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REVIEW ARTICLE

Neurobiology and neurogenetics of dyslexia

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Abstract
Introduction: Dyslexia is a learning disability in which reading (but not any other) impairment is the most prominent symptom. There seems to be a high comorbidity among dyslexia and other learning disabilities, such as SLI, SSD or ADHD.
Development: The nulear deficit in dyslexia appears to correspond to an impairment in phonological processing. Structural and functional studies in dyslexic readers converge to indicate the presence of malformations in the brain areas corresponding to the reading systems, but also a failure of these systems to function properly during reading. Genes linked (or associated) to dyslexia have been shown to be involved in neuronal migration and axon guidance during the formation of the cortex. In the developing cerebral neocortex of rats, local loss of function of most of these genes not only results in abnormal neuronal migration and neocortical and hippocampal malformations, but also in deficits related to auditory processing and learning. While the structural malformations resemble neuronal migration abnormalities observed in the brains of individuals with developmental dyslexia, processing/learning deficits also resemble deficits described in individuals affected by the disease.
Conclusions: On the whole, dyslexia seems to be on a continuum with typical reading at different biological levels (genetic, biochemical, physiological, cognitive). Furthermore, certain elements belonging to some of these levels (mainly -some of the- genes linked or associated to the disease, but also -some of the- neuronal structures whose development is regulated by these genes) would simultaneously belong to those of other cognitive abilities, which give rise to diseases of a different nature (i.e. non- dyslexic impairments) when they are impaired

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Neurobiología y neurogenética de la dislexia

Resumen
Introducción: La dislexia es un trastorno cognitivo que lleva aparejada una competencia lectora reducida y que suele ser comórbido con otros que tienen como característica distintiva un déficit en la capacidad de aprendizaje y de adquisición de competencias específicas (fundamentalmente, trastorno específico del lenguaje, de los sonidos del habla o por déficit de atención e hiperactividad).
Desarrollo: En el caso de la dislexia, el déficit nuclear parece corresponderse con una disfunción del componente fonológico de la memoria de trabajo verbal. El cerebro de los individuos disléxicos presenta diversos tipos de malformaciones estructurales, así como patrones anómalos de actividad cerebral durante las tareas de lectura y deletreo, que conciernen, entre otras, a las áreas que integran el dispositivo de procesamiento cuya actividad se ha asociado con estas actividades en la población no disléxica. Los genes identificados hasta la fecha cuya mutación parece constituir un componente causal (o un factor de riesgo) significativo en relación con el trastorno codifican proteínas que intervienen en la regulación de la migración de determinados linajes neuronales o del proceso de axonogénesis. La disminución del grado de expresión de los correspondientes genes ortólogos produce en el cerebro de los organismos modelo del trastorno alteraciones estructurales y funcionales semejantes a las observadas en los individuos disléxicos. Dichas alteraciones originan, a su vez, déficit auditivos y cognitivos que recapitulan satisfactoriamente los descritos en dichos individuos.
Conclusiones: En conjunto, resulta plausible la hipótesis de que la dislexia vendría a ser, en diferentes niveles de complejidad biológica (genético, bioquímico, fisiológico, cognitivo), y en mayor o menor grado, un extremo del continuo de desarrollo que representa la capacidad de lectura en la población general; al mismo tiempo, algunos de los elementos que integran estos niveles (en particular —varios de—, los genes relacionados con el trastorno, así como —algunas de—las estructuras neuronales cuyo desarrollo está regulado, en buena medida, por los programas que conforman dichos genes) podrían formar parte simultáneamente de los correspondientes a otras capacidades cognitivas, cuya disfunción da lugar a trastornos de diferente naturaleza clínica.

Introduction

The ability to read written texts is acquired thanks to a process of learning and specific training that normally goes on for a long time, even though it ends up with a considerable level of automatism. However, a significant percentage of children do not acquire this ability as a matter of course, in spite of going through the usual learning process and having a normal intellectual capacity in other aspects. Dyslexia is therefore a learning disorder characterised by an obvious difficulty in recognising written words accurately and/or fluently, as if there were a significant loss in the ability to decipher or spell them out.[1] Consequently, the competence finally acquired by dyslexics in these skills does not correlate in the usual way with age, intelligence level, general cognitive abilities, and/or educational stimuli received during their development.[2] Generally, reading difficulties are persistent and do not disappear with time, although they can clearly be alleviated to a certain extent if appropriate corrective therapy is given.[3] Overall, the prevalence of this disorder has been estimated at around 20%of the given population, even though it is considered that 30%35%of them could really have a much lower reading ability than considered basic (namely, that entailing an effective comprehension of what is read).[4] Dyslexia has been reported as a disorder associated to all human language writing systems, including not only those with alphabetical or syllabic characters, but also those of a logographic nature.[5] In the specific case of alphabetical systems, dyslexia has been observed in languages whose orthography is transparent, that is, where there is a practically univocal correlation between phonemes and graphemes, as well as in others where this does not occur.[6]

More and more commonly, one tends to consider dyslexia (and generally all reading difficulties) less as a discrete category (which, apart from other considerations, would make reading ability itself a bimodally distributed ability), but rather that it consists of a particular interval in a continuum that makes up the reading competence. This is

an interval that is conventionally delimited by virtue of certain statistically characteristic measures. People who have reached full reading competence would also form a part of this continuum, together with those who usually are not able to read fluently.[7] This dimensional concept of reading ability means that the impact of dyslexia on individuals can vary. In principle, the groups that can be made according to pedagogical or therapeutic criteria should be mainly arbitrary and-also in principle-devoid of biological validity.[4] However, as is discussed further on, the dimensional concept of the disorder seems to agree fairly well with results derived from genetic analysis. There are other results, obtained from psychometric tests normally used for diagnosis that assess the diverse parameters and abilities relating to reading ability (phonological awareness, ability for phonological and orthographical deciphering, ability to read single words, listeme organisation pattern, and ability to spell). These results seem to show that there are various subtypes of dyslexia,[8] whose differences would consequently exceed the components of the disorder that were merely phenotypic or clinical, by bestowing a neurological and genetic character as well.[9]

A lot of evidence seems to indicate that dyslexia also has an eminently neurobiological origin and is specifically caused by an abnormal development and dysfunction of certain neural circuits. In turn, these structural and functional anomalies would originate, to a certain degree; from the mutation of certain genes.[10] Our first objective was to review succinctly the main structural and functional neural alterations in the brains of individuals who are dyslexic. An additional objective was to discuss the most relevant factors that seem to corroborate the idea that these anomalies have a fundamentally genetic origin (which does not mean that the relevant role played by environmental factors in the appearance and evolution of this disorder should be devalued). Therefore, the main part of the article dissects the nature and function of the genes identified to date that could be considered the main candidates (and not simply mere risk factors) for the appearance of the disorder. The paper's last objective, presented as the conclusion of everything discussed in it, is two-fold: first, an evaluation of the implications that neurological and genetic analyses of dyslexia have for a more precise understanding of its biological nature (and therefore of human cognition); and second, better diagnosis and treatment of this complex condition. In view of these objectives and due to the nature of article review, special care has been taken to search for and choose the references consulted in preparing the document. Two fundamental criteria have been followed: *1)* a direct link to these objectives (and special relevance when referring to them) and how often it is mentioned in the work (as could not be otherwise), but especially *2)* its current relevance. Consequently, preference has been given to the most recent publications and the latest advances produced in relation to the work's objectives and the different questions treated in it. This has gained special importance with regard to the search for, identification of, and molecular and functional characterisation of genes related to the disorder.

