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A neurological model of dyslexia and other domain-specific developmental disorders with an associated sensorimotor syndrome

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Abstract

Given mounting evidence that auditory, visual and/or motor dysfunction may not cause developmental dyslexia, but are often associated with it, the present paper proposes a new neurological model of dyslexia which explains how a specific phonological deficit might arise, and sometimes occur together with a more general sensorimotor syndrome. Based on a review of the neurology of dyslexia, the model specifies that: 1) Genetically determined focal cortical anomalies in specific left perisylvian language areas are the underlying cause of the phonological deficit; 2) This phonological deficit is the primary cause of reading impairment; 3) Under certain hormonal conditions during gestation, these cortical anomalies induce secondary disruption in sensory pathways, notably in the thalamus. The disruption may even extend to further areas, like the posterior parietal cortex and even the cerebellum; 4) When this happens, the individual affected displays one or several components of a sensorimotor syndrome, which may in some cases aggravate the reading impairment. The model generalises to specific language impairment and possibly to other domain-specific developmental disorders, each particular disorder being characterised by the specific location of the brain anomalies.

Introduction

Certain developmental disorders, including dyslexia, specific language impairment (SLI), and autism, are the subject of considerable controversy regarding their neurological and cognitive origins. Certain theoreticians consider them to be domain-specific disorders, arising from congenital dysfunctions circumscribed to certain cognitive components, e.g., phonology, syntax, or mentalising, respectively (Snowling 2000; Gopnik 1997; Frith 2003; van der Lely, Rosen, and McClelland 1998). Others think that these disorders are much more general, and that the seemingly specific components affected are in fact part of a more extended syndrome, usually encompassing the sensory and motor domains (Stein and Walsh 1997; Karmiloff-Smith 1998; Tomblin and Pandich 1999; Gepner and Mestre 2002). Some of these researchers even hold that domain-specific developmental disorders are, in principle, unlikely to exist at all (Thomas and Karmiloff-Smith 2002).

In the case of developmental dyslexia, the predominant theory is that it is due to a specific phonological deficit (Snowling 2000). Nevertheless, this view has been challenged by increasing evidence of sensory and motor disorders in dyslexics, leading to competing theories implicating auditory/temporal processing deficits (Tallal 1980; Farmer and Klein 1995), visual/magnocellular dysfunction (Lovegrove et al. 1980; Livingstone et al. 1991; Stein and Walsh 1997) or motor/cerebellar dysfunction (Nicolson and Fawcett 1990; Nicolson, Fawcett, and Dean 2001). In the face of this highly diverse and inconsistent data set, only one theory so far has attempted to account for all the empirical evidence: the general magnocellular theory, in which a generalised dysfunction of magno-cells affects all sensory pathways and further spreads to the posterior parietal cortex and the cerebellum, thereby encompassing all the known cognitive, sensory, and motor manifestations of dyslexia (Stein and Walsh 1997; Stein 2001).

However, as I have argued elsewhere (Ramus et al. 2003; Ramus 2003), 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 (Ramus 2003; Rosen 2003). 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 more general sensorimotor syndrome occurs more often in the dyslexic than in the general population, but does not by itself play a causal role in the aetiology of the reading impairment (Ramus 2003). According to this view, a complete theory of dyslexia must explain both how a specific phonological deficit might arise, and why a sensorimotor syndrome should be significantly associated with it.

In this paper, I propose a neurological model that serves this purpose. Specifically, it potentially explains how a phonological deficit may arise from genetically determined brain anomalies, in isolation in certain individuals, or in conjunction with sensorimotor impairments in others. This model is compatible with all the known genetic, neurological, and cognitive data available on dyslexia. It easily generalises to SLI and possibly to other domain-specific developmental disorders. It further suggests explanations for a few puzzling issues like co-morbidity between and heterogeneity within disorders, and makes a number of specific predictions yet to be tested.

Insights from anatomical studies and animal models

Post-mortem examination and brain imaging studies have documented many differences between dyslexic and control brains, in the left peri-sylvian cortex (Galaburda et al. 1985; Rae et al. 1998; Eliez et al. 2000; Brown et al. 2001; Leonard et al. 2001), the underlying white matter (Klingberg et al. 2000), the thalamus (Livingstone et al. 1991; Galaburda, Menard, and Rosen 1994), the corpus callosum (Rumsey et al. 1996; Robichon and Habib 1998), the cerebellum (Rae et al. 2002; Finch, Nicolson, and Fawcett 2002), etc. (see Habib 2000 for a comprehensive review). 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, considering the well-known comorbidity between dyslexia and many other disorders (Kadesjö and Gillberg 2001; Kaplan et al. 1998; McArthur et al. 2000). Nevertheless, the functional significance of two types of brain anomalies has been studied in greater detail.

