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

S Mascheretti1,5, A De Luca2,3,5, V Trezzi1, D Peruzzo2, A Nordio2,3, C Marino1,4 and F Arrigoni2

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.

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. Nevertheless, for about 5 to 12% of the population, learning to read is extremely difficult. 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 impairment characterized by impaired reading acquisition in spite of adequate neurological and sensorial conditions, educational opportunities and normal intelligence. This difficulty in reading is often associated with undesirable outcomes for children as well as with social impact and economic burden.

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 psychophysic 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.

GENETICS OF DD

Following earlier descriptions of strong familial aggregation of the disorder, substantial heritability typical of a complex trait has been reported with estimates across DD and DD-related quantitative phenotypes ranging from 0.18 to 0.72. Since the
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 (I1253X) 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. 25,27,50,61-63 The protein encoded by DDX1C1 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 DDX1C1 is related to deficits in both RAP, spatial working memory performance, as well as learning and memory performance. 98 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. 98,95 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. 87,88 Similarly, animal studies have shown that the Glun2b 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 neocortex, 93 mediated by subunit Grin2B. Focused functional investigations of cellular and mouse models uncovered connections between FOXP2 and neurite outgrowth. 77,79 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 structures 102 and modulates the DNA transcription at numerous loci throughout the genome. CNTNAP2 is one of its gene targets 103 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. 105 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 DDX1C1, ROBO1, DCDC2 and KIAA0319 across different brain regions. 106 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.

**IMAGING IN DD**

Postmortem studies in DD patients showed reduced left-right asymmetry of the planum temporale,\(^{1,11}\) as well as neuronal ectopias and architectonic dysplasias in the left perisylvian regions.\(^{1,10}\) 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,\(^{1,12} – 119\) bilaterally in the fusiform gyrus, lingual gyrus, temporo-parieto-occipital junction, frontal lobe, planum temporale, inferior temporal cortex, caudate, thalamus and cerebellum,\(^{1,15} – 118, 126\) and in the right parietal lobe.\(^{1,123, 125}\) 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.\(^{1,13, 116} – 119, 122, 124, 125}\)

**DTI analysis**

Alterations of WM structure have been found in bilateral tracts within the frontal, temporal, occipital and parietal lobes,\(^{1,12, 127} – 129\) in the superior longitudinal fasciculus,\(^{1,30, 131}\) in the left superior corona radiata, in the left centrum semiovale,\(^{1,32}\) in the left inferior frontal gyrus and temporo-parietal WM,\(^{1,132}\) in the left middle and inferior temporal gyri\(^{1,133}\) and in the left arcuate fasciculus.\(^{1,13, 134}\) Moreover, several studies have reported significant differences in the corpus callosum.\(^{1,35, 136}\)

**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.\(^{1,37, 138}\) 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 (Brodman’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).\(^{1,39} – 148\)

Subjects with DD showed abnormal activity during phonological tasks in the left hemispheric temporal areas (Rolandioc 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 gyruus 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).\(^{1,149} – 161\)

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.\(^{1,162}\)

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).\(^{1,152, 153, 163} – 169\)

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.\(^{1,170} – 173\)

The reduced activation of the primary visual cortex, extrastriatal areas and the V5/MT area during fMRI using visual stimuli,\(^{1,174} – 176\) 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.\(^{1,157, 166, 177}\)

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.\(^{1,179} – 181\)

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.\(^{1,150, 169}\)

Results of imaging studies on pre-reading children at risk for DD are in agreement with results found for children with DD.\(^{1,182} – 185\) 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.
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. By focusing mainly on clinical phenotypes, the molecular genetics approach has yielded mixed results, including negative findings for the DD-candidate genes. 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...
| 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 et al.203) |
| 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 et al.203, 204) rs793842 is significantly associated with the thickness of left AG and SG as well as the left LOC (Darki et al.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 et al.203) |
|       |          |      |          |             |         | DCDC2d is significantly correlated with higher GM volumes in left TG, FG, H/PHG, IOPG, IFG, and IMG (Meda et al.200) 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 et al.207) rs1087266 and rs793862 significantly correlate with Broca-Medial-Parietal network in both subjects with SKZ and controls (Jamadar et al.205) |
|       |          |      |          |             |         | During PC, BV677278 complex tandem repeat is associated with left APL 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 SACC, PCG, left PCL and IFG, and rs2143340 with the bilateral APL (Cope et al.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 et al.203) |

