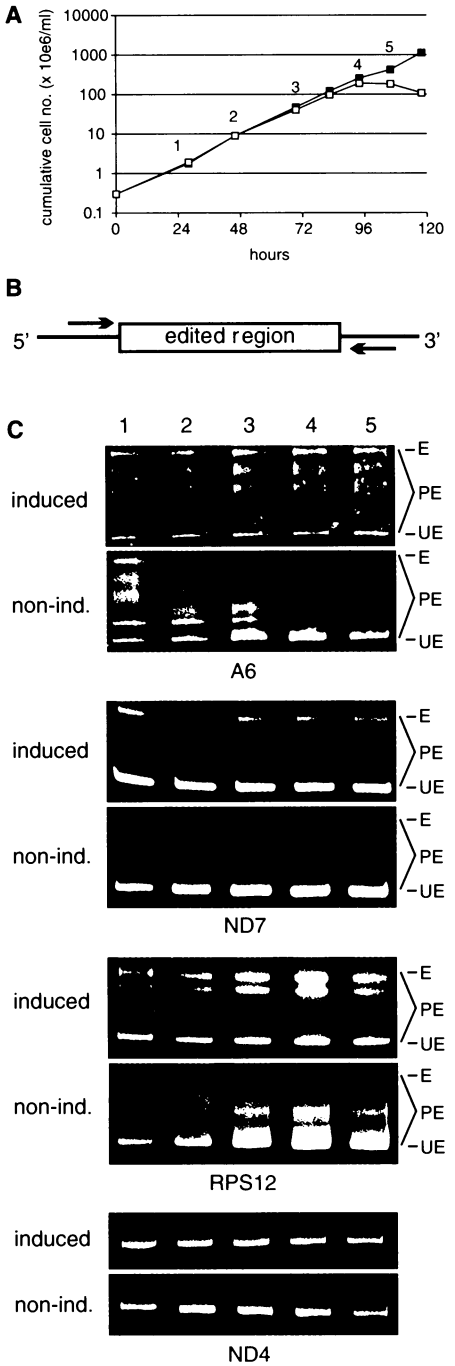

Fig. 4. Loss of TbMP52 blocks RNA editing. (**A**) Growth of induced (black squares) and non-induced (white squares) parasites. Total RNA was prepared from samples taken at the time points indicated (*16*). (**B**) Diagram showing RT-PCR primer locations relative to the edited region. (**C**) Polyacrylamide gel analysis of RT-PCR products from RNAs that are normally edited in bloodforms (A6, ND7, and RPS12) and ND4 RNA, which does not get edited (*16*). Fully edited (E), partially edited (PE), and unedited (UE) molecules were identified by cloning and sequencing.

Table 1. Growth in mice of *T. brucei* with induced or non-induced TbMP52. C57 BL/6 mice were infected by intraperitoneal inoculation with 10^5 cultured bloodstream-form *T. brucei* clones 1B3 or 1-5 (the parental clone with one endogenous allele plus the ectopic allele). Dox (200 μg/ml) and/or 5% sucrose was added to the drinking water beginning 1 week before infection for induction. Parasites were counted with a hemocytometer.

Genotype	dox	Parasites ($\times 10^6$ per milliliter of blood)			
		66 hours	81 hours	105 hours	128 hours
1B3	–	3	1	0	0
	–	16	41	0	0
	+	10	232	*	
	+	0	4	78	955*
1-5	–	26	395	*	
	–	14	239	*	
	+	4	266	*	

*These mice died of the infection or were killed because of high parasitemia.

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Defective Lymphotoxin-β Receptor–Induced NF-κB Transcriptional Activity in NIK-Deficient Mice

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The role of NF-κB–inducing kinase (NIK) in cytokine signaling remains controversial. To identify the physiologic functions of NIK, we disrupted the NIK locus by gene targeting. Although NIK$^{-/-}$ mice displayed abnormalities in both lymphoid tissue development and antibody responses, NIK$^{-/-}$ cells manifested normal NF-κB DNA binding activity when treated with a variety of cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), and lymphotoxin-β (LTβ). However, NIK was selectively required for gene transcription induced through ligation of LTβ receptor but not TNF receptors. These results reveal that NIK regulates the transcriptional activity of NF-κB in a receptor-restricted manner.

apeutic targets for kinetoplastid pathogens, which employ RNA editing (such as African and American trypanosomes and *Leishmania*).