The origin of dyslexia

There have been several theories concerning the origin of dyslexia.[11,12] It has been pointed out that the nuclear deficit of the disorder could be due to the inability to process (and discriminate) extremely rapid acoustic-type sensorial impulses (linguistic and non-linguistic).[13] Likewise, taking into account that reading is an eminently visual activity, which requires correctly processing the aspect and form of the characters comprising the language's written form,[8] it has been said that dyslexia could be largely caused by a deficit in the ability to process visual stimuli.[14] Taking into account the automatism that in time ends up characterising reading ability (particularly in cases where this is based on establishing a correlation between phonemes and graphemes), it has also been said that dyslexia could originate from (or that its appearance could be significantly conditioned by) a cerebellar dysfunction. It should be remembered that the cerebellum, aside from its role in motor control, seems to form part of verbal working memory, which allows short-term handling and storage of linguistically relevant information.[15] It operates by maintaining the lexical elements present in a phrase, thanks to their phonetic properties; that is, by acting like a sort of "silent speech" and thus "refreshing" the phonological representations of the terms.[16] Therefore, especially when the verbal memory load is increased above working capacity in cortical areas (and the reliability of the "silent speech" mechanism is consequently compromised), the cerebellum acts by comparing acoustic phonological representations with the articulation of the "silent speech".[17] Finally, it has been postulated that the origin of dyslexia could be found in a dysfunction in the magnocellular pathway (which intervenes in activating and redirecting attention mechanisms in the higher-level cortical areas). This would give rise to different sensorial deficits, including those of an auditory and visual character mentioned before (although possibly causing a cerebellar dysfunction as well).[18,19] However, the majority of specialists consider that the nuclear deficit of the disorder corresponds to a neural circuit dysfunction that is responsible for the phonological processing ability.[12,20] This capacity is the result of coordinating several related abilities, such as phonological awareness or the ability to decipher, store, and recuperate phonemes. Whenever this phonological deficit is found, we also see that there is inadequate learning of existent compatibilities between phonemes and graphemes, thereby compromising normal acquisition of reading competence.[12,21]

Neurobiology of dyslexia

Neurobiological aspects of the ability to read in the normal population

Overall, data from neuro-imaging analysis seem to indicate that fluent reading is only possible if there is correct interaction between at least 3 main processing systems, located in the left cerebral hemisphere.

The first of these systems is situated in the ventral part of the occipitotemporal region and is integrated by several areas of middle temporal and middle occipital gyrus.[22,23] This area, known as the visual word form area (VWFA),[24,25] receives information from the extra-striate cortex areas of both hemispheres implicated in processing the purely visual stimuli related to the written form of words. One of the main duties this region seems to be guaranteeing a sort of competency in the visual recognition of written words and the sequences these form (in contrast to other visual stimuli) and allowing written texts-and their components-to be perceived quickly during the reading process.[6]

The 2 remaining systems together make up the so-called phonological system.[26] The first of them is located in the dorsal temporo-parietal and from it forms part of the angular and supramarginal gyrus, as well as the posterior areas of the upper temporal lobe area.[22,23] This system is specifically in charge of analysing words; it seems to work as an integrating region where the association between graphemes and phonemes is produced.[27] In turn, the second of the systems that make up the phonological system seems to be composed mainly of the lower front lobe area, particularly Broca's area. It is worth pointing out that this area has progressively stopped being considered as the only causal cortical area of syntactic organisation and speech motor execution. It is now considered as one of the components in verbal working memory, as it is precisely in charge of phonetic tasks of a nature and participates particularly in processing phonetic traits with a phonological value during word reception[28,29] and generation.[30-32] In this way, its role in computation tasks inherent to comprehension and syntactic production is reduced to its intervention in very specific aspects of both processes, fundamentally in tasks related to the application of the so-called transformational rules during the comprehension of speech and specific tasks in creating the process of syntactic hierarchy during its generation.[33] It therefore does not take part directly in the basic combining activity needed to process sentences (generating constituent structure, lexical insertion, etc.).

Neurobiological aspects of reading dysfunction in the normal population

From the neuroanatomical point of view, dyslexia seems to associate itself to various structural anomalies resulting from an abnormal neural migration pattern, which mainly affects the left hemisphere perisylvian areas.[34,35] Among these anomalies ectopia, dysplasia, and microgyria stand out,[34,36] as well as the annexed periventricular nodular heteropias.[37] Likewise, the start of micro-structural white matter degradation has been seen in the temporo-parietal area in dyslexic individuals.[38,39] In certain cases, a change in grey matter volume has also been reported; this would affect certain cortical areas (fundamentally the upper temporal gyrus and the temporo-occipital cortex of the left hemisphere) and would be associated to a modification of its normal activation pattern.[40] In fact, neuro-imaging studies have shown that individuals with dyslexia show various anomalies in the activity and functional organisation of different brain areas that seem to intervene in the reading process (which were referred to previously).[41,42] Consequently, in global terms, we can see less general activity in the left hemisphere and a compensatory over-activation of certain right hemisphere areas. Under-activity particularly concerns the 2 subsystems of the processing system implicated in reading ability that are located in the posterior cerebral areas,[20,22,43] as well as in certain extrastriate cortex areas of the left hemisphere and thalamus; however, these are also located in certain areas of the right hemisphere, centred on the fusiform, post central and temporal gyrus.[44] Over-activity fundamentally corresponds to the previous subcomponent of the processing system that is in charge of reading[20,22,43] (although there are differing opinions[44]), as well as some other cortical areas, mainly located in the right hemisphere, including the inferior frontal gyrus in this hemisphere, the counterpart region to the occipitotemporal system itself (that is, the VWFA[23] area), the anterior insular, and the thalamus.[44]

It has been reported that some of the difficulties that dyslexics characteristically show during (and for) reading, particularly those concerning incorrect establishment of grapheme-phoneme correlation-such as those seen during phonological practice/segmentation-are specifically caused by the incorrect interconnection pattern between the previous processing subsystem and those that follow. This is specifically due to a modulatory activity interruption that comes from the functional relationship that normally exists between fusiform gyrus, inferior frontal gyrus, and the lower portion of the parietal lobe.[45] Additionally, both in individuals who are dyslexic and in inefficient adult readers, who to a great extent read by recurring to memorised words, the occipitotemporal system is found to be connected to several memory systems located in the front lobe of the left hemisphere.[46] This circumstance satisfactorily agrees with the verification that the occipitotemporal subsystem location normally ends up moving to a more posterior and medial position as the age of the individual having the disorder[4] increases. This is probably in relation to the consolidation of irregular processing in this system, in which memory plays a more important role. It is no wonder that precisely this more posterior and medial area is preferentially activated during the reading process in normal people who speak languages that use writing systems of an ideographic or logographic nature, whose characters consequently have to be memorised.[47] This is different to languages using alphabetical or syllabic systems, where the activation pattern, associated to establishing phoneme-grapheme links, is more anterior and lateral than in the aforementioned model. It is also worth pointing out that, in the case of the first type of languages, the functional anomalies detected in dyslexics also seem to differ, to a certain degree, from those observed in individuals who speak alphabetical languages. This means that a greater decrease in activity (also related to a decrease in grey matter volume) is usually detected in the medial area of the frontal gyrus in the left

hemisphere.[48] Finally, we must also point out that some researchers[13,49] have related dyslexia to a dysfunction of certain neural circuits in charge of sensory stimuli processing, in particular those located in the primary visual cortex.

