As but one example, the complex multisubunit transmembrane enzyme cytochrome c oxidase, whose structure has been recently deduced at the atomic level[27], forms a variety of potential water and proton channels in clefts lined by various turns and loops. Even more apt examples of design homology are certain to emerge as the crystal structures of more and more transmembrane proteins, hopefully including ion channels themselves, are successfully resolved.

Concluding remarks

Emerging insights into the function and structure of ion channels support a convergence with classical enzymes. Ion channels catalyse the flux of ions across the cell membrane, and therefore perform the essential function of an enzyme. The structural underpinnings of the catalytic function of ion channels are broadly comparable to those in the active sites of conventional enzymes. The frequency of loops in active site clefts and channel pores enables the design flexibility required for substrate recognition and ion selectivity. Mechanisms of conductance and selectivity differ from ion channel to ion channel[1], yet the loop motif features prominently in the pores of many channels[28]. Likewise, active site clefts and loops are a recurrent structural paradigm in a variety of enzymes that have very different catalytic mechanisms. From these considerations, the functional similarities between enzymes and channels appear to reflect homologous structural design principles.

Selected references

1 **Hille, B.** (1992) *Ionic Channels of Excitable Membranes*, pp. 341–346, Sinauer Associates
2 **Fersht, A.** (1985) *Enzyme Structure and Mechanism* (2nd edn), pp. 121–154, W.H. Freeman
3 **Stryer, L.** (1995) *Biochemistry* (4th edn), W.H. Freeman
4 **Wierenga, R.K. *et al.*** (1991) *Proteins* 10, 33–49
5 **Stuckey, J.A. *et al.*** (1994) *Nature* 370, 571–575
6 **Branden, C. and Tooze, J.** (1991) *Introduction to Protein Structure*, Garland Publishing
7 **Eisenman, G.** (1962) *Biophys. J.* 2, 259–323
8 **Mullins, L.J.** (1959) *J. Gen. Physiol.* 42, 817–829
9 **Tomaselli, G.F., Backx, P.H. and Marban, E.** (1993) *Circ. Res.* 72, 491–496
10 **Sather, W.A., Yang, J. and Tsien, R.W.** (1994) *Curr. Opin. Neurobiol.* 4, 313–323
11 **Guy, H.R. and Durell, S.R.** (1994) in *Molecular Evolution of Physiological Processes* (Fambrough, D., ed.), pp. 197–212, Rockefeller University Press
12 **Chiamvimonvat, N. *et al.*** (1996) *Neuron* 16, 1037–1047
13 **MacKinnon R. and Yellen, G.** (1990) *Science* 250, 276–279
14 **Yellen, G. *et al.*** (1991) *Science* 251, 939–942
15 **Heinemann, S.H. *et al.*** (1992) *Nature* 356, 441–443
16 **Backx, P.H. *et al.*** (1992) *Science* 257, 248–251
17 **Satin, J. *et al.*** (1992) *Science* 256, 1202–1205
18 **Yang, J. *et al.*** (1993) *Nature* 366, 158–161
19 **Stevens, C.** (1991) *Nature* 349, 657–658
20 **Guy, H.R. and Seetharamulu, P.** (1986) *Proc. Natl. Acad. Sci. U. S. A.* 83, 508–512
21 **Lipkind, G. and Fozzard, H.** (1994) *Biophys. J.* 66, 1–13
22 **Lü, Q. and Miller, C.** (1995) *Science* 268, 304–307
23 **Kürz, L. *et al.*** (1995) *Biophys. J.* 68, 900–905
24 **Pérez-García, M-T. *et al.*** (1996) *Proc. Natl. Acad. Sci. U. S. A.* 93, 300–304
25 **Benitah, J-P. *et al.*** (1996) *Soc. Neurosci. Abstr.* 22, 63
26 **Sussman, J.L. *et al.*** (1991) *Science* 253, 872–879
27 **Tsukihara, T. *et al.*** (1996) *Science* 272, 1136–1144
28 **MacKinnon, R.** (1995) *Neuron* 14, 889–892

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PERSPECTIVES

To see but not to read; the magnocellular theory of dyslexia

John Stein and Vincent Walsh

Developmental dyslexics often complain that small letters appear to blur and move around when they are trying to read. Anatomical, electrophysiological, psychophysical and brain-imaging studies have all contributed to elucidating the functional organization of these and other visual confusions. They emerge not from damage to a single visual relay but from abnormalities of the magnocellular component of the visual system, which is specialized for processing fast temporal information. The m-stream culminates in the posterior parietal cortex, which plays an important role in guiding visual attention. The evidence is consistent with an increasingly sophisticated account of dyslexia that does not single out either phonological, or visual or motor deficits. Rather, temporal processing in all three systems seems to be impaired. Dyslexics may be unable to process fast incoming sensory information adequately in any domain.

