982; Geschwind and Galaburda, 1985, 1987).

In the present paper, I will overview the main arguments and experimental data obtained to date in favour of a neurological basis of developmental dyslexia. In this attempt, I shall first successively provide a brief description of the dyslexic syndrome, a sketch of the main aetiological factors and a description of the dyslexic brain. The major part of the presentation will then be devoted to the main theories currently proposed to account for the mechanism of reading impairment. Throughout this review, special emphasis will be placed on morphological and functional *in vivo* investigations of the dyslexic brain. Finally, I will propose a theoretical framework for future studies in this domain.

The definition and clinical spectrum of dyslexia

Developmental dyslexia is defined as a specific and significant impairment in reading abilities, unexplainable by any kind of deficit in general intelligence, learning opportunity, general motivation or sensory acuity (Critchley, 1970; World Health Organization, 1993). It is widely recognized, although not universally (see Shaywitz *et al*., 1992), that dyslexia is more frequent in males (from 2 : 3 to 4 : 5, depending on the study), with significant familial occurrence. Children with this condition often have associated deficits in related domains such as oral language acquisition (dysphasia), writing abilities (dysgraphia and misspelling), mathematical abilities (dyscalculia), motor coordination (dyspraxia), postural stability and dexterity, temporal orientation ('dyschronia'), visuospatial abilities (developmental right-hemisphere syndrome), and attentional abilities (hyperactivity and attention deficit disorder) (Weintraub and Mesulam, 1983; Rapin and Allen, 1988; Dewey, 1995; Gross-Tsur *et al*., 1995, 1996; Fawcett *et al*., 1996). Besides their multiple possible interrelations and associations, all these developmental syndromes share in common their relative 'specificity', i.e. the fact that general intelligence is intact, as reflected in a normal or above normal non-verbal IQ. Depending on the pattern of such associated disorders, verbal and performance IQ may show usual (verbal $<$ performance) or reversed dissociation. Such a dissociation, *per se*, is a good argument in favour of a 'developmental lesion' affecting separately one or several brain circuits or modules specialized in various aspects of cognitive function. Such comorbidity also suggests a common origin involving either genetic factors or prenatal environmental influences, or both (see below). It also has important diagnostic as well as prognosis significance, influencing both evaluation and remediation of the reading disorder.

One aspect of these associated disorders has received particular attention during the last decades, namely the frequency of oral language impairment. A considerable proportion of dyslexic children have known not only more or less severe problems in oral language and speech acquisition, from mere delay to severe dysphasia, but also, as will be developed below, subtle impairment in perception and/or articulation of speech, which is currently considered the most likely mechanism leading to the reading disorders. Accordingly, one of the most widely recognized oral language concomitants of dyslexia is a task known as 'rapid automated naming' where children have to speak aloud as quickly as possible the names of pictures presented on a sheet recurrently in random order (Korhonen, 1995). Finally, it has been suggested that a clinically covert deficit in articulatory efficiency may be demonstrated by adequate testing in most dyslexics (Heilman *et al*., 1996). However, it is important to keep in mind that the relationship between oral language deficits and dyslexia is far from being straightforward since, although these are not the majority, there are dyslexics for whom even sophisticated examination fails to disclose oral language impairment, and, more often, severe dysphasics who learn to read without apparent difficulty.

The reading disorder itself may either appear as primary, thus manifesting at the time when the child learns to read, or as the ultimate and often most worrying feature of an already diagnosed learning disorder. In the large majority of cases, and irrespective of the age of diagnosis, children who fail to achieve normal reading performances make the same type of errors: visual confusions between morphologically similar letters, especially those having a symmetrical counterpart (such as b and d), difficulty in acquiring a global 'logographic' strategy which would allow them to recognize common words presented briefly, and difficulty in generalizing previously learned grapheme to phoneme rules (especially for complex letter clusters). This latter aspect appears as the core dysfunction in dyslexia, since grapheme to phoneme conversion is a critical stage in learning to read (Frith, 1995). This stage is compromised by the two main aspects of neurological dysfunction evidenced in dyslexic children, which affect visual perceptual and phonological processes (see below). Besides cases of obvious dysgraphia due to associated motor and/or coordination–dexterity impairment, the written production of dyslexic children is also stereotyped: phonemic errors in the transcription from oral to written form of letters and syllables, defective spatial arrangement of letters, inversions, omissions and substitutions of letters and/or syllables, aberrant segmentation of words, and weak grammatical development, which all combine to bring about a fuzzy, sometimes incomprehensible production.

Due to the multitude of possible combinations of these basic dysfunctions, a rational remedial approach usually involves specific and specialized teaching best provided by one or more competent professionals (speech therapists, occupational therapists, neuropsychologists and/or specialized educators, depending on the organizational context specific to each country). Finally, after several months or (more often) years of remedial effort, not without unavoidable psychological consequences of this special and longstanding treatment, reading becomes possible, although often clumsy and effortful, sometimes with persisting errors, especially with irregular or exceptional words (surface dyslexia), as well as in the area of comprehension. But the common outcome in adolescence and adulthood is a more or less profound spelling impairment (Treiman, 1985), which will persist as the permanent hallmark of the developmental disorder (and stands as a valuable indicator for retrospective diagnosis of dyslexia in adults). One of the most fruitful contributions of these last years to the analysis and rational therapy of dyslexia has been provided by the neuropsychological approach, through its systematic endeavour to 'dissect' the mechanisms of reading impairment in a given subject in order to develop adequate remedial protocols. One important step has been to individualize the phonological and surface types of developmental dyslexia (Castles and Coltheart, 1993), by analogy to classical subtypes of acquired dyslexia, which are classified according to the rate of errors in reading non-words, which is tightly dependent on a non-lexical phonological procedure, and exception words, which relies on a lexical, visuo-orthographic procedure. However, the distinction between surface and phonological forms of dyslexia has not replaced the old empirical terminology of dysphonetic versus dyseidetic types (Boder, 1973), which remains widely used. (It must be noted here that most dyslexics of the Boder's dyseidetic type probably have a quite special reading disorder where attentional and spatial difficulties interfere with the process of learning to read, rather than constituting a definite, specific incapacity for reading.) It must be noticed, in this regard, that the surface/phonological distinction is only descriptive and devoid of any aetiological assumption as to the underlying brain mechanisms, whereas the dysphonetic/dyseidetic distinction clearly refers to two opposed mechanisms, one related to a speech discrimination deficit, the other to visual perception impairment (see below).

Aetiological considerations

The basic postulate of current research in this field is that dyslexia and related disorders are fundamentally linked to a constitutional characteristic of the brain. Evidence for a genetic origin of dyslexia has been increasingly accumulating during the last few years and will not be reviewed here. The reader is referred to more specific writings by Pennington (Pennington, 1991, 1997, 1999), Schulte-Körne and colleagues (Schulte-Körne *et al*., 1996), Smith and colleagues (Smith *et al*., 1998), and Flint (Flint, 1999), and to recent discoveries regarding the involvement of specific chromosomes (Fagerheim *et al*., 1999; Fisher *et al*., 1999; Gayan *et al*., 1999). It suffices to say for our present purpose that dyslexia is very probably of genetic origin, since it occurs most often in families. However, genetic transmission

is probably complex and non-exclusive. In particular, it is conceivable that different forms of dyslexia may occur within the same family, whereas different genes have been implicated in different aspects of the reading disorders. For instance, it has been suggested that chromosome 15 is related to performance on a single word reading task, while chromosome 6 involvement would be related to a phonological awareness task (Grigorenko *et al*., 1997; see, however, Fisher *et al*., 1999, for an opposite view). Probably more relevant are data obtained recently by Castles and colleagues in a twin sample (Castles *et al*., 1999). These authors compared subjects' scores on exception word reading and non-word reading tasks to build surface and phonological dyslexic subgroups taken at each end of this distribution. Reading deficits were found to be significantly heritable in both subgroups. However, the genetic contribution was much greater in the phonological dyslexics than in the surface dyslexics, suggesting a significant environmental influence for the latter subgroup. The nature of such an environmental influence is still totally speculative, but an attractive hypothesis has pointed to the possible intervention of the prenatal environment (Geschwind and Behan, 1982; see also Bryden *et al*., 1994).

Indeed, from a neurological point of view, the large prevalence of oral or written language deficits among these learning disordered children suggests a special vulnerability of the left hemisphere cortical systems subserving various aspects of language-related abilities to these aetiological factors (Geschwind and Galaburda, 1985). Hormonal factors, such as foetal testosterone levels during late pregnancy, may play a crucial role, and this is possibly reflected in the large male predominance in most of these conditions. However, empirical evidence is lacking for such a hormonal role in the aetiology of dyslexia (Tonnessen, 1997). Another aspect suggested by the Geschwind–Behan–Galaburda theory is related to the putative role of immune factors, based on partial evidence that dyslexia may occur more often in families suffering from various immune diseases (Pennington *et al*., 1987; Hugdahl *et al*., 1990; Crawford *et al*., 1994). In spite of contradictory evidence (Gilger *et al*., 1998), there is currently a consensus towards the conception of a complex link between several traits including non-righthandedness, immune diseases, sex hormones and verbal learning disorders, but the nature of this link, although probably genetic, remains totally speculative (Hugdahl, 1994). Some arguments, however, are derived from animal studies, especially rodent models in which a genetic basis to autoimmune disease has been found in association with cortical anomalies and learning difficulties (Galaburda, 1994). It is noteworthy that one locus implicated in chromosome 6 studies (Cardon *et al*., 1994) is part of the HLA (human leucocyte antigen) complex, known to participate in the immune system control. Finally, it must be observed that these possibly aetiologically relevant associations are not specific to dyslexia, but probably also concern other conditions, such as hyperactivity disorder in which, for instance, male predominance is even larger and the immune link probably also present, with genetic studies pointing to the HLA system (Odell *et al*., 1997).