Anomalies of cell migration called molecular layer ectopias and focal microgyri have been observed by Galaburda and colleagues in the peri-sylvian cortex of dyslexic brains (Galaburda and Kemper 1979; Galaburda et al. 1985; Humphreys, Kaufmann, and Galaburda 1990), predominantly in the left hemisphere, and with a much greater prevalence than in control brains (Kaufmann and Galaburda 1989). 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 disorganization of the subjacent cortical layers. Microgyria 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, the magnocellular layers were more disorganised, with overall smaller cell bodies (Livingstone et al. 1991). Similarly, there was a disproportionate number of small neurons in dyslexics' left medial geniculate nucleus (MGN) (Galaburda, Menard, and Rosen 1994).

It is quite natural to hypothesise that anomalies in the magnocellular layers of the lateral geniculate are the cause of visual deficits, and that anomalies in the medial geniculate are the cause of auditory deficits. There is at least evidence for the latter causal link in rats (Herman et al. 1997). Similarly, it is easy to see cortical anomalies in left peri-sylvian 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 microgyria 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 attention/planning problems, as prescribed by the magnocellular theory. However, this scenario may well be incorrect (Galaburda 1999). 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.

The evidence comes from a whole series of studies on rats and mice. Indeed, it is possible to surgically induce ectopias and microgyria by poking a hole in the external glial limiting membrane of the developing cortex of rats 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 surgically induced microgyria in the frontal, parietal or occipital cortex, subsequently develop anomalies in the MGN: they have more small and fewer large neurons in the MGN than

rats receiving sham lesions, an anomaly similar to that found in dyslexics' MGN (Herman et al. 1997; Peiffer, Rosen, and Fitch 2002). This suggests that the direction of causation is indeed top-down, from the cortex to sensory relays in the thalamus. Furthermore, rats with such an abnormal MGN were found to perform less well in an auditory discrimination task (Herman et al. 1997; Fitch et al. 1994; Fitch et al. 1997; Peiffer, Rosen, and Fitch 2002), which confirms that the observed disruption in the MGN has an impact on auditory capacities. Similar auditory disorders are found in ectopic mice, regardless of the localisation of ectopias (Peiffer et al. 2001), which suggests that this top-down scenario may also occur when cortical malformations have a genetic origin.

Another interesting aspect uncovered in these studies is that only male rats were initially found to have impaired auditory function following early inducement of microgyria (Fitch et al. 1997). Indeed, females rats showed normal auditory performance and did not show a similar anatomical disruption of the MGN in response to the microgyria, even though their cortical lesions were as extended (Herman et al. 1997). Similarly, only male ectopic mice show auditory deficits (Peiffer, Rosen, and Fitch 2002). 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 (Rosen, Herman, and Galaburda 1999).

Finally, the cortical anomalies themselves seem to have an impact on cognitive function: ectopic mice and rats with spontaneous or induced ectopias and microgyria exhibit a variety of learning deficits (Denenberg et al. 1991; Schrott et al. 1992; Balogh et al. 1998; Rosen et al. 1995), including problems with working memory (Boehm et al. 1996; Waters et al. 1997; Hyde, Sherman, Hoplight et al. 2000). Furthermore, the location of the cortical disruption influences the specific type of learning deficit exhibited by the animal (Hyde et al. 2001; Hyde et al. 2002), but not the likelihood of further thalamic disruption and sensory impairment.

To summarise, these results suggest that, in animal models at least, (1) cortical anomalies (microgyria, ectopias) induce secondary anomalies in sensory relays in the thalamus, but (2) only under certain fœtal hormonal conditions. Leaping to the human case, and assuming that early cortical anomalies are directly related to dyslexics' future phonological deficit, these findings suggest that (1) the neural basis for a phonological deficit may exist *prior* to the neural basis for any auditory impairment, and that (2) it may exist *in the absence* of any auditory impairment (when the disruption does not propagate to the thalamus, like in female rats: Herman et al. 1997). Obviously, there are many more conceivable neuro-developmental models of dyslexia than the one most directly suggested by these particular neurological observations and animal models. But, limited as these data are, they seem more compatible with the idea of a specific phonological deficit optionally associated with additional sensorimotor disorders, than with any theory requiring causation of the phonological deficit through other sensory/cognitive disturbances.

I will now spell out and discuss in further detail what a plausible neurological model of dyslexia and other developmental disorders might be, based on this reinterpretation of the anatomical and animal data. It should be emphasised that this model is largely speculative; it attempts to be compatible with all the available data, but given that the available data is not excessively constraining, alternative models are perfectly viable. The goal here is mainly to provide a plausible, testable model that makes specific predictions.