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PERHAPS 15% of normally intelligent boys and 5% of girls fail to learn to read and write as well as would be expected from their general intelligence (specific reading disability, SRD). Learning to read and write taxes our perceptual abilities to the limit – far more than learning to talk. It requires finer visual, auditory and manual skills than almost anything else most of us learn. A sequence of small, minimally redundant, visual symbols must be discriminated and translated into the phonemic sequence of sounds that

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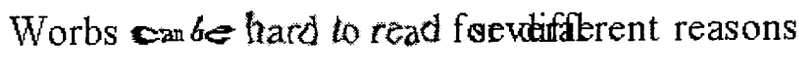


Fig. 1. ***Words can be hard to read for several different reasons.*** *Visual confusions can cause letter reversals ('worbs'), distortion and blurring ('can be hard to read') and superimposition ('for several different').*

comprise each word. It is now clear that a major cause of reading problems is poor ability at distinguishing these phonemes, so that SRD children tend to confuse sounds such as s, sh, th, f and v. Thus, they are significantly worse than controls at discriminating phonemes; young children's phonological skills at the age of five predict their future reading progress, and phonological training speeds their learning to read[1].

However, their problems with phonology do not explain the plethora of other problems that children with specific reading difficulties suffer. They tend to transpose letters ('was' for 'saw', 'god' for 'dog') and produce phonologically implausible non-word guesses, which seem to result from visual confusions (Fig. 1)[2]. They are often remarkably clumsy, with poor balance and delayed motor milestones such as crawling, walking and learning to ride a bicycle[3,4]. Characteristically they have temporal sequencing problems, such as ordering their lives, learning to tell the time, remembering the days of the week, or months of the year. Likewise they are poor at spatial sequencing, having great difficulty with map reading and telling left from right, and failing to become consistently right- or left-handed, together with other signs of weak establishment of lateral dominance[5]. There is often a strong family history and an association with allergies[6]. Recently genetic linkage of SRD with the human leukocyte antigen (HLA) region on the short arm of chromosome 6 has been found[7]. Magnetic resonance imaging has shown that the planum temporale cortical language area, which is normally larger in the left hemisphere than in the right, is symmetrical or even larger on the right than the left in many people with SRD (Ref. 8). In post-mortem brains from severe cases of SRD, abnormal ectopias and microgyrias have been found all over the cerebral cortex, and especially in the temporoparietal association areas[9]. It is clear therefore that specific reading disability is but part of a more general congenital neurological abnormality; hence the neurological term 'developmental dyslexia' is a more appropriate description.

Before the phonological disability of dyslexics was understood it was generally agreed that their reading difficulties were most likely to be the result of a visual-processing defect. In the late 19th century, acquired loss of reading ability was described as 'word-blindness' by Kussmaul. Exactly 100 years ago, Pringle Morgan published the first description of an inability to learn to read in Percy, an otherwise highly intelligent boy[10]; Morgan clearly thought Percy's problems were visual, as he described him as congenitally word-blind. Likewise, in the 1920s Samuel Orton used the term strephosymbolia (twisted signs) to describe his theory that unstable cerebral dominance in developmental dyslexics led to unstable visual representations of letters and their order[5]. Although the evidence in favour of the phonological weakness of dyslexics has dominated the scene recently, it does not diminish the importance of the visual perceptual problems that many dyslexics report.