The dyslexic's brain

The seminal anatomical studies of the Boston school

Undoubtedly, the most significant contribution of these last few decades to the neurology of dyslexia was the description by Galaburda and colleagues of the brains of one (Galaburda and Kemper, 1979), then four (Galaburda *et al*., 1985) brains of male dyslexic subjects. Later on, the same group reported the analysis of three additional female brains (Humphreys *et al*., 1990). To summarize these studies, two main observations were made. First, at the microscopic level, a meticulous analysis of serial coronal slices of the post-mortem specimens, compared with a similar analysis of non-dyslexic brains (Kaufmann and Galaburda, 1989) disclosed specific cortical malformations including ectopias (small neuronal congregations in an abnormal superficial layer location), mainly distributed across both frontal regions and in the left language areas; dysplasia (loss of characteristic architectural organization of the cortical neurons, mainly subjacent to the site of ectopias); and more rarely, vascular micro-malformations. In some instances, these cortical malformations took the appearance of a microgyrus (or micropolygyrus), an aspect also found in the subsequent analysis by Cohen and colleagues of the brain of a dysphasic child (Cohen *et al*., 1989) (It must be noted that, even though the child whose brain was studied by Cohen and colleagues was unequivocally suffering important delays in oral language acquisition, in several of the dyslexics reported by Galaburda *et al*. (1985), oral language was also reported as being delayed.) No ectopias were found in the study by Cohen and colleagues, but the microgyrus, as reported by Galaburda and Kemper (Galaburda and Kemper, 1979), was located in the left temporal cortex. The main lesson drawn from these microscopic observations is that all the brains studied differed from control brains in a way that suggested abnormal cortical development. Since neuronal migration is thought to take place during the sixth gestational month, the mechanism leading to these cortical lesions was presumed to occur before or during this period of the foetal brain development. Finally, in addition to these neuronal abnormalities, the female brains showed glial scars in the border zones between the arterial territories, suggesting a vascular mechanism, supposedly of immune origin (Humphreys *et al*., 1990).

Besides these microscopic anomalies, all the dyslexic brains of the Boston studies, as well as that of the dysphasic child studied by Cohen and colleagues (Cohen *et al*., 1989), displayed a macroscopic peculiarity, namely an absence of the usual left $>$ right asymmetry of the planum temporale. In fact, this small triangular part of the superior surface of the temporal lobe had been reported by earlier anatomists as asymmetrical in the majority of brains, a fact confirmed in

the first such study in the modern area by Geschwind himself (Geschwind and Levistky, 1968; for a review, see Galaburda and Habib, 1987). Since this asymmetry was believed to parallel the functional linguistic preponderance of the left hemisphere, and by reference to the above-mentioned evidence of incomplete lateralization in dyslexics, this region naturally deserved to come under close scrutiny. The prediction was apparently totally confirmed, since all the brains studied displayed this particular symmetrical aspect; however, it is not specific since it is present in roughly one-third of routine brains. In other terms, planum symmetry seemed necessary but not sufficient to define the dyslexic's brain. Although the developmental mechanisms leading to such atypical symmetry still remain a subject of debate (see, for instance, Steinmetz, 1996), these findings, combined with the above-mentioned microscopic features, have been generally considered good evidence of maturational deviance being at the origin of the learning difficulties of dyslexics.

Towards a better understanding of the significance of cortical asymmetries: in vivo *morphological imaging of the dyslexic brain*

Several more recent attempts have been made at replicating these findings, through *in vivo* examination of larger populations of dyslexic individuals using morphological brain MRI. Cortical anatomy can reliably be demonstrated using MRI which provides a unique opportunity to respond to the two main criticisms addressed to results from pathological findings: the limited number of brains analysed and the uncertainty persisting as to the diagnosis and subtype of dyslexia (Hynd and Semrud-Clikeman, 1989). Hopefully, using the remarkable definition of brain MRI to analyse cortical asymmetries in subjects carefully diagnosed and selected should provide clear-cut answers. Several recent studies have yielded complete reviews of the available data, most of them concluding that the evidence is not fully convincing (Beaton, 1997; Morgan and Hynd, 1998; Shapleske *et al*., 1999). Table 1 summarizes the main characteristics and results of these different studies.

Whereas initial studies seemed to confirm pathological findings statistically, with a larger incidence of reversed (or absent) asymmetry, it is noteworthy that more recent ones (using more refined MRI technology) have failed to confirm such a tendency. For instance, the study by Leonard and colleagues, one of the most sophisticated and reliable available, reports an atypical pattern of gyrification in right and left temporal as well as parietal perisylvian cortices (Leonard *et al*., 1993). One intriguing finding in this study is the suggestion that in addition to interhemispheric asymmetry, it would be interesting to consider intra-hemispheric asymmetries, i.e. the relative importance, within each hemisphere, of the temporal and parietal banks of the posterior sylvian fissure.

Among studies finding significant differences between dyslexics and controls, that of Larsen and colleagues was the first to suggest that atypical symmetry in dyslexia is specifically linked to phonological impairment (Larsen *et al*., 1990). They showed that a subgroup of their dyslexics with impaired performance on a non-word reading task had symmetrical planum temporales, whereas those with impaired word recognition did not differ in this respect from controls.

As summarized in Table 1, although there is a global tendency in the literature to confirm *in vivo* the initial neuropathological observations of Galaburda *et al*. (1985), there are notable exceptions when authors fail to find any significant bias towards symmetry in dyslexics. This is especially so in the most recent studies where the surface area of the planum temporale was measured directly. For example, in a study of eight dyslexics and eight controls (all male right-handers) with a MRI-based surface reconstruction technique, Green and colleagues failed to disclose any group difference in asymmetry of the caudal infra-sylvian surface (Green *et al*., 1999). These inconsistencies may relate to the selection of subjects, or to the mode of anatomical measurement. Alternatively, purely environmental factors may act as confounding variables. For example, it has been demonstrated that intensive training in the auditory modality can modify the degree of asymmetry in the posterior auditory region, increasing the size of the left planum (Schlaug *et al*., 1995*a*). This finding is in line with neuroplasticity studies in animals, showing that direct training notably alters the sensory neural maps at the single cell level (Recanzone *et al*., 1993).

In a recent study (Habib and Robichon, 1996) of 16 dyslexic young adults and 14 controls, all male students from the same engineering school (to ensure that both groups had a similar intellectual as well as academic level), we failed to disclose significant differences in planum temporale asymmetry between the two groups. Instead, we found that a parietal area, situated in front of the planum temporale, on the other bank of the sylvian fissure, is less asymmetrical in dyslexics than in controls, and that the degree of asymmetry of this area is inversely proportional to the individuals' performance on a phonological task. [Interestingly, a recent and controversial paper by Witelson and colleagues has found total absence of asymmetry in this region (parietal operculum) on photographs of the brain of Albert Einstein, who was not only a mathematical genius, but also a self-admitted dyslexic (Witelson *et al*., 1999).] This finding suggests that parietal rather than temporal asymmetry may be the most relevant morphological characteristic of the dyslexic brain. It is noteworthy, in this context, that recent functional imaging studies have found dissociations between anatomical preponderance of the left planum temporale and functional asymmetry of the temporal cortex during auditory verbal tasks (Karbe *et al*., 1995). Moreover, it seems that the planum temporale itself is not specifically activated by verbal auditory stimuli, since it responds equally to tones and words during passive listening tasks and more strongly to tones during active listening (Binder *et al*., 1996; Celsis *et al*., 1999).

Finally, as the posterior region of the inferior frontal gyrus

Table 1 *Morphological MRI investigations of cortical asymmetries in dyslexia*

Study	Method	Subjects	Chronological age in years (SD)	Anatomical structure measured	Asymmetries and/or regional abnormalities		
					Dyslexics	Controls	Others
Rumsey *et al.*, 1986	MRI 0.5 T	10 male dyslexics	22.6 (3.34)	Lateral ventricles	R < L: 20% R > L: 40% R = L: 90%		
				Temporal lobes[1]			
Hynd *et al.*, 1990	MRI 0.6 T	10 dyslexics (8 males + 2 females)	9.9 (2.04)	Length of the PT[2]	R < L: 10%	R < L: 70%	R < L: 70%[a]
				Length of the insula	R < L	R > L	R < L
		10 ADD/H (8 males + 2 females)	10.0 (3.36)	Width of frontal lobe	R = L	R > L	R = L
		10 controls (8 males + 2 females)	11.8 (2.0)				
Larsen *et al.*, 1990	MRI 1.5 T	19 dyslexics (ratio: 4 males/1 female)	15.1 (0.3)	Surface of PT	R < L: 31.5% R = L: 68.5%	R <L: 70.5% R = L: 29.5%	
		17 controls (ratio: 4 males/1 female)	15.4 (0.4)				
Duara *et al.*, 1991	MRI 1.0 T	21 dyslexics (12 males + 9 females)	39.1 (11.0)	Postcentral surface[1,3]	(R > L) n.s.	(R = L) n.s.	
				Posterior surface	R > L***	(R < L) n.s.	
		29 controls (15 males + 14 females)	35.3 (10.0)				
Jernigan *et al.*, 1991	MRI 1.5 T	20 L/Li (13 males + 7 females)	8.9 (0.7)	'Inf.-anterior' vol. [4]	R > L**[b]		
				'Sup.-posterior' vol. [5]	R < L**		
		12 controls (8 males + 4 females)	9.0 (0.7)	'Inf.-posterior' vol. [1]	R < L: 45% R > L: 50%; R = L: 5%		
Plante *et al.*, 1991	MRI 0.5 T	8 SLI	5.2	Perisylvian region	R < L: 25%[c]	–†	
		8 normal MRI scans from male subjects selected from a database	–		R > L: 37.5% R = L: 37.5%	– –	
Kushch *et al.*, 1993	MRI 1.5 T	17 dyslexics (9 males + 8 females)	26.2 (15.0)	SSTL[6]: anterior	(R < L) n.s.	R < L ****	
				posterior	(R > L) n.s.	R < L ****	
		21 controls (8 males + 13 females)	33.4 (15.0)	total	(R = L) n.s.	R < L ****	
Leonard *et al.*, 1993	MRI 1.0 T	9 dyslexics (7 males + 2 females)	36 (17.1)	Length of PT[7]	(R < L) n.s.	(R < L) n.s.	(R < L) n.s.[d]
				[T] Temporal length	R < L ****	R < L *	R < L **
		10 unaffected siblings (4 males + 6 females)	25.7 (20.3)	[P] Parietal length	(R > L) n.s.	R > L **	R > L *
				Left intrahemispheric asymmetry[8]	T < P: 22% T > P: 78%	T > P: 100%	T > P: 100%
		12 controls (5 males + 7 females)	37.1 (13.5)	Right intrahemispheric asymmetry[8]	T < P: 55.5% T < P: 44.5%	T > P: 100%	T < P: 40% T > P: 50% T = P: 10%
				Parietal operculum[9]:	LCH[e] RCH[f] Bil[g]	LCH RCH Bil	LCH RCH Bil
				type 3	67%	8%	40%
				type 4	11%	8%	
				Multiple Heschl gyri	22% 33% 11%		10%