A neurological model of dyslexia

Focal anomalies and the phonological deficit

The main claim of the model is that congenital anomalies in specific left peri-sylvian areas are the direct cause of a phonological deficit, which itself is the direct cause of reading impairment.

A simple version of this model attributes the main responsibility to cortical ectopias and microgyria. Galaburda et al. (1985) found most ectopias in the left peri-sylvian cortex. This is indeed where the main brain areas involved in phonology seem to be located: mainly the supramarginal and angular gyri, the posterior superior temporal gyrus, the insula, and the inferior frontal gyrus, although there is debate as to which areas are involved specifically in phonological representations, and which are more concerned with reading or speaking (Paulesu et al. 1996; Paulesu et al. 2001; Poldrack et al. 1999; Binder et al. 2000; Simos et al. 2000; Shaywitz et al. 2002; Temple 2002; Habib 2000; Jacquemot et al. 2003). Note that this does not exclude that areas which become more specifically dedicated to reading (like the left fusiform gyrus, e.g. Cohen et al. 2002) might also be the target of ectopias, although there is currently no such evidence. More generally, the multiplicity of areas involved in phonology and reading, together with the multiple differences found between dyslexic and control brains, makes it plausible that several different patterns of cortical disruption will lead to a reading impairment; this diversity may actually underlie the various manifestations of the phonological deficit in dyslexia.

Unfortunately, work on ectopias and focal microgyria in dyslexia has been scarce (only 8 brains have been dissected so far), so the reality of their involvement needs to be confirmed. However this criticism equally applies to all other neurological differences found in dyslexics. The interest of ectopias is that they have been

replicated in animal models, and this work provides us with some cues about their genetic origin, and their further neurological and functional consequences. Furthermore, their implication in the etiology of dyslexia is further supported by recent findings by LoTurco and colleagues (this volume) (Wang et al. submitted) that a dyslexia susceptibility gene is involved in neural migration, and that its deletion as found in a dyslexic family leads to ectopias. Nevertheless, given the current state of the research on the neurology of dyslexia, it remains entirely possible that other brain anomalies might be as, or even more strongly implicated. In fact many other brain anomalies might themselves be related to ectopias and microgyria, which may indeed be just one manifestation of a wider disruption. For instance, the planum temporale has been argued to be excessively symmetric in dyslexics (Galaburda et al. 1985; Larsen et al. 1990), and this is thought to be closely linked with the presence of ectopias and microgyria (Rosen et al. 1989; Galaburda 2001). Furthermore, increased callosal connections (Rumsey et al. 1996; Robichon and Habib 1998) are also interpretable as a consequence of the excessive symmetry of the planum temporale and/or other cortical areas, as this symmetry is typically manifested by an enlargement of the usually smaller side (Galaburda et al. 1985). Finally, ectopias and microgyria may also be related to the disruption of underlying white matter tracts (Klingberg et al. 2000). Many of the brain anomalies observed in dyslexia may therefore be associated with ectopias and microgyria, and be part of the same disruption. Exactly which part of this disruption plays a significant functional role remains to be established. Quite plausibly, cortical ectopias and microgyria in specific left peri-sylvian areas might affect phonological representations; so might a disrupted planum temporale, as this area is thought to underlie speech representations (Liégeois-Chauvel et al. 1999; Jäncke et al. 2002; Scott and Johnsrude 2003); and disrupted white matter might affect interfaces between phonological and orthographic representations, or between different levels of phonological representation (Paulesu et al. 1996; Klingberg et al. 2000).

Given the current uncertainty on structure/function relationships, the more general version of the present model is not committed to one particular type of brain anomaly, nor to a particular functional interpretation of each anomaly. However, it specifically hypothesises (1) that the disruption is related to ectopias and microgyria, and therefore that it appears very early in development (before the sixth month of gestation in humans); (2) that the functionally significant part of the disruption is *focal*, specific to certain cortical areas or cortico-cortical connections; (3) that these focal anomalies specifically affect the development of phonological and/or orthographic representations/processing; (4) that they are a sufficient cause of reading impairment, without the help of broader sensorimotor dysfunction (see Fig. 1). In essence, this pattern of neurological dysfunction, analogous to that observed in the female rat, gives rise to "pure phonological dyslexia".

Sex hormones and the sensorimotor syndrome

The second claim of the model is that, when the focal anomalies already discussed are present, *and* under certain hormonal conditions at an early stage of brain development, additional disruptions arise in sensory pathways, notably the thalamus, and perhaps subsequently in other areas like the posterior parietal cortex and the cerebellum (Stein and Walsh 1997). These disruptions are responsible for a syndrome consisting of a constellation of sensory, motor and perhaps attentional difficulties.