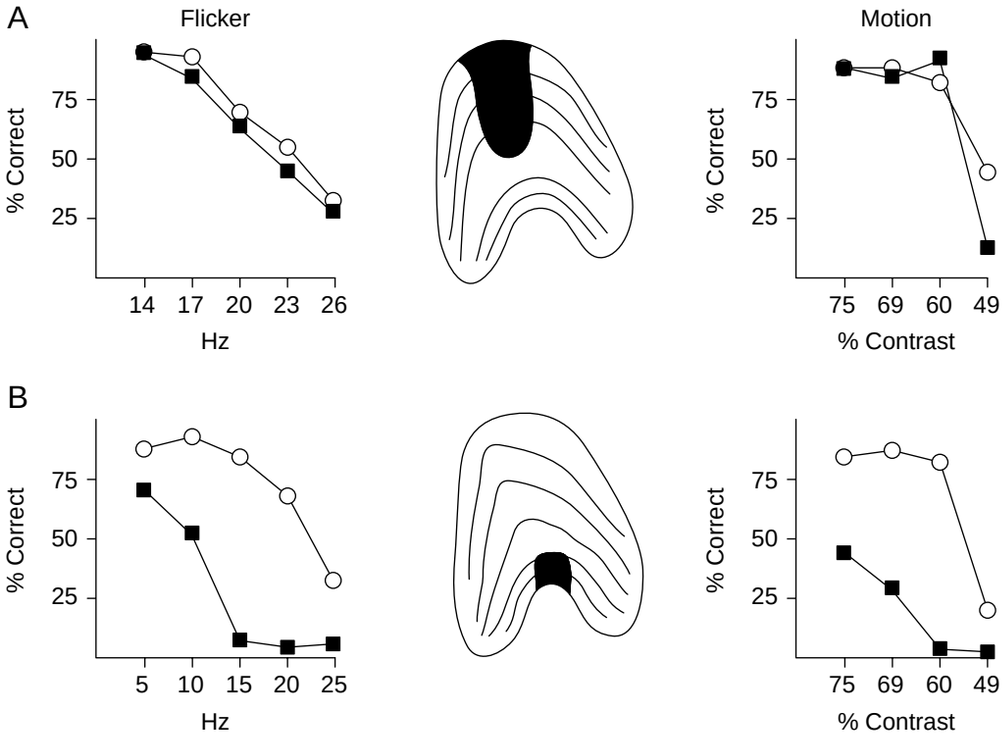


Fig. 2. ***The magnocellular laminae of the lateral geniculate nucleus (mLGN) and visual deficits.*** *The lateral geniculate nucleus (LGN) is a six-layered structure that receives input from the retinal ganglion cells and the primary visual cortex. There are important differences between the relative preferences of the four dorsal parvocellular (P) laminae and the two ventral magnocellular (M) laminae. Cells in the P, but not the M laminae, receive spatially segregated cone-derived inputs from small (P) retinal ganglion cells[11]. M cells have larger receptive fields than P cells and a higher achromatic contrast sensitivity[12]. From the point of view of dyslexia research, the most important differences between the two groups of cells are the faster conduction velocities and the high temporal (transient) sensitivity of the M cells compared with the sustained responses of the P neurones[13]. The laminar organization of the LGN can be exploited to demonstrate the functional significance of the differences between P and M cells. The figure shows the effect of LGN lesions on flicker (left) and motion (right) detection judgements in monkeys. When the parvocellular LGN was lesioned* **(A)**, *the monkeys were unimpaired in the contralateral visual field (filled squares) on either task, compared with their performance in the spared ipsilateral (open circles) visual field. However, when a lesion was made in the magnocellular laminae* **(B)**, *the monkeys were greatly impaired in flicker and motion judgements in the contralateral 'magno-blind' visual field. The opposite pattern of results was obtained when the monkeys were required to detect or discriminate colour, form, size, texture or disparity[14]. The specificity of these findings is mirrored in the specificity of visual deficits reported in dyslexia.* Data replotted from Ref. 14.

The magnocellular theory of developmental dyslexia

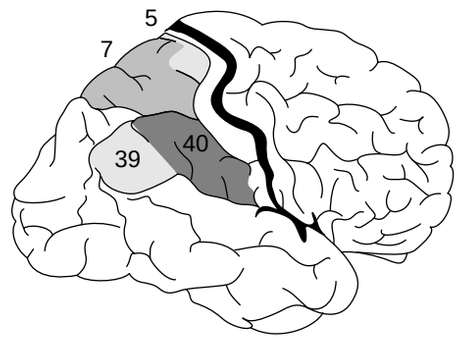
The distinctive characteristics of the visual magnocellular and parvocellular systems (Fig. 2) mean that they can be distinguished psychophysically in intact humans[15]. Lovegrove exploited this to show that most developmental dyslexics have slightly reduced contrast sensitivity at the low spatial frequencies and low luminance levels favoured by the magnocellular system, particularly during flicker, whereas at the higher spatial

frequencies served by the parvocellular, sustained system their contrast sensitivity is normal if not superior to that of normals[16]. These results have been confirmed both psychophysically and by elicited potential recording by numerous other groups, though denied by a few. In addition Cornelissen *et al.*[17] showed another magnocellular, transient deficit in dyslexics, namely impaired visual motion sensitivity even at high contrasts and illumination levels, and this result has been confirmed by both elicited potential[18] and functional magnetic resonance imaging (fMRI)[19] studies. But probably the most convincing evidence is the demonstration by Galaburda and colleagues that the magnocellular layers of the lateral geniculate nucleus (LGN) in five dyslexic brains examined post mortem were disordered, and that the magnocells themselves were over 20% smaller than in control brains[18]. Thus, one can be fairly confident that many dyslexics do have a fundamental impairment of their visual processing.