Table 1 *continued*

Study	Method	Subjects	Chronological age in years	Anatomical structure measured	Asymmetries and/or regional abnormalities		
					Dyslexics	Controls	Others
Schultz *et al.*, 1994	MRI 1.5 T	17 dyslexics (10 males + 7 females) 14 controls (7 males + 7 females)	8.68 (0.64) 8.94 (0.67)	Surface of PT[10]	R < L: 76%	R < L: 71%	
Rumsey *et al.*, 1997*a*	MRI	16 right-handed dyslexic men 14 matched controls	18–40 years	PT and ascending posterior ramus of SF ('planum parietale')	Both groups have: 70–80% leftward PT asymmetry 50–60% rightward planum parietale asymmetry		
Gauger *et al.*, 1997	MRI	11 L/LI and 19 matched controls	5.6–13 years	PT Broca's area (pars triangularis)	• Left pars triangularis significantly smaller in SLI children • More incidence of rightward asymmetry of language structures • Anomalous morphology in these language areas correlated with depressed language ability		
Clark and Plante, 1998	MRI 1.5 T	41 normal adults, including 20 parents of LLI children. Among these, 15 probable (test-identified) dyslexics. 4 probable dyslexics in the non-parent population	30–51 years	Broca's area. 7 types according to gyrification and sulcal patterns	Morphological types including an extra sulcus in the inferior frontal gyrus of test-identified dyslexics (both hemispheres combined)		
Dalby *et al.*, 1998	MRI	17 dyslexics, 6 retarded readers, 12 normal controls	Mean 16 years	3 measures of temporal lobes	L < R or L = R: 82% L > R : 72%[h] for one of the 3 measures (temporal region on coronal slices, cortico-subcortical, including anterior insula)		
Best and Demb, 1999	MRI	Dyslexics with documented magnocellular deficit and normal controls		3 methods on sagittal sections	No difference in asymmetry from normal controls		

ADD/H = attention deficit disorder/hyperactivity; L/Li = language/learning impaired; SLI = specific language impairment; PT = planum temporale. SF = sylvian fissure; inf. = inferior; sup. = superior. [1]Including the PT, among other regions; volumetric measurements (study A) and surface measurements (study D). [2]On axial slices. [3]Measurements were made on an axial slice divided into six areas: anterior polar (prefrontal regions), anterior (premotor regions and Broca's area), anterior central (anterior part of the superior temporal gyrus), posterior central (posterior part of the superior temporal gyrus including the PT), posterior (including the angular gyrus) and posterior polar (lateral occipital cortex and the cuneus of the occipital lobe); positive correlation between the severity of dyslexia and the surface of the right posterior polar brain segment. [4]Prefrontal region below the frontal operculum, including orbitofrontal lobe bilaterally. [5]Region including superior parietal lobe above the parietal operculum. [6]SSTL = superior surface of the temporal lobe, defined as extending from the end of the sylvian fissure to the anterior border of the temporal lobe and divided into two equal anterior and posterior surfaces. [7]Total length: temporal border [T] + parietal border [P]. [8]Intrahemispheric comparison of length of temporal border [T] and length of parietal border [P]. [9]See Steinmetz *et al.*, 1990: four types of configuration of the parietal operculum. [10]The planum temporale is defined as extending from the end of the sylvian fissure to the posterior border of the Heschl gyrus. Other measurements concern the superior surface of the temporal lobe and the volume of the temporal lobe; in order to account for individual variations in overall brain size, the images of brains were enlarged to reach a standard size but no significant difference between the two groups could be pointed out, even for the measurement of the surface of the PT. [a]ADD/H children; [b]L/LI children; [c]SLI children; [d]unaffected siblings; [e]left hemisphere (percentage of cases); [f]right hemisphere (percentage of cases); [g]bilateral abnormalities (percentage of cases); [h]normal controls and retarded readers combined. †Result not reported. *$P < 0.05$; **$P < 0.01$; ***$P = 0.007$; **** $P < 0.001$; n.s. = not significant.

is classically related to language output, the study of its morphology in developmental dyslexics appears to be especially relevant. Paradoxically, such studies are rather sparse. While Galaburda and colleagues have reported at the cytoarchitectonic level the presence of numerous ectopias and dysplasias bilaterally in the inferior frontal gyrus of developmental adult dyslexics (Galaburda *et al*., 1985), others using neuroimaging have shown macroscopic symmetry of the anterior speech region in dyslexic children (Hynd *et al*., 1990). However, Jernigan and colleagues found a significant difference between language-disordered individuals and normal controls in the inferior frontal regions, with reversed direction of asymmetry (Jernigan *et al*., 1991). More recently, Clark and Plante showed a relationship between the sulcal morphology of the inferior posterior frontal gyrus and a family history of developmental language disorders, suggesting an increased risk factor for these disabilities when extra sulci are present in this frontal region (without, however, any lateralized effect) (Clark and Plante, 1998).

In our young engineers population, we recently measured Broca's area asymmetry (Robichon *et al*., 2000) and found a more frequent symmetrical pattern in areas 44 and 45 in dyslexics, and a correlation between this pattern and subjects' non-word reading performance. This result is consistent with functional imaging studies (see below) suggesting a role of the left inferior frontal gyrus in speech perception and rapid auditory processing, as well as in phonological aspects of reading (Fiez *et al*., 1995; Fiez and Petersen, 1998; Price, 1998).

Finally, it appears from this review of anatomical aspects of brain asymmetry in dyslexia that far from resolving questions opened by the initial pathological observations, *in vivo* morphometry using the most refined imaging methods has raised different issues. Tendencies but no strong effects have been shown and only a few aspects of the complex interplay of several factors have been revealed, the majority of which are probably still to be discovered. One potentially interesting avenue could be the use of methods such as diffusion tensor MRI, which would be able to show the directionality of white matter fibres (Klingberg *et al*., 2000).

The interhemispheric deficit theory of dyslexia

These considerations may not apply to another brain structure, the corpus callosum, whose involvement in dyslexia and other developmental disorders has been suspected for a long time. Thus, besides theories pointing to defective brain lateralization, another frequently proposed potential mechanism is abnormal collaboration and/or communication between the hemispheres. This hypothesis relies on well-documented evidence of impaired interhemispheric transfer of sensory or motor information in dyslexics (Gross-Glenn and Rothenberg, 1984; Best, 1985; Gladstone *et al*., 1989; Moore *et al*., 1995; Markee *et al*., 1996). A few studies have looked for a structural concomitant of impaired callosal function by measurement of the mid-sagittal surface of the corpus callosum on MRI scans. Duara and colleagues found a larger total callosal area in female but not male dyslexics and a larger posterior (splenial) area in male and female dyslexics, in 21 adult dyslexics compared with controls (Duara *et al*., 1991). Conversely, Larsen and colleagues failed to demonstrate any difference in callosal measurements, either for total or splenial areas, between 17 dyslexic adolescents and 19 controls (Larsen *et al*., 1992) (for negative evidence, see also Cowell *et al*., 1995; Pennington *et al*., 1999). Hynd and colleagues compared 16 dyslexic children with 16 age-matched controls and only found significant differences in the anteriormost region (genu), which was smaller in dyslexics (Hynd *et al*., 1995). Finally, Rumsey and colleagues found a larger posterior third of the callosum, that included the isthmus and splenium, in 21 dyslexic men than in 19 controls (Rumsey *et al*., 1996).

In our own study of 16 dyslexic men (Robichon and Habib, 1998), we found that (i) our dyslexics' corpus callosum displayed a more rounded and an evenly thicker callosal shape and (ii) only right-handed dyslexics had a larger mid-callosal surface, especially in the isthmus. These findings are globally consistent with the fact that more symmetrical brains may possess more overall (right plus left) brain tissue in temporoparietal regions connected through the posterior part of the callosum. Moreover, they raise the important issue of whether more callosal connections reflect lesser cortical asymmetry, or have a special significance *per se*, for instance in terms of interhemispheric inhibition or collaboration. From a neurodevelopmental point of view, differences in callosal size may reflect hormonal influences during critical periods of development of interhemispheric connections. It has been shown that the size of the mid-posterior part of the callosum is proportional to salivary testosterone concentrations (Moffat *et al*., 1997). Finally, a changed callosal size in dyslexia may also result from intensive remedial therapy, since it has been shown that intensive training may affect callosal morphology (Schlaug *et al*., 1995*b*).

Dyslexia: in search of the neurofunctional defect(s)

Beyond the neuroanatomical aspects reviewed in the previous section, active research is currently in progress from different perspectives in order to elucidate how the dyslexic brain functions or malfunctions. It must be emphasized here that considerable caution is required when attempting to draw any explanatory model of dyslexia from the results reported below, since most of them only reflect statistical tendencies and never represent a systematic rule. As a consequence, all the theories proposed to date suffer from notable exceptions, where a given effect is sometimes only present in a minority of subjects, obviously limiting the impact of such observations. Moreover, finding a relationship between two measured variables does not mean that they are causally tied, so that any theory based on such observations must remain

hypothetical, explaining, at best, only one part of the reality. Another methodological consideration concerns the population studied in some of the works cited in this section. It is possible that researchers advocating different theories have based their observations on more or less different populations, so that their conclusions may differ. This is the case for ophthalmological departments which may artificially isolate a selection-biased population with an unusually important visual contribution to dyslexia; this may also be the case for professionals or institutions receiving younger children, with a disproportionate incidence of oral language deficits. In this regard, arguments drawn from data obtained in so-called language learning impaired (LLI) or specific language impaired (SLI) children, although probably including typically dyslexic individuals, have been criticized as being only loosely representative of the dyslexic population. However, in the present review, we will also consider results obtained in such populations as they possibly provide valuable information on the neurobiological bases of language learning problems in general, and dyslexia in particular.

Neuroscientific research has explored three main pathways during the past decade: the phonological processing theory, the visual theory and the temporal processing theory. In the present section, I will review arguments in favour of each of the three theories in the light of results from studies involving brain functional investigations in dyslexics.

