

Goeddel, M. Rothe, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 9792 (1997).  
 12. S. Miyawaki *et al.*, *Eur. J. Immunol.* **24**, 429 (1994).  
 13. R. Shinkura *et al.*, *Nature Genet.* **22**, 74 (1999).  
 14. N. Garceau *et al.*, *J. Exp. Med.* **191**, 381 (2000).  
 15. S. Fagarasan *et al.*, *J. Exp. Med.* **191**, 1477 (2000).  
 16. The NIK gene was targeted in GS-1 embryonic stem cells by replacing 1.3 kb of DNA containing the first 120 base pairs of exon 1 with a neomycin resistance gene (18). NIK<sup>-/-</sup> mice were maintained on either 129/SvEv or 129/SvEv × C57BL/6 backgrounds. NIK<sup>-/-</sup> mice were more susceptible

to bacterial eye infections but showed no gross abnormalities in growth, behavior, or capacities to reproduce or nurse.  
 17. A. Futterer, K. Mink, A. Luz, M. H. Kosco-Vilbois, K. Pfeffer, *Immunity* **9**, 59 (1998).  
 18. See *Science Online* ([www.sciencemag.org/cgi/content/full/291/5511/2162/DC1](http://www.sciencemag.org/cgi/content/full/291/5511/2162/DC1)).  
 19. K. P. Hoeflich *et al.*, *Nature* **406**, 86 (2000).  
 20. M. Bonnard *et al.*, *EMBO J.* **19**, 4976 (2000).  
 21. T. L. Murphy, M. G. Cleveland, P. Kulesza, J. Magram, K. M. Murphy, *Mol. Cell. Biol.* **15**, 5258 (1995).  
 22. M. Tanaka *et al.*, *Immunity* **10**, 421 (1999).

23. M. A. Meraz *et al.*, *Cell* **84**, 431 (1996).  
 24. J. L. Browning *et al.*, *J. Immunol.* **159**, 3288 (1997).  
 25. H. C. Liou, W. C. Sha, M. L. Scott, D. Baltimore, *Mol. Cell. Biol.* **14**, 5349 (1994).  
 26. We thank J. Browning for LTβR mAb; D. Novack, S. Teitelbaum, and Y. Choi for osteoprotegerin ligand; and W. Sha for the (NF-κB)<sub>2</sub>-Luc reporter construct. Supported by grants from NIH and Tularik Inc. L.Y. is a Postdoctoral Fellow of the Cancer Research Institute.

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# Dyslexia: Cultural Diversity and Biological Unity

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The recognition of dyslexia as a neurodevelopmental disorder has been hampered by the belief that it is not a specific diagnostic entity because it has variable and culture-specific manifestations. In line with this belief, we found that Italian dyslexics, using a shallow orthography which facilitates reading, performed better on reading tasks than did English and French dyslexics. However, all dyslexics were equally impaired relative to their controls on reading and phonological tasks. Positron emission tomography scans during explicit and implicit reading showed the same reduced activity in a region of the left hemisphere in dyslexics from all three countries, with the maximum peak in the middle temporal gyrus and additional peaks in the inferior and superior temporal gyri and middle occipital gyrus. We conclude that there is a universal neurocognitive basis for dyslexia and that differences in reading performance among dyslexics of different countries are due to different orthographies.

Developmental dyslexia is increasingly acknowledged to be a disorder of genetic origin with a basis in the brain (1). However, there continues to be doubt about the universality and specificity of the syndrome because behavioral studies have shown that the nature and prevalence of dyslexia differs across languages (2). The prevalence estimates of dyslexia in different countries seem to be related to the shallowness of the orthography. For instance, using one of the most respected behavioral definitions of dyslexia (word recognition accuracy in relation to IQ), the prevalence of dyslexia in Italy was half that in the United States (3).

