

REVIEW

Neurogenetics of developmental dyslexia: from genes to behavior through brain neuroimaging and cognitive and sensorial mechanisms

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Developmental dyslexia (DD) is a complex neurodevelopmental deficit characterized by impaired reading acquisition, in spite of adequate neurological and sensorial conditions, educational opportunities and normal intelligence. Despite the successful characterization of DD-susceptibility genes, we are far from understanding the molecular etiological pathways underlying the development of reading (dis)ability. By focusing mainly on clinical phenotypes, the molecular genetics approach has yielded mixed results. More optimally reduced measures of functioning, that is, intermediate phenotypes (IPs), represent a target for researching disease-associated genetic variants and for elucidating the underlying mechanisms. Imaging data provide a viable IP for complex neurobehavioral disorders and have been extensively used to investigate both morphological, structural and functional brain abnormalities in DD. Performing joint genetic and neuroimaging studies in humans is an emerging strategy to link DD-candidate genes to the brain structure and function. A limited number of studies has already pursued the imaging–genetics integration in DD. However, the results are still not sufficient to unravel the complexity of the reading circuit due to heterogeneous study design and data processing. Here, we propose an interdisciplinary, multilevel, imaging–genetic approach to disentangle the pathways from genes to behavior. As the presence of putative functional genetic variants has been provided and as genetic associations with specific cognitive/sensorial mechanisms have been reported, new hypothesis-driven imaging–genetic studies must gain momentum. This approach would lead to the optimization of diagnostic criteria and to the early identification of ‘biologically at-risk’ children, supporting the definition of adequate and well-timed prevention strategies and the implementation of novel, specific remediation approach.

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INTRODUCTION

Reading is a cognitive skill unique to humans and crucial for living in the modern society. To be a successful reader, one must rapidly integrate a vast circuit of brain areas with both great accuracy and remarkable speed. This ‘reading circuit’ is composed of neural systems that support language as well as visual and orthographic processes, working memory, attention, motor functions and higher-level comprehension and cognition.¹ Nevertheless, for about 5 to 12% of the population, learning to read is extremely difficult.² These individuals are affected by a complex neurodevelopmental disorder called developmental dyslexia (DD), which represents the most common learning disability among school-aged children and across languages. DD is a lifelong impairment² characterized by impaired reading acquisition in spite of adequate neurological and sensorial conditions, educational opportunities and normal intelligence.³ This difficulty in reading is often associated with undesirable outcomes for children as well as with social impact and economic burden.²

Although the field is immature, the role of genetics in DD is rapidly growing and much has been learned regarding the possible downstream effects of DD risk genes on the brain

structure, function and circuitry. Similarly, cognitive and psychophysical studies have provided initial evidence about the usefulness of testing well-identified cognitive and sensorial deficits associated with and causative of DD to pursue the biological and genetic components of this disorder. Following the increasing findings provided by molecular genetic, cognitive and imaging–genetic studies of DD, this review aims to propose an interdisciplinary, multilevel, imaging–genetic approach to disentangle the pathways from genes to behavior. An interdisciplinary integration of particular cognitive/sensorial, selective genetic, and imaging data, will provide a critically important bridge for ‘connecting the dots’ between genes, cells, circuits, neurocognition, functional impairment and personalized treatment selection, and will pave the way for new candidate gene–candidate phenotype imaging association studies.⁴

GENETICS OF DD

Following earlier descriptions of strong familial aggregation of the disorder,⁵ substantial heritability typical of a complex trait has been reported⁶ with estimates across DD and DD-related quantitative phenotypes ranging from 0.18 to 0.72.⁷ Since the

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early 1980s, at least nine DD risk loci termed *DYX1–DYG9* on eight different chromosomes have been mapped (that is, 1p36-p34, 2p16-p15, 3p12-q13, 6p22 and 6q13-16.2, 11p15.5, 15q21.3, 18p11.2 and Xq27.3) and the involvement of several genes spanning these regions in the etiology of DD has been reported (that is, *DYX1C1*, *DCDC2*, *KIAA0319*, *C2ORF3*, *MRPL19*, *ROBO1*, *FAM176A*, *NRSN1*, *KIAA0319L* and *FMR1*).^{8–13} Apart from these *DYX* loci, other genes implicated in other disorders, before being examined for DD, have also been associated with reading (dis)ability, that is, *FOXP2*, *CNTNAP2*, *DOCK4* and *GTF2I* on chromosome 7,^{14–17} *GRIN2B* and *SLC2A3* on chromosome 12,^{18–20} *ATP2C2* and *CMIP* on chromosome 16,^{15,21} *PCNT*, *DIP2A*, *S100B* and *PRMT2* on chromosome 21.^{21–23} Recent genome-wide association and sequencing studies further strengthened the role of previously identified DD-candidate genes^{22,24,25} and identified novel associations with markers spanning new chromosomal regions.^{12,22,24,26–30} Among all these genes, nine DD-candidate genes have been replicated in at least one independent sample: *DYX1C1*, *DCDC2*, *KIAA0319*, *C2ORF3*, *MRPL19*, *ROBO1*, *GRIN2B*, *FOXP2* and *CNTNAP2*.^{8–12,18,20,31} Interestingly, initial evidence has been provided of the presence of putative functional genetic variants influencing the expression of some of the above-described DD-candidate genes. A functional effect of two single-nucleotide polymorphisms (SNPs) in *DYX1C1*, rs3743205 (-3G → A) and rs57809907 (1249C → T), has been hypothesized on the basis of bioinformatics predictions.³² In particular, the -3G → A SNP is located in the binding sequence of the transcription factors Elk-1, HSTF and TFII-I, and affects the Kozak sequence, which has a major role in the translation process. The coding 1249C → T-SNP truncates the protein and thus likely disrupts its functionality.³² These two *DYX1C1* variants have been associated with DD and DD-related phenotypes,^{32–34} although opposite patterns of effects^{35–42} and negative findings⁴³ have also been observed. A three-SNP risk haplotype spanning across *TTRAP*, *THEM2* and *KIAA0319* genes, has been described, that is, rs4504469, rs2038137 and rs2143340.⁴⁴ This risk haplotype is associated with 40% lower levels of the expression, splicing or transcript stability of any of the *KIAA0319*, *TTRAP* or *THEM2* genes as compared with the non-risk haplotype.⁴⁴ Furthermore, it has been shown to associate with DD in three independent clinical samples,^{44–47} as well as in two large unselected samples.^{48,49} Further characterization of *KIAA0319* has led to the identification of a marker in the risk haplotype, that is, rs9461045, found to be strongly associated with DD and to influence gene expression, possibly due to the alteration of the binding site to transcriptional silencer OCT-1 by luciferase-based assays.⁴⁷ Interestingly, a 168-base pair purine-rich region in the intron 2 of the *DCDC2* gene harboring a highly polymorphic, short-tandem repeat (BV677278) has been reported.⁵⁰ This non-coding region might serve as a regulatory node as it contains 131 putative transcription factor binding sites, is rather conserved across species and has the capacity of enhancing activity, as BV677278 changes the reporter gene expression from the *DCDC2* promoter in an allele-specific manner.⁵¹ Although more work is needed to confirm it, Powers et al.⁵² recently identified the BV677278-binding protein as the transcription factor ETV6, confirmed BV677278 as a regulatory element and proposed 'regulatory element associated with dyslexia 1' (READ1) as a new name. As such, READ1 could substantially act as a modifier of *DCDC2* gene expression. A naturally occurring deletion in intron 2 of the *DCDC2* gene (hereafter, *DCDC2d*), encompassing READ1, has been associated with DD and DD-related phenotypes,^{34,37,46,50,53,54} although negative findings have also been reported.^{41,55} In accordance with works showing that cognitive traits can be useful in the search for the susceptibility genes of neurodevelopmental disorders,⁵⁶ two recent psychophysical studies showed that *DCDC2d* specifically influences the inter-individual variation in motion perception both in children with DD^{57,58} and in normal readers.⁵⁸ Finally, one of the most informative reports of a specific