The central role of phonological disorders in developmental dyslexia

One of the most robust discoveries in the domain of cognitive mechanisms leading to dyslexia is the repeated demonstration that the core deficit responsible for impaired learning to read is phonological in nature and has to do with oral language rather than visual perception. The deficit is in the ability to manipulate in an abstract form the sound constituents of oral language, so-called phonological awareness (or meta-phonology). Whereas most children are able to perform tasks requiring segmenting words in smaller units (syllables and partly phonemes) well before reading age, dyslexic children are still unable to do so even after several months of reading and writing (Liberman, 1973; Bradley and Bryant, 1983). Lundberg and colleagues (Lundberg *et al*., 1988) showed improved reading abilities in children previously trained in such exercises and these observations are the basis of the widespread use of oral language exercises for the rehabilitation of reading and spelling disorders. An important concept of the phonological processing theory is that there is a deficit at the level of phoneme representation itself. For instance, several researchers have found that dyslexics are poorer than age-matched controls (and also than controls matched for reading age) at tasks that require processing of subtle differences between phonemes that are acoustically similar to each other. This is best exemplified in tasks of categorical perception when children have to categorize as 'ba' or 'da' an artificial acoustic continuum between the two syllables. A number of studies (Godfrey *et al*., 1981; Werker and Tees, 1987; Reed, 1989) have shown a deficit in this task in a proportion of dyslexics that is variable across different studies. The deficit is generally found for items situated close to the intercategorical boundary, especially articulatory oppositions (/ba/–/da/; /da/–/ga/), or less often voice-onset oppositions such as /ba/–/pa/ (Manis *et al*., 1997). The latter authors showed such deficits are found specifically in a subgroup of dyslexic children with a phonological awareness deficit (as assessed in a task in which subjects had to pick out a phoneme within a non-word said aloud by the examiner). Manis and colleagues concluded that inadequate representations of phonemic units resulting from such perceptual deficits could prevent dyslexic children from using and normally manipulating phonological information, thus impairing their ability to acquire phonological prerequisites to learning to read (Manis *et al*., 1997). As will be developed below, phonemic processing impairment in dyslexia may even stem from a more elementary general auditory problem with the detection of stimuli with certain temporal properties. A defect in sensitivity to auditory frequency modulation has been shown in dyslexia and found to be related to the rate of errors in a non-word reading task (Witton *et al*., 1998), a result not replicated in another study (Bishop *et al*., 1999). Recently, Helenius and colleagues have shown that the illusion of 'stream segregation', normally obtained when two pure tones are repeated rapidly in alternation, is present in adult dyslexics even at much slower rates (Helenius *et al*., 1999). This can be taken as an equivalent to the phenomenon of sensory persistence reported below for the visual modality.

Demonstration of a visual processing deficit: the 'magnosystem' theory

Besides the multitude of deficits demonstrated in phonological and orthographic aspects of reading, researchers have sought part of the mechanism of reading disorders within the domain of visual perception, using tools primarily designed for investigations of visual function. Several lines of evidence argue in favour of this strategy.

First, clinical studies have long reported that most dyslexics make errors that follow visual rather than strictly phonetic laws, e.g. confusions between symmetrical (b/d) or visually close (m/n) letters, and that at least some of them may derive from purely perceptual impairments. Although such errors are present in most children with otherwise typical phonological problems, they can also occur predominantly or even exclusively in some, a situation often referred to as visuoattentional dyslexia (Valdois *et al*., 1995). Accordingly, the characterization of a 'dyseidetic' subgroup of dyslexics (Boder, 1973) supposed a visual deficit at the origin of the disorder with preferential use of a phonetic strategy when

reading. A reverse dissociation was proposed for 'dysphonetic' dyslexics.

Up to 75% of dyslexic children may be affected by ophthalmological problems that disturb binocular vision, ocular tracking or motion perception, to the point that ophthalmological remedial methods have even been proposed as treatment in the past. However, each of these problems can be interpreted as a consequence rather than a cause of reading impairment if one considers that these various abilities develop in normal readers partly under the influence of reading itself.

Such an explanation does not hold, however, for more elementary perceptual abnormalities repeatedly reported in dyslexic children. Globally, visual perceptual studies have shown that dyslexic children process visual information more slowly than normal readers. For instance, there are studies that show longer visual persistence at low spatial frequencies (Lovegrove *et al*., 1980*a*, *b*), or a slower flicker fusion rate (Martin and Lovegrove, 1987). However, the best demonstration of a low-level visual deficit in dyslexics is that of altered contrast sensitivity. Dyslexics may need 10-fold lower spatial frequencies to perceive the same contrast as non-dyslexic children. This contrast sensitivity deficit may affect 75% of dyslexics, especially those with evidence of an associated phonological deficit (Lovegrove *et al*., 1980*a*, *b*, 1982, 1990; Eden *et al*., 1996*b*; Cornelissen *et al*., 1998). Contrast sensitivity deficit (but not abnormal visual persistence) could even be specific to a dysphonetic subgroup of dyslexics, being absent in dyslexics classified as dyseidetic or mixed (Slaghuis and Ryan, 1999). Moreover, visual detection of motion, another function usually ascribed to the magnosystem, has been found correlated to performance of a lexical decision task (Cornelissen *et al*., 1998), a finding interpreted as reflecting variations in lettering position encoding.

Several researchers have suggested that deficits observed in psychophysical experiments may be accounted for by reference to the distinction between sustained and transient visual channels (for a review, see Stein and Walsh, 1997) [More precisely, during reading, the activity in the transient channel (magnosystem) would be inhibited at each ocular saccade by activity in the sustained channel (parvosystem). If such inhibition does not occur, visual processing of a given letter within a word would be compromised by abnormal persistence of the preceding letter(s).] Since these channels can be distinguished by their preferred spatial frequencies, their temporal properties and their contrast sensitivity, it has been suggested that the impairment observed in dyslexics both in contrast sensitivity and visual persistence may result from disturbance in the transient system, which mediates perception of global form, movement and temporal resolution. As a confirmation of this hypothesis, Livingstone and colleagues have provided electrophysiological and neuro-anatomical evidence of an alteration of the magnocellular component of the visual pathway (M-system), and shown the absence of specific electrical responses to high spatial frequency and low contrast visual targets in dyslexic children who responded normally to targets with greater contrast and lower spatial frequency (Livingstone *et al*., 1991). In the same article, they report that the dyslexic brains previously shown by Galaburda and colleagues (Galaburd *et al*., 1985) to display cortical changes, also display subtle abnormalities in the neuronal organization of the lateral geniculate nucleus (the thalamic relay of the retinocortical pathway). Consistent with the M-system theory, only neurons of the magnocellular part of the nucleus were abnormally atrophied, whereas the parvocellular part of the nucleus was intact. These neuropathological findings, however, have never been replicated, a deficiency that represents an obvious limitation to any line of argument based on such neuropathological evidence. More recently, Jenner and colleagues failed to find a specific involvement of the magnocellular component of the primary visual cortex, but reported an absence in dyslexics of the asymmetry in neuronal size found in normals, namely more large cells in the left occipital lobe (Jenner *et al*., 1999).

To summarize, the considerable research effort currently devoted to visual theories of dyslexia may seem disproportionate, since almost all in the field agree that phonological impairment is the crucial phenomenon. Indeed, if the pathognomonic dysfunction in visual dyslexia is in the rapid recognition of written words (Lovett, 1987; Siegel, 1993), current theories of reading emphasize the development of word decoding skills, which in turn rely heavily on basic language skills, particularly phonological skills (Bentin, 1992; Rack *et al*., 1993; Siegel, 1993). Actually, the magnosystem theory, again triggered by results coming from neuropathological studies (Livingstone *et al*., 1991; Galaburda and Livingstone, 1993), is eminently fragile even if negative results are still scarce (see, for instance, Johannes *et al*., 1996; Spinelli, 1997; Barnard *et al*., 1998; Jenner *et al*., 1999). In particular, recent attempts at correlating a psychophysical deficit in the realm of presumably M-dependent visual functions with behavioural performance is not always convincing, especially since the neuropsychological profile of the patients is ill-defined (Talcott *et al*., 1998). Finally, a recent review of the available literature on contrast sensitivity (Skottun, 2000) concludes that there is more negative than positive evidence for the existence of a deficit in contrast sensitivity in dyslexia.

Probably the more attractive feature of the M-deficit theory is that it can be extended to other sensory channels, since there is some evidence that the magno/parvo distinction also exists anatomically and functionally for other sensory modalities. Thus, Galaburda and colleagues have shown that, just as the M-pathway may be specifically affected in the dyslexics' lateral geniculate, the same may be true for the medial geniculate, situated on the auditory pathway (Galaburda *et al*., 1994). In this view, dyslexia would be a 'pathology of the magnosystems', which could account for phonological as well as visual impairment.

The 'temporal (rate)-processing' theory of dyslexia

Another very attractive hypothesis, which possibly may reconcile the phonological and visual deficit accounts, postulates that the different levels of impairment reported above all stem from a unique basic deficit, involving processing by the brain of the rate and temporal features of various kinds of stimuli. In other terms, these children's brains would be fundamentally unable to process rapidly changing or rapidly successive stimuli either in the auditory or the visual modality. Tallal and Piercy have thus demonstrated that children with LLI are poor at processing stimuli that incorporate brief, rapidly changing components, especially when these changes occur in the tens of milliseconds time range that characterizes the acoustics of ongoing speech (Tallal and Piercy, 1973).

As a consequence, the hypothesis posits that these children's language problems result from their inability to perceive the rapid acoustic elements included in human speech, namely, the formant transitions whose duration is as short as a few tens of milliseconds. Moreover, this rate processing constraint would be both non-specific to language, since it also concerns non-verbal sounds, and non-modality dependent, since it has also been demonstrated using visual and sensory-motor tasks (Tallal *et al*., 1985).

However, most available evidence comes from auditory experiments. In particular, Tallal and Piercy found that children with LLI were impaired in discriminating syllables /ba/ versus /da/ that naturally incorporate 40 ms duration formant transitions (Tallal and Piercy, 1974). However, these same children were unimpaired in discriminating these syllables when formant transitions were artificially expanded from 40 to 85 ms (Tallal and Piercy, 1975).

Tallal and colleagues were able to correctly classify 98% of children as normal or language-impaired on the basis of six variables involving rapid perceptual and production abilities (Tallal *et al*., 1985). Many dyslexics, with or without obvious oral language involvement, also manifest rate processing problems (e.g. Tallal, 1980; Wolff, 1993; Tallal *et al*., 1995; Stein and Walsh, 1997). Farmer and Klein have reviewed five studies, including 10 different experiments involving temporal order judgement in dyslexia, five in the visual modality and five in the auditory modality (Farmer and Klein, 1995). In all studies significant group differences were found, except for one auditory condition (vowels, which acoustically do not incorporate rapid changes) and in one visual experiment (symbols). The same authors also reviewed six studies involving discrimination of stimulus sequences. In nine out of 15 conditions tested, dyslexics were significantly poorer than controls.

During the last few years, the temporal processing theory of dyslexia has been rather severely contested, especially on the basis of the apparent initial confusion between such different concepts as time duration and sequential processing. Thus, Mody and colleagues (Mody *et al*., 1997) designed several studies in order to test the validity of the initial findings of Tallal and Piercy (Tallal and Piercy, 1975). They compared poor and good readers on a similar task using either classical /ba/–/da/ pairs or other pairs presumed to be phonetically more contrasting (/da/–/sa/ and /ba/–/sha/). Only on the former and not on the latter two pairs did dyslexics perform less well than controls, leading the authors to the conclusion that it is the phonetic distance not the temporal order difficulty which is reflected in the dyslexic's poor performance in temporal order judgement tasks.