The research just reviewed suggests that the "hormonal conditions" may reduce to an elevated concentration of testosterone in the fetal environment (Rosen, Herman, and Galaburda 1999). More generally, it has been proposed that testosterone plays an important role in brain development, notably by slowing the growth of the left hemisphere, and that it is involved in a number of brain and cognitive anomalies (Geschwind and Behan 1982). There is also indirect evidence that a high concentration of fetal testosterone is associated with autism (Manning et al. 2001), another disorder with a high incidence of the sensorimotor syndrome (Spencer et al. 2000; Milne et al. 2002; Milne et al. in press). Fetal testosterone is therefore a likely candidate as a mediator for the sensorimotor syndrome. Nevertheless, the situation may be more complex. Indeed, other gonadal steroids like progesterone and estrogen have been shown to influence brain development, usually in positive ways (Hall, Pazara, and Linseman 1991; Roof et al. 1994). It may be that testosterone acts by attenuating the protective effects of these other hormones (Fitch et al. 1997), which suggests that sex differences in the neurophysiological response to cortical damage may result from a complex interaction of several hormones. Finally, it could also be that these “hormonal conditions“ are a matter of hormone receptors in the brain rather than hormone concentration per se (Geschwind and Galaburda 1985). This will all be matter for future research.

The hypothesis is therefore that, under certain hormonal conditions to be precisely defined, focal cortical anomalies may induce further disruption in the thalamus, and more particularly in the medial geniculate nucleus (as demonstrated in male rats: Rosen, Herman, and Galaburda 1999), as well as in the lateral geniculate nucleus (as suggested by dyslexics' brains: Livingstone et al. 1991). This would be the direct cause of subtle auditory and visual deficits. Although it has been suggested that sensory dysfunction might be specifically or predominantly magnocellular (Galaburda, Menard, and Rosen 1994; Livingstone et al. 1991; Stein and Walsh 1997), as pointed out earlier the empirical evidence seems inconclusive. The model is therefore neutral to this issue. The sensory disorders in question might well be magnocellular, parvocellular, a combination of the two, or

perhaps this dichotomy serves no meaningful purpose in the characterisation of the deficit: this is a matter for future research. The main claim is that these sensory disorders arise optionally, under certain conditions in certain individuals only, and on top of the phonological deficit.

Similarly, Stein & Walsh (1997) proposed that the magnocellular disruption further extends to the posterior parietal cortex and to the cerebellum. Again, this might well be true, but the model is neutral to this issue. If this is true (and even if the abnormalities are not specifically magnocellular), this might explain further visuo-attentional (Hari, Renvall, and Tanskanen 2001) and motor (Fawcett, Nicolson, and Dean 1996) problems also evidenced in some dyslexics (see Fig. 1).

Obviously, when present, the sensorimotor syndrome may in principle aggravate the situation of the dyslexic child. In particular, a severe auditory deficit might aggravate the phonological deficit (Ramus et al. 2003). Visual or visuo-attentional deficits might also aggravate the reading impairments (Stein and Walsh 1997). However, it should be noted that in both cases the proposed causal links are still speculative and await further evidence.

Extension of the model to other developmental disorders

Dyslexia and SLI have two features in common: first, relatively specific cognitive deficits; and second, the additional presence of a sensorimotor syndrome in part of the population. The model presented here seems perfectly suited to explain all disorders that share these two features.

Indeed, nothing in this model restricts the possible loci of focal anomalies to areas subserving language. I hypothesise that, in humans like in mice (Hyde et al. 2001), what makes each developmental disorder unique is the location of the focal anomalies. In this view, what makes, say, a dyslexic child qualitatively different from an SLI child, has little to do with differences in low-level perception or the like, but depends on whether the cortical areas affected implement, say, processing of speech sounds, or of syntactic structure or lexical items. The model proposed for dyslexia therefore generalises quite naturally to SLI, and possibly to other specific disorders like developmental dyscalculia (Shalev and Gross-Tsur 2001) or prosopagnosia (Galaburda and Duchaine 2003). Certain cases of autism, dyspraxia and ADHD might also be explained within the same framework, insofar as the focal anomalies under discussion may arise in the brain areas involved in mentalising, motor control or attention respectively. On the other hand, disorders like Williams, Down or fragile-X syndromes clearly do not fit into this class of specific developmental disorders (Donnai and Karmiloff-Smith 2000; Korenberg et al. 2000).

