

## **Neurobiology of dyslexia : A reinterpretation of the data**

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### **Keywords**

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### **Teaser**

A new model that attempts to explain how a specific phonological deficit may arise from genetically determined brain anomalies, in isolation in certain individuals, and together with sensorimotor impairments in others.

### **Abstract**

Theories of developmental dyslexia differ on how to best interpret the great variety of symptoms (linguistic, sensory, motor) observed in dyslexic individuals. One approach views dyslexia as a specific phonological deficit, which sometimes co-occurs with a more general sensorimotor syndrome. The present review of 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 may generalise to other neuro-developmental disorders, and may further explain heterogeneity within each disorder and co-morbidity between disorders.

Developmental dyslexia is a mild hereditary neurological disorder which manifests itself as a persistent difficulty in learning to read in children with otherwise normal intellectual functioning and educational opportunities. Researchers typically attempt to characterise 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 neuro-developmental 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 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 generalised dysfunction of magno-cells affects all sensory pathways and prolongs itself in the posterior parietal cortex and the cerebellum[1]. Quite uniquely, this theory accounts for reading disability both through auditory/phonological and visual-spatial deficits, and encompasses all the 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 data set. 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 does 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***

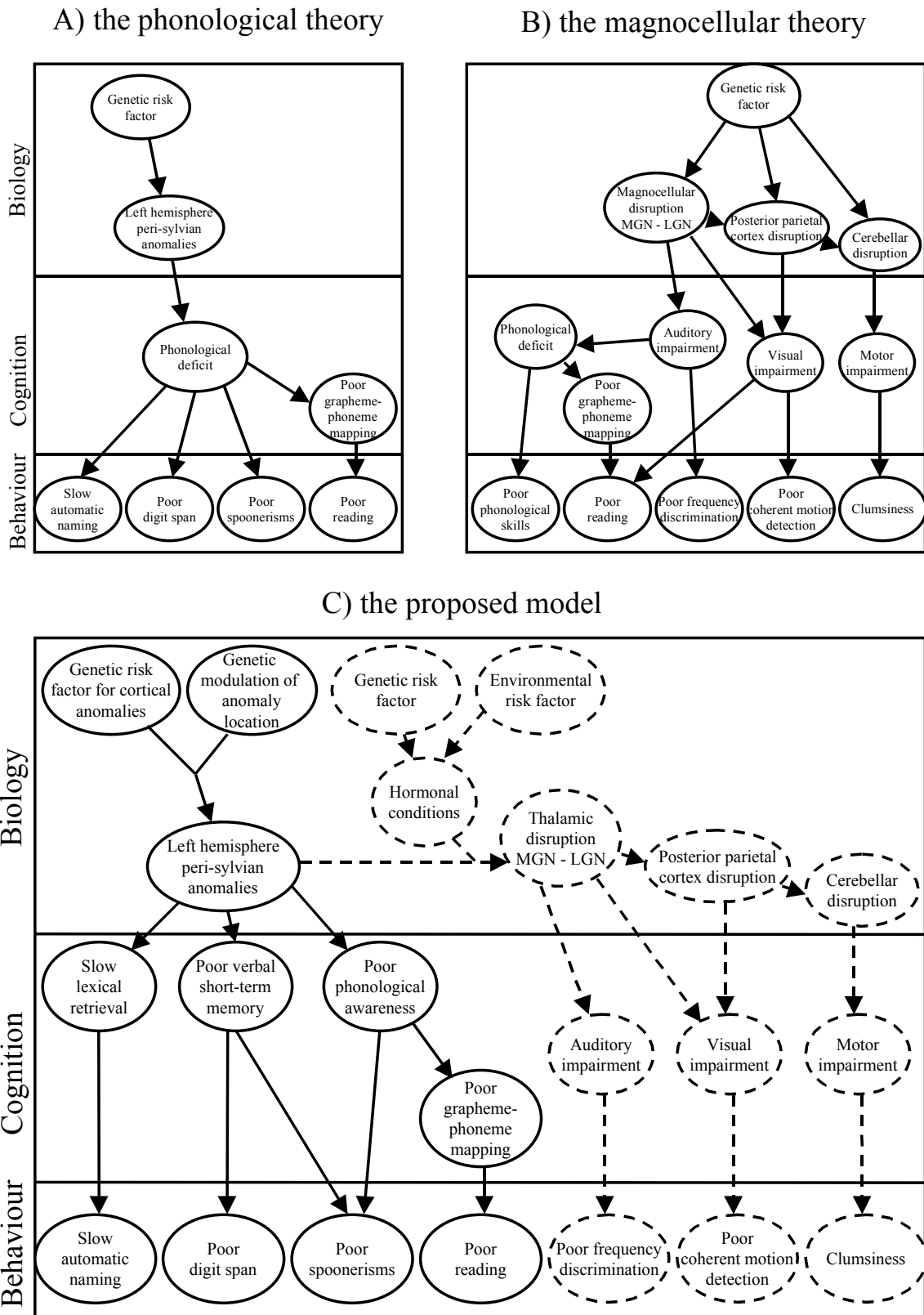
Post-mortem examination and brain imaging studies have documented many differences between dyslexic and control brains, in the left peri-sylvian cortex, the underlying white matter, the thalamus, the corpus callosum, the cerebellum, etc. [see 14,15 for reviews]. In most cases, the functional significance of 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 anomalies 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 peri-sylvian 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 have escaped into the molecular layer of the cortex through a breach in the external glial limiting membrane, accompanied by mild disorganisation of the subjacent cortical layers (Figure 2). Microgyri are more severe disturbances where the organisation of all layers of the cortex is severely affected. Cytoarchitectonic anomalies have also been observed in dyslexics' thalamus: in the lateral geniculate nucleus (LGN), the magnocellular layers were more disorganised and with smaller cell bodies[9]. Similarly, there was a disproportionate number of small neurons in dyslexics' left medial geniculate nucleus (MGN)[20].