The posterior parietal cortex

The magnocellular impairments that have been found in dyslexics are very mild and are often demonstrated using very low contrasts, low light levels or unusual motion conditions that are not found during normal reading. How could such slight impairments lead to difficulties with reading? The answer probably lies in the anatomical connections from the magnocellular laminae of the LGN (mLGN) to the posterior parietal cortex (PPC). It is true that much intermingling of parvo and magno processing occurs in the cortex[20], but the PPC is dominated by m-like properties: sensitivity to direction of movement[21]; sensitivity to direction of gaze[22]; and relative insensitivity to colour or visual form. Slight impairments of mLGN performance or organization might, therefore, multiply up to greater deficits in PPC function. The PPC is known to be important for normal eye-movement control, visuospatial attention and peripheral vision – all important components of reading[23–27]. It is also a region which, if damaged, results in acquired reading disorders[28] (Fig. 3).

A



B

Function	Lesion	Dyslexia?
Spatial localization	Mislocalization	+
Spatial orientation		
Self	Topographical agnosia	+
Objects	Letter reversals	+
Direction of visual attention	Neglect	+
Directed auditory attention	'Cocktail party' problems	+
Visuomotor co-ordination	Clumsiness	+
Visuoverbal association	Acquired alexia	+
Attention to multiple objects	Simultanagnosia	?

Fig. 3. ***Functions of the posterior parietal cortex (PPC) and their relations to dyslexia.*** *The different shading patterns show the separate subareas of the PPC. Damage to each region can produce specific deficits: spatial mislocalization may be associated with damage to areas 5 and 7; spatial disorientation with damage to areas 5, 7 and 39; neglect with damage to areas 39 and 40; 'cocktail party' problems with damage to area 40; visuomotor co-ordination with damage to areas 5, 7 and 39; and visuoverbal association with damage to area 40.*

Eye movements

One important function of the magnocellular system is to help control eye movements. Hence, the impaired magnocellular function of dyslexics might destabilize binocular fixation; letters might then appear to move around and cause visual confusion. It has been found that often the binocular control of dyslexics is poor. Their eyes are unsteady when they are attempting to view small letters; hence their vision is unstable and they tend to make visual reading errors. They make less of this kind of error if they are given larger print[2].

In addition, dyslexics make fewer visual reading errors if one eye is occluded and they read with only one eye. Monocular occlusion relieves the confusion caused by two images moving around independently. Reading with only one eye not only reduces the visual errors made by many dyslexic children, but the majority of 8–10-year old dyslexic children with unstable binocular control who use only the right eye for all reading and number work for a few months can improve their fixation permanently[29]. The reading of those whose binocular control stabilizes has been shown to progress twice as fast as those whose control remains unstable, and this result has been confirmed in three separate studies. This simple treatment is not effective in older children. But it shows that the ocular motor consequences of the magnocellular defect in dyslexics are not irreversible; they can be remedied by rational treatment directed at their mechanism, if it is given early enough.

Many dyslexics complain that words and letters move around, blur and merge with each other. Breitmeyer suggested that their impaired transient system fails to inhibit the products of each reading fixation provided by the parvocellular system during the saccadic eye movements between them[30]. This would lead to superimposition of successive images, hence serious visual confusion. Williams *et al.* provided some support for this idea by demonstrating that dyslexics do have slightly reduced backward metacontrast masking[31]. However, lack of transient on sustained inhibition is unlikely to explain their visual confusion. Saccadic suppression seems to be an exclusively magnocellular function, and parvocellular sensitivity is not reduced during saccades[32]. Furthermore, like patients with lesions of the parietal cortex[33], dyslexics characteristically confuse neighbouring letters, whereas the seven-letter spaces traversed by the average reading saccade would predict confusions between letters similarly far apart.

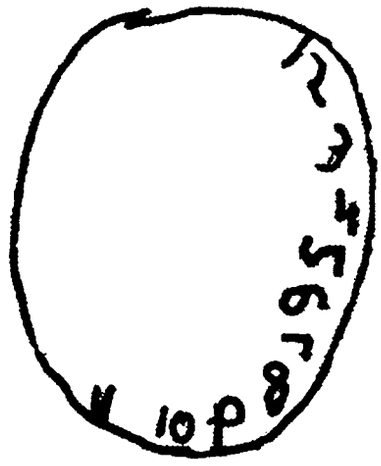


Fig. 4. ***Left neglect in a dyslexic child.*** *The child's age was 7 years 11 months, with a reading age that was retarded by 20 months. The child's I.Q. was 92.*

Attention

Dyslexics are impaired on a range of attention tasks that depend upon parietal cortex functioning[34]: the Posner task[35]; perceptual grouping[36]; visual search[37]; and also inhibition of stimuli that are not the focus of attention[24]. Attention is, of course, sensitive to the nature of visual stimuli. Patients with visual neglect following damage to the parietal cortex commonly make fewer errors on the contralesional side of words than non-words[38], which suggests that attention is apportioned according to stimulus type (word or non-word) and that parietal cortex mechanisms must be linked with the word-recognition systems resident in the temporal lobe[39].