However, as pointed out by Denenberg, the study by Mody and colleagues suffers from the fact that the statistical power required to challenge previously established evidence may not be reached in this study (Denenberg, 1999). Moreover, the selection of their 'poor reader' group may be misleading, as is the case for several other studies in the literature.

In order to test the validity of a link between temporal processing and phonological deficit, Nittrouer carried out several tasks including a non-verbal sequencing task adapted from that of Tallal and colleagues (Tallal *et al*., 1980) and a 'stop closure detection' task using a discrimination between the words /say/ and /stay/ (Nittrouer, 1999). None of these tasks was found significantly impaired in otherwise severely phonologically affected children.

Other studies have tried to test the temporal processing hypothesis by using artificially modified auditory stimuli. In their study of 15 dyslexic boys and 15 non-dyslexic controls taken from the same school (mean age 15 years 2 months), McAnally and colleagues tested the influence of artificially stretching or compressing synthesized consonant–vowel–consonant (CVC) stimuli on the performance of these children at discriminating between 11 different CVC syllables (McAnally *et al*., 1997). Although dyslexics tended to perform poorly compared with controls, this deficit was found to be independent of the time characteristics of the stimuli. These authors conclude that 'limited exposure of children with dyslexia to time-stretched synthetic CVC syllables did not improve their ability to identify the stimuli correctly'. This result obviously questions the validity of significant results obtained by Tallal and colleagues (Tallal *et al*., 1996) and Merzenich and colleagues (Merzenich *et al*., 1996) with a temporally based remedial method, results which have been partly replicated more recently by our group (Habib *et al*., 1999) [See, however, the work by Bradlow and colleagues (Bradlow *et al*., 1999) discussed in the headed MMN section.] Moreover, we recently obtained preliminary results suggesting that artificially slowing each element of a consonant cluster may improve dyslexic children's ability to discriminate and reproduce the sequence of the two consonants (De Martino *et al*., 2000). Work is still in progress to try and elucidate these apparent inconsistencies.

Other dimensions of the temporal theory

Neurological accounts of dyslexia usually ascribe at least some of the symptoms observed to a left-hemisphere

dysfunction. That the left hemisphere is a good candidate for subserving the role of rapid processing of brief stimuli is also widely admitted (for the most recent evidence, see Belin *et al*., 1998; Liegeois-Chauvel *et al*., 1999). Adult aphasics with acquired left-hemisphere damage are also impaired on rate processing tasks, and the degree of impairment is correlated with the extent of the language impairment (Tallal and Newcombe, 1978). In addition, older adults who often report difficulty understanding speech despite normal hearing, exhibit a temporal sequencing decrement (Trainor and Trehub, 1989). There is, thus, converging evidence to suspect that the left hemisphere is specifically pre-wired to support the function of processing transient sensory events, especially when these events become meaningful through their temporo-spectral characteristics. Therefore, the notion that dyslexia may in fact be a 'dyschronia' (Llinás, 1993) has emerged during the last few years. One group of such studies has concerned the competence of dyslexic children in fine motor skills. The first evidence in this area has come from early studies by Stambak, showing that dyslexic children perform significantly worse than normal in tasks where they have to reproduce a rhythmic tapping sequence (Stambak, 1951). More recently, Nicolson and Fawcett have repeatedly shown that dyslexic children differ significantly even from reading-age controls in tasks involving automation of motor skill, motor reaction times, speed of naming and even in pure body motor balance (Fawcett and Nicolson, 1992, 1994; Nicolson and Fawcett, 1993, 1994). Although initially emphasizing a possibly specific automation defect in dyslexia, these authors currently favour the thesis of a cerebellar involvement, especially in view of evidence of time estimation deficits in dyslexics, a function thought to depend on the activity of the cerebellum (Nicolson *et al*., 1995; Fawcett *et al*., 1996). This position has been reinforced by recent results which Nicolson and colleagues (Nicolson *et al*., 1999) and others (Rae *et al*., 1998) have obtained with functional imaging, both studies showing abnormal metabolism in the right cerebellum in dyslexics.

Finally, in clinical practice, there are numerous circumstances where dyslexic children seem to have trouble with various aspects of temporal processing, well beyond the sole sensory motor level. For instance, it is very usual to find severe delays in time duration awareness, sequential naming problems for concepts pertaining to time (such as the days of a week), errors in time relocation of memories, and vagueness of temporal distance or remoteness appreciation. It is not rare to see a parent of a dyslexic child, who was formerly dyslexic, admitting his or her own persisting problems occasionally emerging when confronted by situations where time constraints have to be handled. Hence, the term dyschronia could apply to dyslexia from more than one point of view. Whether or not these different levels of 'temporal features' impairment are dependent on the same mechanism is not yet known, but represents a reasonable and testable hypothesis.

Contribution of electrophysiological studies to the understanding of the neurology of dyslexia

Recent years have seen a growing use of electrophysiological techniques in research on the neurobiological mechanisms underlying language-learning disorders. As speech processing and reading are complex cognitive skills, entailing several levels of brain organization, these processes can be difficult to differentiate with behavioural measures. Event-related potentials (ERPs) provide sensitive neurophysiological measures of the timing and cortical utilization of different stages of cognitive processing, and thus are well suited for investigations of the levels of cognitive processing required for reading. ERPs have been shown to be valuable in the study of normal cognitive development, as well as in the investigation of cognitive disturbances in childhood (e.g. Martineau *et al*., 1992; Stauder *et al*., 1993; Taylor, 1995). Most studies were devoted to 'classical' electrophysiological events such as mismatch negativity (MMN), P300 and N400 (for a review of peculiarities of ERPs in childhood, see Taylor, 1995). However, some works also described abnormalities of earlier events such as N1, P2 or N2 in dyslexic or LLI children, but these will not be reviewed here.

MMN

The MMN is an ERP characterized by a negative deflection with a frontocentral distribution, that peaks between 100 and 250 ms after stimulus onset. The MMN is thought to be generated in the supratemporal auditory cortex and is elicited in situations where any physically deviant auditory stimulus occurs randomly and infrequently in a series of homogeneous, or standard, stimuli (Näätänen *et al*., 1978). It can be elicited independent of attention and by very small acoustic changes. The MMN therefore reflects an automatic 'change-detection response' (Kraus *et al*., 1995) and may be used to investigate, at a pre-attentive level, whether the auditory system has distinguished between two stimuli.

Using the MMN evoked response, Kraus and her colleagues have obtained evidence suggesting auditory deficits in certain children with learning problems (Kraus *et al*., 1996). Using speech stimuli from two continua (/da/ to /ga/ and /ba/ to /wa/), these authors found that learning-impaired children were poorer in speech discrimination than were normal controls, and that impaired discrimination was correlated with diminished MMNs. In other words, children who were poor at discriminating certain speech contrasts also showed reduced or absent MMNs. The MMN is a correlate of auditory processing at pre-attentive levels, so these findings suggest discrimination deficits in some learning-impaired children originate in the auditory pathways before conscious perception. Several studies using a similar paradigm have consistently shown reduced MMN in learning disordered children (for review, see Leppänen and Lyytinen, 1997). For instance, Schulte-Körne and colleagues presented 12-year-old dyslexics and controls with either language stimuli (85%

standard /da/, 15% deviant /ba/) or pure tones (standard 1000 Hz, deviant 1050 Hz) (Schulte-Körne *et al*., 1998). The MMN response differed between the two groups only for the language stimuli. These results point to a specific deficit of pre-attentive mechanisms for language processes as a possible source of these children's difficulties learning to read. In the perspective of testing the temporal processing hypothesis, Bradlow and colleagues have measured the MMN response to an auditory contrast /da/–/ga/ and found diminished responses in dyslexic children compared with controls (Bradlow *et al*., 1999); yet, when the transition duration of the stimuli was lengthened to 80 ms the dyslexics' response became closer to that of controls. Interestingly, this effect was not present when only the behavioural performance on the same stimuli was recorded, suggesting that the temporal deficit may be too subtle to appear clinically while clearly manifesting through electrophysiological investigation.

Recently, Kujala and colleagues have used the MMN response to test the hypothesis of a basic auditory dysfunction in eight adult dyslexics compared with eight controls (Kujala *et al*., 2000). They contrasted two stimulus conditions, one so-called 'tone-patterned' where four 500 Hz tones were displayed in such a way that the third one was either close to the fourth (standard pattern) or closer to the second tone (deviant pattern). In the other condition ('tone-pair' condition), the stimuli were made of only two tones separated by either 150 (standard) or 50 (deviant) ms. Only in the tone-patterned condition did dyslexics differ from controls, in such a way that the too-early (deviant) tone failed to elicit a MMN in dyslexics, whereas the two groups did not differ in the tone-pair condition. The authors' conclusion was that dyslexic adults have problems in discriminating temporal sound features only when they are 'surrounded by other stimuli, such as phonemes in words'.

Finally, one potentially useful application of this method has been proposed by Leppänen and Lyytinen who compared the MMN in 6-month-old infants with and without familial risk of learning disorder (Leppänen and Lyytinen, 1997). Children genetically at risk displayed reduced MMN amplitudes in the left electrodes only, suggesting a predictive value of this pattern for the later occurrence of dyslexia.

P300

In another group of electrophysiological studies of developmental language impairments, the amplitude and/or latency of the P300 component has been compared. The P300 is elicited in 'odd-ball' tasks where subjects must attend to a train of frequently occurring stimuli and respond at the presentation of a different, infrequent deviant stimulus. This event is related to conscious processing and evaluation of stimuli as well as memory updating. Several studies have reported a smaller or later P300 in developmental dyslexics (Taylor and Keenan, 1990) and in children with attention-deficit disorder (Holcomb *et al*., 1985), suggesting inefficient processing of task-relevant stimuli. Duncan and colleagues found P300 abnormalities among adults with childhood dyslexia only in those also suffering from attention-deficit disorder (Duncan *et al*., 1994). Since attention deficits are present in many dyslexics, it is difficult to determine the respective contribution of the two disorders to the ERP abnormalities (Taylor, 1995).

N400

An anomalous N400 has been observed in many studies of developmental language disorders (Stelmack *et al*., 1988; Neville *et al*., 1993). The results, however, are inconsistent making interpretation difficult. Stelmack and colleagues, for example, found a reduced N400 in dyslexics, which the authors interpreted as a 'failure to engage long-term semantic memory' (Stelmack *et al*., 1988). Other investigators (Neville *et al*., 1993), on the other hand, found an enhanced N400 in language-impaired children. More recent observations (M. Besson, personal communication) suggest that the N400, classically obtained when brain activity is recorded while normal subjects read incongruous sentences ('the mother holds the child in her nostrils') but not with recordings during reading of sentences with congruous endings ('. . . in her arms'), is elicited in dyslexics on congruous endings as well. This would mean that semantic integration could be deficient or more effortful in dyslexics, or, alternatively, that when reading dyslexics use semantic strategies not used by normal readers.