It is quite natural to hypothesise 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 peri-sylvian areas as the underlying cause of phonological, and perhaps other cognitive difficulties.

Figure 1. Three causal models of the aetiology of developmental dyslexia.

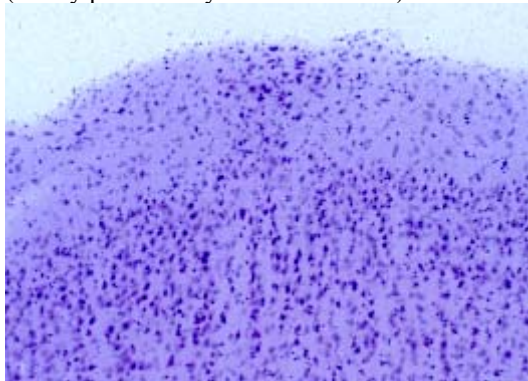
Bubbles represent traits at the biological, cognitive and behavioural levels of description. Arrows represent causal relationships between traits. Only a subset of all possible behavioural manifestations are represented. (A) The phonological theory. (B) The magnocellular theory. (C) The proposed model. Solid lines are used for core traits of developmental dyslexia, dashed lines for optional, associated traits. Cases of co-morbidity with other developmental disorders (e.g., SLI) are not represented. LGN: lateral geniculate nucleus. MGN: medial geniculate nucleus.



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 may 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), i.e., that the cortical anomalies engender the thalamic anomalies.

**Figure 2. A molecular layer ectopia in a dyslexic subject.**

(kindly provided by Glenn D. Rosen).



### ***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 have led to a number of important findings.

First of all, 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 dyslexics' MGN[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 were found to perform 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 ectopic mice[25], which suggests that this top-down scenario may also occur when cortical malformations have a genetic origin. Extrapolated to dyslexia, these findings suggest that the neural basis of the phonological deficit may be primary, while the neural basis for sensory impairments would be secondary.

Another interesting aspect uncovered in these studies is that only male rats and mice were initially found to have impaired auditory function following microgyri or ectopias[26,27]. Indeed, female rats showed normal auditory performance and did not show a similar anatomical disruption of the MGN in response to the microgyri, even though their cortical lesions were as widely distributed[22]. It was then found that this sex difference had a hormonal basis; indeed, female rats that were androgenised by injection of testosterone during gestation showed disrupted MGN and impaired auditory function like males[28]. This therefore suggests that the neural basis for the phonological deficit may 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: ectopic 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, while sensory impairments can be expected to arise regardless of the cortical locus and specific type of cognitive deficit.

