

Neurobiology of dyslexia: a reinterpretation of the data

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Theories of developmental dyslexia differ on how to best interpret the great variety of symptoms (linguistic, sensory and motor) observed in dyslexic individuals. One approach views dyslexia as a specific phonological deficit, which sometimes co-occurs with a more general sensorimotor syndrome. This article on the neurobiology of dyslexia shows that neurobiological data are indeed consistent with this view, explaining both how a specific phonological deficit might arise, and why a sensorimotor syndrome should be significantly associated with it. This new conceptualisation of the aetiology of dyslexia could generalize to other neurodevelopmental disorders, and might further explain heterogeneity within each disorder and comorbidity between disorders.

Developmental dyslexia is a mild hereditary neurological disorder that manifests as a persistent difficulty in learning to read in children with otherwise normal intellectual functioning and educational opportunities. Researchers typically attempt to characterize dyslexia at the genetic, neurobiological and cognitive levels of description, and to uncover causal pathways between the different levels.

One notable aspect of dyslexia that puzzles theorists and causes much confusion is the variety of symptoms that are consistently associated with it: problems with reading, of course, but also problems with phonology (the mental representation and processing of speech sounds), sensory difficulties in the visual, auditory and tactile domains, problems with balance and motor control, and more [1,2]. Another puzzle is that dyslexia is frequently comorbid with other neurodevelopmental disorders, such as specific language impairment (SLI), attention deficit hyperactivity disorder (ADHD) or dyspraxia [3,4].

This plurality of symptoms has led to two broad approaches to dyslexia. One has been to concentrate on one particular cognitive symptom thought to reflect the most direct causal explanation: for instance, in the phonological theory of dyslexia [5] (Figure 1a), a specific deficit in the representation and processing of speech sounds is thought to cause difficulty in learning and handling the relationship between letters and speech sounds (grapheme–phoneme correspondences). Within this approach, the other symptoms of dyslexia are

considered as simple comorbid markers, without causal relationship with the reading disability.

Conversely, the alternative theoretical approach gives a primary explanatory role to the sensory and/or motor symptoms. This approach has led to the formulation of theories of dyslexia tracing the causes of reading disability back to auditory (temporal) processing deficits (via the phonological deficit) [6,7], visual (magnocellular) dysfunction [8,9] and/or motor (cerebellar) dysfunction [10,11]. The culminating point of this approach has been the unification of its different variants under the general magnocellular theory (Figure 1b), in which a generalized dysfunction of cells in the magnocellular pathway affects all sensory modalities and prolongs itself in the posterior parietal cortex and the cerebellum [1]. Uniquely, this theory accounts for reading disability both through auditory–phonological and visual–spatial deficits, and encompasses all known cognitive, sensory and motor manifestations of dyslexia.