The transcription factor NF-κB is activated by a variety of cell surface receptors (*1*). Although different receptors often use distinct combinations of intracellular proteins to initiate NF-κB activation, the signals converge downstream into a common pathway

that leads to activation of the IκB kinase (IKK) complex and the phosphorylation and degradation of IκB (inhibitor of NF-κB) (*2–8*). The upstream kinases that activate the IKK complex are not defined (*1, 9*). However, the serine-threonine kinase NIK has been suggested to fulfill this role (*10, 11*). NIK was identified by its interaction with TRAF2, an adapter protein that interacts with TNF receptors (*10*). NIK was thought to be an integral component of the NF-κB signaling pathway because, when overexpressed in cells, wild-type NIK interacted with the IKK subunits IKKα and IKKβ, enhanced IKK complex kinase activity (*5*), and caused ligand-independent activation of NF-κB (*10, 11*). Moreover, kinase-inactive NIK inhibited NF-κB activation in cells treated with a variety of ligands (*10, 11*). Recent studies of alymphoplasia (*aly/aly*) mice, which have defective lymphorganogenesis and express a point mutant form of NIK that retains catalytic potential, suggest that NIK may function in NF-κB activation in a cell- or receptor-specific manner (*12–15*). However, the presence of the catalytically active mutant NIK protein in the *aly/aly* mouse makes it difficult to draw firm conclusions about the precise functional role of this protein.

To determine whether NIK plays an obligatory role in signal-induced NF-κB activation, we generated $NIK^{-/-}$ mice by gene targeting (*16*). Disruption of the NIK gene was verified by Southern and Western blot analyses. Although $NIK^{-/-}$ mice were born in Mendelian proportions and were grossly normal, they displayed abnormal lymphorganogenesis similar to that observed in *aly/aly* mice and mice lacking the LTβ receptor (LTβR) (*12, 17*). Specifically, they lacked all lymph nodes (including cervical, inguinal, mesenteric, popliteal, and axillary lymph nodes) and did not develop Peyer's patches (*18*). In addition, they showed an abnormal architecture of spleen and thymus, and formed only poor antibody responses upon immunization (*18*).

To assess whether NIK was required for TNF or IL-1 signaling, we treated $NIK^{-/-}$ or wild-type mouse embryonic fibroblasts (MEFs) with each ligand and assessed NF-κB DNA binding activity by electrophoretic mobility-shift assay (EMSA). No substantial differences were observed between the two cell types, even when different durations of stimulation or different doses of cytokine were used (Fig. 1, A and B). Moreover, activation of the IKK complex and c-Jun NH_2-terminal kinase (JNK) enzymes, which are known to be stimulated by these ligands, occurred equivalently in $NIK^{-/-}$ and wild-type MEFs (Fig. 1C). TNF and IL-1 also induced comparable biologic responses in $NIK^{-/-}$ and wild-type cells, including apoptosis (Fig. 1D) and production of IL-6 (Fig. 1E) or nitric oxide (Fig. 1F). Thus, NIK does not play an obligate role in either TNF or IL-1 signaling in fibroblasts. This conclusion was generalizable to other cell types from the $NIK^{-/-}$ mouse, such as bone marrow–derived macrophages (BMMs) and T cells, which developed wild-type levels of NF-κB DNA binding activity after TNF stimulation (Fig. 2A).

We also considered the possibility that NIK functioned to induce NF-κB DNA binding activity in a receptor-specific manner. As shown by EMSA, MEFs and BMMs from $NIK^{-/-}$ and wild-type mice formed equivalent amounts of DNA binding complexes after treatment with a variety of known NF-