loss of *CNTNAP2* function has come from a study of an old-order Amish population in which 13 probands were found to carry the same homozygous point mutation within *CNTNAP2*, that is, 3709delG.⁵⁹ This change introduced a premature stop codon (11253X) predicted to produce a non-functional protein.^{59,60}

Recent evidence has shown that DD-susceptibility genes affect neuronal migration, neurite outgrowth, cortical morphogenesis and ciliary structure and function.^{25,27,50,61–82} In particular, *ROBO1* is known to be an axon guidance receptor regulating the connections between brain hemispheres.^{25,61–63} The protein encoded by *DYX1C1* has been linked to neuronal migration, estrogen receptor transport and cilia structure and functions.^{64–66,71,74,78,81} Animal studies showed that *in utero* RNAi of *DYX1C1* is related to deficits in both RAP, spatial working memory performance, as well as learning and memory performance.^{9,83} The expression pattern of *KIAA0319* in the developing neocortex is consistent with its hypothesized role in neuronal migration, and recent bioinformatics analysis has suggested its involvement in ciliary functions.^{69,70,72,75,79,80,84} The embryonic RNAi of *KIAA0319* expression results in RAP and spatial learning deficits.^{9,85} The *DCDC2* gene encodes a protein with two DCX domains which are essential for neurite outgrowth and neuronal migration and it is involved in ciliary functions.^{27,50,67,81,86} *DCDC2* knockout mice show impairments in visuospatial memory, visual discrimination and long-term memory, auditory processing, working memory and reference memory.^{9,87,88} Similarly, animal studies have shown that the *Gln2b* subunit is required for neuronal pattern formation in general and for channel function and formation of dendritic spines in hippocampal pyramidal cells in particular.^{68,89–91} Recently, *DCDC2* knockout mice were shown to have increased excitability and decreased temporal precision in action potential firing,⁹² as well as increased functional excitator connectivity between layer 4 lateral connections in the somatosensory neocortex⁹³ mediated by subunit *Grin2B*. Focused functional investigations of cellular and mouse models uncovered connections between *FOXP2* and neurite outgrowth.^{73,77} *FOXP2* was first implicated in a family segregating a severe form of dyspraxia of speech, designated the KE family.^{94,95} Since its original identification, many studies reported that rare variants disrupting one copy of *FOXP2* cause language-based learning (dis)abilities-related impairment.³¹ Mice carrying mutant *Foxp2* exhibit abnormal ultrasonic vocalizations as well as other disorders including developmental delay, deficits in motor-skill learning and impairments in auditory-motor association learning.^{96–101} *FOXP2* encodes a forkhead domain transcription factor expressed in several brain structures¹⁰² and modulates the DNA transcription at numerous loci throughout the genome. *CNTNAP2* is one of its gene targets¹⁰³ and it has recently been implicated in a broad range of phenotypes including autism spectrum disorder, schizophrenia, intellectual disability, DD and language impairment.¹⁰⁴ *CNTNAP2* encodes a cell-surface neurexin protein, that is, *CASPR2*, implicated in neuronal connectivity at the cellular and network level, interneuron development/function, synaptic organization and activity and migration of neurons in the developing brain.¹⁰⁴ Recently, a genetic knockout of the rodent homolog *Cntnap2* has been associated with poor social interactions, behavioral perseveration and reduced vocalizations, as well as with delayed learning and cross-modal integration.^{105,106} In contrast, little is known about the *C2ORF3* and *MRPL19* candidate genes. *C2ORF3* protein is suggested to have a potential function in ribosomal RNA (rRNA) processing,¹⁰⁷ and, as for *MRPL19*, is highly expressed in all areas of fetal and adult brain.¹⁰⁸ Furthermore, their expression was strongly correlated with *DYX1C1*, *ROBO1*, *DCDC2* and *KIAA0319* across different brain regions.¹⁰⁸ All these findings depict DD as a disorder at the mild end of the spectrum of a number of pathways producing developmental disturbances in neuronal positioning and axonal outgrowth,¹⁰⁹ consistent with the neuroanatomical

findings of focal architectonic dysplasia and neuronal ectopias in the brains of people with DD.¹¹⁰

IMAGING IN DD

Postmortem studies in DD patients showed reduced left–right asymmetry of the planum temporale,¹¹¹ as well as neuronal ectopias and architectonic dysplasias in the left perisylvian regions.¹¹⁰ More recently, magnetic resonance imaging (MRI) has been extensively used to investigate both morphological, structural and functional brain abnormalities in DD patients (Figure 1). Being noninvasive and allowing *in vivo* studies, MRI is a unique and valuable tool for disentangling tissue modifications and functional (re)organization in developmental disorders like DD. Among different MRI-based techniques, voxel-based morphometry (VBM) is used to quantify gray and white matter (GM and WM, respectively) volumes, while diffusion tensor imaging (DTI), which probes water diffusivity in the micron scale, detects alterations in WM structure and indirectly in the architecture of fiber pathways. Finally, functional MRI (fMRI) investigates brain activations during cognitive and sensory tasks, and when at rest.