Due to therapeutic implications, we must emphasise that carrying out auditory process exercises and oral linguistic training (which stimulates processing phonological tasks) in individuals who are dyslexic normally results in an increase in cortical area activity that is implicated in the phonological process together with a compensatory over-activation of other cortical areas.[50] These 2 increases seem to mitigate the symptoms associated to the disorder. This circumstance also indicates that the processing system implicated in reading tasks is plastic enough (even in adults) to guarantee achieving sufficient ability to discriminate contrasting phonological characteristics as long as the stimulation is appropriate.[13,50-52].

Neurogenetics of dyslexia

Dyslexia heritability

Dyslexia has a complex genetic and environmental base.[49] Generally, genetic factors seem to explain 30%-70% of the variability in reading ability observed in the normal population.[53] It seems appropriate to confirm something like this in certain aspects of this ability, particularly certain endophenotypes of the disorder (that is, any quantifiable component of the area found between the condition and the genes, which can appear as a cognitive, neuroanatomical, neurophysiological, endocrinal or biochemical character[54]), such as: *1)* phonological processing ability (for which genetic contribution has been calculated at 60%-70% when assessed in terms of pseudoword reading ability); *2)* orthographic processing ability (whose contribution for this would be between 30% and 60%),[55,56] or *3)* spelling ability (where heritability would be 75%).[57] Likewise, heritability coefficients of the different cognitive processes that intervene in reading (and consequently the different end phenotypes of the disorder) are related among themselves in such a way that, for example, the abilities for phonological and orthographical deciphering would cover up to 60%[8] which would suggest that a part of the genes implicated in these processes would presumably be the same. This would agree with (and explain to a great extent) the existence of an overlapping activation pattern in the cerebral centres in charge of this type of processes.[58] It has also been seen that genetic factors influencing general intelligence or linguistic competence (*à la* Chomsky) are similarly relevant in reading competence.[59,60]

The transmission pattern of dyslexia, based on the heritability analyses carried out through the standard methods (transmission of the condition in family group studies, regression studies that compare dyslexia prevalence in groups of twins, whether identical or not, etc.) indicates that the disorder is not normally transmitted as a Mendelian character and is a heterogeneous condition from a genetic point of view.[61] Consequently, different genes are implicated in its appearance.[62] This type of analysis has been extended to different endophenotypes of the disorder (and to reading competence in general). For example, it has been suggested that the ability for pseudoword repetition would be inherited codominantly and there would be 2 (or sometimes 3) genes implicated. Whereas, for example, considering phonological deciphering ability, there would be a polygenic background and 2 genes would probably be involved.[63] In any case, it should be remembered that the heritability level of the disorder depends to a great extent on the environmental factor exposure level, which must be considered a risk for its appearance. This, in the specific case of dyslexia, makes the heritability observed inversely proportional to the age of the individuals affected.[64]

Dyslexia-related loci and dyslexia candidate genes

This significant heritability that characterises dyslexia (which is different than in other cognitive disorders) has significantly stimulated the efforts to try to identify and structurally characterise hypothetical genes whose mutation could be a significant causal component of the disorder. For this, positional cloning is normally used, which allows the phenotype anomaly to be associated to a specific chromosomal fragment, which later sequences itself, so as to determine the nature of the gene (or genes) contained in it. The main methodological tool in positional cloning is linkage or association analysis, which consists of determining dyslexia co-heritability with a sufficiently raised number of polymorphic genetic markers (generally SNP, single nucleotide polymorphisms), whose position in each chromosome is known. In the case of linkage analysis, the process starts with a group of people whose family relationships are known, which notably reduces the number of genetic markers needed to delimit the area of interest.[49] In contrast, association analysis is applied to populations consisting of individuals whose family relationship is unknown, which in turn means that a much greater number of polymorphic markers must be used.[65] The response capacity of association analysis has been increased to a great extent by the recent development of the so-called GWAS (genome-wide association studies). These studies, by using the whole genome, not only make linkage analysis unnecessary, they also allow researchers to simultaneously determine the existence and location of multiple loci susceptible to the disorder, instead of having to exclusively centre on one (or several).[66] Linkage and association analysis have a clear advantage in making it possible to establish genotype/phenotype correlations when there is an absence of precise data concerning aetiology of a certain disorder. However, it should be remembered that it is also certain that the precision and relevance of these results are found to be conditioned by several factors (for a more complete review, see Benítez-Burraco[67]); one of the most important is the group of criteria used to define, characterise, and assess the affected phenotype.[10] Using a battery of psychometric tests is becoming more and more frequent in the

identification, characterisation, and selection of the right phenotypes (instead of opting to restrict oneself to a categorical definition of the disorder and its phenotypes, as was previously done). This is precisely what has allowed dyslexia to be treated, in the sense indicated previously, as a variable continuum (and as an extreme of the continuum that makes up the general population's reading ability) and consequently apply quantitative analysis methods to its genetic analysis. This has brought about the identification of the corresponding quantitative trait loci (QTL), that is, loci associated to quantitative traits. These represent statistically significant confidence intervals where one gene or various genes, whose dysfunction under certain environmental conditions and in a certain population give rise to the phenotype studied or constitute a risk factor for its appearance, are located in a specific chromosomal area.[68-71] Apart from that, in certain cases this type of analysis has been made easier or complemented with a detailed study of places where chromosomal rearrangement has occurred, as Karyotype exams of certain individuals affected by the disorder seem to indicate. The analysis of this nature can reach a considerable degree of resolution; for example, through fluorescent *in situ* hybridization (FISH), it is consequently possible to detect translocations where chromosomal fragments of only 100kb are implicated.[66]

Linkage and association studies in particular, have identified several loci that, if they exist, are potentially related to dyslexia (DYX1 to DYX9, according to the Human Gene Nomenclature Committee [http://www.gene.ucl.ac.uk/nomenclature/], although the corresponding analysis has only been replicated in 4 of them: DYX1, DYX2, DYX5, and DYX6),[66] as well as a great many additional loci that could attribute a susceptibility to the disorder. From 3 of these loci (DYX1, DYX2, and DYX5), it has been possible to clone and identify a total of 4 genes considered dyslexia candidate genes. Detailed functional studies are being conducted on these genes to try and clear up their physiological role and establish the way their mutation contributes to the appearance of dyslexia.[66] As discussed further on, this type of research seems to confirm that all the genes identified up till now have a link to dyslexia. Genetic character analyses have likewise confirmed that in this aspect the disorder would constitute only an extreme, in quantitative terms, of the genetic factor (and environmental) group implicated in the normal population's reading ability (although it is possible that some of the genes that confer susceptibility to dyslexia do not directly influence the reading ability of the non-dyslexic population[72]).