It is clear that many attention-related functions contribute to reading. Crowding effects can disrupt letter and word recognition[40]; also accurate fixation and saccade control are required[24–27]; and selective attention to a word or string of words necessitates concentrated focal attention and controlled shifts of attention. The case for attentional deficits consequent upon abnormal functioning of the parietal cortex is strengthened by the close correspondence between the types of attentional deficits observed in dyslexia and those due to damage to the parietal cortex (Fig. 4).

Peripheral vision

The peripheral visual system plays an important part in reading. A page of text in, say, a small paperback contains approximately 2000 distracting stimuli. In normal vision the ability to identify stimuli diminishes with retinal eccentricity. In dyslexic subjects, however, the fall-off in peripheral identification might be less pronounced[23], and there is some evidence that restricting the field of view can yield improvements in reading[41]. The peripheral visual field is, of course, emphasized in the parietal visual areas.

Acquired reading disabilities

It is something of a puzzle that the contribution of impaired visuospatial and visual attentional processing to acquired reading disorders following posterior parietal lesions has received itself very little attention, and most effort has been expended on phonological explanations for acquired language disorders. Yet acquired dyslexias with a phonological basis are relatively rare. On the other hand, visuospatial neglect is a common result of loss of right parietal cortex function; and, although not often emphasized, most patients with neglect have reading problems. As Fig. 4 shows, left neglect can also be a feature of developmental dyslexia.

The similarities between the visual performance of patients with acquired dyslexia and developmental dyslexia are wide-ranging, non-trivial and, notwithstanding the dangers of making too simple a comparison between the two conditions, impressive. They include eye-movement abnormalities, left neglect, failure to distinguish between rotated letters[42], crowding effects[33], and of course reading problems.

Animal studies also support the suggestion of some correspondence between dyslexia and parietal cortex damage. Monkeys with PPC lesions, whilst able to discriminate between different visual stimuli such as a square and a triangle, are unable to discriminate between left–right reversals or rotated versions of the same stimuli [for example, < and >, or b and d (Ref. 43)], an important ability in humans for successful reading. Writing reversals and b–d confusions are errors commonly observed in dyslexics, but usually attributed to phonological problems.

Negative evidence

There have been some failures to find clear magnocellular impairments in dyslexics[44–46], but several factors need to be considered in evaluating them. First, transient system deficits are not all or none; one has to use appropriate stimulus parameters to observe them. For example, deficits in contrast sensitivity might be observed only at low but not high luminance levels. Failure to account for this lies behind some of the negative findings with young dyslexic subjects[44]. Luminance conditions might also explain differences between studies of visual masking. Those in which differences between dyslexic and normal readers have been found tended to use low-luminance displays[31,47,48], whereas the one report that disputes the finding used high-luminance displays[45]. Until performance over a wide range of conditions is known one should be wary of confusing absence of evidence with evidence of absence of a role for the transient system in dyslexia.

The failure to find evidence supporting the transient system hypothesis of visual deficits frequently rests on another error in data interpretation: treating all transient system functions as equivalent. Usually, dyslexics are tested on a number of tests related to mLGN functioning. If they are not deficient on all of them, or there is low correlation between the tests, it is concluded that mLGN deficits do not exist or are not relevant to reading[44,49]. In one experiment dyslexics were tested on four tests of transient system function. Dyslexics were significantly different in two of the experiments, yet the author concluded that the two in which they did not differ challenged the transient system hypothesis. But it should come as no surprise that abnormalities in some LGN neurones produce only some LGN-related deficits.

A more measured conclusion is that the heterogeneity of dyslexics causes heterogeneity of their performance. Dyseidetic dyslexics tend to make visually related errors[2], for example reading 'talc' for 'talk' or 'gob' for 'god', whereas dysphonetics have difficulty

with reading unfamiliar or non-words, when phonetic analysis is at a premium. It is important therefore to ensure that appropriate tests are chosen for each kind of dyslexic. Thus, Borsting *et al.*[50] recently reported reduced visual contrast sensitivity in dyslexics with both visual and phonological deficits ('dysphoneidetics'). But those with only one of these problems had normal sensitivity.