In the rat model, thalamic disruption arises under high fetal testosterone conditions, whether microgyria are located in the parietal, frontal or occipital lobe (Herman et al. 1997). Similarly, in male ectopic mice, auditory deficits are found regardless of ectopia location (Peiffer et al. 2001). According to the present model, this further explains why a similar sensorimotor syndrome seems to appear across a whole range of developmental disorders, and typically only in a subset of individuals within each disorder, whether dyslexia, SLI or other (Hill 2001; Kadesjö and Gillberg 2001; McArthur and Bishop 2001; Milne et al. 2002; Ramus 2003; O'Brien et al. 2002; Milne et al. in press). I specifically hypothesise that the sensorimotor syndrome arises in any individual who presents with both the focal brain anomalies and the hormonal conditions discussed in the preceding section, regardless of the specific type of cognitive deficit.

Heterogeneity and co-morbidity

In the brains examined by Galaburda and colleagues (Galaburda et al. 1985), several dozens of ectopias spread over large cortical areas were found in each subject. This may seem at odds with the presumed specificity of the cognitive deficit. But this depends on the precise functional consequences of such cortical anomalies: it may well be that only a critical concentration of ectopias in one area produces any significant cognitive disruption; or that disruption occurs only when an area is affected bilaterally. Nevertheless, it is perfectly likely that several distinct cognitive systems are disrupted within a dyslexic individual: indeed, as already mentioned there is more than one component to the phonological and reading systems, and nothing prevents a dyslexic from presenting other cognitive deficits unrelated to reading. Together with clinicians' strategy of sorting cases into a few basic diagnostic categories, this seems consistent both with the well-known heterogeneity within disorder and co-morbidity between disorders.

Within disorder: It seems to be the case that none of the usual diagnostic categories reflect homogeneous cognitive profiles. For instance, dyslexics' phonological deficit typically has three main manifestations: poor phonological awareness, poor verbal short-term memory, and slow automatic naming, which are significantly associated but may be partly independent (Wolf et al. 2002). This is consistent with the view that this triad of impairments reflects distinct disruptions of, say, the left posterior superior temporal gyrus, the left inferior frontal gyrus, and the angular/supra-marginal gyri respectively. Similarly, SLI is typically characterised by any combination of poor grammar, vocabulary, and/or speech articulation, which can be seen as reflecting distinct impairments of the syntactic, lexical, or articulatory systems. Finally, assuming that the number of focal anomalies may vary between individuals, the model is consistent with the existence of both

individuals with a multi-faceted disorder, and others with a purer subtype, like pure phonological dyslexia (Wolf et al. 2002) or Grammatical-SLI (van der Lely and Stollwerk 1997).

Between disorders: Of course, multiple focal anomalies may span several cognitive domains as well as sub-systems of the same domain. For instance, both phonological and syntactic systems may be affected, in which case the resulting disorder can be interpreted as a co-morbid case of dyslexia and SLI. This helps explain why between one third and one half of children with a developmental disorder also qualify for the diagnosis of another one (Kadesjö and Gillberg 2001; Kaplan et al. 1998; Hill 2001; McArthur et al. 2000).

Predictions of the model

Brain anomalies in other developmental disorders

Further research should reveal much more on the brain anomalies underlying dyslexia and other developmental disorders. While the present model is specified sufficiently loosely to accommodate a variety of outcomes, it also makes specific predictions: that a whole class of domain-specific disorders are characterised by focal brain anomalies, the differences between disorders reducing to differences in the localisation of the anomalies. As far as SLI is concerned, the sample studied by Galaburda et al. (1985) actually included individuals whose profile was more that of co-morbid dyslexia and SLI than of pure dyslexia, which is consistent with the observed distribution of cortical anomalies across language areas. More generally, MRI anatomical studies are globally consistent with the idea that brain anomalies of a similar nature, but not identical, are present in SLI and dyslexia (Plante et al. 1991; Jernigan et al. 1991; Gauger, Lombardino, and Leonard 1997; Leonard et al. 2002). The little that is known about developmental dyscalculia suggests that it might also fit into the same class of neurodevelopmental disorders, possibly with abnormalities in inferior parietal cortex (Levy, Reis, and Grafman 1999; Dehaene et al. 2003); so might developmental prosopagnosia and associated visual recognition difficulties, with abnormalities in posterior inferior temporal cortex (Galaburda and Duchaine 2003). However much more research is needed to confirm the hypothesis that all these disorders are the product of similar neurological disruptions but in different anatomical localisations or configurations. On the other hand, research on such disorders as autism and ADHD has led to rather different neurological hypotheses (Bailey et al. 1998; Kemper and Bauman 2002; Krause et al. 2003; Castellanos et al. 2002), 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. Furthermore, the model predicts that thalamic abnormalities will be found in a sub-population only of each disorder, in parallel with the sensorimotor syndrome, but unrelated to the specific nature of the cognitive deficits.