The contribution of brain functional imaging to the neurology of dyslexia

Table 2 summarizes 13 studies published to date in which images of the functioning brain from a group of dyslexics and a group of matched non-dyslexic controls have been compared. It must be noted, first, that most of these studies have involved adults with a past diagnosis of learning disorder mainly affecting reading abilities, so that it is highly difficult to retrospectively ascertain the type and intensity of the disorder. Secondly, these studies did not take into account the diversity of clinical forms of dyslexia and thus are exposed to the possible pitfall of putting together cases with different pathophysiological mechanisms. The variety of imaging methods, from magnetoencephalography to functional MRI (fMRI), as well as multiple techniques and experimental designs even across studies using one method, render fragile any attempt to draw firm conclusions from this overview. However, some important information has been already obtained.

Brain activation during phonological tasks in dyslexics

The first study to use PET and ^{15}O-labelled water in dyslexics was that of Rumsey and colleagues (Rumsey *et al*., 1992).

Table 2 *Summary of studies using various functional imaging techniques in dyslexics*

Study	Method	Subjects	Chronological age in years (SD)	Imaging technique	Functional activation	Results	Conclusions
Rumsey *et al.*, 1987	^{133}Xe inhalation	14 men with severe dyslexia, 14 controls	22.0 (3.5)	Cerebral blood flow measurements, 16 collimated probes on each side of the scalp	Semantic classification task Line orientation task	Increased L>R asymmetry. Reduced anterior to posterior difference	Inadequate bihemispheric integration
Flowers *et al.*, 1991	^{133}Xe inhalation	69 controls (39 males + 30 females) 83 adults with known past learning disabilities 33 dyslexic adults 27 borderline 23 nondisabled	29.8 (7.5) 33.8 (5.7) 33.8 (4.3) 32.2 (5.3)	Cerebral blood flow. 8 detectors on each hemisphere	Verbal memory task. Auditory perception task. Spelling analysis task (indicate for each heard word whether or not it has 4 letters)	Spelling task: hypoactivation in the left superior temporal region. Hyperactivation in a more posterior temporoparietal region	Dyslexics may use a different strategy due to structural inefficiency in Wernicke's area
Gross-Glenn *et al.*, 1991	[^{18}F]FDG-PET	11 adult dyslexics (all males) 14 controls (all males)	30.3 (8.3) 27.6 (6.4)	Regional cerebral metabolic values. 32 regions in each hemisphere	Serial word reading during 30 min, one every 5 s	Bilateral hyper-activation lingual gyrus (controls more leftward asymmetry). Relative right frontal hypoactivation, controls more rightward asymmetry	Location of alteration is different from that of classical acquired dyslexia, suggesting different mechanisms
Hagman *et al.*, 1992	[^{18}F]FDG-PET	10 dyslexic adults, 10 matched controls	39.1 (11.0) 35.3 (10.0)		Identify the target syllable 'da' within a series of 6 different stop consonant-vowel syllables	Bilateral increase in metabolism in medial temporal regions	More effortful processing in dyslexia. Suggest involvement of fibres connecting internal and lateral (auditory) aspects of the temporal lobes
Rumsey *et al.*, 1992	$H_2{}^{15}O$-PET	14 dyslexics 14 controls	27 (5) 26 (5)	ROI method 49 regions analysed	Rhyme detection task (experimental task). Control task: discrimination of intensity of a simple tone	Failure to activate left posterior temporal and inferior parietal regions. Hyperactivation in right temporal cortex	Support the hypothesis of left temporoparietal dysfunction
Rumsey *et al.*, 1994*a*	$H_2{}^{15}O$-PET	15 dyslexics 20 controls	27 (5) matched	Idem	Listening to pairs of sentences differing in grammatical construction, but indicating whether or not they have the same meaning.	Reduced blood flow at rest in left temporoparietal cortex. Activation in anterior language regions not different from controls	
Rumsey *et al.*, 1994*b*					Listening to paired sequences (3–4 tones), had to indicate which were identical	Reduction of normal right frontotemporal hyperactivity	Dyslexics may have more widespread deficits also involving circuits in right frontotemporal region
Paulesu *et al.*, 1996	$H_2{}^{15}O$-PET	5 dyslexics 5 controls	25.2 (1.5) 27.2 (2.2	Whole-head PET scanning, analysis with SPM software	2 experimental tasks involving subvocal rehearsal of series of letters: (a) Rhyming task (subparticulation, no memory); reference task: shape similarity with Korean letters; (b) Memory task (subarticulation, keeping sounds in immediate memory); reference task: visual short-term memory with Korean letters	(a) Normal: left perisylvian zone including precentral, areas 44 inf and 45, sup. temp. gyrus; dyslexics: anterior part only. (b) Left perisylvian, wider zone in temporoparietal region, including parietal operculum. Dyslexics: posterior part only (Heschl's gyrus and parietal operculum)	In both tasks insular cortex thought to be crucial to convert non-segmented phonology (Wernicke's area) into segmented phonology (Broca's area). Inf. parietal region may correspond to phonological store, implicated in memory task. Dyslexia may result from disconnection between posterior and anterior language areas

Table 2 *continued*

Study	Method	Subjects	Chronological age in years (SD)	Imaging technique	Functional activation	Results	Conclusions
Eden *et al.*, 1996*a*	fMRI	6 dyslexics 8 controls	25.5 (6.2) 26.8 (6.2)	BOLD 1.5 MRI apparatus 30 5-mm contiguous, coronal slices	Reference task: fixation of a central cross. Motion task (magno-stimulus): low contrast array of black dots on a grey background all moving in the same direction. Pattern task (parvo-stimulus): stationary, high contrast patterned stimulus	Controls: bilateral motion sensitivity in the region V5/MT. Dyslexics: 5: no activation in this region. 1: unilateral activation. No group difference for stationary pattern	Dyslexics fail to activate motion area V5/MT. This finding provides neurophysiological basis for the M-cell system perceptual deficit in dyslexia. Could be one manifestation of a basic disorder in the processing of temporal properties of stimuli
Salmelin *et al.*, 1996	MEG	6 dyslexics (3 males + 3 females), 8 controls (4 males + 4 females)	19–35 years 18–37 years	Whole-head MEG 122 SQUID sensors	Finnish words and non-words presented for 300 ms every 3 s	Dyslexics fail to activate a left inferior temporo-occipital region normally responding 180 ms after presentation of words. Left inferior frontal lobe activates within 400 ms in 4/6 dyslexics and no controls	Corresponds to impaired perception of visual word form. Could result from compensatory silent articulation of the misperceived visual word form
Rumsey *et al.*, 1997*b*	$H_2{}^{15}O$-PET	17 right-handed dyslexic men, 14 matched controls	18–40 years mean 27 (8)	Whole-head PET scanning. Statistical analysis with SPM	One visual fixation control task and 4 experimental tasks divided into 'phonological' and 'orthographic'. 2 pronunciation tasks: read pseudo-words (phonological) and read irregular words (orthographic). 2 decision-making tasks: which one of 2 written pseudowords (e.g. 'bape'-'baik') sounds like a real word (phonological) and which one of 2 written forms of a real word ('hoal' or 'hole') is correct (orthographic).	Globally 30% more voxels activated and 50% more voxels deactivated in dyslexics as in controls. Pronunciation tasks: reduced activations and unusual deactivations in bilateral temporal mid- to posterior temporal cortex + left inferior parietal cortex. Decision making tasks: no significant differences between dyslexics and controls	Diffuse extension of activated and deactivated areas is related to greater difficulty of tasks in dyslexics compared with controls. Overall differences in magnitude rather than location in the comparison between phonological and orthographic versions of the tasks may be due to common mechanism underlying the deficit in dyslexics
Demb *et al.*, 1997, 1998	fMRI	5 dyslexics (3 males + 2 females), 5 controls (3 males + 2 females)	22.2 (2.9) 26.8 (6.1)	BOLD on 1.5 T scanner. 8 adjacent 4-mm slices centred on the occipital region. Retinography measurements on computationally flattened representations of each brain + psychophysical measures of M-pathway functioning (speed discrimination thresholds) + 5 reading measures	Visual stimulation in conditions 'known to preferentially stimulate M-pathways' (especially low luminance level, moving gratings) as opposed to control stimuli 'designed to elicit strong responses from multiple pathways' + a separate study similar to moving dots experiment in Eden *et al.* (1996)	fMRI responses in both V1 and MT+ are lower in dyslexics across the full range of contrasts explored, with larger differences at higher contrasts, especially in V1. Strong negative correlation between MT+ activity and discrimination thresholds. Weaker but significant correlation for V1 (both dyslexics and controls). Strong correlation between MT+ activity in M-condition and reading speed (both dyslexics and controls)	There is a strong 3-way correlation between V1 and MT+ brain activity, speed discrimination thresholds and reading speed

Table 2 *continued*

Study	Method	Subjects	Chronological age in years (SD)	Imaging technique	Functional activation	Results	Conclusions
Shaywitz *et al.*, 1998	fMRI	29 dyslexics (14 men, 15 women), 32 normal readers (16 men, 16 women	16–54 years 18–63 years	1.5 T echo-planar imaging 9-mm slices, 17 brain ROI 'that previous research had implicated in reading and language'	5 tasks ordered hierarchically: line orientation judgement, letter-case judgement, single letter rhyme, non-word rhyme, semantic category judgement	Group/task interaction in 4 ROI: posterior STG (Wernicke's area), angular gyrus (BA 39), striate cortex (BA 17), IFG (Broca's area) and marginally in 2 more regions: inferior lateral extra-striate and anterior inferior frontal. Relative increase of activation in phonological versus orthographic tasks is greater in posterior regions (areas 21, 40, 39, 37) in normal readers and in anterior regions (BA 44–47 and 11) in dyslexics	Dyslexics demonstrate a functional disruption in an extensive system in posterior cortex encompassing both traditional visual areas and traditional language regions, a portion of association cortex. Overactivation even for the simplest phonological tasks in Broca's area in dyslexics is consistent with the role of this area in phonological processing and probably represents increased effort in performing these tasks
Horwitz *et al.*, 1998	$H_2{}^{15}O$-PET	17 right-handed dyslexics, 14 normal readers all males	27 (8) 25 (5)	Spatial normalization into stereotactic space (Talairach and Tournoux). Calculation of inter-regional correlations within each condition between one voxel representative of the angular gyrus and all other brain voxels	Pseudoword reading task (read aloud), exception word reading task (read aloud) self-paced on a computer screen	(1) Pseudoword reading large correlations between left angular gyrus and temporo-occipital extra-striate areas including motion area (V5/MT), lingual and fusiform gyri, inferior frontal (BA 45) superior temporal (BA 22). (2) Exception word reading: idem for extrastriate, just miss significance for Wernicke's and Broca's areas. Dyslexics: all correlations absent or much less marked	Suggest functional disconnection of left angular gyrus from Wernicke's area and inferior frontal cortex.