DYX1

The DYX1 locus corresponds to 15q21 and correlates not only with reading ability (isolated words) but also with spelling, although apparently it would not do so with any specifically phonological dyslexia endophenotypes.[73-75] The mutation of the *DYX1C1* gene in this area (caused by a translocation that interrupts its sequence) cosegregates with the disorder in the family analysed by Taipale et al.[76] The gene is made up from 10 exons and its transcription seems to give way to different mRNA (with sizes varying between 1kb and 5kb) thanks to a process of alternative maturity. The main mRMA of the gene encodes a protein of 420 amino acids, whose most relevant characteristic is the presence of 3 tetratricopeptide repeats (TPR) domains in their carboxyl-thermal area.[76] These are regulatory factor characteristics that function integrated into multi-protein complexes, given that they are responsible for protein-protein interactions.[77] A multi protein complex intervenes in gene expression regulation, integrated by genetic regulators TFII-I, PARP1, and SFPQ.[78] The *DYX1C1* gene is expressed in different tissues, including lung, hepatic, testicular, and brain. In the case of the brain, and in an organism such as the rat, the orthologous gene is expressed during embryonic development in the whole forebrain, primarily in the neocortex, hippocampus, and choroid plexus, as well as the cerebellum and striatum.[79] In turn, the protein DYX1C1 is preferentially located in the nucleus of certain neurons and in the glial cells of the cerebral cortex.[76] It has been shown that it could specifically intervene in radial neuronal migration regulation.[80] This hypothesis has been recently confirmed thanks to the confirmation that in rats a decrease in the transcripted value of the *DYX1C1* gene during embryonic development, induced by RNA interference (RNAi), significantly changes the normal migration pattern of neurons in the periventricular region. This altered migration pattern initially stops the migratory process of certain neuron groups, and later causes the appearance of, specifically, an abnormal bimodal migratory pattern. This, in turn displaces certain neurons to a lesser degree than usual and they are constrained in the white matter and cortical layer VI, while the majority of them are displaced further away than their usual destination.[79] An example of other structural changes associated to gene expression decrease is the presence of ectopia in the molecular layer of the cortex, affecting several cortex layers. Another example consists of the appearance of a hippocampus malformation, which brings about a change in its normal anatomical organisation and affects a quarter of pyramidal neurons; this specifically results in the appearance of localised heterotopias, particularly in the CA1 area.[79] In rats, the neuron changes associated to decreased *DYX1C1* gene messenger RNA (mRNA) values are not confined to the structural plane, but are also accompanied by significant behavioural changes. These consist fundamentally of a decrease in the processing capacity of complex auditory stimuli that occur during both childhood and adulthood (preferentially associated to malformations that affect the cortex), as well as decreased ability for spatial capacity (linked, in this case, to hippocampus malformations).[81]

The relationship between the *DYX1C1* gene and dyslexia seems to be also confirmed by the fact that dyslexic people studied up till now have had up to 8 different polymorphisms detected in its gene sequence, 2 of which seem to be unequivocally associated with the disorder and have

important functional consequences. The first of them (–3G→A) affects the gene promoter area and modifies the putative binding sequence of the multi-protein complex integrated by the genetic regulators TFII-I, PARP-1, and SFPQ.[78] These specifically produce a change in the binding level of factor TFII-I to the promoter (and consequently to gene expression),[78] as well as of the transcription factors Elk-1 and HSTF (one must take into account that factor Elk-1 is a transcription activator that in an organism such as a rat has been related to learning tasks[82,83]). The second polymorphism (1249G→T) would give rise to a truncated protein that could not be functional,[76] given that the absent fragment seems to be necessary and sufficient to promote normal radial neuron migration.[80] Aside from this, it has been indicated that these 2 polymorphisms (as well as other different ones, situated in both the gene promoter area and modifies the putative binding sequence of the multi-protein complex integrated by the genetic regulators TFII-I, PARP-1, and SFPQ.78 These specifically produce a change in the binding level of factor TFII-I to the promoter (and consequently to gene expression),78 as well as of the transcription factors Elk-1 and HSTF (one must take into account that factor Elk-1 is a transcription activator that in an organism such as a rat has been related to learning tasks[82,83]). The second polymorphism (1249G→T) would give rise to a truncated protein that could not be functional,[76] given that the absent fragment seems to be necessary and sufficient to promote normal radial neuron migration.[80] Aside from this, it has been indicated that these 2 polymorphisms (as well as other different ones, situated in both the gene promoter area in the encoder one) are mainly correlated to the dyslexia endophenotype that corresponds to short term memory dysfunction.[84,85] At any rate, one should also state the fact that many researchers have questioned the link of the *DYX1C1* gene to the disorder.[86] They claim that there is a significant percentage of dyslexic individuals who have none of these polymorphisms, while it has been detected in non-dyslexics who show many gene sequence changes. It has even been reported that it could really be another gene that corresponds to QTL for the dyslexia existing in 15q21.[10]

DYX2

A second locus for the disorder seems to be in the 6p22[87-89] area. It corresponds to a QTL related to several dyslexia components, including those of a phonological and orthographical nature[87] that are particularly linked to the most serious variants of the condition.[90] Several association studies have made it possible to progressively delimit the chromosomal fragment implicated, until suggesting that there are 2 genes that could correspond to locus DYX2. The first would be *DCDC2*, located in 6p22.1, which is mainly expressed in the entorhinal cortex, inferior temporal cortex, medial temporal cortex, hypothalamus, amygdala, and hippocampus.[91] It was initially suggested that there was a relationship between dyslexia and certain polymorphisms of this gene and, to a lesser degree, between the disorder and specific deletions that affected intron 2, which had eliminated several binding tandem motives to the transcription factors PEA3 and NF-ATp that intervene in the cerebral development regulation.[91] (In mouse PEA3, it specifically intervenes in the arborisation regulation of the peripheral motor neurons,[92] while NF-ATp modulates the axonogenesis implicated in establishing neuron connections during embryonic development[93]). However, the spatial expression pattern seems to be the same in dyslexic and non-dyslexic individuals. Consequently, it has been indicated that gene mutation could give rise in dyslexics to a protein function deregulation, caused by a change in normal gene expression values.[91] The *DCDC2* gene encodes a protein that has 2 doublecortin (DCX) domains implicated in microtubule binding,[94] which are similar to those existing in the DCX protein. A DCX mutation gives rise to a type of lissencephaly and seems to intervene in neuron migration regulation.[95] It has consequently been proposed that the DCDC2 protein could also participate in neuron migration regulation, intervening particularly in determining the correct position of neurons in several cortex layers. This could have a modulator role in this regulatory system, instead of being an essential component, as would be the DCX case.[91] This hypothesis seems to be corroborated by the confirmation that in rats a decrease in knockdown (RNAi-induced *DCDC2* gene expression*)* in cortical neuron progenitor cells in the embryo ventricular area causes a serious alteration in the normal neuronal migration pattern, which to a great extent affects the pyramidal neurons of the hippocampus. Among the consequences of this alteration, one should mention: *1)* the appearance of a bimodal migratory pattern (in which up to a third of neurons exceed their usual destination in their migration, while a tenth of them hardly leave the ventricular area); *2)* a significant change in the normal cerebral cortex organisation pattern; and *3)* the appearance of heterotopic neurons in the periventricular area.[96] Schumacher et al[97] have confirmed the relationship between the *DCDC2* gene with the most serious dyslexia variant, while Wilcke et al[98] have recently done so with less serious non-dysphonetic dyslexia variants (which are consequently dyseidetic).

