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Neurogenetics and auditory processing in developmental dyslexia

Anne-Lise Giraud[1,2] and Franck Ramus[3]

Dyslexia is a polygenic developmental reading disorder characterized by an auditory/phonological deficit. Based on the latest genetic and neurophysiological studies, we propose a tentative model in which phonological deficits could arise from genetic anomalies of the cortical micro-architecture in the temporal lobe.

Addresses
[1] Inserm U960, Département d'Etudes Cognitives, Ecole Normale Supérieure, 29 rue d'Ulm, 75005 Paris, France
[2] Department of Neuroscience, University of Geneva, Rue Michel-Servet 1, 1211 Genève 4, Switzerland
[3] Laboratoire de Sciences Cognitives et Psycholinguistique, Ecole Normale Supérieure, EHESS, CNRS, 29 rue d'Ulm, 75005 Paris, France

Corresponding author: Giraud, Anne-Lise (annelise.giraud@gmail.com)

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Introduction

Dyslexia is a reading disorder of polygenic origin affecting 3–7% of school children, defined by marked difficulties in the acquisition of reading despite normal intelligence, perception and educational opportunities [1]. In most cases, dyslexia is accompanied with a phonological deficit, for example, difficulties in tasks involving speech sounds and dysfunctions of the left perisylvian language network [2] and/or subcortical auditory relays [3,4]. Understanding how diverse genetic variations can cause a cognitive disorder as specific as dyslexia is the challenge we are currently facing. Animals in which dyslexia genes have been knocked out exhibit both disturbed neuronal migration in auditory cortex and impaired auditory processing. We review the current literature and describe a putative mechanistic model linking neuronal micro-architecture of the auditory cortex to specific alterations of phonological processing.

Molecular genetics of dyslexia and related cognitive and brain phenotypes

Between 2003 and 2006, a first series of genes (*DYX1C1*, *ROBO1*, *KIAA0319* and *DCDC2*) were found to be associated with dyslexia [5]. Since then, additional candidate genes have been proposed, raising the number to about 15 [6,7].

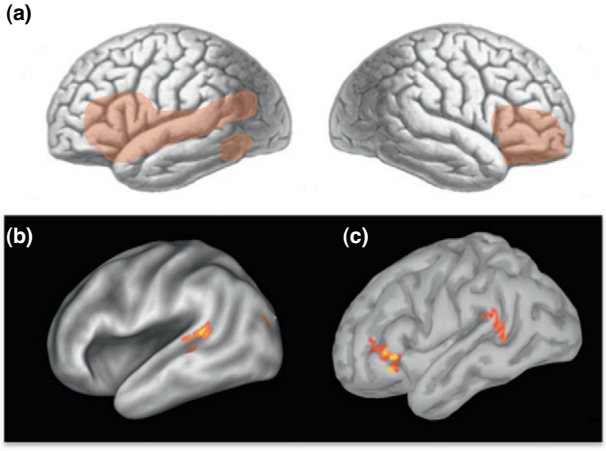
Several of the identified susceptibility alleles have recently been associated not only with the diagnosis of dyslexia but also with reading or spelling phenotypic variability within the general population. A few studies showed *KIAA0319*, *DYX1C1*, *DCDC2* and *CMIP* to be associated with normal variations in reading ability [8–12]. These studies remain to be replicated, as there are statistical issues and inverted effects on some alleles [13].

Beyond reading and spelling, other cognitive phenotypes relevant to dyslexia seem to be influenced by dyslexia candidate genes. For instance, verbal short-term memory, that is, the ability to store and recall a series of verbal items, has also been associated with *DYX1C1*, *ROBO1* and *DCDC2* in both dyslexic children and their siblings [14–17]. One study further suggested linkage between rapid automatised naming, that is, the ability to rapidly name a series of pictures, and region 6p21, neighbouring the loci of *KIAA0319* and *DCDC2* [18].