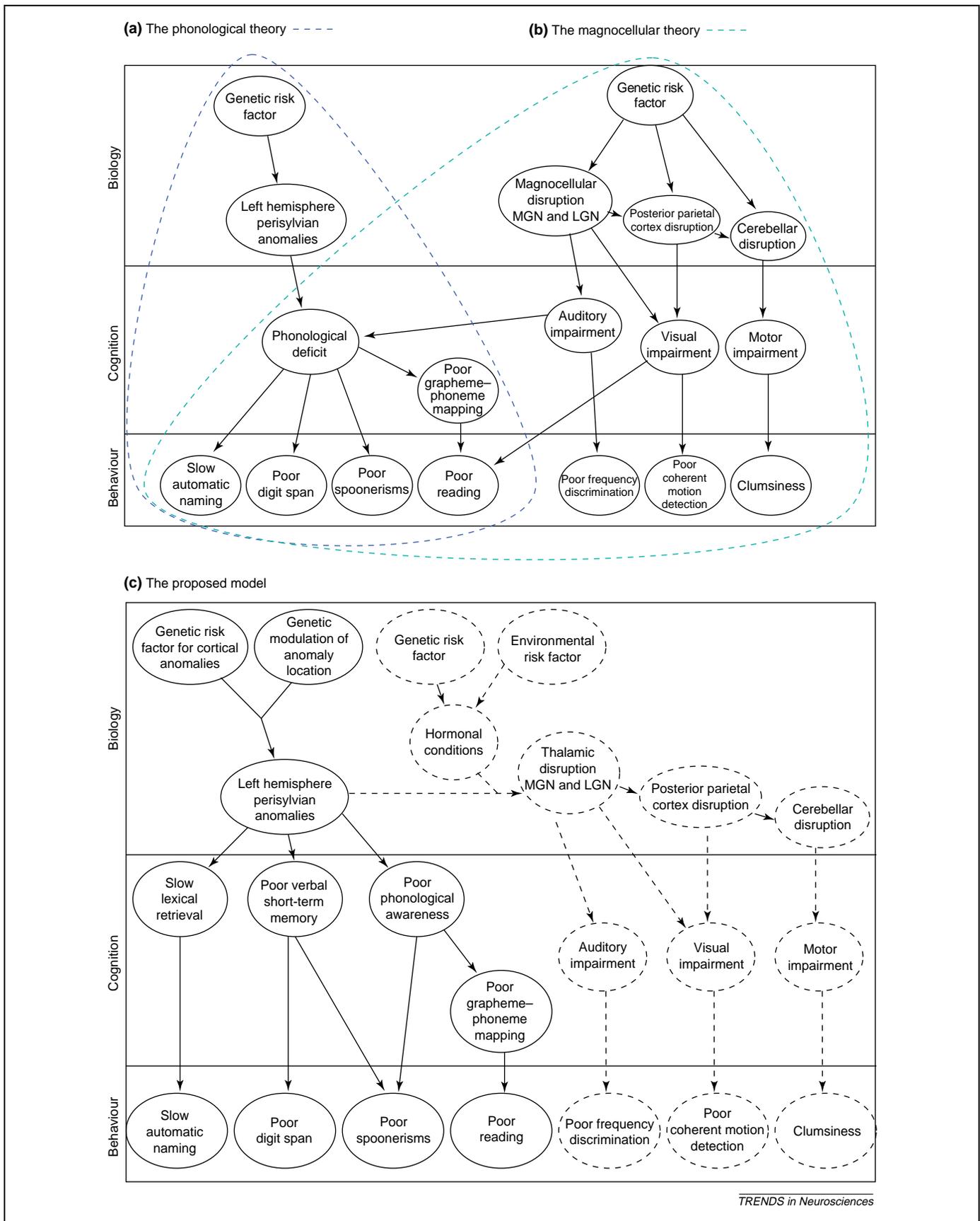
However, as I have argued elsewhere [2,12], the magnocellular theory only partly succeeds in explaining the whole dataset. In particular, it fails to explain why the prevalence of sensorimotor dysfunction is so much lower than that of the phonological deficit in the dyslexic population. Even within the subset of dyslexics affected by sensory and/or motor disorders, the causal relationship with the reading impairment is far from clear [2,13]. On the basis of a comprehensive review of the literature, I have previously advocated that dyslexia is, in most individuals, explained by a specific phonological deficit; furthermore, a general sensorimotor syndrome occurs more often in the dyslexic than in the general population, but does not by itself play a significant causal role in the aetiology of the reading impairment [2]. This paper reviews the neurobiology of dyslexia and argues that the available data do indeed support this view, by explaining both how a specific phonological deficit might arise and why a sensorimotor syndrome should be significantly associated with it.

Data from anatomical studies

Post-mortem examination and brain imaging studies have documented many differences between dyslexic and control brains, for example in the left perisylvian cortex, the underlying white matter, the thalamus, the corpus callosum, and the cerebellum (see Refs [14,15] for reviews). In most cases, the functional significance of

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Figure 1. Three causal models of the aetiology of developmental dyslexia. Ovals represent traits at the biological, cognitive and behavioural levels of description; arrows represent causal relationships between traits. Only a subset of all possible behavioural manifestations is represented. **(a)** Traits and relationships postulated by the phonological theory. **(b)** Traits and relationships postulated by the magnocellular theory. **(c)** The proposed model. Solid lines are used for core traits of developmental dyslexia, dashed lines for associated traits that are not necessarily present in each affected individual. Cases of comorbidity with other developmental disorders (e.g. specific language impairment) are not represented. Abbreviations: LGN, lateral geniculate nucleus; MGN, medial geniculate nucleus.

these brain differences has not been elucidated. It is not even clear which of those differences are specifically relevant to dyslexia, given comorbidity issues. Nevertheless, the functional significance of two types of brain anomaly has been studied in greater detail.