VBM analysis

By applying VBM, altered GM density has been identified in several areas, that is, in the left temporal and parietal regions,^{112–119} bilaterally in the fusiform gyrus, lingual gyrus, temporo-parieto-occipital junction, frontal lobe, planum temporale, inferior temporal cortex, caudate, thalamus and cerebellum,^{115,118–126} and in the right parietal lobe.^{123,125} Moreover, VBM analysis has revealed altered WM density in the bilateral temporal and frontal lobes, in the left cuneus and arcuate fasciculus, and in the right precuneus and cerebellum.^{113,116–119,122,124,125}

DTI analysis

Alterations of WM structure have been found in bilateral tracts within the frontal, temporal, occipital and parietal lobes,^{124,127–129} in the superior longitudinal fasciculus,^{130,131} in the left superior corona radiata, in the left centrum semiovale,¹³² in the left inferior frontal gyrus and temporo-parietal WM,¹³³ in the left middle and inferior temporal gyri¹¹³ and in the left arcuate fasciculus.^{113,134} Moreover, several studies have reported significant differences in the corpus callosum.^{135,136}

fMRI analysis

fMRI has had an important role in understanding the pathophysiology of DD by analyzing the brain areas activated while performing specific tasks. The brain activations associated with the reading process have been extensively analyzed using fMRI, as well as other reading-related functions, such as phonological processing, integration of letters and speech, visual perception and attention, working memory and acoustic stimuli.^{137,138} Depending on the task performed during fMRI, several altered activation patterns have been reported.

With reading-related tasks, altered activations were found in the DD subjects in the left hemispheric temporo-parietal regions (Brodmann's areas (BAs) 20, 21, 37, superior and middle temporal gyrus, operculum, supplementary motor area), and in the bilateral frontal and occipital areas (BAs 44 and 45, inferior and middle frontal gyrus, visual areas and extrastriate cortex).^{139–148}

Subjects with DD showed abnormal activity during phonological tasks in the left hemispheric temporal areas (Rolandic operculum, middle and superior temporal gyrus, fusiform gyrus, planum temporale and Wernicke's area), in bilateral parietal (superior and inferior parietal gyrus, BA40), frontal (BAs 44 and 45, middle and inferior frontal gyrus, precentral gyrus, superior medial

gyrus and prefrontal cortex), occipital cortex (middle and superior occipital gyrus, lingual gyrus, calcarine sulcus, BAs 18 and 19, striate cortex), cerebellum, and right hemispheric subcortical structures (putamen, basal ganglia).^{149–161}

During semantic tasks, diffuse activations have been reported in DD subjects in the left hemispheric temporal (BA22, fusiform gyrus, parahippocampal gyrus and middle and superior temporal gyrus) and occipital (V5/MT), as well as bilateral parietal (inferior parietal lobule, supramarginal gyrus), frontal (BAs 44 and 45, precentral gyrus, superior frontal gyrus) cortex, cerebellum and subcortical structures.¹⁶²

Children with DD showed altered activations during auditory tasks in the right temporal areas (middle and superior temporal gyrus, BAs 41 and 42, Heschl gyrus, superior temporal cortex), anterior insular cortex, cingulate cortex, thalamus and cerebellum, in the left occipital (cuneus) and parietal (inferior parietal region, supramarginal gyrus, angular gyrus) regions and in bilateral frontal areas (supplementary motor area, inferior and middle frontal gyrus, precentral gyrus, inferior frontal sulcus, prefrontal cortex).^{152,153,163–169}

Working memory-related tasks elicited altered activations in the bilateral parietal (superior parietal cortex, inferior parietal lobule) and frontal (BA46, prefrontal cortex, inferior frontal gyrus) areas in children with DD.^{170–173}

The reduced activation of the primary visual cortex, extrastriate areas and the V5/MT area during fMRI using visual stimuli,^{174–176} as well as increased right frontal activation in areas 44 and 45 (ref. 152) have been consistently reported in subjects with DD. Visual spatial tasks elicited altered activation in the right temporal (temporal pole, fusiform gyrus, temporal gyrus, motor/premotor cortex) and frontal (precentral gyrus, frontal gyrus) areas, and in bilateral parietal (intraparietal sulcus, inferior and superior parietal lobes, precuneus), occipital (cuneus, BAs 17–19), subcortical structures (putamen, basal ganglia), anterior cingulate and cerebellum.^{157,166,177,178}

Altered activations in bilateral temporal (inferior temporal cortex), parietal, frontal (middle frontal cortex), occipital (striate and extrastriate visual cortex) and cingulate cortex have been reported during attentional tasks in children with DD.^{179–181}

Interestingly, the fMRI activation patterns in response to tasks requiring the processing of several demands (visuospatial, orthographic, phonologic and semantic) showed that subjects with DD tend to process using the visuospatial areas instead of the normal language processing areas.^{150,169}

Results of imaging studies on pre-reading children at risk for DD are in agreement with results found for children with DD,^{182–185} suggesting that neural alterations in DD predate reading onset, reflect the differential developmental trajectory of reading brain networks and may serve as early biomarkers of risk for DD.

Given the heterogeneity of imaging modalities and findings, it is difficult to summarize MR results into a unifying perspective (Figure 1). According to previous findings showing a consistent link between reading and both subcortical structures and cortical systems, structural techniques (VBM and DTI) identify temporo-parietal and, partially, middle frontal areas as the targets of cerebral derangement that may occur in DD, whereas more anterior and occipital areas seem to be less frequently involved. It is even harder to sum up the findings derived from functional MR studies. In broad terms, a pattern of cerebral hypoactivation seem to prevail over hyperactivity during task-based fMRI. Circuits involving temporo-basal, parietal and frontal lobes are more frequently impaired, without a clear lateralization between the left and right hemispheres.

The details about the study design and results are reported in Supplementary Information 1 and 2.

