Review

Developmental Dyscalculia: heterogeneity might not mean different mechanisms

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Research indicates that developmental dyscalculia (DD; a mathematical deficiency) involves a single brain area abnormality – in the intraparietal sulcus. This is surprising because, (i) the behavioural deficits are heterogeneous, (ii) multiple problems are most common in most cases (co-morbidity) and (iii) different aspects of intact number processing are represented in different brain areas. Hence, progress in the study of DD might be limited by conceptual issues. This work looks at biological and cognitive findings within DD and delineates frameworks for studying the neurocognitive basis of DD. We offer three alternative frameworks. These proposed frameworks have the potential of facilitating future discussions, work in the field and have implications for studies of similar disorders like dyslexia and attention-deficit/hyperactivity disorder.

From pure developmental dyscalculia to co-morbidity

Most diagnostic criteria use the term developmental dyscalculia (DD) to describe moderate to extreme difficulties in fluent numerical computations that cannot be attributable to sensory difficulties, low IQ or educational deprivation [1,2]. Epidemiological studies have indicated that DD is as common as reading disorders and affects 3.5%–6.5% of the school-age population [2]. Paradoxically, DD is an unexpectedly neglected area by both clinicians and researchers, despite its importance in health management [3], schooling, everyday life and employment.

Current research points to a single biological marker in DD: an intraparietal sulcus (IPS) abnormality (Figure 1) [4–6]. This is surprising because cognitive deficits seen in DD are heterogeneous [7], and functional brain imaging and brain lesion studies demonstrate that various aspects of intact number processing undoubtedly involve not only the IPS but also additional brain areas [8–10].

Recently, Wilson and Dehaene [11] wrote a review revolving around the idea of DD being because of a core numerical deficit (Boxes 1 and 2) involving a single brain area (similar to the first framework we propose later). They still suggested that other subtypes of DD could exist and would involve brain areas other than the IPS. Our departure point is heterogeneity in etiology and in the manifestation of maths difficulties. Accordingly, we critically evaluate the core problem and offer additional frameworks of thought (Figure 2) [12].

We would like to draw a distinction between DD and mathematical learning disabilities (MLD). Both are disorders in mathematics with no other non-numerical disorder. The term DD is reserved here for a deficit in core numerical abilities (e.g. difficulty in processing quantities) and a relatively specific malfunction at the behavioural level (first framework; Figure 2a). By contrast, MLD are caused by several cognitive deficits such as deficient working memory, visual-spatial processing or attention. Accordingly, DD and MLD would manifest in different behaviours at early stages of development. However, they sometimes manifest in similar behaviours later in life because of the influence of various developmental factors [13] such as schooling.

We offer three alternative frameworks for the origin of DD or MLD and their cognitive deficits. These frameworks can direct theoretical work and help reveal the causal relationship between neurocognitive mechanisms and behaviour. The first framework indicates that a single restricted biological deficit gives rise to a specific developmental disorder (Box 1). However, as is the case with many developmental disorders, multiple problems are most common and pure disorders apply to a minority of cases only. Hence, two other frameworks are suggested. The second framework indicates a variety of cognitive deficits because of a single or multiple instances of biological damage (Box 3). Each cognitive deficit produces a different mathematical deficiency and as a whole, they create the behavioural manifestations of MLD. The third framework indicates that the neurocognitive damage that causes DD could produce other behavioural disorders that are unrelated to DD, namely co-morbidity (e.g. DD + dyslexia) (Figure 2).

It should be noted that very little is known about the molecular biological origins of DD or MLD and there are very few longitudinal studies that examine developmental aspects of these disorders. We emphasize brain dysfunction as a possible origin. However, DD or MLD can involve genetic or environmental factors. Accordingly, the links between the biological, cognitive and behavioural levels are, in most cases, tentative.

In what follows we outline three frameworks, demonstrate their viability and explore important barriers to embracing the particular frameworks.