Anomalies of cell migration (molecular layer ectopias and focal microgyri) have been observed by Galaburda and colleagues in the perisylvian cortex of dyslexic brains [16–18], predominantly in the left hemisphere, and with a much greater prevalence than in control brains [19]. Ectopias consist of 50–100 neurons (and glia) that, in the course of neural migration, have missed their target in the cortex and have escaped into the molecular layer through a breach in the external glial limiting membrane, accompanied by mild disorganization of the subjacent cortical layers (Figure 2). Microgyri are more severe disturbances where organization of all layers of the cortex is severely affected. Cytoarchitectonic anomalies have also been observed in the thalamus of dyslexics: in the lateral geniculate nucleus (LGN), the magnocellular layers were more disorganized and contained smaller cell bodies [9]. Similarly, there was a disproportionate number of small neurons in left medial geniculate nucleus (MGN) of dyslexics [20].

It is natural to hypothesize that anomalies in the magnocellular layers of the LGN are the cause of visual deficits, and that anomalies in the MGN are the cause of auditory deficits. Similarly, it is easy to see cortical anomalies in left perisylvian areas as the underlying cause of phonological, and perhaps other, cognitive difficulties.

In this anatomical evidence, one can therefore see direct neurological support for auditory and magnocellular theories of dyslexia. The implicit causal (bottom-up) scenario is that anomalies in the thalamus engender ectopias and microgyri in certain cortical areas to which the thalamus is connected. At the cognitive level, this would translate into the auditory deficit causing a phonological deficit, and into the basic visual deficit causing visual–spatial attentional problems, as prescribed

by the magnocellular theory. However, this scenario might well be incorrect [21]. Indeed, Galaburda and colleagues have found that, at least in animal models, the causal direction seems to be the opposite (top-down) – that is, the cortical anomalies engender the thalamic anomalies.

More insights from animal models

In rats, one can surgically induce ectopias and microgyri by poking a hole in the external glial limiting membrane of the developing cortex during late neocortical neuronal migration. There are also strains of mutant mice that spontaneously develop similar malformations. Investigation of these animal models has led to several important findings.

First, newborn rats with microgyri in the frontal, parietal or occipital cortex subsequently develop anomalies in the MGN: they have more small and fewer large neurons than rats receiving sham lesions, a disruption similar to that found in the MGN of dyslexics [22,23]. This suggests that the direction of causation is indeed top-down, from the cortex to sensory relays in the thalamus. Furthermore, rats with this type of abnormal MGN performed less well in an auditory discrimination task [22–24], which confirms that the observed disruption in the MGN has an impact on auditory capacities. Similar auditory disorders are found in mice with ectopias [25], suggesting that this top-down scenario might also occur when cortical malformations have a genetic origin. Extrapolated to dyslexia, these findings suggest that the neural basis of the phonological deficit could be primary, whereas the neural basis for sensory impairments would be secondary.

Another interesting aspect uncovered in these studies is that only male rats and mice with microgyri or ectopias were initially found to have impaired auditory function [26,27]. Female rats showed normal auditory performance and did not show a similar anatomical disruption of the MGN, even though they presented with microgyri as severe as those in males [22]. It was then found that this sex difference had a hormonal basis; indeed, female rats that were androgenized by injection of testosterone during gestation showed MGN disruption and impaired auditory function in the same way as males [28]. This therefore suggests that the neural basis for the phonological deficit can occur either with or without the secondary sensory impairments, depending on whether certain hormonal conditions are met.

Finally, the cortical anomalies themselves seem to have an impact on cognitive function: mice and rats with spontaneous or induced ectopias and microgyri exhibit a variety of learning deficits [29–32], including problems with working memory [33–35]. Furthermore, the location of the cortical disruption influences the specific type of learning deficit exhibited by the animal [36,37], but not the likelihood of further thalamic disruption and sensory impairment [25]. This suggests that the location of cortical abnormalities will be crucial to the nature of the cognitive deficits observed in dyslexia, whereas sensory impairments can be expected to arise regardless of the cortical locus and specific type of cognitive deficit.