At the macroscopic level, dyslexia is associated with alterations of human cortical neuroanatomy [19,20]. Broadly speaking, the alterations are suggestive of a disconnection syndrome as they affect the white and grey matter sitting in the fronto-temporo-parietal network that is involved in reading. Recently, dyslexia candidate genes have been shown to be associated with such neuroanatomical variations. *DCDC2* deletion is associated in healthy adults with increased grey matter volumes across a large network of cortical regions [21], which might in part overlap with the location of ectopias that have been observed post-mortem in dyslexic individuals [22] (Figure 1a). White matter volume is also affected by variations of *KIAA0319*, *DYX1C1* and *DCDC2*, particularly so in the posterior fibre tracts that lie within the superior longitudinal fasciculus and the corpus callosum, and those linking the left medial temporal gyrus with angular and supramarginal gyri [23••] (Figure 1b). The location of these structural differences is consistent both with previous neuroanatomical (VBM and diffusion) studies [24•] as well as with functional neuroimaging studies of reading and dyslexia [25,26].

A haplotype composed of dyslexia-susceptibility alleles within the *KIAA0319* region has recently been associated with the left–right asymmetry of brain activations for reading in temporal cortex using fMRI (Figure 1c). Adult, healthy carriers of the susceptibility haplotype show less leftward functional asymmetry than controls, hence

Figure 1



(a) Cortical location of ectopias in human dyslexics. Modified from Ramus [61]. The affected zone roughly corresponds to the location of anomalies of the grey and underlying white matter. (b) Polymorphism of the SNP rs17243157 cluster (KIAA0319/TTRAP/THEM2 locus) is associated with functional asymmetry of the STG/STS during reading. Healthy subjects with variants of this SNP (single-nucleotide polymorphism) have reduced asymmetry. Courtesy Philippe Pinel, see Pinel *et al.* (2012). (c) Deficit in auditory steady state response to a noise modulated at 30 Hz in dyslexics. The deficit is found in the left prefrontal and temporal cortices. Note the overlap with both the location of ectopias (a) and the location of the variance in neural activity related to KIAA0319 polymorphism during reading (b). Modified from Lehongre *et al.* (2011).

displaying a phenotype closer to that of dyslexic readers than to that of controls [27••]. The same study further showed that variations of *FOXP2* are associated with activations of the left inferior frontal gyrus and the left precentral cortex [27••]. This gene was previously associated with developmental verbal dyspraxia [28,29], but also recently with dyslexia [30].

Dyslexia-susceptibility alleles have been related to *neurofunctional* phenotypes, for instance with electrophysiological responses to speech sounds. The auditory mismatch negativity (MMN) to minimally different syllables seems reduced in carriers of susceptibility alleles. MMN is a pre-attentive electrophysiological component that reflects change detection in the sensory environment. It corresponds to an increase in evoked responses when a stimulus does not conform to expectations generated by previous repetitions, for example, in an oddball paradigm. Using a whole-genome association study, the variability of MMN in dyslexia was associated with an intergenic marker on Chr. 4 that was related to the transcription of *SLC2A3* on Chr 12, a DNA region coding for the main cerebral glucose transporter in neurons, which had not previously been associated with dyslexia [31]. Another study found abnormal MMN in two individuals carrying three rare variants within *DCDC2* and between *DCDC2* and *KIAA0319* in dyslexia-linked region 6p22 [32]. Consistent with earlier findings [33,34], both studies found the genetic effects to affect the late (300–700 ms) MMN component, but not the early one (100–200 ms). This presumably reflects intact auditory discrimination ability, but alterations at later stages of auditory/phonological processing.