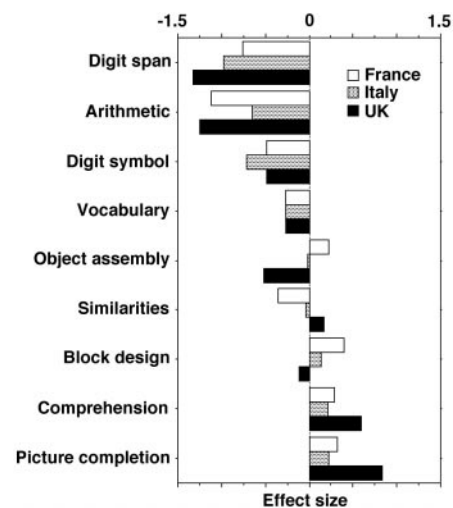
Current theories of dyslexia favor a neurocognitive explanation with the implicit assumption of a universal application. There is considerable agreement that a causal link between brain abnormality and reading difficulties involves phonological processing deficits (4, 5). The cause of these deficits is, however, less clear. Recently, more general perceptual problems have been postulated, either auditory (6) or visual deficits associated with dysfunction of the magnocellular system of the brain (7). At a neurological level, it has been shown that dyslexics have microscopic cortical abnormalities, particularly in the perisylvian language areas in the form of cortical ectopias and dyslamination of cortical layers (8). These diffuse neurological abnormalities may reduce corticocortical connectivity, as suggested by recent positron emission tomography (PET) and magnetic resonance imaging (MRI) studies (9, 10). Until now, most of the biological studies used English-speaking subjects; none have directly compared dyslexics across different orthographies.

In languages with transparent or shallow orthography (e.g., Italian), the letters of the alphabet, alone or in combination, are in most instances uniquely mapped to each of the speech sounds occurring in the language (11). Learning to read in such languages is easier

than in languages with deep orthography (e.g., English and French), where the mapping between letters, speech sounds, and whole-word sounds is often highly ambiguous (12, 13). Adult skilled readers show a speed advantage in shallow orthographies (14, 15). Differences have also been demonstrated at the physiological level (15).

Our aim was to contrast dyslexic and normal adult readers in deep (English and French) and shallow (Italian) orthographies in order to explore similarities and differences at both the behavioral and neurophysiological level. If dyslexia has a universal basis, then substantial similarities should be found, either at the cognitive or the brain level, or both. We investigated single-word reading at explicit and automatic levels, because differential response to the written word is the most widely agreed defining behavioral feature of dyslexia. Given that stimuli differ between different orthographies, and given that orthographic depth affects reading difficulty, any commonality found in underlying physiological responses in dyslexics would be strong evidence for a unitary biological basis.

Normal controls and subjects with dyslex-



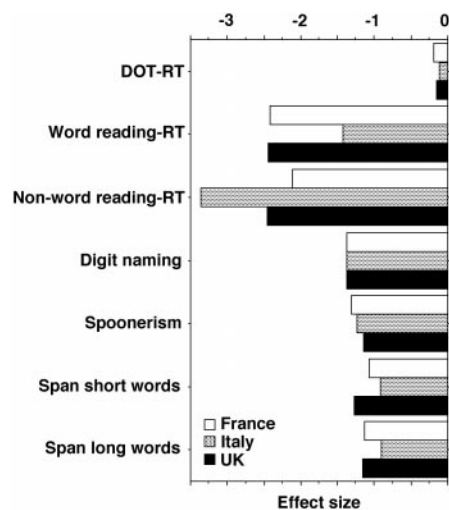
**Fig. 1.** Effect size (Z-scores) of the differences between dyslexic and normal readers in each country on Wechsler scale subtests. Z-scores were derived from the group differences expressed in standard deviation (SD) units using pooled SDs. Negative Z-scores represent impaired performance. The dyslexics were only impaired on subtests involving phonological short-term memory.