However, for other researchers[99,100] the statistically significant relationship between dyslexia and chromosome 6 would happen in specifically the 6p22.2 area, very close to the previous one, where the *KIAA0319* gene is found. This gene is mainly expressed in nerve tissue,[101] with the peculiarity that, at least in mice, it does so during neocortex development, coinciding with the neural migration process.[102] The gene encodes a highly glycosylated membrane protein (either N-glycosylated or O-glycosylated), which contains several PKD repeats (which seem to intervene in the interaction between neurons and glial cells) and which will act *in vivo* in a dimeric way, thanks to there being various cysteine-rich areas in its sequence located in both inside and also in the transmembrane domain surroundings.[103] In rats, an RNAi-induced decrease in mRNA values causes the majority of the neurons to remain detained in the proliferative ventricular area.[102] In view of all this evidence, it has been proposed that the protein KIAA0319 would

intervene in the interaction and adhesion phenomena that take place between neurons and radial glial cell fibres. In this way, the migration of certain cerebral cortex neuron populations is regulated during embryonic development. In any case, one should bear in mind that the maturity pattern of the gene seems complex, because at least 3 alternative transcripts are detected *in vivo*. Two of these transcripts would give rise to proteins that lack transmembrane domain,[104] with the peculiarity that 1 of them (the KB form, which exclusively lacks amino acids encoded by exon 19) would secrete itself outside the cell. This would mean it might function as a component of a signal transduction route, as suggested by the MANSC and PKD domains present in the protein.[103]

With regard to the causal relationship between dyslexia and gene mutation, a positive correlation between certain haplotypes and a decrease in gene expression has been established.[102] The relationship between the disorder and certain mutations that specifically affect the area that regulates its expression, particularly that situated far above the first exon, has also been demonstrated.[105] Recent studies have not only related *KIAA0319* gene mutation with the appearance of dyslexia, but they have indicated that this gene plays a relevant role in the development of (and in the natural variability associated to) the reading ability of the general population.[61,106]

It is possible that each of these 2 genes influences a certain component of dyslexia, as the *DCDC2* gene seems to show a greater relationship to the dyslexia endophenotype corresponding to spelling ability, while *KIAA0319* does the same with that which corresponds to the seriousness of the disorder and perhaps also with that of phonological deciphering ability. Apart from that, the indications that both genes could physiologically interact are also significant[105,107] and one of the most relevant indications in this respect is the fact that certain studies point to that the most significant association in this chromosome 6 area with dyslexia is that it would take place specifically with certain SNPs located precisely in the regulatory area of the *KIAA0319 gene*.[105] However, for other researchers, despite these promising results, not only the *DCDC2* gene but also the *KIAA0319* gene make up simple risk factors for the disorder, whose relevance would depend on the analysed person's genetic background or even on the process followed for the analysis.[108]

DYX3

The third locus for dyslexia is located in chromosome 2, possibly in the 2p16-p15 area[109], although the 2p11 area[110] and even the 2q22.3[111] have also been indicated as probable. Francks et al[112] set out a 60-75 Mb fragment of the first of these areas as the possible DYX3 locus. It would be fundamentally associated to the phonological awareness endophenotype, likewise ruling out that the dyslexia candidate genes would be 2 of those present. This is particularly true in the case of SEMA4F, which encodes the protein implicated in determining the direction of axon growth cone development, and *OTX1*, which encodes a homeotic transcription factor implicated in the regulation of forebrain specification and regionalisation. Anthoni et al[113] have recently suggested that locus associated to dyslexia present in this chromosome could correspond to a 157kb fragment situated in the 2p12 area, in such a way that the 2 risk haplotypes identified by them (which overlap each other and have a joint surface area of 16kb) would be found specifically in the chromosome area consisting of the *MRPL19* and *C2ORF3* genes on the one hand, and *FLJ13391* on the other. This region would have certain long-distance regulators for the expression of the genes *MRPL19* and *C2ORF*. Several research results seem to point to this, including the following factors that should be mentioned: *1)* the fact that the linkage imbalance observed is greater in the specific case of these 2 genes; *2)* the circumstance that genes *MRPL19* and *C2ORF3* co-express themselves in several areas of the adult brain; *3)* the confirmation that *C2ORF3* expression satisfactorily correlates with that of other genes related to dyslexia, particularly with genes *DYX1C1, ROBO1* and *DCDC2,* while *MRPL19* does so with *KIAA0319; 4)* the fact that none of the non-synonymous changes detected in the encoding sequences have a significant relationship with the disorder; and *5)* the fact that, in people heterozygous for risk alleles, *MRPL19* and *C2ORF3* gene expression would be less than that detected in normal heterozygotes.[113] In brain tissue, *MRPL19* gene expression seems to give rise to a single transcript,[113] which encodes one of the proteins that the mitochondrial ribosomes[114] integrate. In turn, *C2ORF3* mRNA seems to suffer some type of alternative processing,[113] with the main mRNA encoding a protein of 781 amino acids of unknown function.[115]

DYX4

This fourth locus of the disorder is found in the 6q11.2-q12 area. It is mainly related to spelling ability and phonological encoding,[116] even though no gene has been cloned from it yet.

DYX5

The fifth locus of the disorder corresponds to the chromosomal area 3p12-q13. The *ROBO1* gene, considered as the fourth main dyslexia candidate gene identified until now, is located in this area. and a correlation between the disorder and lower gene expression has therefore been established.[117] Several facts indicate that the protein encoded by the *ROBO1* gene could intervene in axon growth regulation, probably in those that cross from one brain hemisphere to the other.[117,118] In *Drosophila,* for example, the orthologous gene *ROBO* encodes a membrane receptor that forms part of a signal transduction chain implicated in the regulation of axon and dendrite growth.[119] However, in mice, the *ROBO1* gene (fundamentally expressed in the cerebral cortex and the developing thalamus) does so in a way complementary to Slit, a negative regulator of axon growth. It has been reported that the Robo1 protein specifically intervenes in growth

regulation of fibres projected outside the brain cortex together with those that form part of the thalamocortical projections.[120] Finally, in *Xenopus laevis*, the Slit-Robo receptor binding seems to inhibit the stimulating effect that netrin-1 has on axon genesis. This consequently contributes to modulating the competitive effect that signals of attraction and repulsion have on the speed and direction of axon growth.[121]

It is worth mentioning that locus DYX5 has also been related to what is known as speech-sound disorder (SSD).[122] This is a cognitive dysfunction whose most normal clinical manifestation is making errors in the generation of speech sounds, caused by many different problems, which while they affect articulation, mainly concern phonological and/or linguistic processing.[123] The SSD locus in the 3p12-q13 area has been particularly correlated to the dyslexia endophenotype that corresponds to phonological memory.[124]

DYX6

This locus corresponds to the chromosomal area 18p11.2[125], although in this case it has also been impossible to identify any candidate gene from it.[126] Nevertheless, the linkage analysis carried out up till now suggests that it is one of the most promising loci from a statistical point of view. It is especially linked to the endophenotypes in single word reading ability and phonological awareness.[25]

DYX7

The seventh dyslexia locus is found in the 11p15.5 area and linkage analysis that point to it was carried out by Hsiung et al.[127] Among all the many genes in this area, those suggested as dyslexia candidates are: *1)* the *SCT* gene, which encodes so-called secretin, a neuropeptide of the VIP/glucagon family, whose activity is necessary for normal brain development[128,129]; *2)* the *STIM1* gene, that presumably intervenes in regulation of nervous system development and in response to external stimuli and encodes a protein that seems to participate in many cellular interactions and signal transduction processes[130]; *3)* the *MTR1* (*TRPM5*) gene, whose functional characteristics and physiological role would be similar to those of the STIM1[131] gene; and *4)* the *HRAS* gene, which encodes a GTPase that takes part in a signal transduction chain implicated in long-term potentiation regulation, synaptic plasticity, and neural growth and differentiation,[132] and whose mutation is also related to autism.[133]