ROI = region of interest; STG = superior temporal gyrus; IFG = inferior fusiform gyrus; BOLD = blood-oxygen level dependent; MEG = magnetoencephalography.

However, this study (as well as two more from the same group, see Table 2), used a region of interest method for analysis which limits the scope of the results since it is always possible to overlook a peak of activation situated outside chosen regions with this method. Moreover, since the choice of regions of interest is dictated by preconceived ideas, the outcome of such studies is inevitably weakened by a risk of tautology. However, the results were important and have served as a basis for subsequent studies.

Fourteen adult dyslexics and 14 control subjects performed a rhyming task in which they had to press a button each time two words, within a pair presented binaurally through headphones, were judged to rhyme. Rhyming tasks are classically thought to explore some aspects of phonological awareness. To achieve such a task, subjects must concentrate on the sound form of the word endings, keep them in short-term memory and compare them according to phonological similarity. Such a task is especially difficult to perform for adult dyslexics who usually compensate by trying to resort to visual-orthographic mechanisms. For instance, non-rhyming pairs such as 'shoe'/'toe', that are orthographically similar, and others such as 'head'/'said' which rhyme but are orthographically dissimilar are particularly puzzling for many dyslexics, showing high error rate in this task. In the study by Rumsey and colleagues, the task is made intentionally easy by avoiding such conflicting pairs (Rumsey *et al*., 1992). The main result is that dyslexics fail to activate a 'left temporoparietal region' activated in controls performing the task. Moreover, an interaction between group and condition for the left inferior and right anterior frontal regions was suggested in that dyslexics showed a trend to relative deactivation in these regions, whereas controls showed a non-significant increase in activity. Finally, dyslexics showed an activation compared with controls in a right-middle temporal region. From these results, the authors conclude that the main dysfunctional region in dyslexia is situated in the temporal cortex of the left hemisphere, and that this defect is related to their core phonological deficit.

The first ^{15}O PET study of dyslexics using whole-brain scanning and voxel-based analysis is that of Paulesu and colleagues (Paulesu *et al*., 1996). These authors used the same experimental paradigm as in a previous study (Paulesu *et al*., 1993) comparing a rhyming and a memory condition. When subjects have to remember six letters successively flashed on a screen ('memory' condition), they try to pronounce them subvocally, in order to put them in the auditory phonological store postulated in classical models of working memory (Baddeley, 1986). In another ('rhyming') condition, previously used by Sergent and colleagues (Sergent *et al*., 1992), subjects pronounce letters mentally, but uniquely this task has no memory requirement and consists of a decision whether the name of a letter rhymes with a target letter 'b' ('b' rhymes with 'c', not with 'h'). In normal individuals, both conditions activate a large perisylvian area, including Broca's and Wernicke's areas, whereas parietal operculum activation is specific to the memory condition.

Paulesu and colleagues found a specific pattern of activation in their five dyslexics, compared with five controls (Paulesu *et al*., 1996). In the memory task, dyslexics showed blood flow increases only in the posterior part (inferior parietal cortex) of the large perisylvian area activated in controls, whereas in the rhyming task, these patients only activated its anterior part (Broca's area). The common finding with both tasks was the absence of activation of insular cortex. This led the authors to an interpretation of dyslexic deficits in terms of disconnection between anterior and posterior zones of the language area. Since such impaired activation of the insular cortex has not been replicated by other functional imaging studies of dyslexics, this hypothesis awaits further evidence. Likewise, most studies published to date have shown increased rather than reduced activity close to Broca's area during phonological tasks in dyslexics. However, the finding of reduced left superior temporal activation is consistent with other more recent studies (see below). Finally, the disconnection hypothesis has gained additional credence following a recent study (Horwitz *et al*., 1998) showing that some areas, especially the angular gyrus, fail to co-activate in dyslexics.

Brain functional anatomy of reading in dyslexia

Three important functional imaging studies of reading in dyslexics have been reported in the last few years, one using the PET method with ^{15}O radiotracer, the second one using fMRI, and the third (historically the first), with magnetoencephalography.

Comparing 17 right-handed dyslexics and 14 controls, Rumsey and colleagues performed a PET study which, unlike their previous studies, used a voxel-based whole-brain imaging technique (Rumsey *et al*., 1997*b*). The main objective of their study was to try to contrast orthographic and phonologic processes in reading. This was done using two different paradigms, one named 'pronunciation', where participants had to read aloud pseudowords (presumably relying on phonological processing) and irregular words (calling for orthographic processing). The other group of tasks, called 'decision making tasks', consisted of having participants read two words or non-words with either a phonological instruction (decide which one of two non-words sounds like a real word) or an orthographic one (decide which of two homophone forms of a same word is correctly spelled). Besides differences in the global volume of activation between the two groups (more brain tissue activated in dyslexics), the only significant changes observed in dyslexics were reduced activations and unusual deactivations in left posterior temporal/inferior parietal areas, in the 'pronunciation' paradigm. The authors comment on the absence of any difference between the locations of brain activation with the word and non-word versions of the tasks, which could result, they suggest, from a common mechanism for both kinds of reading errors in dyslexia. Finally, in another report of the same experiment (Rumsey *et al*., 1999),

these authors show that activation in only one region, the left angular gyrus, was correlated with reading skill, and that the direction of this correlation was opposite in controls (positive) and dyslexics (negative correlation). They conclude from this result that the left angular gyrus is 'the most probable site of a functional lesion in dyslexia'.

With fMRI, using imaging parameters that were not optimal (9-mm thick slices, 17 regions of interest 'that previous research had implicated in reading and language'), Shaywitz and colleagues proposed to 29 dyslexics and 32 controls a complete series of tasks tapping various levels of processing in reading: a line orientation judgement task, presumably exploring low-level perceptual mechanisms; a letter-case judgement, presumed to reflect orthographic mechanisms; a single letter rhyme and a non-word rhyme task, exploring the phonological level of processing; and a semantic category judgement task (Shaywitz *et al*., 1998). The main result was that in normals there was relative overactivation with phonological tasks (in comparison with orthographic ones) in posterior regions [posterior temporal, Brodmann area (BA) 21; supramarginal and angular gyri, BA 39 and 40; and inferior lateral temporal region, BA 37], and a reversed pattern (greater anterior than posterior activation when contrasting phonological and orthographic processing) in dyslexics. The authors propose a general explanation for posterior hypoactivation in dyslexics, that it is 'due to actual disruption in a system in charge of phonological processes', whereas Broca's area hyperactivation reflects 'increased effort required of dyslexics in carrying out phonological analysis'.

Finally, probably the most informative study on brain functioning during reading tasks in dyslexics is that of Salmelin and colleagues (Salmelin *et al*., 1996). These authors used the method of magnetoencephalography to compare six dyslexics and eight controls on various reading tasks involving Finnish words and non-words presented for 300 ms every 3 s. Since this method provides only an approximate location for the presumed sources of recorded signal, one must remain cautious about information on the actual brain regions involved. However, the remarkable temporal resolution of the method makes it a valuable complement to other imaging methods, which can only provide information about processes occurring within a period of time of several seconds. Whereas normal controls activated a left inferior temporo-occipital region 180 ms after the presentation of words, dyslexics totally failed to activate this same region. Moreover, a left inferior frontal area activated within 400 ms in four out of six dyslexics, but in none of the controls.

This result is of great importance because it clarifies data obtained by other methods whose interpretation had remained obscure. For instance, the inferior temporo-occipital activation is reminiscent of activation of BA 37 found in several studies. Since it appears as early as 180 ms after the presentation of a word, it is likely to represent early visual processing or immediate phonological processing occurring before any conscious recognition has occurred. That dyslexics do not activate this process suggests either an inability to achieve these early operations of global word-form perception or inefficient immediate phonological extraction. On the other hand, abnormal activity in Broca's area could result from compensatory silent articulation of a misperceived visual word form. These results thus provide information about the time course of reading in two areas already suspected to be dysfunctional in dyslexia, allowing a more complete discussion of their role.

A recent study by Brunswick and colleagues using ^{15}O-PET to investigate explicit and implicit reading in dyslexic adults and normal readers came to similar conclusions (Brunswick *et al*., 1999). In both reading conditions, dyslexics activated two regions to a lesser degree than controls: left basal temporal lobe (area 37) and left frontal operculum. In the explicit reading condition, they overactivated a left pre-motor region situated 20 mm lateral to the area of reduced activation. This finding confirms that Broca's area is one of the most important brain regions at the origin of the learning impairment in dyslexics, but that this important role is probably not unique, since different cortical zones within this anatomical region display different patterns of functional activation. Involvement of Broca's area is reminiscent of the above-mentioned evidence of motor-articulatory deficit in dyslexia (Heilman *et al*., 1996).

Using the same inclusion criteria as in Brunswick's study, we recently conducted a parallel study in French-speaking dyslexics and matched controls (J. F. Démonet *et al*., unpublished results). The only region to show greater activation in controls than in dyslexics on reading tasks was precisely the left inferior temporal region, exactly at the junction between lateral and mesial aspects of the temporal lobe. It is noteworthy that this region is ideally located to serve as an interface between areas associated with processing visual features of written words (especially the more mesial extrastriate cortex), other temporo-occipital regions involved in complex visual processing (including the motion area which is in close vicinity), and more dorsal language areas in the middle and superior temporal gyri, possibly subserving grapheme-to-phoneme transformation. One plausible role which could be attributed to this crucial region could be that of mediating the visual entry into the linguistic system, combining orthographic, lexical and phonological information about words. Unpublished observations show that this region also activates with stimuli given in the auditory modality when subjects have to perform an orthographic computation on the heard words. Such data are also compatible with this formulation. Finally, the same region has been found activated with Japanese kanji characters, suggesting that its role is probably more orthographic than phonologic (Uchida *et al*., 1999).

fMRI study of motion perception in dyslexia

By reference to theories based on psychophysical and electrophysiological evidence of a deficit in the magnocellular component of the visual pathways, Eden and colleagues

designed an fMRI experiment contrasting two visual conditions that differentially activate the magnosystem and the parvosystem (Eden *et al*., 1996*a*). The experimental condition (M-stimulus) consisted of a moving dot task, where participants had to look passively at an array of dots moving on a computer screen. In the reference task (P-stimulus), they had to look at a stationary pattern. The first condition is supposed to activate the magnosystem preferentially, especially the human area V5 (MT) which has been shown in earlier experiments to be in the posterior part of the inferior temporal sulcus. As expected, normal controls activated this area bilaterally with the M-stimulus, but not with the P-stimulus, whereas dyslexics failed to activate this region even in the moving-dot condition. The authors' conclusion is that their data provide a direct demonstration of a magnocellular deficit in dyslexia, which could be one manifestation of a basic disorder in the processing of temporal properties of stimuli (Eden *et al*., 1996*b*).