### ***Scaling up to dyslexia***

Although the data reviewed above 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):

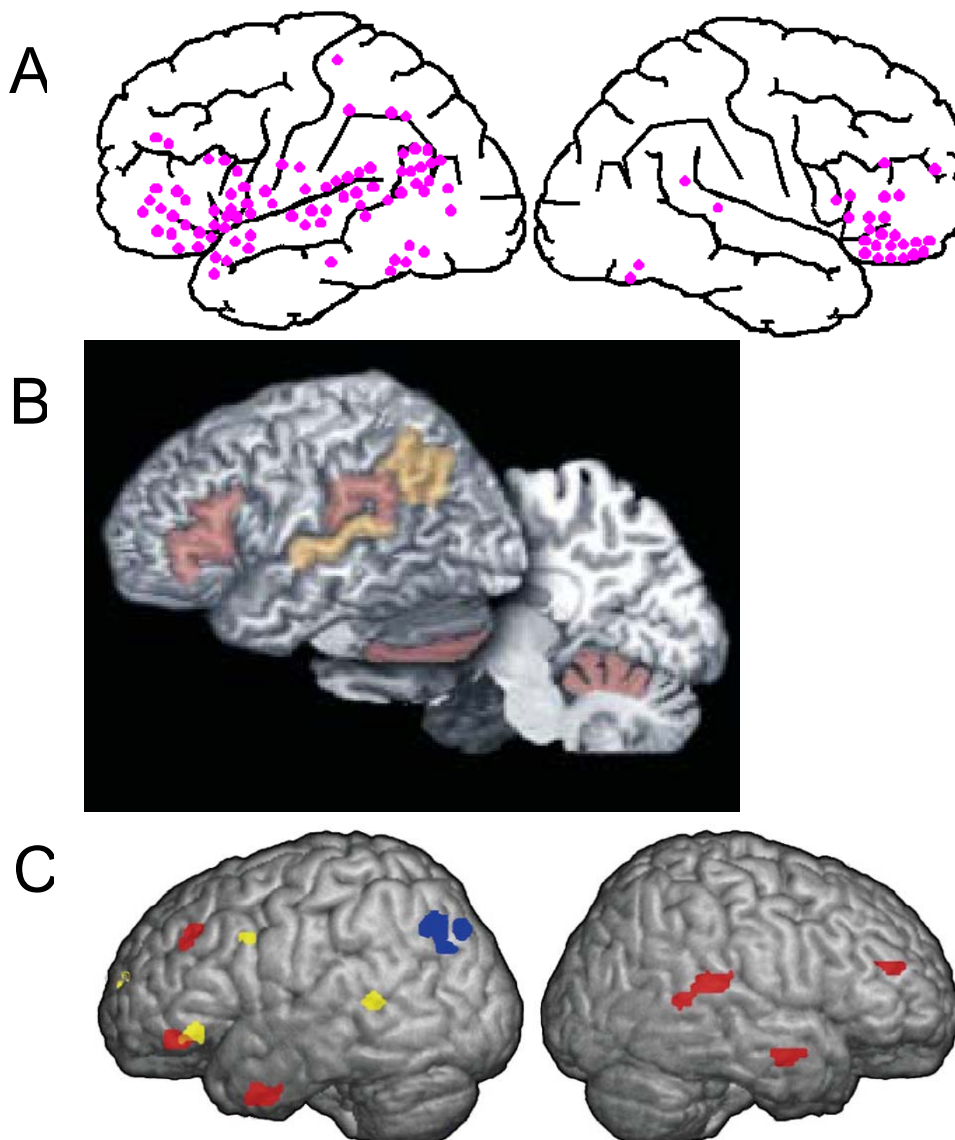
- Genetically driven focal cortical abnormalities such as ectopias and microgyri, in specific locations of left perisylvian cortex involved in phonological representations and processing, are the primary cause of dyslexia (Figure 3). This is consistent with 1) anatomical studies of dyslexic brains showing loci of cortical abnormalities; 2) functional brain imaging studies showing that the very same areas are involved in phonological processing, and show abnormal activation in dyslexics; 3) ectopic mouse models as discussed above; 4) 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[38].
- Under certain hormonal conditions (which may or may not reduce to elevated levels of fetal testosterone), the disruption propagates to the thalamus, provoking additional (and optional) sensory impairments. This is consistent with 1) rat and mouse models; 2) the fact that sensory disorders are present in some, but not all, dyslexic individuals.