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ia were matched for age and IQ, and all had achieved tertiary levels of education. This ruled out certain causes of reading impairment, e.g., poor general ability or poor education, that often bedevil the diagnosis of dyslexia. It also ensured that all participants could perform the simple word-reading task in the scanning experiments to a satisfactory level. In France and the United Kingdom, we recruited volunteers who had been diagnosed as dyslexic and had documented histories of reading and spelling difficulties. In Italy, such diagnosis is rare among university-level adults, and we therefore used a screening procedure to identify individuals showing impaired reading speed and defective phonological processing. The criteria for inclusion in the Italian dyslexic group involved two stages. First, about 1200 students were given group tests of spelling and stress assignment, a test where subjects have to mark the stressed syllable of 90 printed multisyllabic words (16). Those scoring in the bottom 10% were then assessed individually on word and nonword reading speed, digit naming, short-term memory, and spoonerisms, all of which are tests thought to be sensitive to phonological processing deficits (4). Those who performed in the bottom 10% (of a normative sample based on 40 consecutive students) on three or more of the six tasks were classified as dyslexic. These same experimental tests were also used with the French and English samples (16, 17).



**Fig. 2.** Effect size (Z-scores) of the differences between dyslexics and controls on experimental reading and phonological tests. Z-scores were derived from the group differences expressed in SD units using pooled SDs. There were no differences in simple reaction time (RT) for a dot appearing on a computer screen. However, all other tasks showed impairments in the dyslexics (negative Z-scores). Note that Italian dyslexics differ strongly from their controls on nonword reading, even though they perform better on this task (fewer errors) when compared to French and English dyslexics.

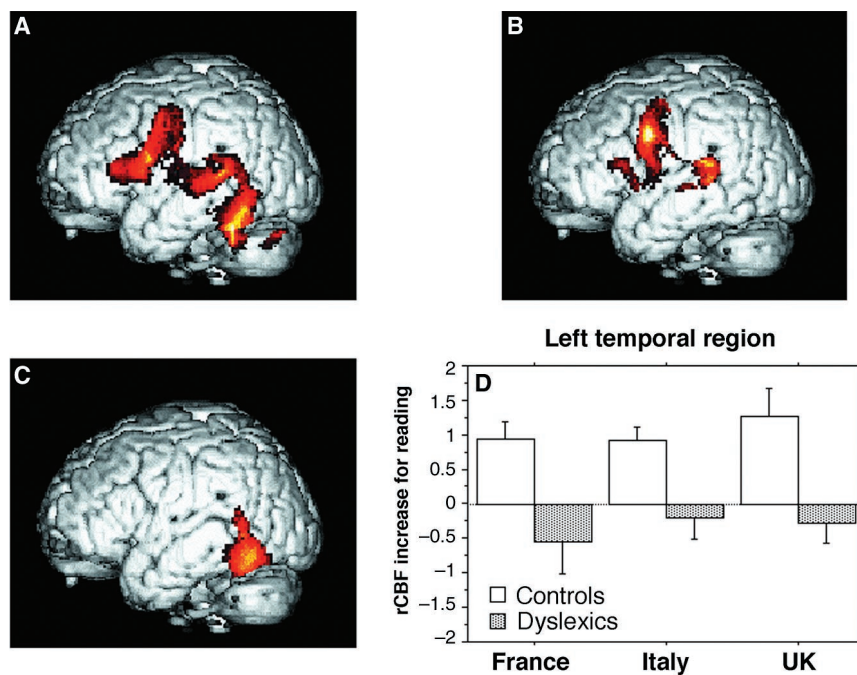
The results of the Wechsler intelligence test scales for adults (WAIS) [Fig. 1 and Web table 1 (16)] demonstrate a characteristic pattern that has been found previously (18): the dyslexics performed most poorly on those subtests that involve phonological short-term memory (digit span, arithmetic, and digit symbol). On all other subtests, dyslexics showed unimpaired performance. This was similar across the three countries and suggests that we were comparing like with like.

Performance on the reading and phonological tests is shown in Fig. 2 and in Web table 1 (16). There was a consistent advantage on the reading tests in favor of the Italian dyslexic sample when compared to the French and English dyslexic samples. In particular, the Italian dyslexics showed fewer errors for both words and nonwords (Mann-Whitney U test:  $P < 0.001$ ). Yet, as Fig. 2 shows, Italian dyslexics performed significantly worse than their controls on reading and phonological tasks, and differed as much as did the English and French dyslexics from their controls. This and the fact that the French and English dyslexics had not been selected for phonological impairments, sup-

ports the idea that dyslexia is associated with a phonological deficit. Moreover, this deficit appears to be independent of orthography.