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Table 1. (Continued)

| Locus | Location | Gene           | Function                                                                 | Reliability                      | Imaging | Results                                                                 |
|-------|----------|----------------|--------------------------------------------------------------------------|-----------------------------------|---------|--------------------------------------------------------------------------|
|       |          |                | 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., 2003, 2004) | Functional |         |                                                                          |
| rs9461045 is associated with cortical thickness in the left orbitofrontal region and FA in the CC (Eicher et al., 2008) |         |                | rs17243157 is associated with asymmetry in functional activation of the STS (Pinel et al., 2007) |         |         |                                                                          |
| 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., 2002). |         |                | 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., 2008). |         |         |                                                                          |
| rs917235 and rs6732511 show suggestive association with cortical thickness in the left middle temporal region and cortical volume in the right fusiform region, respectively. rs2298248 is associated with cortical thickness in the right middle temporal region and with cortical volume in the right inferior temporal region (Eicher et al., 2008). |         |                |         | rs917235 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., 2003, 2004) |         |         |                                                                          |
| rs6980093 is associated with higher levels of activation in the bilateral IFG during both reading and speech listening tasks (Pinel et al., 2009) |         |                | 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., 2017). |         |         |                                                                          |
Table 1. (Continued)

| Gene | Function | Location | Structural Imaging | Reliability |
|------|----------|----------|--------------------|-------------|
| DCDC2 | deletion in intron 2 of the DCDC2 gene | 14q32.33 | Two independent samples (British and German) | Functional connectivity at the cellular and network level, interneuron development/function, synaptic organization and activity, migration of neurons |
| ISPD | deletion in intron 1 of the ISPD gene | 11p15.5 | Two independent samples (British and German) | Functional connectivity at the cellular and network level, interneuron development/function, synaptic organization and activity, migration of neurons |

Abbreviations: AC, auditory categorization; AF, arcuate fasciculus; AG, angular gyrus; AIPL, anterior inferior parietal lobe; ASD, autism spectrum disorder; BA, Brodmann’s area; CC, corpus callosum; DCC17F; 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; LOG, lateral occipital gyrus; MCG, middle occipital gyrus; PCG, posterior cingulate gyrus; PCL, paracentral lobule; SACG, superior anterior cingulate gyrus; SG, supramarginal gyrus; SKZ, schizophrenia; SLF, superior longitudinal fasciculus; STS, superior temporal sulcus; TG, temporal gyrus; WM, white matter.
subjects with SKZ and healthy controls. In healthy adults, an allelic variation in the DCDC2 gene has been associated with individual differences in cortical thickness, 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). 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, and with inter-individual variations in functional connectivity in a Broca-medial parietal network. Furthermore, in healthy adults, DCDC2 has been associated with altered GM volumes in reading/language-related brain regions especially in the left hemisphere, and with both common and unique alterations of WM fiber tracts in subjects with DD. In an fMRI study, Cope et al. 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 DCDC2 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. 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. 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. 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, common variants spanning this gene were associated with altered levels of activation in temporoparietal and inferior frontal brain areas during both reading and speech listening tasks in DD samples. CNTNAP2 has been associated with structural brain connectivity and brain activation in BA7, BA44 and BA21 during a language processing task in healthy individuals. Moreover, it has been significantly associated with FA in the uncinate fasciculus of subjects with SKZ, with reduction of GM and WM volume and low FA in the cerebellum-fusiform gyrus, occipital and frontal cortices, and with modulations in functional frontal lobar connectivity 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, 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 aforementioned imaging–genetic studies, 10 have used 1.5T scanners, eight were performed with 3T scanners, and one acquired with a 4T scanner. Two of them used similar acquisition protocols and performed VBM to investigate GM, 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. Nevertheless, DTI analysis can provide parameters that are more specific to WM microstructure than VBM, 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. One of the studies 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. 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, 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. For example, the ADNI (Alzheimer’s Disease Neuroimaging Initiative) 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.\textsuperscript{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.\textsuperscript{2186,229,231} 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 mechanisms or with universal effects (that is, all/many-risk gene function in this region). Identifying the dots connecting putative mechanisms or with universal effects (that is, all/many-risk gene function in this region).

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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–genetics 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9,12,31} By implementing a ‘gene hunting’ strategy,\textsuperscript{6} 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.\textsuperscript{12,23,125} 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,\textsuperscript{201,202} multivariate pattern analysis,\textsuperscript{227}...
endophenotype ranking value, polygenic risk score, 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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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)