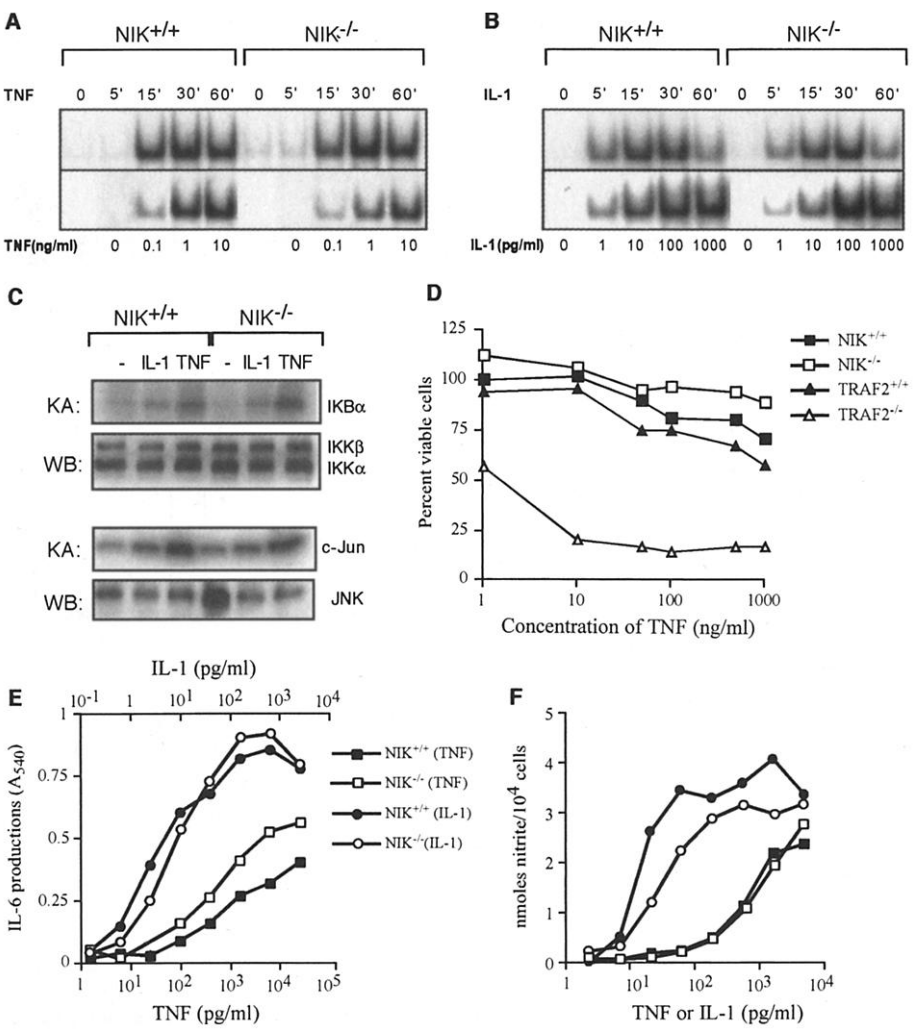

Fig. 1. $NIK^{-/-}$ MEFs display unimpaired signaling and biologic responsiveness to murine TNF and IL-1β. (**A** and **B**) Comparable activation of NF-κB DNA binding activity in $NIK^{-/-}$ or wild-type MEFs treated with TNF (A) or IL-1 (B) (10 ng/ml each) for the indicated numbers of minutes (top panel), or treated with the indicated doses of cytokines for 30 min (bottom panel). EMSA was performed as described using a probe derived from the immunoglobulin κ promoter (*21*). (**C**) In vitro kinase assays showing comparable activation of the kinase activity (KA) of the IKK complex and JNK in $NIK^{-/-}$ or wild-type MEFs incubated for 5 min with either IL-1 (50 ng/ml) or TNF (100 ng/ml). The IKK complex and JNK were immunoprecipitated, and kinase activities in the immunoprecipitates were determined using recombinant IκB or c-Jun proteins as substrates. IKKα, IKKβ, and JNK protein levels were assessed by Western blotting (WB). (**D**) $NIK^{-/-}$ and wild-type MEFs are similar in their sensitivity to TNF-dependent cytotoxicity. This assay was performed on cycloheximide-treated MEFs as described (*22*). $TRAF2^{-/-}$ MEFs were used as a pathway control. (**E**) Unimpaired cytokine-induced IL-6 production in $NIK^{-/-}$ cells. $NIK^{-/-}$ or wild-type MEFs were stimulated with various amounts of TNF or IL-1 for 24 hours, and IL-6 levels in culture supernatants were determined using the IL-6–dependent T1165 cell line. (**F**) Normal TNF- or IL-1–induced nitric oxide production by $NIK^{-/-}$ cells. MEFs were cultured with various amounts of TNF or IL-1 in the presence of murine interferon-γ (250 ng/ml), and the level of nitrite in the supernatants was determined as described (*23*).