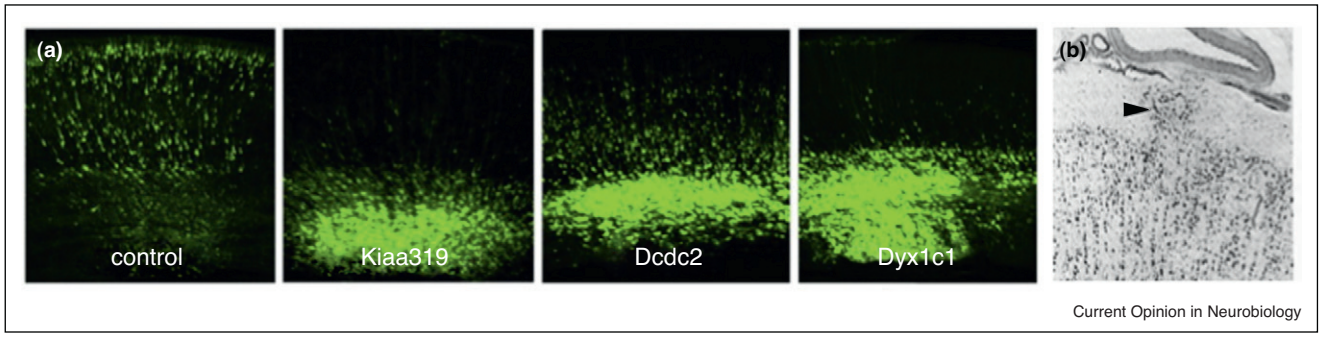
Dyslexia candidate genes influence cortical neuronal migration and microcircuits

The neural effects of the genetic markers identified in humans are now being explored in non-human animals. Candidate genes can be artificially inactivated and the neural consequences followed up from microscopic to functional levels. RNA interference experiments in rodent models suggest that all four primarily identified genes (DYX1C1, ROBO1, DCDC2, KIAA0319) appear to regulate neocortical development, in particular neuronal migration [7,35–37], which provides a nice connection with earlier post-mortem studies that indicated disrupted cortical architecture in the brains of dyslexic individuals, in particular over the temporal lobe [38].

The inactivation of DYX1C1, DCDC2 and KIAA0319 produces a clustering of neurons in the ventricular zone. Some neurons seem trapped and have difficulty migrating to their cortical target (Figure 2a), while other neurons seem to move beyond their target in superficial layers and produce ectopias [37] (Figure 2b). Many different cell types, not normally present in superficial layers, can be observed in ectopias. These neurons and interneurons establish abnormal vertical and horizontal connectivity, and hence disrupt local microcircuits [37]. In the long term, the distribution of neurons within the cortex seems to be skewed, with an over-representation in layers 1, 5 and 6 and in the underlying white matter, at the expense of layers 3 and 4 [39]. Rodent models additionally provide interesting functional information. Auditory and learning functions, but not working memory, appear impaired in a KIAA0319 RNAi mouse model [40•]. When DYX1C1 is inactivated, both auditory function [41] and working memory appear impaired, whereas when DCDC2 is mutated, only memory deficits arise independent of detectable cortical architecture anomaly [42]. Cortical disruptions associated with KIAA0319 and DYXC1 seem to consistently induce auditory dysfunctions, yet their expression pattern is not wholly consistent with auditory impairments [43]. The cortical anomalies observed in mouse models rather loosely fit with the location of ectopias in humans over the temporal and inferior prefrontal lobes (Figure 1a), reflecting the limits of animal models in dyslexia research.

Many more details are needed to complete the picture, but it seems reasonable to assume that firstly cortical micro-circuitry is disrupted in regions that present

Figure 2



(a) Abnormal neuronal migration in embryonic neocortex: 'control' shows the normal position of neurons. 'KIAA0319', 'DCDC2' and 'DYX1C1' panels show abnormal migration following RNAi knockdown of candidate genes. After Gabel *et al.* (2012). (b) Ectopia in human cortex: the arrow indicates abnormal neuronal migration. Galaburda *et al.* (1979).