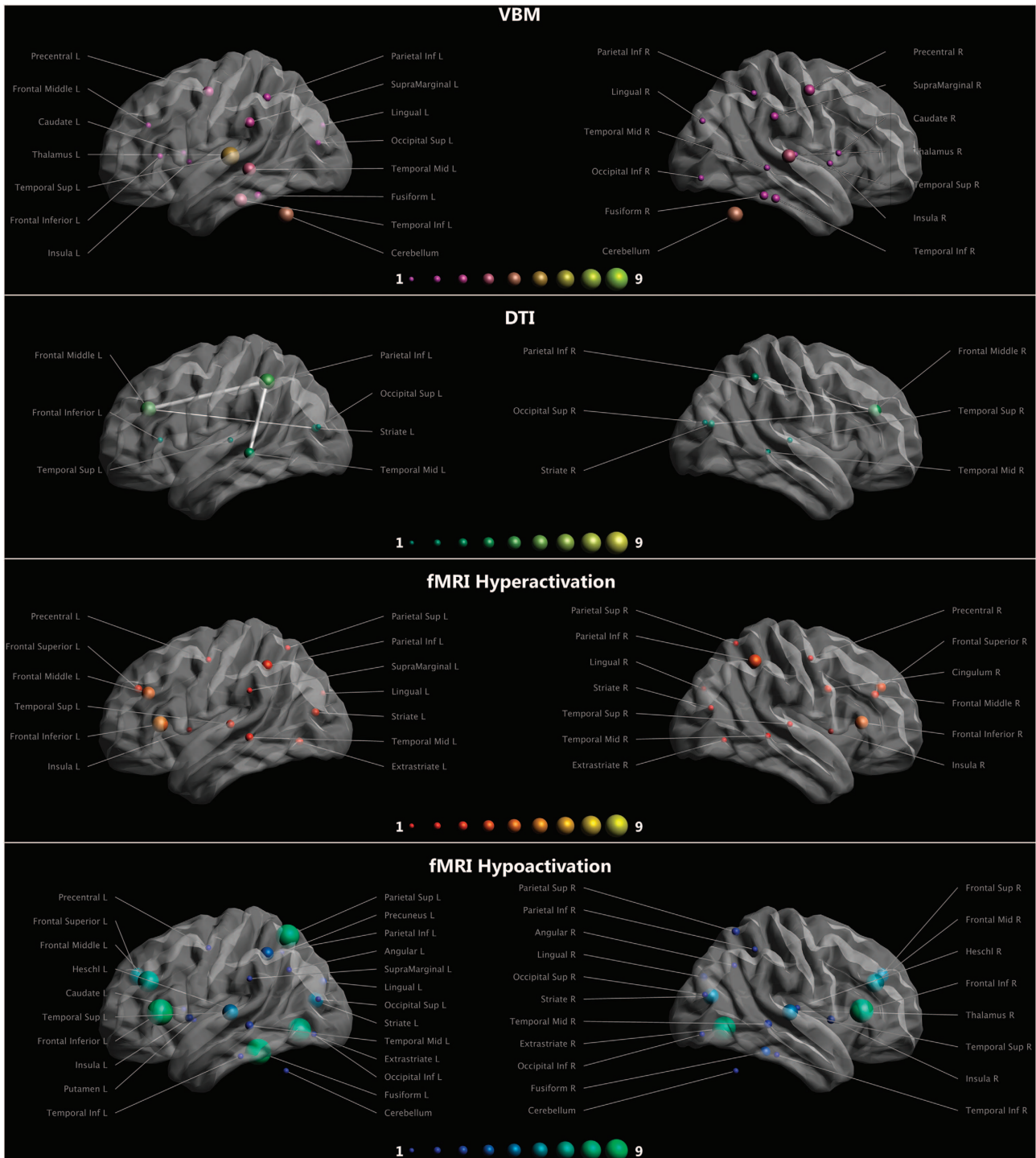


Figure 1. Rows show the findings obtained with structural and functional MR techniques in DD subjects. The size and the color of the spheres reflect the amount of papers reporting differences in the specified area. Longitudinal fasciculi and arcuate fasciculus are shown as edges. fMRI findings are not divided by task. Task specific findings are available in Supplementary Tables 1 and 2. DD, developmental dyslexia; fMRI, functional magnetic resonance imaging. Figure was created with ExploreDTI (<http://exploredti.com>). DTI, diffusion tensor imaging; VBM, voxel-based morphometry.

IMAGING–GENETICS IN DD

Taken together, these findings show how neuroimaging and genetic research have substantially enhanced understanding of the mechanisms underlying atypical reading development. Despite the successful characterization of DD-susceptibility genes, we are far from achieving a comprehensive understanding of the

pathways underlying the development of DD.¹⁸⁶ By focusing mainly on clinical phenotypes, the molecular genetics approach has yielded mixed results,¹⁸⁷ including negative findings for the DD-candidate genes.^{42,188–190} This could be ascribed to at least three possible sources: (1) as complex traits are substantially polygenic, with each variant having a small effect, larger sample