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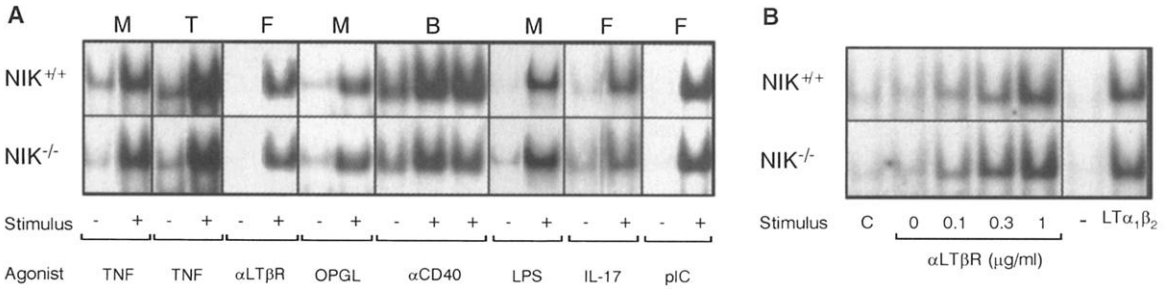
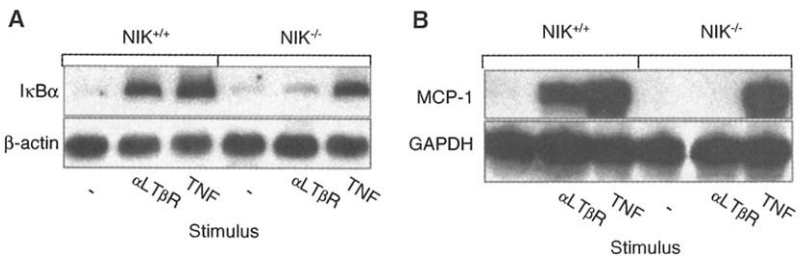


Fig. 2. Induction of NF-κB DNA binding activity in NIK$^{-/-}$ cells after stimulation with different agonists. (**A**) NIK$^{-/-}$ or wild-type BMMs (M), T lymphocytes (T), fibroblasts (F), or B lymphocytes (B) were stimulated with TNF (10 ng/ml, 30 min), LTβR mAb (*24*) (αLTβR; 1 μg/ml, 1 hour), osteoprotegerin ligand (OPGL; 100 ng/ml, 15 min), antibody to CD40 (αCD40; 10 μg/ml, 1 and 4 hours), lipopolysaccharide (LPS; 10 μg/ml, 1 hour), IL-17 (100 ng/ml, 30 min), or polyinosinic-polycytidylic acid (pIC; 100 μg/ml, 2 hours). NF-κB DNA binding activity was then assessed by EMSA. (**B**) NIK$^{-/-}$ or wild-type MEFs were stimulated with the indicated doses of LTβR mAb, irrelevant mAb (C, 1 μg/ml), or $LT\alpha_1\beta_2$ (Sigma; 100 ng/ml) for 1 hour and assayed by EMSA.



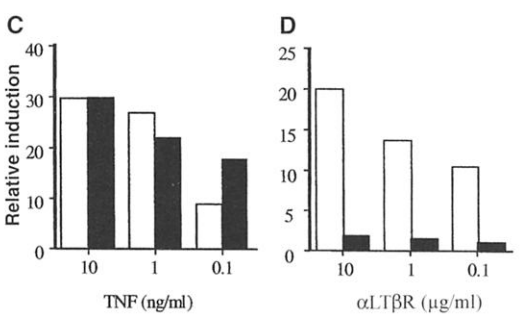


Fig. 3. Failure of NIK$^{-/-}$ cells to transcribe NF-κB–regulated genes after LTβR stimulation. (**A**) IκBα or β-actin gene expression was determined by Northern blotting for NIK$^{-/-}$ or wild-type MEFs treated for 8 hours with buffer, LTβR mAb (αLTβR, 1 μg/ml), or TNF (10 ng/ml). (**B**) RNA samples prepared as in (A) were assayed for gene expression using the RiboQuant multiprobe ribonuclease protection assay system and mCK-5 template (Pharmingen). In wild-type cells, the gene encoding MCP-1 was the only gene induced among those represented in the mCK-5 template upon LTβR mAb treatment. (**C** and **D**) Immortalized MEFs were transiently transfected using SuperFect reagent (Qiagen) with 1 μg of an $(NF\text{-}\kappa B)_2$-Luc reporter construct (*25*) together with 1 μg of pRL-TK (Promega) for transfection normalization. The transfected wild-type cells (open bars) or NIK$^{-/-}$ cells (filled bars) were stimulated with TNF (10 ng/ml) (C) or LTβR mAb (1 μg/ml) (D) for 6 to 8 hours, and luciferase activity was determined and normalized. Data are presented as relative induction of luciferase activity over the unstimulated control.