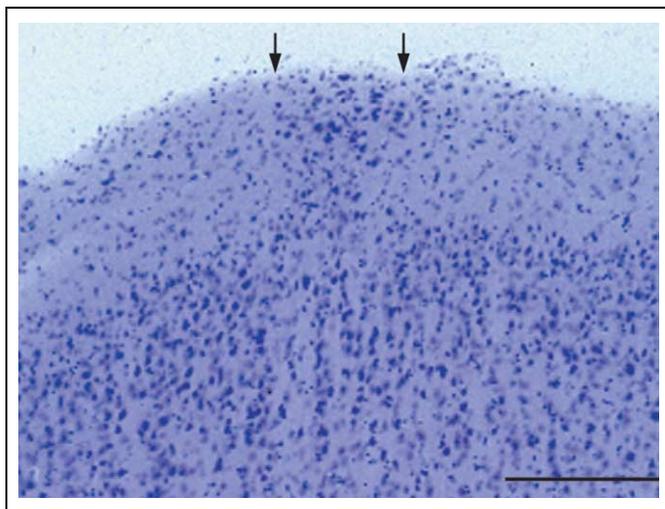


Figure 2. A molecular layer ectopia in a dyslexic subject. Neurons and glia have escaped into the molecular layer of the cortex, through a breach in the external glial limiting membrane, to form an ectopia (between the two arrows). Scale bar, 250 μ m. Micrograph kindly provided by Glenn D. Rosen.

Scaling up to dyslexia

Although the data already reviewed here are not sufficiently constraining to specify a single neurobiological model of dyslexia, they seem most compatible with one based on the following hypotheses (Figure 1c):

- Genetically driven focal cortical abnormalities such as ectopias and microgyri, in specific areas of left perisylvian cortex involved in phonological representations and processing, are the primary cause of dyslexia (Figure 3). This is consistent with: (i) anatomical studies of dyslexic brains showing loci of cortical abnormalities; (ii) functional brain imaging studies showing that the very same areas are involved in phonological processing, and show abnormal activation in dyslexics; (iii) mouse models with ectopias, as already discussed; and (iv) recent findings that the dyslexia susceptibility gene *DYX1C1* is involved in neural migration, and that the deletion found in a dyslexic family disrupts its function (Y. Wang *et al.*, unpublished).

- Under certain hormonal conditions (which might or might not reduce to elevated levels of foetal testosterone), the disruption propagates to the thalamus, provoking additional (and optional) sensory impairments. This is