Our PET data link the psychological findings to brain physiology. Two regional cerebral blood flow (rCBF) PET activation experiments (19), one on explicit and one on implicit reading (15), were conducted with a total of 72 participants. In all, six groups of normal controls and six groups of dyslexics were scanned (six subjects per group, four groups from each country). We combined the results of the two experiments, so that we only report the most reliable activations elicited by exposure to print (20).

For normal controls, and in line with previous results (21), we identified a number of cortical language areas of the perisylvian cortex (Broca's area and Wernicke's area including the planum temporale), the left middle and inferior temporal gyri, and the fusiform gyrus (Web table 2 and Fig. 3A). Activations were also seen in the cerebellar hemispheres and in subcortical gray structures (thalami and basal ganglia). These areas represent the common activation for exposure to printed material relative to baseline. The same analysis ap-



**Fig. 3.** Brain areas activated in normal and dyslexic readers from three countries: United Kingdom, France, and Italy. Activations are rendered on a standard brain in standard stereotactic space. The first row shows the activations revealed by conjunction analysis (29) of the independent effects of reading minus baseline in the six groups of normal controls (A) and in the six groups of dyslexics (B) (see also Web table 2). (C) The figure shows the brain areas that were significantly more active in all normal compared to all dyslexic readers. The conjunction analysis accepted only those group differences that replicated across explicit and implicit reading experiments ( $P < 0.001$  corrected for spatial extent). Stereotactic coordinates (the distances in mm from the anterior commissure) and Z-scores of left hemispheric areas showing statistically significant differences were ( $x, y, z$ ; Z-score): superior temporal gyrus ( $-54, -50, 14$ ; 3.7); middle temporal gyrus ( $-60, -56, 0$ ; 5.3); inferior temporal gyrus ( $-52, -60, -14$ ; 5.06); and middle occipital gyrus ( $-52, -64, -6$ ; 4.15). (D) Bar graph illustrates the profile of rCBF increases for reading in control and dyslexic groups from the three countries. The plot is based on average rCBF values from the entire region that was significantly more active in the controls [see (C)]. Error bars indicate 1 standard error.

plied to the dyslexic readers revealed a greatly restricted pattern of activation. This is illustrated in Fig. 3B, whereas Web table 2 shows the coordinates of the peak activations (16).

A direct comparison of the areas of activation in normal controls and dyslexics (Fig. 3C) identified a large region in the left hemisphere of significantly greater activation for the controls ( $P < 0.001$  corrected for spatial extent), with the maximum peak in the middle temporal gyrus and additional peaks in the inferior and superior temporal gyri and middle occipital gyrus (Web table 2) (16). There were no areas of significantly greater activation in dyslexics compared to controls.

We also explored whether there were orthography-specific effects in the dyslexic groups. Our previous study of skilled Italian and English readers showed that Italians have greater activation in left superior temporal regions (15), which have been associated with processing phonemes (22). In contrast, and for nonwords in particular, English normal readers had greater activations in left posterior inferior temporal gyrus and anterior inferior frontal gyrus, areas which have been associated with word retrieval during both reading and naming tasks (23–25). This result was confirmed when the French group was added. However, when dyslexic readers were compared across orthographies, no such differences were evident. This is most likely because dyslexics have a less developed reading system that cannot adapt to some subtle specific requirement of their orthography.

Reduced activation in the left middle, inferior, and superior temporal cortex and in the middle occipital gyrus was the robust universal feature of dyslexia for word reading in the three language groups; reduced activation in this region was found previously with PET and functional MRI in English-speaking dyslexics (26, 27) and with magnetoencephalography in Finnish-speaking dyslexics (28).