Auditory temporal processing

Visual impairment is thus an important component of developmental dyslexia; and any understanding of the problem that does not consider basic visual processing will be incomplete. It is likely that the phonological defect might also be caused by a more basic auditory processing impairment.

Although the auditory system does not have an anatomically distinct magnocellular pathway, there is an auditory subsystem, characterized by large neurones, responsible for analysing acoustic transients. Discrimination between phonemes requires extremely precise frequency analysis. At the frequencies found in speech such accurate frequency tracking is carried out by auditory neurones that are phase locked to each peak of the acoustic wave. It has recently been shown that the ability of many dyslexics to discriminate closely spaced frequencies by phase locking, and to detect phase differences between the ears, is significantly worse than in normal controls[51]. Thus, their problems with phonological analysis might result from an impairment in low-level auditory transient processing, which is analogous to their visual magnocellular defect. Galaburda and colleagues have recently shown that, like visual magnocells, auditory magnocells in the medial geniculate nucleus are abnormal in dyslexic brains[52].

The auditory impairment of dyslexics might affect their auditory attention. The parietal attention system is supramodal[53]; patients with parietal lesions are impaired on the Posner task when given invalid cues irrespective of whether the cue is visual or auditory, and this is probably true of dyslexics also.

General timing hypothesis

Thus, developmental dyslexics often have both auditory and visual transient processing defects that lead to reduced ability to focus attention in either domain. There is some evidence suggesting that magnocellular temporal processing deficits are not confined to vision and audition, but extend to other systems, such as vestibular and motor, as well. Dyslexics are notoriously clumsy and uncoordinated, their writing is appalling, their balance is poor, and they show other 'soft' cerebellar signs, such as reach and gaze overshoot, and muscle hypotonia[3]. The cerebellum is a major target of m-type efferents. It is possible therefore that in dyslexics a particular magnocellular neuronal cell line that plays a major role in temporal processing in all sensory, sensorimotor and motor systems throughout the brain might be selectively damaged during early development. The most likely mechanisms would be genetic impairment of their development or immunological attack *in utero*[54].

Concluding remarks: parts in the sum of dyslexia

Of course, dyslexics display a wide variety of symptoms; and so we are faced with the question whether a single explanation, impaired temporal processing, can really underlie this diversity of deficits and individual differences. How can weak phonological processing, unstable visual perception, bizarre spelling, untidy writing, clumsiness, forgetfulness, distractibility and poor spatial organization all submit to a single explanation? It is still possible that dyslexia results from several different impairments. But the main aim of this article has been to convince you that it is possible that dyslexics suffer from one fundamental abnormality that has many different manifestations. One should not be surprised if this unifying thread is subtle, nor that it may eventually be found at a lower level than the perceptual and cognitive systems that have been the main focus of research efforts to date.