Post-mortem dissection, high-resolution MRI, diffusion-tensor imaging and proton-MR spectroscopy studies will all be important tools to test these predictions. But they will be useful only insofar as the anatomical measures are matched with comprehensive and reliable cognitive testing, in order to test precisely the postulated structure-function correspondences within each individual.

Sex-ratio

It is commonly accepted that males are more affected by dyslexia than females (e.g., Flannery et al. 2000), although this has been challenged (Shaywitz et al. 1990). Within the magnocellular theory, the finding that thalamic disruption was mediated by fetal testosterone in the mouse model has been interpreted as a possible explanation for the uneven sex ratio in dyslexia (e.g., Herman et al. 1997).

In the present model, the cause of reading impairment has been shifted away from the thalamus to the cortical anomalies. In this view, the sex-ratio of dyslexia has little to do with fetal hormones, but is tightly related to possible sex differences in cortical anomalies. It turns out that the female dyslexic brains that were dissected showed fewer ectopias than male ones, and were characterized instead by a large number of small myelinated glial scars (Humphreys, Kaufmann, and Galaburda 1990). This may imply that females are less likely to have a phonological deficit, and that the deficit will be less severe on average in females, or alternatively that females require more severe neuropathology in order to exhibit behavioral problems, thereby explaining the uneven sex-ratio. But the exact functional significance of these differences in cortical anomalies is unknown, so it is at present impossible to predict the theoretical sex ratio of the phonological deficit.

However, because of the hormonal mediation leading to the thalamic disruption, the model does predict an increased prevalence of the sensorimotor syndrome in males. More precisely, irrespective of the actual male/female ratio in dyslexia, it predicts that this ratio will be increased in the subpopulation with a sensorimotor syndrome, as compared to the subpopulation without it. And it predicts just the same for the sensorimotor syndrome 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.

Markers of fœtal hormonal conditions

Another prediction of the model is that if one could measure the relevant hormonal conditions in human fetuses, 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). Unfortunately, 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 would still be measurable in the child or even in the adult. One such marker has been proposed: the ratio between the length of the second digit and that of the fourth digit (2D:4D ratio) would be inversely correlated to foetal testosterone levels (Manning et al. 1998), and has been shown to be significantly lower in autism than in the general population (Manning et al. 2001). Furthermore, a recent study replicated this result and found that within a group of autistic-spectrum disorder children, the 2D:4D ratio was correlated with their performance in coherent motion detection and in manual dexterity (Milne et al. in press). Obviously, such results are to be taken with caution considering the very indirect relationship between the two measures. Their interpretation may be further complicated by the fact that, as was evoked earlier, the determining hormonal conditions might not be simply a matter of testosterone concentration.

Genetics

Because developmental disorders like dyslexia and SLI have a strong genetic basis, the model predicts that ectopias and other relevant focal anomalies must arise under genetic control. This is indeed confirmed by studies of autoimmune mice that spontaneously develop ectopias (Sherman et al. 1990; Sherman et al. 1994), and by recent findings on the role of the Dyx1c1 dyslexia susceptibility gene (Wang et al. submitted). Furthermore, unless total cross-heritability across 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 (Denenberg et al. 1991), but the exact mechanisms influencing their location are not known yet.

On the other hand, fœtal hormonal conditions may be partly genetically determined, but are also more likely to be influenced by external factors. The model therefore predicts a lower heritability of the sensorimotor syndrome than of specific cognitive deficits. The possibility that some cases of sensorimotor dysfunction are due to genetically-determined cortical anomalies in visual, auditory or motor cortex, or in the cerebellum, may attenuate this prediction. Nevertheless, it is currently consistent with the finding that the phonological deficit is highly heritable (both in dyslexia and SLI), while auditory and visual deficits are not, or to a much lower extent (Bishop et al. 1999; Davis et al. 2001; Olson and Datta 2002).

It is also notable that all the specific cognitive disorders under consideration here have a complex genetic etiology involving several regions on different chromosomes (e.g., Fisher and DeFries 2002), unlike Williams, Fragile-X, Down syndromes, etc., which all have a simple genetic etiology with wide-ranging cognitive consequences. In the light of the present model, one way to understand the relationship between complex genetic etiology and specific cognitive deficit is to speculate that in dyslexia and other specific disorders, certain genes are general risk factors for the occurrence of focal anomalies like ectopias, while other genes influence the precise location of such anomalies, for instance by generating molecular gradients interacting with ectopia risk factors. Yet other genes might be risk factors for the hormonal conditions leading to the sensorimotor syndrome. These hypotheses broadly predict that the genes implicated in all these specific cognitive disorders will be partly shared (those acting as general risk factors for cortical anomalies), and partly specific to each disorder (those influencing brain localization). The more specific predictions are potentially testable using current mouse models.