Why did we find a reduction of activity? We consider two possibilities. One is the disconnection hypothesis (9, 10) which assumes that the connections between the different components of the language system are weak. If so, this could result in reduced activation of the major components of the system with the consequence of slower processing of spoken and written language. Another explanation is that the brains of dyslexics are more idiosyncratic in modularizing the reading system. The reduced activation in dyslexics, i.e., more restricted in extent and significance, could be due to more variability in the individual pattern of activation. These two explanations are not mutually exclusive. If there were diffuse differences in organization, the acquisition of written language would be slow in consequence and subject to idiosyncratic strategies.

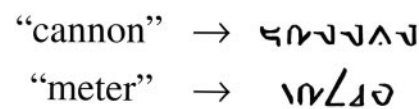
Is dyslexia a disorder with a universal neuro-

anatomical basis, or is it a different disorder in shallow and deep orthographies? Our results are clear-cut. They show that dyslexia has a universal basis in the brain and can be characterized by the same neurocognitive deficit. Clearly, the manifestation in reading behavior is less severe in a shallow orthography. However, our results show that if more sensitive tests were available, the neurocognitive deficit would be detected. Although Italian dyslexics read more accurately than French or English dyslexics, they showed the same degree of impairment on reading latencies and reading-related phonological tasks relative to their controls. We conclude that a phonological processing deficit is a universal problem in dyslexia and causes literacy problems in both shallow and deep orthographies. However, in languages with shallow orthography, such as Italian, the impact is less, and dyslexia has a more hidden existence. By contrast, deep orthographies like that of English and French may aggravate the literacy impairments of otherwise mild cases of dyslexia.

References and Notes

1. S. D. Smith, P. M. Kelley, A. M. Brower, *Hum. Biol.* **70**, 239 (1998).
2. K. Landerl, H. Wimmer, U. Frith, *Cognition* **63**, 315 (1997).
3. S. D. Lindgren, E. De Renzi, L. C. Richman, *Child Dev.* **56**, 1404 (1985).
4. S. Brady, D. Shankweiler, *Phonological Processes in Literacy* (Erlbaum, Hillsdale, NJ, 1991).
5. M. Snowling, *Dyslexia* (Blackwell, Oxford, 2000).
6. P. Tallal, *Brain Lang.* **9**, 182 (1980).
7. J. Stein, V. Walsh, *Trends Neurosci.* **20**, 147 (1997).
8. A. M. Galaburda, G. F. Sherman, G. D. Rosen, F. Aboitiz, N. Geschwind, *Ann. Neurol.* **18**, 222 (1985).
9. E. Paulesu et al., *Brain* **119**, 143 (1996).
10. T. Klingberg et al., *Neuron* **25**, 493 (2000).
11. A. Lepschy, G. Lepschy, *La Lingua Italiana* (Bompiani, Milano, Italy, 1981).
12. U. Frith, H. Wimmer, K. Landerl, *Sci. Stud. Reading* **2**, 31 (1998).
13. G. Cossu, M. Gugliotta, J. Marshall, *Reading Writ.* **7**, 9 (1995).
14. R. Frost, L. Katz, S. Bentin, *J. Exp. Psychol. Hum. Percept. Perform.* **13**, 104 (1987).
15. E. Paulesu et al., *Nature Neurosci.* **3**, 91 (2000).
16. A complete description of the methods and results is available at [www.sciencemag.org/cgi/content/full/291/5511/2165/DC1](http://www.sciencemag.org/cgi/content/full/291/5511/2165/DC1).
17. Behavioral study: Male, right-handed students with tertiary education participated in the study. Italy: 40 controls (mean age, 21.5; SD, 2.4); 18 dyslexics (mean age, 21.7; SD, 2.3). France: 18 controls (mean age, 28.2; SD, 4.8); 18 dyslexics (mean age, 27.2; SD, 5.9). United Kingdom: 18 controls (mean age, 23.5; SD, 2.9); 18 dyslexics (mean age, 23.6; SD, 4.7). All subjects were tested with the WAIS. Reading accuracy and speed, and phonological processing were also assessed. Words and nonwords were presented on a computer, and naming latency was recorded via a voice-key. All words had two or three syllables, avoiding irregular patterns. Nonwords were created from the words by maintaining the "word envelope" while changing internal consonants. Simple reaction times for a dot stimulus provided a baseline. Spoonerism task: Subjects heard pairs of words with the instruction to repeat back the two words after having swapped the initial sound around (e.g., Basket and Lemon repeated as Lasket and Bemon). Auditory short-term memory: Subjects recalled 10 lists of six short words and 10 lists of six long words. Digit naming time: Participants read aloud, as fast as possible, strings of 50 single digits.
18. S. Naidoo, *Specific Dyslexia* (Pitman, London, 1972).