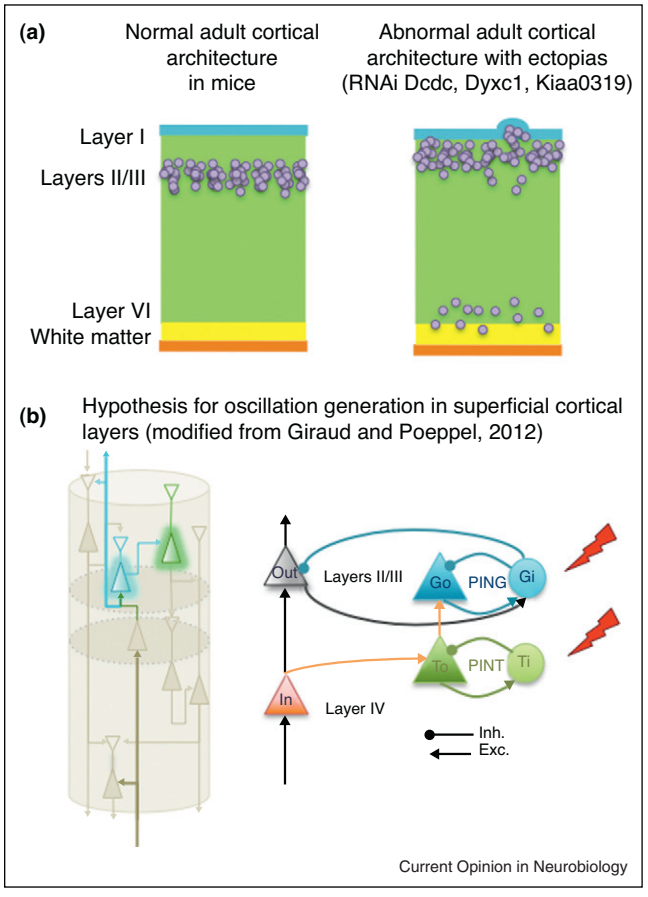
anomalies of neuronal migration (temporal and inferior prefrontal lobes in humans), whether ectopias, heterotopias, or other alterations of neurons' distribution, and secondly that these cortical anomalies somehow affect auditory function. Yet, how do anatomical anomalies impact on auditory function, and translate into a reading deficit, are issues that remain open.

A mechanistic hypothesis for linking genetic cortical anomalies and the phonological impairment in dyslexia

Further exploring the specific functional consequence of cortical microcircuitry anomalies could represent a promising research avenue. Migration anomalies likely disrupt the physiology of neuronal interactions within and across cortical layers and columns [44], and subsequently impair synchronous neuronal activity emerging from specific interactions across neurons and interneurons [45,46••] (Figure 3a). In auditory cortices, synchronous bursts of neural activity occur at specific frequencies in the delta/theta (1–7 Hz) and the low-gamma (20–40 Hz) ranges. This ensemble activity appears as so-called *neural oscillations* in intra-cortical or scalp encephalographic recordings (multiunit neuronal activity, ECoG, EEG, MEG, etc). In auditory cortex theta- and low-gamma activity are detected in superficial cortical layers [47–49] (Figure 3b). Because neurons in temporal cortex ectopias establish abnormal connectivity with the cortical layers situated underneath, they likely disrupt the generation of delta/theta and gamma oscillations [37,50].

Anomalies in delta/theta and gamma oscillation generation could have important consequences on phonological processing. The most relevant acoustic modulation in speech signals is the syllabic rate, which falls within the delta/theta range. In addition, psycholinguistics shows that the brain segments speech into phonemes, which occur in natural speech at a rate of about 20–30 Hz, that is, within the low-gamma range. In sum, the theta and

Figure 3



(a) Left panel: normal adult cortical architecture. Neurons controlled by the dyslexia genes migrate to layers II/III. Right panel: after RNAi knockdown of dyslexia genes, neurones end up in layer I and beyond forming ectopias. Modified from Gabel *et al.* (2012). (b) Hypothesis for theta and gamma oscillation generation from superficial cortical layers. Modified from Giraud and Poeppel (2012). The red arrows indicate the level where anatomical anomalies could alter cortical oscillatory function.