Clinical implications

Current diagnostic categories are undermined by the heterogeneity within and the overlap between categories, as well as by the occasional focus on associated deficits as part of certain diagnostic procedures (e.g., clumsiness in dyslexia (Fawcett and Nicolson 1996)). They do not do justice to the variety of cognitive impairments that may arise, and their different possible combinations. Although dyslexia, SLI, autism etc. may remain convenient umbrella terms based on the most salient cognitive trait, a possibly more useful approach to learning disabilities would be in the form of a check-list enumerating all attested cognitive, sensory, and motor deficits, each child being characterised by his own combination of marks (and severity ratings) in the list. This would, in essence, replace ever imperfect labels with a comprehensive, individual neuro-cognitive profile.

Attempts at remediation might also gain from such an approach. The present model suggests that there is little point proposing auditory, visual or motor training schemes as general treatments for dyslexia and SLI, since many of these children do not have sensory or motor impairments. The comprehensive diagnostic approach

could nevertheless draw attention to sensorimotor impairments when present, which might justify treatment in their own right insofar as they are themselves a cause of trouble.

General discussion

It may be observed that the present model much resembles the traditional neuropsychological model for acquired brain lesions, in that it postulates focal disruptions causing specific cognitive deficits, assuming a rather tight fit between brain area and function, even if the function is not yet developed at the time of the disruption. Some might argue that this makes the model highly implausible (Paterson et al. 1999; Thomas and Karmiloff-Smith 2002; Goswami 2003). I would like to argue otherwise. The tight fit between brain area and function seems to be a basic fact about brain organisation and development. Even for those functions that clearly have no evolutionary basis (e.g., orthographic processing), there seems to be one area of the brain that is more appropriate than others (e.g., orthographic representations reliably settle in a very specific sub-region of the left fusiform gyrus: Cohen et al. 2002), presumably because not all areas of the brain have the optimal representational, computational and connectional properties required for each particular function. And these properties of brain areas are largely genetically determined.

Certainly, when the optimal area for a particular function is disrupted, there can be a significant amount of compensation through brain plasticity, and more so in developmental than in acquired disorders. Indeed, it is well-known that the right hemisphere can take over some linguistic functions from a dysfunctional or removed left hemisphere (Vargha-Khadem and Polkey 1992; Bates et al. 1997; Frith and Vargha-Khadem 2001). Functional brain imaging suggests that this does happen in dyslexics too, as they show less activation than controls in their disordered left temporo-parietal junction and inferior frontal gyrus, but more in the right counterpart areas (Shaywitz et al. 1998; Simos et al. 2002). But for all the hype about brain plasticity and reorganisation, dyslexics, left-hemispherectomised children as well as ectopic mice remain significantly and specifically impaired, demonstrating that no other brain area does the job as well as the optimal one. What is known about brain development and plasticity is therefore entirely compatible with the idea that the congenital disruption of a limited brain area will lead to long-lasting disruption of the cognitive function that it would subserve under normal development.

Skeptics may further argue that it is unlikely that the effects of an early focal brain anomaly would remain circumscribed to that particular area and cognitive function, again because of plasticity (Karmiloff-Smith 1998; Thomas and Karmiloff-Smith 2002). But this again overlooks the fact that brain plasticity is far from total. Of course, development occurs and produces knock-on effects: in dyslexia, for instance, the phonological deficit alters the development of the orthographic system, and may also impact on the acquisition of vocabulary. Yet, there is no reason to expect that it should have consequences on *all* areas of the brain (after all, dyslexics are not overall mentally retarded). Indeed, this is not observed in the case of congenital focal brain lesions which can also lead to relatively specific cognitive deficits in humans (Curtiss, de Bode, and Shields 2000; Stromswold 2000; Daigneault and Braun 2002), just like in ectopic mice with focal cortical anomalies (Hyde, Sherman, Hoplight et al. 2000; Hyde et al. 2001; Boehm et al. 1996; Hyde, Sherman, Stavnezer et al. 2000; Hoplight et al. 2001). The female rat model further demonstrates that disruption in one cortical area does not necessarily produce changes just one synapse away (Herman et al. 1997). The hypothesis of a specific cognitive deficit remaining specific throughout development therefore seems perfectly plausible and compatible with current knowledge in developmental neuroscience.