19. K. Friston, in *Human Brain Function*, R. Frackowiak, K. Friston, C. Frith, R. Dolan, J. Mazziotta, Eds. (Academic Press, San Diego, CA, 1997), pp. 25–41.
20. PET experiments: There were two PET scan experiments involving 72 of the aforementioned subjects (17) (36 subjects for each experiment, 24 for each country, half of whom were dyslexics). In the explicit reading experiment, subjects read bisyllabic words and nonwords aloud. In the implicit reading experiment, participants performed a feature detection task. Subjects detected the presence or absence of ascenders (graphic features which go above the midline of the word, e.g. "b," "l," and "t" as opposed to "a," "c," and "o") within visually presented words, nonwords, and false font strings. The false fonts were created by substituting letters in the real words with nonletters matched for size and presence or absence of ascenders (e.g., see "cannon" and "meter" in Scheme 1). Subjects pressed one key with their right-hand index finger if one or more ascender was present, and another key with their right middle finger if no ascenders were present. These studies



Scheme 1.

were approved by the ethics committees of the Institute of Neurology (London) and Institute H San Raffaele (Milan). Informed consent was obtained after the nature and possible consequences of the studies were explained to the volunteers. Data analysis: rCBF was measured by recording the distribution of radioactivity following the intravenous injection of  $^{15}\text{O}$ -labeled water ( $\text{H}_2^{15}\text{O}$ ). Twelve consecutive scans were obtained for each subject in each experiment. Task-related differences in rCBF were examined using Statistical Parametric Mapping (SPM96) software (Wellcome Department of Cognitive Neurology, London, UK) on stereotactically normalized and smoothed PET images. For each experiment, data were analyzed according to a random effects model: replications of each task were collapsed into average images to give one average scan per reading task per subject. The analysis was based on a 2 (controls versus dyslexics)  $\times$  3 (French, English, Italian subjects)  $\times$  2 (implicit, explicit reading)  $\times$  3 (words, nonwords, baseline) factorial design. The pattern of activation associated with reading was identified as the conjunction of the six main effects of reading (reading minus baseline) in each of the six groups of controls (Fig. 3A) and in each of the six groups of dyslexics (Fig. 3B). We then calculated the differences between controls and dyslexics as the conjunction of the six groups  $\times$  task interaction effects (Fig. 3C). The interaction effects were computed on the voxels identified by the linear contrast of the relevant main effects.

21. C. Price, in (19), pp. 301–328.
22. J. Démonet, J. Fiez, E. Paulesu, S. Petersen, R. Zatorre, *Brain Lang.* **55**, 352 (1996).
23. C. Price, C. Moore, G. Humphreys, R. Frackowiak, K. Friston, *Proc. R. Soc. London Ser. B* **263**, 1501 (1996).
24. R. Vandenberghe, C. Price, R. Wise, O. Josephs, R. S. Frackowiak, *Nature* **383**, 254 (1996).
25. R. Poldrack, A. Wagner, M. Prull, J. Desmond, G. Glover, J. Gabrieli, *Neuroimage* **10**, 15 (1999).
26. J. Rumsey, K. Nace, B. Donohue, D. Wise, M. Maisog, P. Anderson, *Arch. Neurol.* **54**, 562 (1997).
27. S. E. Shaywitz et al., *Proc. Natl. Acad. Sci. U.S.A.* **95**, 2636 (1998).
28. R. Salmelin, E. Service, P. Kiesilä, K. Uutela, O. Salonen, *Ann. Neurol.* **40**, 157 (1996).
29. C. Price, K. Friston, *Neuroimage* **5**, 261 (1997).
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