Selected references

1 **Bradley, L. and Bryant, P.** (1983) *Nature* 301, 419–421
2 **Cornelissen, P. *et al.*** (1991) *Dev. Med. Child Neurol.* 33, 755–762
3 **Nicholson, R.I. and Fawcett, A.J.** (1995) *Dyslexia* 1, 19–36
4 **Miles T.R.** (1993) *Dyslexia*, Whurr Wyke
5 **Orton, S.T.** (1925) *Arch. Neurol. Psychol.* 14, 582–615
6 **Hugdahl, K., Synnevag, B. and Satz, P.** (1990) *Neuropsychologia* 28, 673–679
7 **Cardon, L.R. *et al.*** (1994) *Science* 266, 276–279
8 **Steinmetz, H. *et al.*** (1991) *Ann. Neurol.* 29, 315–319
9 **Galaburda, A.M. *et al.*** (1985) *Ann. Neurol.* 18, 222–233
10 **Morgan, W.P.** (1896) *Br. Med. J.* 2, 1378
11 **Wiesel, T. and Hubel, D.H.** (1966) *J. Neurophysiol.* 29, 1115–1156
12 **Shapley, R.M. and Perry, V.H.** (1986) *Trends Neurosci.* 9, 229–235
13 **Schiller, P.H. and Malpeli, J.G.** (1977) *J. Neurophysiol.* 40, 428–445
14 **Schiller, P.H., Logothetis, N.K. and Eliot, C.R.** (1990) *Visual Neurosci.* 5, 321–346
15 **Kulikowski, J.J. and Tolhurst, D.J.** (1973) *J. Physiol.* 232, 149–162
16 **Lovegrove, W.J. *et al.*** (1980) *Science* 210, 439–440
17 **Cornelissen, P. *et al.*** (1995) *Vis. Res.* 35, 1483–1494
18 **Livingstone, M.S.** (1991) *Proc. Natl. Acad. Sci. U. S. A.* 88, 7943–7947
19 **Eden, G.F. *et al.*** (1996) *Nature* 382, 66–69
20 **Schiller, P.H.** (1996) *Behav. Brain Res.* 76, 21–35
21 **Motter, B. and Mountcastle, V.B.** (1981) *J. Neurosci.* 1, 3–26
22 **Galletti, C., Battaglini, P. and Fattori, P.** (1991) *Eur. J. Neurosci.* 3, 452–461
23 **Geiger, G. and Lettvin, J.Y.** (1987) *New Engl. J. Med.* 316, 1238–1243
24 **Morris, R.K. and Rayner, K.** (1991) in *Vision and Visual Dyslexia* (Stein, J.F., ed.), pp. 223–242, Macmillan
25 **Olson, R.K., Conners, F.A. and Rack, J.P.** (1991) in *Vision and Visual Dyslexia* (Stein, J.F., ed.), pp. 243–250, Macmillan
26 **McConckie, G.W. *et al.*** (1991) in *Vision and Visual Dyslexia* (Stein, J.F., ed.), pp. 251–262, Macmillan
27 **Pavlidis, G.** (1991) in *Vision and Visual Dyslexia* (Stein, J.F., ed.), pp. 263–270, Macmillan
28 **Kinsbourne, M. and Warrington, E.K.** (1962) *J. Neurol. Neurosurg. Psychiatry* 25, 339–344
29 **Stein, J.F. and Fowler, M.S.** (1985) *Lancet* 337, 69–73
30 **Breitmeyer, B.G.** (1980) *Psychol. Rev.* 87, 52–69
31 **Williams, M.C., Molinet, K. and Le Cluyse, K.** (1989) *Clin. Vision Sci.* 4, 137–144
32 **Burr, D.C., Morrone, M.C. and Ross, J.** (1994) *Nature* 371, 511–513
33 **Shallice, T. and Warrington, E.K.** (1977) *Neuropsychologia* 15, 31–41
34 **Valdois, S.** (1995) *Cognitive Neuropsychol.* 12, 31–67
35 **Brannan, J. and Williams, M.C.** (1987) *Percept. Psychophys.* 41, 23–28
36 **Williams, M.C. and Bologna, N.** (1985) *Percept. Psychophys.* 38, 367–374
37 **Ruddock, K.H.** (1991) in *Vision and Visual Dyslexia* (Stein, J.F., ed.), pp. 58–83, Macmillan
38 **Brunn, J.L. and Farah, M.J.** (1991) *Cognitive Neuropsychol.* 8, 59–75
39 **Nobre, A.C., Allison, T. and McCarthy, G.** (1994) *Nature* 372, 260–263
40 **Atkinson, J.** (1991) in *Vision and Visual Dyslexia* (Stein, J.F., ed.), pp. 44–57, Macmillan
41 **Geiger, G., Lettvin, J.Y. and Fahle, M.** (1994) *Vis. Res.* 34, 1223–1233

42 Riddoch, M.J. and Humphreys, G.W. (1988) *Cognitive Neuropsychol.* 5, 289–315
43 Walsh, V. and Butler, S.R. (1996) *Behav. Brain Res.* 76, 127–142
44 Walther-Muller, P.U. (1995) *Perception* 24, 919–936
45 Gross-Glenn, K. *et al.* (1995) *Visual Neurosci.* 12, 153–163
46 Victor, J.D. *et al.* (1993) *Visual Neurosci.* 10, 939–946
47 Williams, M.C., Le Cluyse, K. and Bologna, N. (1990) *Clin. Vision Sci.* 5, 335–343
48 Edwards, V.T. *et al.* (1996) *Vis. Res.* 36, 1037–1045
49 Evans, B.J., Drasdo, N. and Richards, I.L. (1994) *Vis. Res.* 34, 1913–1926
50 Borsting, E. *et al.* (1996) *Vis. Res.* 36, 1047–1053
51 McAnally, K.I. and Stein, J.F. (1996) *Proc. R. Soc. London Ser. B* 263, 961–965
52 Galaburda, A.M., Menard, M.T. and Rosen, G.D. (1994) *Proc. Natl. Acad. Sci. U. S. A.* 91, 8010–8013
53 Farah, M.J. *et al.* (1989) *Neuropsychologia* 27, 461–470
54 Stein, J.F. (1994) *Int. J. Psychophysiol.* 18, 241–249