This thalamic disruption may or may not be specifically magnocellular[1,9]; this point is a subject of debate[39] and is not particularly crucial to the present model. Similarly, Stein & Walsh propose that the magnocellular disruption further extends to the posterior parietal cortex and the cerebellum[1]. If this is true, then this might well explain the visuo-spatial 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 the neurobiological data seems perfectly compatible with this view and able to explain how this might be.

### 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 from Ref. [15]). (C) Brain areas activated during performance of the main phonological skills impaired in dyslexia: phonological awareness (yellow), rapid serial naming (red), verbal short-term memory (blue) (reproduced with permission from Ref. [40]).



## ***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, dyslexics' phonological deficit is usually described as having three main components: poor phonological awareness (ability to consciously access and manipulate speech sounds), 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[40] (Figure 3C). Interestingly, the observed distribution of ectopias in dyslexic brains quite closely matches this network (compare with Figure 3A) as well as larger-scale structural anomalies (Figure 3B). But note that dyslexic brains vary in terms of both the number of ectopias they present, and their distribution. This suggests that there may 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[41]. In brief, variation in the symptoms of the phonological deficit may straightforwardly reflect variation in the distribution of the underlying cortical abnormalities.

## ***Generalising to other developmental disorders***

From these premises, one may 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 may provide a way to explain other neuro-developmental disorders than dyslexia. For instance, ectopias in areas involved in syntax, morphology and/or the lexicon might engender the various manifestations of specific language impairment (SLI). Similar abnormalities in the relevant areas may also be able to explain developmental dyscalculia, developmental prosopagnosia, and at least some forms of autism, ADHD or dyspraxia.

It is particularly interesting to note that like in dyslexia, a certain proportion of individuals affected by the disorders mentioned above present with just the same sort of sensorimotor impairments[3,42-46]. Animal models suggest a straightforward explanation for this: in both mice and rats, thalamic disruption occurred under the conjunction of high fetal testosterone and ectopias or microgyri, *whatever the location of these cortical abnormalities*.

Therefore, the present model not only potentially explains the specific cognitive deficits characterising 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 may be explained accordingly.

## ***Generating new predictions***

One straightforward prediction of the model is that a whole class of domain-specific developmental disorders are characterised by similar focal brain anomalies, the differences between disorders reducing to differences in localisation. 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 and Figure 3], but owing to resolution limitations they are currently insufficient to seriously test it. On the other hand, research on the neurobiology of autism and ADHD has shown rather different types of abnormalities[47,48], 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 to 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 data sets 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 to be found (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 may want to look for markers of foetal hormonal conditions that persist throughout development. A possible one is the ratio between the length of the second and that of the fourth digit (2D:4D) which has been shown to be inversely correlated to foetal testosterone levels[49], and significantly lower in autism than in the general population[50]. A recent replication further found that the 2D:4D ratio was more specifically correlated with autistic children's performance in visual and motor tasks[51], which is consistent with the model (applied to autism), although still very preliminary and indirect.

The high heritability of developmental disorders like dyslexia and SLI is consistent with the clear genetic origin of ectopias and related focal anomalies[38,52,53]. 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.

On the other hand, 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 vs. phonological deficits) [54-56].

It is also notable that all the specific cognitive disorders under consideration here have a complex genetic aetiology involving several regions on different chromosomes (e.g. [57]). One way to understand this is to speculate that in these disorders, certain genes are general susceptibility factors for focal anomalies like ectopias, while 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.

## **Conclusion**

The model outlined here is both compatible with all the available cognitive and neurobiological evidence, and, quite uniquely, 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. In order 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 a number of 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 and associated deficits, cause and 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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