gamma frequencies that the auditory cortex tends to spontaneously generate coincide with the two major phonological rates. This is so because the articulation system has presumably adapted to auditory sensitivity during the evolution of spoken language [51]. While the auditory system is capable of detecting modulations at rates much higher than 20–40 Hz [52,53], high frequency modulations do not yield temporally distinct cortical neural events (synchronous neural activity), which could be individually referred to and mentally manipulated as 'auditory representations'. Short phonemes (e.g. stop-consonants) occurring over about 20 ms might be the shortest linguistic element that the cortex can represent and manipulate in a stable way, even though subphonemic elements can be detected and discriminated. Alterations in oscillation rates in auditory cortex might therefore directly translate into abnormal syllabic and phonemic representations, and constitute an interesting potential endophenotype of dyslexia, bridging the expression of genetic anomalies with impairments in the phonological domain.

Dyslexic individuals produce abnormal auditory cortical responses in the delta range [54]. Functionally, this disruption translates in a reduced ability to detect acoustic rise-times, a cue relevant to phonological processing [54–56]. Dyslexic individuals also show abnormal auditory responses to sounds that carry modulations in the low gamma range (20–35 Hz) [46••,56]. They lack a specific low-gamma steady state response in left auditory cortex, and present bilateral abnormal responses at a higher rate (near 60 Hz), which could indicate that they have finer-grained phonemic representations than controls (or infra-phonemic representations). A direct consequence could be that they perceive, store and mentally manipulate subphonemes. This hypothesis is seductive as it could also account for verbal working memory deficits [46••]. Assuming that dyslexics can memorise an equivalent number of items as controls, they might appear impaired in auditory memory tasks simply because for a given acoustic stream, the amount of auditory representations that are attempted to be manipulated is higher than in controls.

Disruptions of neuronal migration occur in utero, and are therefore assumed to disrupt auditory cortical organisation very early on. Accordingly, auditory functional anomalies have been observed well before dyslexia manifests as a reading disorder [57,58], as well as in siblings of dyslexic children, thus reflecting shared endophenotypes [34]. Why auditory cortical anomalies would prevent some children from learning to read and not others remains unclear. The genetic background, as well as other sources of variability, may all play a role in accounting for individual differences. There likely exists a high variability in the capacity to compensate for disrupted phonological processing, which could further contribute to the heterogeneity of the symptoms. Accordingly phonological performance in dyslexics parallels the amount of functional compensation by the right hemisphere [46••].

While these deficits in speech-relevant neural oscillations may seem to imply that dyslexic individuals' phonological representations are fundamentally disrupted or in an inadequate format, this is not necessarily so. Indeed, careful analysis of the psycholinguistic evidence suggests that dyslexics' phonological representations may be normal, but less available for some purposes [59]. Neuronal oscillations may reflect the parsing of phonological representations equally well, making certain units more readily available for the purpose of later stages of processing and more difficult tasks. These more difficult, later stages may include phonological awareness and verbal short-term memory, on which dyslexic individuals show notorious difficulties. They may also include the learning of associations with visually stored symbols, which is the basis of reading acquisition.

Conclusion

Despite new trails in pinpointing the determinants of dyslexia, no direct causal relationship between genetic markers and auditory oscillations is definitely established. The next step should target experiments in animals involving genetic manipulations and dedicated neurophysiological recordings targeting neural oscillations. Finally, the neural oscillation hypothesis is not incompatible with other hypotheses, and the emergence of symptoms during reading acquisition naturally also point to the visual modality [60]. It appears obvious that irrespective of whether the primary endophenotype lies in the visual or auditory modality, we need to understand whether and how the two modalities interact in symptom development when there is a common genetic background.

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