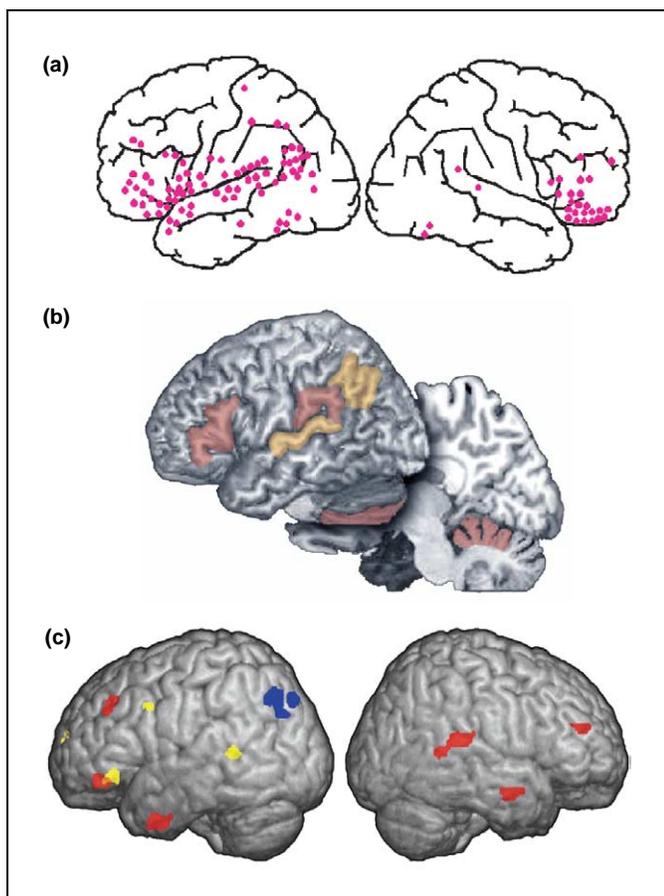


Figure 3. Neurobiology of developmental dyslexia. (a) Overall distribution of cortical ectopias observed across different dyslexic subjects (kindly provided by Glenn D. Rosen). (b) Brain areas activated in oral language tasks and exhibiting structural differences between dyslexics and controls. Areas in orange are supported by one published study, areas in red by more than one. Reproduced, with permission of Sage Publications, Inc., from Ref. [15]. (c) Brain areas activated during performance of the main phonological skills impaired in dyslexia: phonological awareness (yellow), rapid serial naming (red) and verbal short-term memory (blue). Reproduced, with permission, from Ref. [39].

consistent with rat and mouse models and the fact that sensory disorders are present in some, but not all, dyslexic individuals. Whether this thalamic disruption is specifically magnocellular is a subject of debate [1,9,38] and is not particularly crucial to the present model. Similarly, Stein and Walsh propose that the magnocellular disruption further extends to the posterior parietal cortex and the cerebellum [1]. If true, this might well explain the visuospatial and motor symptoms observed in certain dyslexics.

In summary, not only do cognitive studies suggest that dyslexia is a specific phonological deficit associated with an optional sensorimotor syndrome, but also the neurobiological data seem perfectly compatible with this view and able to explain how this might be.

Explaining heterogeneity within dyslexia

One essential aspect of the proposed model is that it assumes that focal cortical abnormalities disrupt the development of the particular cognitive function(s) that would normally recruit those areas. Of course, there is not one single area assumed to be involved in phonological processing that would be disrupted in dyslexia. Rather, the phonological deficit of dyslexics is usually described as having three main components: poor phonological awareness (the ability to access and manipulate speech sounds consciously), slow lexical retrieval (evidenced in rapid serial naming tasks) and poor verbal short-term memory (as tested by digit span or non-word repetition). Each of these phonological skills in turn involves a whole network of cortical areas [39] (Figure 3c). Interestingly, the observed distribution of ectopias in dyslexic brains closely matches this network (compare Figure 3a with Figure 3c) as well as larger-scale structural anomalies (Figure 3b). But note that dyslexic brains vary in terms of both the number and the distribution of their ectopias. This suggests that there might be several ways to become dyslexic, depending on which subset of the phonological skills network is affected. This is indeed consistent with data showing that the different components of the phonological deficit vary partly independently and provide additive contributions to the reading disability [40]. In brief, variation in the symptoms of the phonological deficit might straightforwardly reflect variation in the distribution of the underlying cortical abnormalities.

Generalizing to other developmental disorders

From these premises, one might of course expect focal cortical abnormalities to sometimes arise outside the phonological network. By the same logic, one would then predict disruption to the development of the corresponding cognitive functions. This could provide a way to explain neurodevelopmental disorders other than dyslexia. For instance, ectopias in areas involved in syntax, morphology and/or the lexicon might engender the various manifestations of SLI. Similar abnormalities in the relevant areas might also explain developmental dyscalculia, developmental prosopagnosia, and at least some forms of autism, ADHD or dyspraxia.

It is particularly interesting to note that, as in dyslexia, a certain proportion of individuals affected by the

disorders just mentioned present with just the same sort of sensorimotor impairments [3,41–45]. Animal models suggest a straightforward explanation for this: in both mice and rats, thalamic disruption occurred under the conjunction of high foetal testosterone and ectopias or microgyri, whatever the location of these cortical abnormalities.

Therefore, the present model potentially explains not only the specific cognitive deficits characterizing many developmental disorders, but also the fact that these disorders are associated with an optional sensorimotor syndrome: in all disorders, additional hormonal conditions are the mediating factor to the sensorimotor symptoms.

Explaining comorbidity between disorders

Finally, the postulated structure–function relationship also provides an explanation for the typical comorbidity between different developmental disorders. Indeed, nothing restricts the distribution of cortical abnormalities within a given cognitive domain. If ectopias span, say, both the phonological and the syntactic systems, then the outcome would be a case of comorbid dyslexia and SLI. All other observed comorbidities can be explained accordingly.