However, the most appealing candidate in this respect seems to be the *DRD4* gene, which encodes the dopamine D4 receptor. There are at least 3 reasons for this: *1)* because in the case of this gene, the statistical linkage analysis value is particularly high [127]; *2)* the fact that certain polymorphic variants of the gene (mainly the one known as the DRD4 VNTR genotype, characterised by the presence of 7 tandem repetitions of a 48 pb fragment located in exon 3) have been related to the disorder through attention deficit and hyperactivity disorder (ADHD)[134-137]. This would agree satisfactorily with the comorbidity often seen between dyslexia and ADHD,[138,139] particularly that which corresponds to some of its endophenotypes, such as inattention (but not to hyperactivity-impulsiveness)[140]; and *3)* because the gene expresses itself in the hippocampus and the frontal cortex,[141,142] which are brain areas that intervene in executive functions, linguistic processing, memory, and attention. However, it should indicated that until now no statistically significant link has been detected between dyslexia and any of the alleles of the DRD4 genotype associated to ADHD.[127] This means that in the case of the first of these disorders, other polymorphic variants from the gene or even another close gene might be implicated.

DYX8

The eighth dyslexia locus corresponds to the chromosomal area 1p34-p36.[143,144] This locus presents the peculiarity that it has a gene homologous to *KIAA0319,* called *KIAA0319L,* one of whose haplotypes seems to have a quite a significant relationship with certain dyslexia endophenotypes. This is particularly true of reading efficiency (a compound parameter that jointly assesses identification ability and deciphering of isolated words) and with quick naming of objects and colours.[145] The locus has also been related to ADHD.[146]

DYX9

The ninth and last dyslexia locus is found in Xq27.3.[147] The interest that it has lies in the fact that several indications seem to show that in the case of this disorder there should be risk alleles associated to gender[148]; one of the most relevant is the greater prevalence of males in the condition.[149] It should also be taken into account that this area has been related to what is known as the fragile X (chromosome) syndrome,[150] one of the most frequent forms of hereditary mental retardation, which includes many speech disturbances[151,152] among its characteristic symptoms but also those of a linguistic nature.[153] Furthermore, these speech disturbances are caused by transcription silencing through *FMR1* gene methylation in the majority of cases.[154] This gene encodes a regulator capable of modulating interpretation in up to 4%of the cerebral genes through the formation of complex ribonucleoproteins (mRNP) in the neural nucleus.[155] It therefore plays a crucial role in neural plasticity regulation,[156,157] thanks to its role in determining the proper establishment and appropriate functioning of dendritic spines.[158]

Other dyslexia-related loci

As well as the previous loci, it has been suggested that there is a significant statistical link between dyslexia and certain areas of chromosomes 7 and 13, particularly in areas 7q32.2,[110] 13q12,[159] 13q21,[160] and 13q22.1,[125] as well as areas 18q22.2-q22.3 and 21q21-q22.[125] However, neither of these results has been replicated up to now.

There is no doubt that area 7q32.2 is of particular interest, given that its deletion seems to entail, among other symptoms, an anomalous language development as occurs with those described by Sarda et al[161] and Zeesman et al,[162] which affect the areas 7q31.2-7q32.3 and 7q31.2-7q32.2 respectively. This phenotype anomaly certainly seems to be caused specifically by haploinsufficiency of the *FOXP2* gene located in 7q31, which encodes a transcription repressor that seems to regulate certain aspects of this neural differentiation process. These are particularly needed for the correct organisation and/or normal functioning of certain cortical-thalamus-striate circuits associated to motor planning, sequential behaviour, and procedural learning; they are consequently relevant for linguistic stimuli processing. As is well known, gene mutation leads to receptive and expressive difficulties of many kinds, which have generally been described as a orofacial dyspraxia linked to development or a spastic dysarthria, but that include specifically linguistic character deficits that affect (among other aspects) the ability to store relevant phonological information in the verbal working memory and perhaps in the sequential articulation process units with a phonological value, which is particularly relevant in the case of dyslexia.[163-166] It is true that even in cases where the analysis seemed to suggest there was a relationship between dyslexia and the 7q32 area, it has been possible to find individuals having a mutated *FOXP2* gene.[110] In addition, we cannot yet discard the hypothesis that these supposed mutations could have affected some of the regulatory regions of the gene. In any case, the conclusions of the analysis carried out in this respect currently point to the fact that none of the loci related to specific language impairment (SLI) would really overlap with those related to dyslexia.[167] This is true despite having frequently seen that individuals showing SLI normally end up presenting some form of dyslexia during their development. In fact, it has been indicated that this comorbidity between SLI and dyslexia could be explained by the fact that, to a great extent, the first seems to have also been caused by a deficit in short-term phonological memory and perhaps by a deficit in temporal resolution ability as well.[168] For this reason, a great part of the loci related to the "canonical" SLI forms (that is, not associated to *FOXP2* gene mutation) are still particularly appealing *a priori* in the case of dyslexia, as happens especially with locus SL1. This is associated to 3 variables that assess reading ability and, consequently, phonological working memory; locus SLI3, associated to the endophenotype SLI "reading ability disorder", and an additional locus situated in 17q23 and associated to the phenotypic component "reading problems". Whether the end the *FOXP2* gene is or is not implicated in the appearance of dyslexia, what is certain is that, bearing in mind all these facts, it has been suggested that both disorders should have a partially common genetic base.[169] All the shared genes would therefore be mainly those that take part in establishing and making short-term phonological memory function.[168] On the other hand, it is still significant that certain chromosomal rearrangements that affect this area-especially balanced chromosome translocations t(1;7)(q21.3;q34) and t(7;22)(q32;q11.2)-have been correlated to the Coffin-Siris syndrome.[170,171] This has been characterised by, among other symptoms, a moderate mental retardation that on occasions means slower language emergence, although linguistic ontogeny seem to end up completing itself normally in some people.[172]

Regarding areas present in chromosome13, it is equally significant that the13q21 area in particular, where one of the QTL related to SLI is actually located–specifically locus SLI3, which, as previously indicated, is found to be strongly associated to the endophenotype for reading ability deficit.[160] As far as the13q12 area, one should take into account that the 13q13.2-q14.1 area, particularly, corresponds to an autism locus (AUTS3) that shows a statistically significant linkage to a subtype of this disorder that includes among its distinctive symptoms several types of specifically linguistic deficits.[173] The area 13q13.2-q14.1 includes at least 4 genes that express themselves in the brain and whose products are presumably implicated with its development: *NBEA, MAB21L1, DCAMKL1,* and *MADH6 (SMAD9)*[174] (for a complete review on this area, see Benítez-Burraco[175]). On the other hand, the *CENPJ*[176] gene is found in 13q12.2, which corresponds to locus MCPH6 and encodes a J protein associated to the centromere, which would be implicated in microtubule nucleation.[177,178] This gene mutation gives rise to a primary microcephaly, a congenital microcephaly subtype where there are characteristically no serious neurological changes or dysmorphias[179] and in which abnormal cortical volume reduction is specifically due to a decrease in the number of neurons.[180] However, there is again no evidence of a possible relationship between this gene and dyslexia to date.