Within the framework of the present model, a sensory explanation of dyslexia, in order to be viable, has to make the following assumptions: 1) that a sensory dysfunction is present in all dyslexics at birth, but recovers in most of them to the point that it is detectable only in a minority by school-age; 2) that in dyslexics who remain auditorily impaired, some factor also alters the relationship between the severity of the auditory deficit and that of the phonological deficit (as there is no reliable relationship at school-age: Rosen 2003); 3) that the ectopias and concomitant brain anomalies observed in dyslexics' language areas *do not* by themselves cause any phonological deficit (since these anomalies exist before the sensory disruption); 4) that the phonological deficit itself is not reflected by any additional physical disruption in those areas affected by the aforementioned anomalies, or, if it is, such disruption has so far gone unnoticed. Although such a conjunction of unlikely facts may appear implausible, it is of course possible that they will all turn out to be true. Further research should indeed aim to test these assumptions and more generally evaluate the respective predictions of the two competing frameworks, the sensorimotor one, and the domain-specific one.

The model outlined here opens up new avenues of research aiming to uncover the precise links between specific genes, brain anomalies and cognitive deficits. But 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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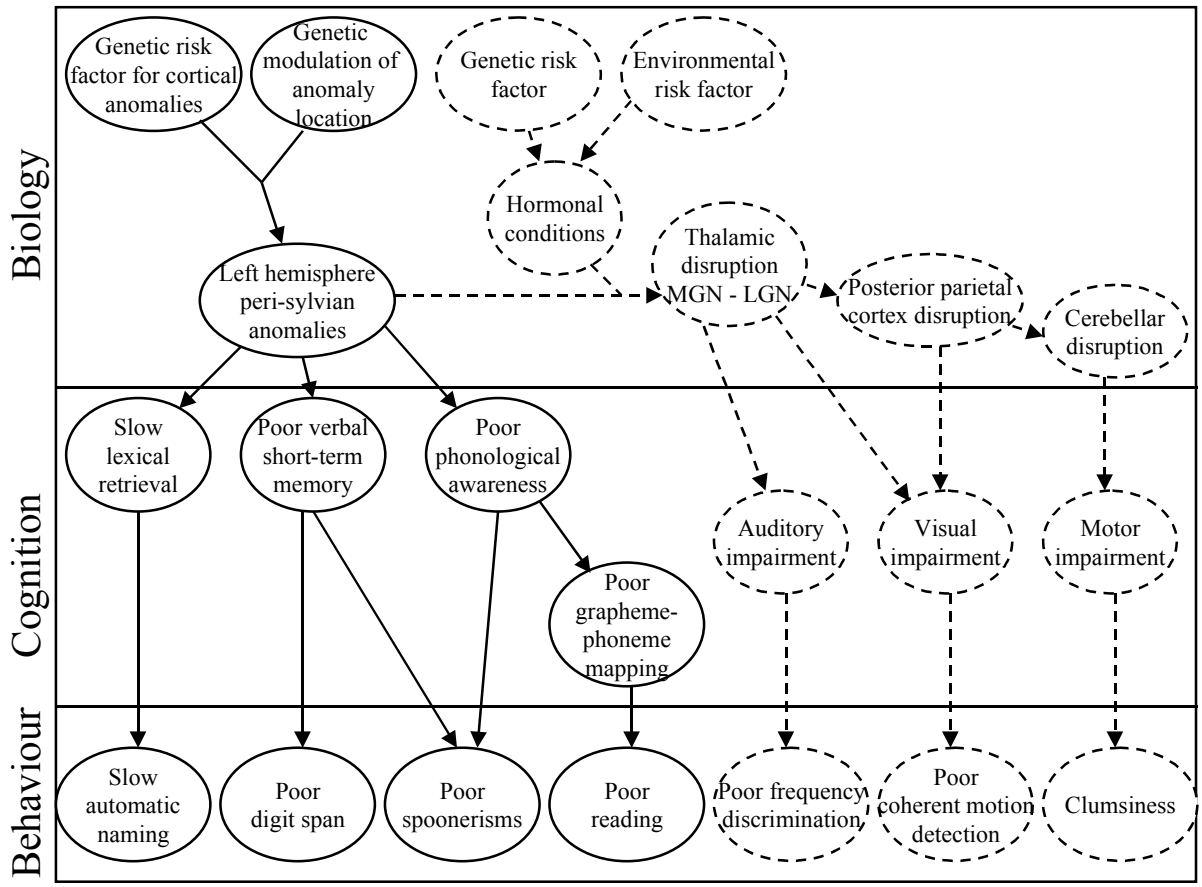
Figure

Figure 1. A causal model of the aetiology of developmental dyslexia. Bubbles represent traits at the biological, cognitive and behavioural levels of description. Arrows represent causal relationships between traits. Solid lines are used for core traits of developmental dyslexia, dashed lines for optional, associated traits. Only a subset of all possible behavioural manifestations are represented. Cases of co-morbidity with other developmental disorders (e.g., SLI) are not represented. LGN: lateral geniculate nucleus. MGN: medial geniculate nucleus.



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