κB–activating stimuli (Fig. 2A). In contrast, NIK$^{-/-}$ B cells developed normal levels of NF-κB DNA binding activity after 1 hour of treatment with antibody to CD40 but showed reduced levels (relative to wild-type cells) 4 hours after stimulation. However, because B cells in NIK$^{-/-}$ mice are abnormal, it is not possible to determine whether this defect is attributable to an abnormality in signaling or cellular development. Because mice lacking NIK displayed a phenotype that was similar to LTβR-deficient mice, we studied LTβR signaling in the former in more detail. NIK$^{-/-}$ MEFs produced wild-type levels of NF-κB DNA binding activity after treatment with different doses of LTβR monoclonal antibody (mAb) or with the natural ligand for the LTβR (i.e., the $LT\alpha_1\beta_2$ complex) (Fig. 2B). Thus, NIK is not required for promoting NF-κB DNA binding activity by a variety of receptors on different cells.

We next examined whether NIK regulates the transcriptional activity of the activated NF-κB complex. To test this hypothesis, we monitored the capacity of TNF or LTβR mAb to induce expression of representative NF-κB–responsive genes in wild-type and NIK$^{-/-}$ cells. In wild-type MEFs, both LTβR mAb and TNF induced the genes encoding IκBα (Fig. 3A) and monocyte chemoattractant protein–1 (MCP-1, Fig. 3B). These genes were also induced by TNF in NIK$^{-/-}$ cells. In contrast, neither gene was induced in NIK$^{-/-}$ MEFs after LTβR mAb stimulation. Further experiments tested whether this unresponsiveness was due to a defect in the transcriptional activity of the NF-κB complex. Using a luciferase reporter gene construct driven by an NF-κB responsive element, we found that TNF induced comparable levels of luciferase in wild-type and NIK$^{-/-}$ MEFs (Fig. 3C). Reporter gene activation was also consistently observed in wild-type MEFs treated with LTβR mAb (Fig. 3D). In contrast, no reporter activity was observed in NIK$^{-/-}$ MEFs treated with a wide range of doses of LTβR mAb (Fig. 3D). Thus, even though engagement of LTβR induces normal DNA binding activity of NF-κB in NIK$^{-/-}$ cells, the activated NF-κB in these cells cannot transactivate (at least some) NF-κB–regulated genes.

These results show that NIK is not the common upstream kinase that activates IKKs in the NF-κB signaling pathway, as previously proposed (*10, 11*). Rather, NIK acts in a receptor-selective manner, and its function is limited in the case of the LTβR to promoting the transcriptional action of the NF-κB complex. Hence, the function of NIK in LTβR signaling may be similar to that of glycogen synthase kinase–3β or the T2K/TBK1/NAK kinase, which function in TNF and IL-1 signaling to induce NF-κB transcriptional activity without altering IκB degradation or NF-κB nuclear translocation (*19, 20*). Thus, different receptors that signal through NF-κB may use distinct serine kinases to regulate the transcriptional activity of the activated NF-κB complex. In this manner, the NF-κB signal emanating from each type of receptor may be slightly different and thereby effect distinctive cellular response patterns after receptor stimulation.

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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-

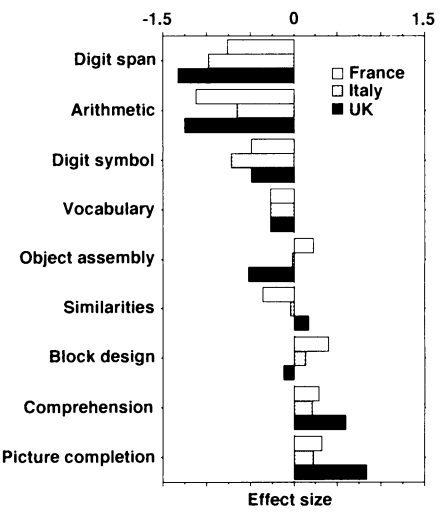

Fig. 1. Effect size (Z-scores) of the differences between dyslexic and normal readers in each country on Wechsler scale subtests. Z-scores were derived from the group differences expressed in standard deviation (SD) units using pooled SDs. Negative Z-scores represent impaired performance. The dyslexics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

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