Table 1. Imaging genetic studies in DD

Locus	Location	Gene	Function	Reliability	Imaging	Results
DYX1	15q21	DYX1C1	Neuronal migration, estrogen receptor transport, and cilia structure and function	Ten independent samples (Finnish, British, two Italian, German, Canadian, Australian, American, Indian, Chinese)	Structural	rs3743205 is significantly correlated with the inferior cerebellar network in both subjects with SKZ and in controls; the magnitude of the relationship did not differ between groups. On the contrary, the gender-matched subsample showed a stronger correlation in subjects with SKZ compared with controls (Jamadar <i>et al.</i> ²⁰¹) rs3743204 is significantly associated with WM volume of the temporo-parietal region containing WM pathways connecting the MTG with the inferior parietal lobe, that is, the SLF and the posterior part of CC (Darki <i>et al.</i> ^{203, 204})
DYX2	6p22.3-p21.3	DCDC2	Neurite outgrowth, neuronal migration and ciliary functions	Ten independent samples (two American, two British, German, Australian, Canadian, Italian, Chinese, Indian)	Structural	rs793842 is significantly associated with WM volume of the temporo-parietal region containing WM pathways connecting the MTG with the inferior parietal lobe, that is, the SLF and the posterior part of CC (Darki <i>et al.</i> ^{203, 204}) rs793842 is significantly associated with the thickness of left AG and SG as well as the left LOC (Darki <i>et al.</i> ²⁰⁴) rs1087266 is significantly correlated with the superior prefrontal, occipital and temporal networks in subjects with SKZ but not in controls. rs793862 is significantly correlated with the superior cerebellar network in both subjects with SKZ and in controls; the magnitude of the relationship did not differ between groups. On the contrary, in the gender-matched subsample the correlation in subjects with SKZ do not reach significance while it is significant in controls (Jamadar <i>et al.</i> ²⁰¹) DCDC2d is significantly correlated with higher GM volumes in left TG, FG, H/PHG, IOPG, IFG, and IMG (Meda <i>et al.</i> ²⁰⁶) DCDC2d is associated with FA decreases in the bilateral ILF and in the genu of the CC in subjects with DD, and with FA reductions in the genu of the CC bilaterally and in the body of the CC in the right hemisphere, in the left ILF, AF and IFOF, and in the right IFOF, and in the body and splenium of CC in controls (Marino <i>et al.</i> ²⁰⁷) rs1087266 and rs793862 significantly correlate with Broca-Medial-Parietal network in both subjects with SKZ and controls (Jamadar <i>et al.</i> ²⁰²)
		KIAA0319	Neuronal migration and ciliary functions		Structural	During PC, BV677278 complex tandem repeat is associated with left AIPL and right LOTG. During AC, BV677278 complex tandem repeat is associated with right LOTG. During reading tasks, BV677278 complex tandem repeat is nominally associated with the SACG, PCG, left PCL and IFG, and rs2143340 with the bilateral AIPL (Cope <i>et al.</i> ¹⁹⁹) rs4504469 is significantly correlated with the superior cerebellar network in both subjects with SKZ and in controls; the magnitude of the relationship did not differ between groups. On the contrary, in the gender-matched subsample the correlation in subjects with SKZ do not reach significance while it is significant in controls (Jamadar <i>et al.</i> ²⁰¹)
					Functional	

Table 1. (Continued)

Locus	Location	Gene	Function	Reliability	Imaging	Results
					Functional	rs6935076 is significantly associated with WM volume of the temporo-parietal region containing WM pathways connecting the MTG with the inferior parietal lobe, that is, the SLF and the posterior part of CC (Darki et al., ^{203, 204})
					Functional	rs9461045 is associated with cortical thickness in the left orbitofrontal region and FA in the CC (Eicher et al., ²⁰⁸)
					Functional	rs17243157 is associated with asymmetry in functional activation of the STS (Pinel et al., ²⁰⁵)
					Structural	rs2038136 and rs2038137 significantly correlate with the left Broca-superior/inferior parietal network in controls, and with the left Wernicke-fronto-occipital network in both subjects with SKZ and controls. rs4504469 is significantly correlated with the bilateral Wernicke-fronto-parietal network in controls (Jamadar et al., ²⁰²)
DYX3	2p16-p15	MRPL19 and C2ORF3	rRNA processing	Two independent samples (Finnish and German)	Structural	rs917235 is significantly associated with WM structure in the posterior part of the CC and cingulum, connecting large parts of the cortex in the parietal, occipital and temporal lobes (Scerri et al., ²⁰⁶)
DYX4	6q11.2-q12	—	—	—	—	—
DYX5	3p12-q13	ROBO1	Axon guidance receptor regulating the connections between brain hemispheres	Four independent samples (Finnish, Australian, Italian, Indian)	—	—
DYX6	18p11.2	MCSR, DYM, NEDD4L	—	—	—	—
DYX7	11p15.5	—	—	—	—	—
DYX8	1p36-p34	KIAA0319L	—	—	—	—
DYX9	Xq27.2-q28	—	—	—	—	—
No locus named	12p13.1	GRIN2B	Neuronal pattern formation, channel function and formation of dendritic spines in hippocampal pyramidal cells	Two independent samples (German and Italian)	Functional	rs2160517, rs219931, rs11055792, rs17833967 and rs12814951 are associated with the dorsolateral prefrontal cortex activity during a working memory tasks (Pergola et al., ²⁰⁹)
No locus named	7q31	FOXP2	Neurite growth and branching, transcriptional regulation	Two independent samples (American and German)	Functional	rs6980093 is associated with higher levels of activation in the bilateral IFG during both reading and speech listening tasks (Pinel et al., ²⁰⁵)
						rs12533005 modulates the activation in occipital and inferior temporal brain areas, the AG, the insula and inferior frontal brain areas, during phonological and visual processing tasks (Wilcke et al., ¹⁷)

Table 1. (Continued)

Locus	Location	Gene	Function	Reliability	Imaging	Results
No locus named	7q35	CNTNAP2	Neuronal connectivity at the cellular and network level, interneuron development/function, synaptic organization and activity, migration of neurons	Two independent samples (British and German)	Structural	rs7794745 is associated with altered structural brain connectivity in a general population sample (Dennis et al. ²¹¹) and with reduction in GM and WM volume and FA in the cerebellum, FG, occipital and frontal cortices in subjects with ASD (Tan et al. ²¹⁴) rs2710126 is associated with FA in the uncinate fasciculus in subjects with SKZ (von Hohenberg et al. ²¹³) rs2710102 is associated with modulation of frontal lobar connectivity in subjects with ASD autism spectrum disorder (Scott Van-Zeeland et al. ²¹⁵), and with increased brain activation in BA7, BA44 and BA21 during a language processing task in healthy individuals (Whalley et al. ²¹⁴) rs7794745 is associated with brain activation in BA7, BA44 and BA21 during a language processing task in healthy individuals (Whalley et al. ²¹⁴)

Abbreviations: AC, auditory categorization; AF, arcuate fasciculus; AG, angular gyrus; AIPL, anterior inferior parietal lobe; ASD, autism spectrum disorder; BA, Brodman's area; CC, corpus callosum; DCDC2d, deletion in intron 2 of the DCDC2 gene; DD, developmental dyslexia; FA, fractional anisotropy; FG, fusiform gyrus; GM, gray matter; H/PHG, hippocampal/parahippocampal gyrus; IFG, inferior frontal gyrus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; IMG, inferior medial gyrus; IOPG, inferior occipito-parietal gyrus; LOC, lateral occipital cortex; LOTG, lateral occipital temporal gyrus; MTG, middle temporal gyrus; PC, print categorization; PCG, posterior cingulate gyrus; PCL, paracentral lobule; SACCg, superior anterior cingulate gyrus; SG, supramarginal gyrus; SKZ, schizophrenia; SLF, superior longitudinal fasciculus; STS, superior temporal sulcus; Tg, temporal gyrus; WM, white matter.