The loci discussed up till now have been identified principally through population samples composed of individuals affected by the disorder (in categorical terms). However, there are some additional loci that have been identified thanks to applying linkage analysis and association to samples corresponding to nuclear endophenotypes of dyslexia. Besides those previously mentioned regarding SLI and SSD, it is worth pointing out specifically that those associated to phonological memory (assessed by a pseudoword repetition test) include areas 4p12 and 12p and probably also 17q.[181]

Other dyslexia candidate genes (or genes that should at least be considered as risk factors)

Analysing certain chromosomal rearrangements has led to the identification of additional dyslexia candidate genes (or genes whose mutation could favour the appearance of the disorder in certain individuals and/or populations): This is the particular case of genes *PCNT, DIP2A, S100B*, and *PRMT2,* located in an approximately 300 kb fragment belonging to the 21q22.3 area (located at only 5 Mb from that previously related to the disorder by Fisher et al[125]), whose deletion has recently been related to dyslexia.[182] The most promising gene in this respect seems to be *DIP2A,*

which encodes a protein that forms part of the so-called recycling route of the AMPA-type glutamate receptor.[183,184] This seems to play a crucial role in synaptic plasticity regulation,[184] which is in turn necessary for cognitive processes (such as learning and memory) that depend on hippocampus activity[184] and seem to be affected in dyslexic people.[185] In mice, the orthologous gene is abundantly expressed in the central nervous system, once the identity of different brain areas is established. That is why it has been pointed out that the role played by the Dip2 protein could consist of proportioning certain axon positional signals, which would be determinant for both their normal growth and correctly establishment of neural interconnection patterns.[186] In turn, the *PCNT* gene (which was found only partly deleted in individuals examined by Poelmans et al[182]) encodes the so-called pericentrin 2, which regulates the gamma tubulin binding to the centrosome nucleus during the microtubule nucleation, a fundamental stage for normal spindle development during mytosis.[187] It should be remembered that many cognitive disorders caused by mutation of genes encoding proteins that interact with the microtubules have been described (such as the *ASPM, CYLN2* or *MAPT* genes[188]); likewise, some genes related to dyslexia itself and the genes *DCX* and *FLNA* have been indicated (see further on).

Conclusions

Current knowledge concerning the neural and genetic causes of dyslexia is a step in allowing us to observe, with a greater base, the (complex) aetiology of this disorder. It also makes it possible to observe the way in which the brain circuits related to different aspects of cognition emerge and organise themselves during development. The general framework that results from this growing corpus of genetic, biochemical, histological, anatomical, and physiological data is that the mutation of certain genes (among which *DYX1C1, DCDC2, KIAA0139,* and *ROBO1* are probably included) lead to dysfunctional proteins that produce certain changes in the normal migration and interconnection pattern in certain neural populations. These in turn bring about specific anatomical and physiological changes in certain brain areas, which consequently cause abnormal speech sound processing, but–above all–give rise to a dysfunction in the phonological component of the verbal working memory. The peculiarity is that the first of these 2 deficits contributes to reinforcing the scope of the second during the initial development stages, even though it generally ends up disappearing as the individual ages.[189,190] The causal relationship between the dyslexia candidate genes (or those that can be considered as risk factors for its appearance) identified up till now and the cognitive dysfunctions characteristically associated to this disorder has been corroborated and reinforced in the last few years thanks to the development of animal models and, in particular, thanks to the results derived from different RNAi experiments carried out on rodents. The most significant conclusion in this respect has been that the structural changes caused by a decrease in orthologous gene expression are substantially similar to those described in the brains of individuals with dyslexia, with the possible exception of *ROBO1,* on which there is no data available to date. However, these changes are also observed (especially in periventricular nodular heterotopia aggregates) in individuals affected by other illnesses caused by an abnormal cortical neural migration; an example is what is called periventricular heterotopia,[191] where, significantly, a lower reading ability is found as one of its distinctive symptoms, even in cases where the intellectual quotient is normal.[192] It is likewise of no less significance that this condition is caused by a mutation of the *FLNA* gene, which encodes a filament-1 (a phosphoprotein implicated in the same way as DCDC2 in regulation of microtubule dynamics and, particularly, in establishing cross reactions among the actin filaments, which seem to be necessary for correct cell movement regulation. This fact, coupled with the situation that the expression of the gene is particularly high during brain cortex development, seems to corroborate the hypothesis that the FLNA protein could also be essential during embryogenesis for correct regulation of neural migration up to the final destination in the brain cortex.[191] Aside from this, and at a higher biological complexity level, orthologous gene inactivation in dyslexia candidate genes also gives rise to dysfunctions that also greatly recapitulate those observed in dyslexic people, as they bring about a deficit of an auditory and cognitive nature that has to, just as properly, correlate with that observed in individuals with dyslexia.[190]

A particularly relevant, very important question consequently arises[10]: nothing less than the reason why the mutation of specific genes gives rise to a specific cognitive disorder. The genes in question are ones seemingly controlled by the general aspects of the migration and neural interconnection process and that are not only expressed in brain areas specifically integrated with the processing system related to reading (as described before), but also in other different areas, both during embryonic development and in adulthood. The cognitive disorder referred to is one that, up to a certain point, is clinically homogenous (although it is true that, as pointed out at the start of this review, several subtypes could exist) and seems to affect certain specific cognitive abilities. So why do these specific mutated genes cause this specific cognitive disorder? (And this question is posed without even considering the fact–a most significant one–that hardly any of these regions can be characterised as being exclusively in charge of a certain type of process because these areas seem to have more of a multifunctional character, taking into account the amount of resolution available through the non-invasive neuroimaging techniques currently used in their in *vivo* analysis.)

This question firstly links to some of the problems discussed in this article related to the definition of the dyslexic phenotype. However, it is also clear that it necessarily refers to the way that the genes intervene in brain development and function (as is characterised later in this article) as well as with the following in particular:

1) the limitations to which the clinical categorisation of the disorder must face when defining a syndrome on the basis of the homogenisation of the dysfunctions observed in a group of individuals, a categorisation that consequently will not always properly grasp (and that will usually leave aside) the (relative) phenotypic variability that is in fact noticed among individuals affected by the disorder.
2) the existence itself of different subtypes of the disorder (pointed out earlier in this article), which cannot be explained jointly by referring to a sole etiological hypothesis either.
3) the comorbidity often observed between dyslexia and other cognitive disorders that start in infancy and display a learning ability deficit and specific competency acquisition as a common characteristic (particularly SLI, SSD and ADHD).

The previous factors have led to the suggestion that instead of describing dyslexia as an independent, clinically homogeneous disorder, it might be more appropriate to describe it as a particular subtype of a cognitive disorder or, if you wish, as a specific manifestation of a more general cognitive deficit. This would mean that there would be other subtypes or manifestations that would correspond to what we have traditionally been describing as comorbid disorders of dyslexia and even as different subtypes of it. Alternatively (although, in reality it would be better to say in a complementary manner), it has also been pointed out that, just as in the case of other illnesses with a significant hereditary component (and including other language disorders), what has been characterised as a discrete clinical entity could really correspond to a conglomeration of different disorders with similar symptoms caused by different deficits. This would mean that each of these deficits would increase the probability of suffering a disorder susceptible to being clinically characterised as dyslexia. In the specific case of this condition (and although the deficit that would have a nuclear character would involve phonological processing ability, as also seems to be true in the case of SLI and probably SSD), auditory or visual character deficits would decisively contribute to increasing its incidence and/or seriousness.