Generating new predictions

One straightforward prediction of the model is that a whole class of domain-specific developmental disorders is characterized by similar focal brain anomalies, the differences between disorders reducing to differences in localization. Unfortunately, post-mortem work has been extremely limited past the original studies. Brain imaging studies of dyslexia, SLI and dyscalculia are certainly compatible with the present prediction [15] but, owing to resolution limitations, they are currently insufficient to test it seriously. Research on the neurobiology of autism and ADHD has shown rather different types of abnormalities [46,47], but this does not exclude the possibility that certain cases of these disorders might be explained by focal anomalies of the same nature as dyslexia in relevant brain areas.

Because of the steroid hormonal mediation leading to the thalamic disruption, the model also predicts an increased prevalence of the sensorimotor syndrome in males (regardless of the actual sex ratio in dyslexia). More precisely, it predicts that the male:female ratio will be increased in the subpopulation with a sensorimotor syndrome, as compared with the subpopulation without it (in dyslexia as well as in other developmental disorders). Such predictions could be easily tested by carrying out post-hoc analyses on already existing datasets including reliable individual data on sensory and/or motor measures.

Another prediction of the model is that if one could measure the relevant hormonal conditions in human foetuses, and relate these measures to later outcome measures of sensorimotor functions, there would be significant correlations (more than with measures of each specific cognitive deficit). Only major longitudinal studies including all the relevant measures will be able to test this prediction. In the meantime, one might want to look for markers of foetal hormonal conditions that persist

throughout development. A possible one is the ratio between the lengths of the second and fourth digits (2D:4D ratio), which is inversely correlated to foetal testosterone levels [48] and significantly lower in autism than in the general population [49]. A recent replication further found that the 2D:4D ratio was more specifically correlated with the performance of autistic children in visual and motor tasks [50], which is consistent with the model (applied to autism), although the evidence is still very preliminary and indirect.

The high heritability of developmental disorders such as dyslexia and SLI is consistent with the clear genetic origin of ectopias and related focal anomalies [51,52] (Y. Wang *et al.*, unpublished). Furthermore, unless total cross-heritability between different disorders is shown, the model also predicts that the precise location of cortical anomalies is under genetic control. This is consistent with the fact that different strains of mutant mice have ectopias in different locations [29], but the exact mechanisms influencing their location are still unknown.

By contrast, foetal hormonal conditions are more likely to be influenced by non-genetic factors. The model therefore predicts a lower heritability of the sensorimotor syndrome than of specific cognitive deficits, which is indeed the case (for auditory and visual versus phonological deficits) [53–55].

It is also notable that all the specific cognitive disorders under consideration here have a complex genetic aetiology, involving several regions on different chromosomes [56]. One way to understand this is to speculate that in these disorders, certain genes are general susceptibility factors for focal anomalies such as ectopias, whereas other genes control the precise location of such anomalies, for instance by generating molecular gradients interacting with ectopia susceptibility factors. This broadly predicts that the genes implicated in all these specific cognitive disorders will be partly shared (those acting as general susceptibility factors), and partly specific to each disorder (those determining specific brain locations). The more specific predictions are potentially testable using current mouse models.

Concluding remarks

The model outlined here is compatible with all the available cognitive and neurobiological evidence and, uniquely, also offers potential explanations for the association between specific cognitive developmental disorders and sensorimotor manifestations, heterogeneity within each disorder, and comorbidity between disorders.

Future research should now aim to uncover the precise links between specific genes, brain anomalies and cognitive deficits. To meet that challenge, research on developmental disorders will have to complete a methodological revolution that has only recently begun: the production and analysis of reliable individual data at all levels of description. Indeed, the present model suggests that several genetic, neurological and cognitive traits are consistently associated with dyslexia and other disorders, without actually explaining them. This implies that the usual studies focusing on group differences and correlations between measures are doomed to confuse core with

associated deficits, and cause with correlation. The future belongs to longitudinal studies that will be able to trace causal pathways throughout development, across genetic, neurological and cognitive measures, and within each individual subject.

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