sizes are needed,¹⁹¹ (2) the pathway from genes to phenotypes is not straightforward (see for example, 'the missing heritability problem')¹⁹² and can be influenced by incomplete linkage disequilibrium between causal variants and genotyped SNPs,¹⁹³ environmental, gene-by-gene and gene-by-environment effects,^{2,186} (3) it is unlikely that a single model connects all the DD-candidate genes and their corresponding proteins at the molecular level, therefore several etiological cascades involved in neuronal migration and neurite outgrowth contributing to DD likely exist.¹⁹⁴

An alternative approach is to focus on the phenotypes thought to reflect lower-level processes, hypothesizing that individual differences in the areas responsible for reading acquisition might be important end points, better reflective of the underlying biology and more tractable to genetic mapping than behavioral phenotypes.^{56,195} In addition, the brain is the most complex of all organs, and behavior is not merely the sum of the phenotypic output of complex interactions within and between endogenous and exogenous environments during development. Therefore, more optimally reduced measures of functioning (hereafter, intermediate phenotypes—IPs) should be more useful than behavioral 'macros' in studies pursuing the biological and genetic components of neurodevelopmental disorders.¹⁹⁶ Genetic determination of an IP will likely be less complex than determination of the related behavioral/clinical phenotype, as the latter incorporates multiple neural systems and is influenced by multiple genes and environmental etiologic variables.¹⁸⁶ Even if concerns have been raised about how to interpret the relationship between IPs and psychiatric disorders,¹⁹⁷ such use of IPs has had a crucial role in improving the knowledge of the gene to phenotype gap in other neurodevelopmental disorders (for example, schizophrenia—SKZ, autism spectrum disorder).¹⁹⁵

Imaging data provide a viable IP for complex neurobehavioral disorders like DD, reducing the inherent complexity of brain functioning and of the intricate clinical outcome of these disorders.^{56,196–198} Performing joint genetic and neuroimaging studies in humans, where the association between genotypes and brain phenotypes can be tested, is an emerging strategy to link DD-candidate genes to brain structure and function. To date, imaging–genetic studies, including both structural and functional imaging, have focused on at least one of the above-described DD-candidate genes and on the proposed functional variants spanning them (Table 1).^{17,199–215} Although some of the studies involving DD-candidate genes have been carried out on populations other than DD (that is, healthy subjects, SKZ), they have been taken into consideration for the purpose of this review, that is, to propose an interdisciplinary, multilevel, imaging–genetic approach to disentangle the pathways from genes to behavior, by focusing on selective, functional genetic variants and particular, well-defined cognitive/sensorial phenotypes. Structural MRI studies have shown that in subjects with SKZ and controls, *DYX1C1* and *KIAA0319* genes are significantly correlated with the inferior and superior cerebellar networks,²⁰¹ with WM volume in the left temporo-parietal region,^{203,204} and with cortical thickness in the left orbitofrontal region in typically developing children.²⁰⁸ A pilot resting-state fMRI study failed to find a significant link between *DYX1C1* markers and functional connectivity of language-related regions in both subjects with SKZ and healthy controls.²⁰² Functional MRI studies showed associations between *KIAA0319* and asymmetry in functional activation of the superior temporal sulcus,²⁰⁵ and the inter-individual variability in activation of reading-related regions of interest (that is, the right and left anterior inferior parietal lobe)¹⁹⁹ during reading-related tasks in two independent samples of subjects with DD and normal readers. Moreover, *KIAA0319* was found to influence functional connectivity in language-related regions (that is, a left Broca-superior/inferior parietal network, a left Wernicke-fronto-occipital network and a bilateral Wernicke-fronto-parietal network) in both

subjects with SKZ and healthy controls.²⁰² In healthy adults, an allelic variation in the *DCDC2* gene has been associated with individual differences in cortical thickness,²⁰⁴ and in fiber tracts, which are commonly found altered in neuroimaging studies of reading and DD (that is, the connection of the left medial temporal gyrus with the angular and supramarginal gyri, the superior longitudinal fasciculus and the corpus callosum).²⁰³ Interestingly, in a sample of subjects with SKZ and controls, *DCDC2* was found to be associated with distributed cortical structural abnormalities in language-related superior prefrontal, temporal and occipital networks,²⁰¹ and with inter-individual variations in functional connectivity in a Broca-medial parietal network.²⁰² Furthermore, in healthy adults, *DCDC2d* has been associated with altered GM volumes in reading/language-related brain regions especially in the left hemisphere,²⁰⁰ and with both common and unique alterations of WM fiber tracts in subjects with DD.²⁰⁷ In an fMRI study, Cope et al.¹⁹⁹ found significant associations between *DCDC2*-READ1 and brain activations in the left antero-inferior parietal lobe and in the right lateral occipital temporal gyrus during reading tasks, and a nominally significant association between *DCDC2d* and activation in the left antero-inferior parietal lobule. Further imaging-genetic studies investigated the effects of *C2Orf3/MRPL19* and *GRIN2B* genes upon neuroanatomical structures. By using VBM, Scerri et al.²⁰⁶ revealed that WM volume in the bilaterally posterior part of the corpus callosum and the cingulum varied depending on one variant in the *C2Orf3/MRPL19* region. Finally, in healthy individuals, *GRIN2B* correlated negatively with dorsolateral prefrontal cortex activity during a working-memory-related task.²⁰⁹ Imaging-genetics of *FOXP2* and *CNTNAP2* has implicated common genetic variants spanning these genes. Multiple imaging studies of the KE family have found both structural and functional alterations in subjects with dyspraxia of speech and the mutant *FOXP2*.^{216–219} Even if no evidence for effects of *FOXP2* on variability in brain structures in a sample of >1300 people from the general population have been recently reported,²¹⁰ common variants spanning this gene were associated with altered levels of activation in temporo-parietal and inferior frontal brain areas during both reading and speech listening tasks in DD samples.^{17,205} *CNTNAP2* has been associated with structural brain connectivity and brain activation in BA7, BA44 and BA21 during a language processing task in healthy individuals.^{211,212} Moreover, it has been significantly associated with FA in the uncinate fasciculus of subjects with SKZ,²¹³ with reduction of GM and WM volume and lower FA in the cerebellum, fusiform gyrus, occipital and frontal cortices,²¹⁴ and with modulation in functional frontal lobar connectivity²¹⁵ in subjects with a diagnosis of autism spectrum disorder.