LETTERS TO THE EDITOR

Updating the functional model of the basal ganglia

Chesselet and Delfs have tried to update the well known dual circuit model of the functional organization of the basal ganglia[1]. This is important, having regard to the popularity of this model[2]. They have hit on the weakest point of the model, namely the direct relationship between the observations of an increased discharge rate in subthalamic neurons of primates treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)[3] or 6-hydroxydopamine (6-OHDA)-lesioned rats[4] and a hypothesized decrease of pallidal activity. In the dual circuit scheme, the external pallidum (GPe) in primates [the globus pallidus (GP) in rats] is believed to be a simple relay with spiking activity strongly linked to changes in the discharge rate of inhibitory striatal neurons projecting to the pallidum. Chesselet and Delfs have clearly summarized the various objections to this assumption. They have reminded us of the importance of the feedback projection from the subthalamic nucleus (SThN) to the GPe, and emphasized that projections to the internal pallidum (GPi), substantia nigra pars reticulata (SNr) and reticular thalamic nucleus arise from the GPe in addition to the well known projection to the SThN. This leads to the suggestion that the GP can act as an integrative structure with functions that are not restricted to the control of subthalamic activity, an idea suggested also by Parent and Hazrati[5].

However, there is a sense of incompleteness in this review. Although the main interest of Chesselet and Delfs focuses on the GPe, they have not taken into account the numerous anatomical reports, arising from teams in Oxford and Quebec, that have appeared in the past two years. Some other failures and omissions in the current model of functional organization of the basal ganglia could also have been mentioned on the basis of reports published previously. One important purpose of an update, if nothing else, is to point out the *terrae incognitae* in order to promote further research in the field.

First, I wonder why they forget about the thalamic inputs to the basal ganglia; the main one being the thalamostriatal projection. This last part of the 'Nauta–Mehler' loop has been abundantly described in numerous anatomical reports published in the 1960s and 1970s (for a review, see Ref. 6). In addition, projections arising from the parafascicular nucleus reach two other targets in the basal ganglia: the GP (Refs 7,8) and the SThN (Refs 9,10), possibly through collaterals of the thalamostriatal projections[11]. The thalamostriatal projection always appears in the diagrammatic representations and is mentioned by Chesselet and Delfs but always without commentary. Could this be related to the lack of obvious anatomopathological observations following lesions of intralaminar nuclei? In fact, crude and extensive lesions on the thalamus cannot be limited to the intralaminar nuclei. Consequently the pathological cases cannot provide information on their physiological function. We have demonstrated that stimulation of the parafascicular nucleus induces a monosynaptic excitation of subthalamic neurons through glutamate neurotransmission[12,13]. We have further demonstrated that the thalamic input to the GP also produces an excitatory effect on the pallidal neurons (O.K. Hassani, M. Mouroux and J. Féger, unpublished observations). Such excitatory inputs could be a driving force for these substriatal structures. Similarly, the corticosubthalamic excitatory input has rarely been taken in account in the model, although it has been suggested that it is able to produce an early excitation of the substriatal structures[14,15]. Alternatively, because the intralaminar nuclei receive an important projection from the cerebral cortex, the centre médian-parafascicular complex is also able to produce an early excitatory effect in response to a cortical input in a similar way to the subthalamic nucleus. The occurrence of this thalamic input to the pallidal neurons provides further evidence of the integrative functions of the GP.

In one part of their review, Chesselet and Delfs raise the possibility that the pattern of spiking activity could be more important than the mean discharge rate in determining synaptic efficacy. They suggest that a shift from a regular to a bursting activity in pallidal neurons could result from an increased activity of subthalamic inputs. This explanation seems appropriate regarding the action of the subthalamic projection on dopamine-containing neurons in the substantia nigra[16]; however, changes in the pattern of spiking in pallidal neurons cannot result only from an increased release of glutamate by the subthalamic terminals because, in our experiments, pharmacological activation of the subthalamic nucleus[17] did not induce a bursting pattern in recorded pallidal neurons, even when their discharge rate was increased by 112%. Similarly, pharmacological activation of the parafascicular nucleus, which provides an excitatory and probably glutamatergic input to the GP, induced an increase by 142% of the spiking activity in the GP but did not induce a bursting pattern. The bursting activity observed in pallidal neurons in 6-OHDA-lesioned rats[4,18,19] seems equally explicable by reference to the importance of the reciprocal relationship between the GP and the SThN (Ref. 20), which provides a strong negative feedback control.

In conclusion, the update offered by Chesselet and Delfs presents the very same simplifications emphasized by Albin *et al.* in their critical reappraisal[21] as being dangerous for this model. Maybe it is important to follow the wishes expressed by Albin and destroy the dual circuit model and construct a new one. Like an artist covering a previous sketch with a white coat of paint, we may have to go beyond the current models, built with boxes and + or – arrows, and think of the basal ganglia organization as a network with sequences of activation and inhibition in both space and time.

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