On the other hand, the difficulty presented in achieving a precise clinical separation between the different language disorders (but also among these and others that simultaneously affect the different and/or general cognition aspects) does not differ from other controversies of the same qualitative nature. Examples of these are:

1) Controversies around the true nature and real scope of the disassociations would presumably be seen in the individuals affected by linguistic (as well as cognitive) disorders acquired in the sense that the linguistic competence dysfunction observed in–for example–the majority of aphasic individuals seems to affect the general language aspects and not so much specific grammatical entities such as those defined by linguistics[193] (for a more detailed discussion, see Benitez-Burraco[67]).
2) Controversies that likewise refer to cognitive disorders linked to development. An exemplary case would be Williams-Beuren syndrome, where supposedly only the visuospatial type of cognition is affected, while linguistic competence would be substantially preserved.[94]
3) Controversies observed regarding the real consequences for linguistic competence a mutation of certain genes affecting cognition would entail, as can be the exemplary case of *FOXP2* in relation to language.[67,163-166]
4) Controversies stemming from the relevant confirmation of linguistic dysfunctions associated to many of these disorders that can vary along the ontogeny and in response to corrective therapy.

However, despite these difficulties, it is no less certain that in a disorder such as dyslexia: *1)* a characteristic discrepancy between reading ability development and the manner and the rhythm in which the rest of the cognitive capacities are acquired is typically seen during ontogeny; *2)* all individuals affected by the disorder show very similar cerebral malformations and abnormal brain activation patterns during reading tasks; and *3)* although (as commented before in the article) the neural processing system implicated in reading tasks is sufficiently plastic, it is hardly ever able to completely correct all dysfunctions associated to a dyslexic disorder (independently of what type of therapy has been followed).

Finally, focusing specifically on comorbidity, given the data that we currently have, the most plausible explanation is that comorbid disorders must share some sort of underlying deficit. This deficit could sometimes be caused by the same brain dysfunction, caused by the mutation of the same gene. This is what would happen, for example, in the case of SSD and dyslexia related to phonological memory and locus DYX3 (where the *ROBO1* gene is located). Another example is what seems to happen with SSD and certain autism subtypes that seem to have a linguistic character deficit (although we should probably also include the syndromes of Angelman and Prader-Willi here) related to the 15q11-13 area.[175,195] This factor would mean that some of the neural circuits comprising part of the processing devices that depend on cognitive capacities affected in these disorders could be the same. Consequently, the development and operating capacity of biological complexity levels related to these cognitive abilities could be regulated, to a certain extent, by partially-overlapping genetic programmes. In the specific case of dyslexia and comorbid disorders (especially SLI and SSD), shared genes would therefore fundamentally be those that take part in regulating development and establishing the general interconnection pattern of the neural circuits causing short-term phonological memory.[168]

In light of everything that has previously been discussed, it seems reasonable to report that it is advisable not to continue thinking of dyslexia as a disorder caused by the dysfunction of circuits, structures or neural devices that specifically cause reading and spelling ability, which would work autonomously with respect to other circuits,

structures or devices implicated in processing information of a linguistic or even non-linguistic nature. Therefore, based on the general characterisation of cognition by Marcus,[196] as well as linking biological foundations to reading competency, what is relevant in neural terms is not just that there are specific portions of brain tissue devoted exclusively to processing information related to encoding and deciphering graphemes (although it is possible that some may exist), but that there is an exact design of a specific interconnection pattern. This could connect neural circuits, structures, and devices that should really be seen as computation mechanism subcomponents used in resolving many varied tasks. These tasks would of course include those related to reading. On the other hand, one must consider that only initial properties of a neural system (of reading) of this nature and created in this way would really be suitable for setting up and operating a development programme (and. to a great extent, one that was genetically coded). This programme would (solely) be in charge of regulating proliferation, migration, and, to a certain point, structural and functional specialisation of the neurons that constitute the diverse circuit structures and areas that make up this system. This could be achieved basically thanks to the programmed induction of axon and dendrite growth, as well as by establishing synaptic contacts among neurons. However, the synaptic interconnection patterns generated in this way would have an excessively generic character ("the X-type neurons have to connect to the Y-type ones"), so as to end up generating a fully working neural architecture.[9] Consequently, the itinerary of development and final characteristics for this system, responsible for reading competence, would be necessarily and substantially conditioned by the way that those initial characteristics were remodelled through the individual's life according to the environmental ambience in which he or she grows up and the stimuli (educational and/or therapeutic) that she or he receives (something ultimately possible thanks to the plasticity-always controlled and limited-inherent to the majority of neural structures).

Something similar should be confirmed with the genes identified up till now, whose mutation seems to constitute a significant causal component (or a risk factor) in the appearance of dyslexia. In this case, what is also relevant is not so much the identity of and the physiological role played by these genes, but fundamentally the exact characterisation of the architecture of the genetic programme to which they form belong This genetic architecture joins with other factors (such as epigenetic nature, those related to maternal heritability, those derived from the dynamics of the development process itself-and which make up the ontogenetic environment, those concerning the remaining levels of the biological substrate complexity of reading ability, as well as those of environmental nature), contributing to regulate the development (and to a certain extent, the functioning) of circuits and neural structures that integrate the processing systems that make reading possible. The most plausible hypothesis regarding this programme is that the majority of genes that form part of it would have a pleiotropic nature. This would signify that they would undertake different functions in different places and times during the organism's ontogeny. (In this sense, it is important to emphasise that all the dyslexia candidate genes identified to date are expressed not only in other brain areas apart from those that are not integrated in the neural system implicated in reading ability, but these candidate genes are also expressed outside the central nervous system.) Simultaneously, the candidate gene products would also act in a coordinated fashion (in space and time) to give rise to a basic neural architecture in this processing system (polygenism). Ultimately, this conception of the role played by genes in neural substrate development whose dysfunction brings about dyslexia would make it possible to explain its phenotypic heterogeneity and its genotypic variability, which results in there being various subtypes as well as different candidate genes and different genetic risk factors in different populations and for different subtypes. This also means the possibility that some of these risk alleles are present in non-affected individuals, that certain affected individuals do not show the same risk alleles, and that some individuals that show the same risk alleles present different degrees of affectation. This concept would likewise make it possible to explain the comorbidity observed between dyslexia and other language and cognition disorders. Consequently, on the one hand, in a polygenic context like this, the contribution of each dysfunctional product to the abnormal phenotype will always be (in general terms) small, very unpredictable, and conditioned by the contribution of the multitude of other genes. Such dysfunctional contribution will also be conditioned by the molecular and ontogenic context and by the environmental stimuli the individual receives during development. On the other hand, in an again pleiotropic context, a defective gene will simultaneously form part of 2 (or more) different genetic programmes; this means that its mutation will affect development (and function) of 2 (or more) structural circuits or neural devices at the same time and, consequently, 2 (or more) cognitive processes concurrently. This in turn will lead to clinical symptoms that are susceptible to being interpreted as characteristics of 2 (or more) different cognitive disorders.

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Conflict of interest

The author declares no conflict of interest.

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