LIMITATIONS OF CURRENT IMAGING-GENETIC STUDIES

Clearly, neuroimaging is playing a fundamental part in disentangling the role of genetic variants in the etiology of complex cognitive functions like reading. However, the complexity of the 'reading circuit' is still far from being completely understood, as revealed by the heterogeneous and sometimes conflicting results of brain MRI studies.

Study design and data processing are important factors increasing complexity and heterogeneity in neuroimaging research. The inclusion of subjects with an unknown genetic profile will likely enhance inter-subject variability, as different DD genes may cause different deficits in different, particular cognitive and sensorial phenotypes (see 'Genetics of DD' paragraph). Nevertheless, even if some imaging-genetic studies of DD have been proposed,^{17,199–215} the number of these works is still too low to draw definitive conclusions about the role of each DD-candidate gene.

Moreover, it is interesting to note some technical evidence that might limit the integration of these results. Of the 19

forementioned imaging-genetic studies, 10 have used 1.5T scanners,^{199,203–206} eight were performed with 3T scanners^{200–202,205,207–209,215} and one acquired with a 4T scanner.²¹¹ Two of them used similar acquisition protocols and performed VBM to investigate GM,^{200,201} but their results were only partially overlapping. These different findings may be owing to the different disorders included in the studies (that is, DD and SKZ) and/or to the different analysis pipelines (linear regression versus independent component analysis). Genetic data can be integrated with every parametric map derived from MRI, whether a simple measure of volume, a microstructure-related metric or a measure of chemical properties. Three of the aforementioned studies integrated genetic data in the VBM analysis of WM volume as an attempt to reveal genetically related alterations, limiting the analysis of DTI data to the detection of the major fiber bundles included in altered WM areas.^{203,204,206} Nevertheless, DTI analysis can provide parameters that are more specific to WM microstructure than VBM,²²⁰ including fractional anisotropy (FA) and measures of diffusivity along different spatial axes. These maps can be analyzed similarly to VBM, but may provide additional characterization of the genetic effect at the microstructural level. To date, only three studies have used DTI-derived maps to detect voxel-based WM modifications related to DD-candidate genes.^{207,208,214} One of the studies²¹³ computed FA maps and tried to perform region-of-interest-based analysis of covariance regression with the SNPs of *CNTNAP2*; however, only one genotype was a significant predictor of FA in the uncinate fasciculus after Bonferroni correction, despite the relatively high number of subjects included in the study ($n = 125$). Further studies with rigorous advanced diffusion MRI protocols (that is, high-field magnets, multiple directions and b-values) and populations with a specific genetic characterization are therefore needed. Moreover, more complex diffusion-based techniques, such as NODDI (Neurite Orientation Dispersion and Density Imaging), have recently provided more specific metrics of GM and WM in several applications.^{221–223} The application of NODDI or other affine techniques might be beneficial to the study of DD, providing additional disentanglement of the connections between genetic variations and structural alterations.

Similar considerations apply to fMRI, where the choices of stimuli and the analysis pipeline are fundamental. To date, functional imaging-genetic studies of DD have investigated the effects of DD-candidate genes only during reading tasks,^{199,205,209} irrespective of the deficits each DD gene is likely to produce (see 'Genetics of DD' paragraph). Moreover, while task-based fMRI might help investigate the effects of DD-candidate genes on specific brain functions through correlation analysis or linear regressions, resting-state fMRI might offer a more reproducible/reliable approach to the investigation of genetic effects on brain functionality. It is worth noticing that while imaging-genetic studies are at their early stages in DD, they are more popular in the context of other diseases.^{224–227} For example, the ADNI (Alzheimer's Disease Neuroimaging Initiative)²²⁸ has performed MRI and positron emission tomography acquisitions with genetic profiling in more than 1000 subjects over time. Along with genetic profiling, the success of the initiative is strongly supported by the standardization of multicentric acquisition protocol and processing methods, all factors that are unfortunately still lacking in imaging-genetic studies on DD.

TOWARD A NEW APPROACH

As aforementioned, learning to read requires the accurate, fast and timely integration of different neural systems supporting different cognitive and sensorial processes. Molecular genetic studies have consistently identified DD-candidate genes and provided initial evidence of the presence of putative functional genetic variants influencing gene expression. Recent findings in

both animal and humans studies support the role of specific genetic variants on the different cognitive and sensorial processes underlying reading acquisition. Similarly, neuroimaging data can be considered IPs to genetics in identifying the causes of DD.¹⁹⁸ New studies must therefore gain momentum to understand the function of neuronal migration genes and their relationships with specific cognitive and sensorial vulnerability, and to establish links between such susceptibility variants and neuroanatomical phenotypes. Following a probabilistic and multifactorial etiological model of reading acquisition, the emergence of DD is rooted at multiple levels, and may reflect the global failure of interacting mechanisms, each with degrees of impairment that vary across children.^{2,186,229–232} It is therefore reasonable to predict a low specificity and high heterogeneity of imaging findings, especially when dealing with small sample sizes. Furthermore, according to this model, the fundamental role of genetics in the selection of homogeneous DD subtypes population suitable for imaging investigation appears reasonable. The integration of specific cognitive/sensorial, selective genetic and imaging data can lead to the identification of regions with gene- and cognitive/sensorial-specific effects (that is, only a risk genetic variant alters structure/function in this region tapping specific cognitive/sensorial mechanisms) or with universal effects (that is, all/many-risk gene function in this region). Identifying the dots connecting putative functional genetic variants, neuroanatomical structures and functions, and reading-related cognitive/sensorial pathways, will be important areas for imaging-genetics research in the future and will pave the way for new candidate gene-candidate phenotype imaging association studies.⁴ However, some have argued that neuroimaging studies reporting effects of candidate genes are also at risk for false-positive effects due to small sample sizes, and questions about the statistical power of imaging techniques may be risen.^{233,234} Some possible strategies could be used to overcome such variability. First, accordingly to what is proposed in this review, an alternative way to avoid false positives is to focus on selective variants with known molecular function and to take into account the increment in effect sizes enabled by careful selection of phenotypes.^{235,236} By narrowing the search space to genes that are likely to have a role—and whose functions have more chance of being understood—the power of the study is directly increased, as is its practical value for neuroscience and medicine.²³⁵ The identification of what constitutes a phenotype is crucial as the identification of the phenotype itself. Going beyond classical association studies, where heterogeneous patient groups selected by clinical symptoms are compared with controls, is crucial to identify reliable biomarkers and to guide the diagnosis of neurodevelopmental disorders.⁴ More specific, elementary, straightforward IPs may help to interpret the results of genetic studies of psychiatric diseases,²³³ increasing the statistical power in smaller sample size.²³⁶ Recent studies on relatively small samples show that using IPs can be very useful for researching susceptibility genes in DD^{26,237,238} and for explaining their effects on the phenotypic variance.^{35,57,58} Second, there is a growing perception of reproducibility as a fundamental building block in science. Some have argued that small individual studies—when replicated—may lead to useful observations to address the impact of genetic variation on a neural system that is abnormal in a given illness, despite the problem of false-positive findings. An alternative strategy is to recruit large data sets through multi-center studies. Many neuroimaging consortia have been recently established (for example, the ADNI, the functional Brain Imaging Research Network, the Mind Clinical Imaging Consortium, the Enhancing Neuroimaging Genetics through Meta-Analysis consortium, the Pediatric Imaging Neurocognition Genetics study) to expand the promise of imaging-genetic studies and to detect factors that affect the brain that could hardly be detected by single site studies.^{12,235} However, as some limitations apply (for example, it is difficult to aggregate data from cohorts that are