Demb and colleagues have replicated these findings in five adult dyslexics with a similar fMRI method, but with localization of the different areas by a more accurate technique that uses computational flattening of each brain (Demb *et al*., 1997, 1998). Speed discrimination thresholds were measured psychophysically for each participant to determine as accurately as possible the efficiency of the magnocellular pathway. Finally, five reading tasks were administered in order to evaluate the impact of the magnodefect on reading performance. Stimuli were low luminance level, moving gratings, known to preferentially stimulate M-pathways, as opposed to control stimuli 'designed to elicit strong responses from multiple pathways'. The results showed that fMRI responses in both V1 and MT+ were less in dyslexics across the full range of contrasts explored, with larger differences at higher contrasts, especially in V1. Moreover, there was a strong negative correlation between MT+ activity and discrimination thresholds, as well as a weaker but significant correlation for V1 (in both dyslexics and controls). Finally, a strong correlation was found between MT+ activity in the M-condition and reading speed (in both dyslexics and controls).

Taken together, these results obtained in the visual modality in dyslexics have been suggested as a potential brain marker for dyslexia (see, however, Vanni *et al*., 1997 for negative results with magnetoencephalography). However, it must be noted that neither Eden and colleagues (Eden *et al*., 1996*a*) nor Demb and colleagues (Demb *et al*., 1998) have characterized their dyslexic adults by the neuropsychological form of dyslexia. For instance, it would have been interesting to know whether pure phonological dyslexics, with a prevalent grapheme-to-phoneme conversion deficit, are more or less impaired in their ability to activate their visual motion area. On the other hand, it would be important to know whether magnocellular impairment impinges specifically on the possibility of using global, whole-word strategies in reading, which could suggest a causal link between the perceptual deficit and learning disorder. On the contrary, if even purely phonological dyslexics fail to activate their motion area, this could mean that both visual deficit and phonological impairment stem from a common mechanism, as, for example, suggested by the temporal processing theory.

The temporal processing deficit theory: a working hypothesis and perspectives for remediation

As mentioned above, although sometimes criticized (Studdert-Kennedy and Mody, 1995; Mody *et al*., 1997; Nittrouer, 1999), the temporal processing theory remains one of the most attractive—although largely speculative—explanations available to date that accommodates the clinical and neuropsychological complexity and diversity of dyslexia, as well as the neurological and physiological data. Moreover, it represents a plausible basis for trying to reconcile data obtained from the neuropsychological approach, pointing to a phonological deficit, and those demonstrating a visual impairment. Although the population covered by the term 'dyslexic' may seem rather heterogeneous (some having mainly phonological problems, some not, some suffering from motor clumsiness, others being excellent at all kinds of motor tasks, some clearly performing poorly on spatial tasks, others managing beyond the average performance of non-dyslexic subjects), it remains tempting and clinically intuitive to try and explain all these cases, including some falling outside the strict definition of dyslexia, through a unique general framework. The temporal theory potentially offers such a useful framework. I will propose here that, beyond the sole sensory-motor dimension of such evidence, the temporal processing theory would be extended to other more cognitive characteristics of the dyslexic's brain functioning.

Difficulties for processing time in its different dimensions is an amazingly universal characteristic of the dyslexic individual. Thus, it is plausible that a general difficulty for the brain (most probably in the left hemisphere) is to integrate rapidly changing stimuli. Such a difficulty could account for (i) an impaired perception of transient auditory stimuli, such as consonants; (ii) a deficit in generation or judgement of temporal order; and (iii) deficits in multiple stages of reading that utilize rapid processing, e.g. visuospatial letter arrangement, global word-form perception, integration of successive relative word positions during oculomotor scanning. In this context, the central feature of phonological awareness could appear as a typically sequential activity requiring at the same time intact phoneme representation, efficient temporal processing of the phonemic constituents and adequate maintaining of information in short-term memory.

Even apparently more complex cognitive functions, such as awareness of time passing, processing of sequences of successive events or duration judgement, also probably necessitate intact temporal coding of information. Therefore, in the absence of a satisfactory explanation for such common findings in dyslexics, which can be formulated in terms of

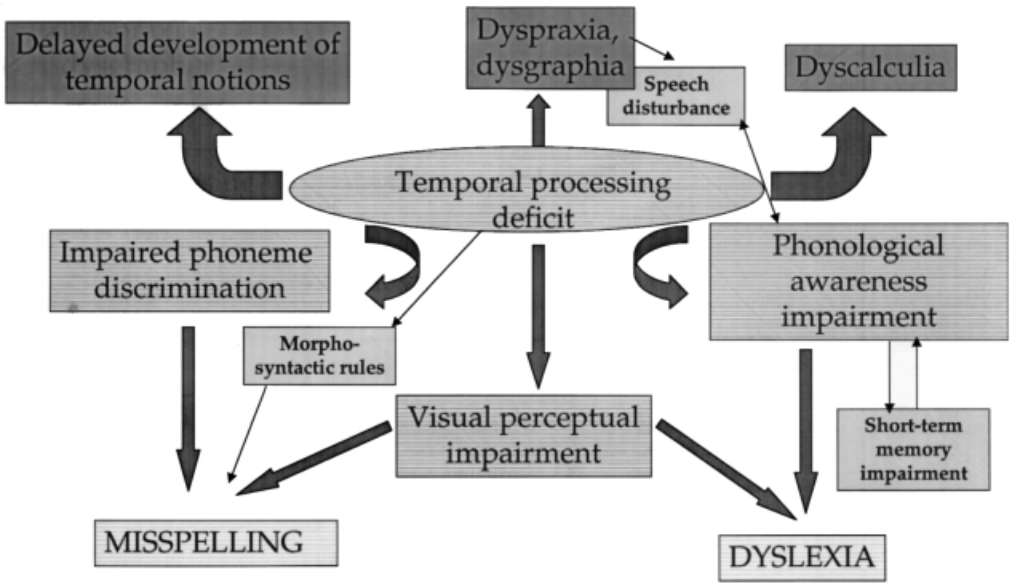

Fig. 1 A postulated mechanism for dyslexia and associated developmental disorders.

impaired or delayed 'temporal notions', one can reasonably hypothesize that they also stem from a developmental deficiency in the brain networks devoted to various aspects of time coding. It is also conceivable that developmental dyscalculia, which is often associated with severe forms of dyslexia, may implicate such time processing-dependent cognitive processes: the concept of number (Spelke and Dehaene, 1999), including the mental representation of quantities, may rely heavily on integration of sequential processing into a more abstract form, and thus require adequate temporal coding of numerical information. Finally, fine motor coordination, as exemplified in bimanual rapid alternation tasks (Wolff *et al*., 1990*b*; Wolff, 1993) or more specifically in graphomotor gestures, probably relies on such time-dependent mechanisms and thus on time-coding brain structures, if they exist. The often associated occurrence of dysgraphia may therefore be accounted for in this context (although the reason why some even severe dyslexics may have normal graphic abilities remains obscure). It is not trivial to remark that such general motor coordination impairment has also been suspected as underlying articulatory deviance observed in dyslexics' oral productions (Wolff *et al*., 1990*a*). Automation of orthographic rules, whose impairment is the almost inevitable outcome of all types of dyslexia, may itself require intact sequential processing to first build an efficient phoneme–grapheme correspondence procedure, and then achieve adequate mastering of the morphosyntactic features of one's native language, since syntax itself is eminently dependent on temporal integration of successive events, although to a variable extent in different languages. Figure 1 illustrates how different elements of the dyslexic syndrome may tentatively be accounted for by a general temporal coding deficit.

From a neurobiological point of view, one may speculate that the dyslexic brain, perhaps due to abnormal maturational neuronal migration and assembly and/or connectivity, especially in the left-hemisphere language areas, is normally unable to hold any kind of functions requiring temporal simultaneity and/or coordination between even remote neuronal zones. Synchrony of activity between groups of neurons is viewed as one of the fundamental features of electrical activity of the brain (Llinás, 1993). Furthermore, it is possible that the same general brain property is also responsible for processing all kinds of brain signals whose significance relies on their temporal characteristics. Moreover, such temporal coordination of activity in different, even remote, cortical regions probably requires control from one or more 'pacemaker' structures able to homogenize spontaneous or evoked activity in groups of neurons normally functioning in concert. Anatomically, the cerebellum appears as one of the best candidates to carry out this task, since spontaneous rhythmic activity and remote propagation of this activity has been clearly demonstrated there (Llinás, 1993; Ivry, 1997). Recent evidence of reduced cerebellar activity in dyslexics performing a motor learning task (Nicolson *et al*., 1999) provides an interesting basis for further testing of this hypothesis in normal readers and dyslexics.

Other contributing evidence has also been obtained from neuroimaging in normal readers. Fiez and colleagues have shown that activation of Broca's area is obtained in a similar way when subjects have to listen to consonants and rapid non-verbal stimuli, but not when they listen to steady-state vowels without rapid acoustic changes (Fiez *et al*., 1995). Belin and colleagues have used auditory activation with PET to show that non-verbal sounds containing rapid (40 ms) or extended (200 ms) frequency transitions yield different patterns of activation in the auditory cortex, bilateral symmetry for slow-transition stimuli and left unilateral activity for rapid transitions (Belin *et al*., 1998). Similar experiments in dyslexics would certainly provide valuable

information about the temporal processing hypothesis in dyslexia and are currently in progress. For example, it is important to know whether or not dyslexics recruit different brain areas or a different amount of brain tissue depending on the temporal properties of a speech or non-speech signal. Magnetoencephalography, due to its excellent temporal resolution, may be an ideal tool for this purpose (Nagarajan *et al*., 1999). Finally, such functional imaging studies in dyslexics, that have only been performed for the moment in adults, could be of great value in children, especially as neurobiological markers of therapy efficacy, for example, in relation to the recently proposed training methods using acoustically modified speech to improve temporal processing deficits in dyslexics (Merzenich *et al*., 1996; Tallal *et al*., 1996; Habib *et al*., 1999).

In the context of the hypothesis discussed above, it would be of great interest to seek a relationship between the degree of temporal processing impairment at the most basic level and patterns of temporal impairment at a cognitive level, and to evaluate the efficiency of training methods on each of these levels. Obviously, however, one important issue for future research will be to try and understand why a supposedly common basic temporal deficit yields such different manifestations and why these manifestations are so variable in their association with the reading impairment.

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