heterogeneous in terms of duration of illness and demographics, spoken languages, ethnic differences in allele frequency), novel, harmonized data analysis and meta-analysis protocols checking for the effects of possible confounders, are crucial to the success of these projects.^{235,239} Third, it would help to develop an interdisciplinary multilevel approach aimed at defining MRI protocols heavily guided by genetics and cognitive findings. The best outcomes result from cooperation within a multidisciplinary team to address the different levels of investigation underlying such complex neurodevelopmental disorders.^{240,241} Nonetheless, addressing the statistical power problem in imaging studies is nontrivial. We depicted DD as a heterogeneous disease, and the MRI findings also reported the same to date (Figure 1). Generally speaking, the estimation of the minimum sample size required to highlight structural or functional imaging alteration is prohibitive. One may argue that some areas, that have been reported more consistently in literature, are more consistently altered and thus require a smaller sample size to be detected. The problem is worsened by the variability introduced by MRI techniques and methods as the multiple comparisons correction, that greatly limits the comparability of results across studies. New candidate gene-candidate phenotype imaging association studies should integrate investigations of the effects of selective genetic variants upon neuroanatomical pathways underlying the specific reading-related cognitive and sensorial processes each gene is supposed to target by applying the most sensitive and robust neuroimaging techniques. Future hypothesis-driven imaging-genetic studies should therefore take advantage of recent genetic findings in both animal and human studies to focus their attention on innovative interdisciplinary analyses of well-defined, specific cognitive and sensorial, imaging and selective genetic data. In this way, the effect of a known genetic diversity, naturally occurring among human populations, is studied by brain imaging to determine whether one of its forms can cause a difference in the level of such cognitive/sensorial phenotypes and hence could make people more vulnerable to neurodevelopmental disorders.⁴ A fruitful outcome is particularly possible when fMRI is used to examine the neurobiological effect of a well-validated gene. If DD-candidate genetic variants are selectively associated with inter-individual variation in one of the reading-related processes at brain level, children carrying these genetic variants would be considered as 'biologically at-risk'. Early identification of these children would be crucial to defining adequate and well-timed prevention strategies.^{197,242} Furthermore, candidate gene-candidate phenotype might be fundamental to understanding the relationship between traditional diagnostic categories and the new classifications of mental disorders based on dimensions of observable behavior and neurobiological measures.^{186,187,195,196,198} Neuroimaging may provide evidence for or against existing theories, or provide unique and sensitive insight unexplained solely by behavioral measures.¹⁹⁸ Although producing interesting results, the hypothesis-driven approach of imaging genetics represents a way for validation/replication studies of selective genes and do not reveal other genetic contributors to the overall neurobehavioral reading deficits nor the imaging phenotype changes associated with DD.^{4,12,31} By implementing a 'gene hunting' strategy,⁴ hypothesis-free approach, similar to those commonly seen in human genetics such as genome-wide association studies and new DNA sequencing technologies, could detect common variants with small effect sizes and could reveal new genes and pathways, rare and *de novo* variants, that contribute to alterations in brain imaging phenotypes, and how they contribute to the ultimate neurobehavioral phenotypes.^{12,31,235} However, the question that arises from imaging-genetics as a hypothesis-free field is how to use and analyze such large and diverse datasets. Data reduction or hypothesis-free processing methods, such as parallel independent component analysis,^{201,202} multivariate pattern analysis,²²⁷

endophenotype ranking value,²⁴³ polygenic risk score,²⁴⁴ as well as new analytical methods to collapse and/or integrate a variety of data types into relevant risk models (for example, support vector machine analysis) are potentially needed.

CONCLUSION

This review aimed to highlight the promising imaging–genetics approach as a way to unravel new insights behind the pathophysiology of reading (dis)ability. As the presence of putative functional genetic variants influencing the expression of some of the DD-candidate genes has been provided and as genetic associations with specific, well-defined cognitive/sensorial mechanisms have been reported, current knowledge of genetics of DD could help target imaging more selectively. The integration of particular cognitive/sensorial, selective genetic and imaging data, as well as the implementation of candidate gene–candidate phenotype imaging association studies would result in a better consideration of what constitutes a phenotype. Clearly, such an approach is essentially interdisciplinary given the multiple levels of analysis simultaneously achieved. Even if there are weaknesses despite strengths in this perspective, such hypothesis-driven approach in imaging–genetics as a field would lead to the optimization of criteria to diagnose DD and to the early identification of ‘biologically at-risk’ children. This means the definition of adequate and well-timed prevention strategies and the implementation of novel, specific and evidence-based remediation approach training specifically the reading-related cognitive/sensorial impairment. These insights will aid in the earlier detection of children with DD and aid their overall academic and remediation potential. Naturally, these developments should be considered in parallel with the advance made by the hypothesis-free approach that will aid in the identification of new mechanisms (genetic and imaging) that contribute to reading deficits in DD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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