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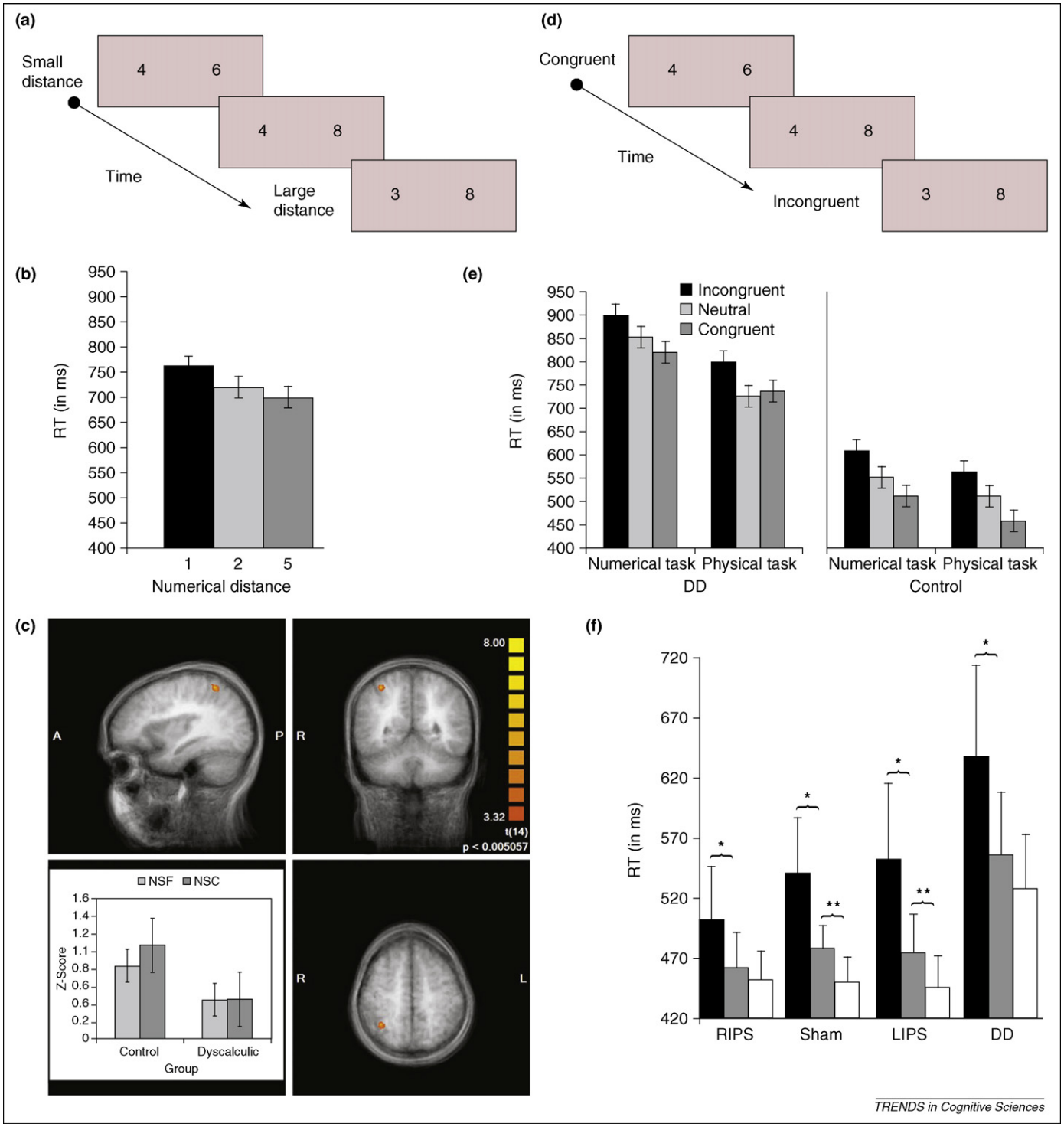

Figure 1. The distance and size congruity effects. **(a)** A typical task that produces the distance effect (DE). When participants are asked to compare two digits, they respond faster when the digits are numerically further apart from one another (e.g. 3–8) than when they are closer (e.g. 4–6). This negative correlation between reaction time and numerical distance is termed DE [56]. DE is considered to reflect access to an analogue representation of numerosity. **(b)** Typical behavioural results, which appear both in DD subjects and controls [17,18]. **(c)** DE involves IPS activation [57]. Right IPS DE for comparisons of non-symbolic stimuli (NSF, non-symbolic far distance; NSC, non-symbolic close distance) is reduced in children suffering from DD [5]. **(d)** Trials in the numerical Stroop task are characterized by independent manipulation of both numerical and physical distances. The two dimensions can be congruent (e.g. 4–6) or incongruent (e.g. 3–8) [58]. Participants process both dimensions automatically; they cannot ignore either dimension and respond faster to the congruent trials than to the incongruent trials [58–60]. **(e)** Typical and atypical behavioural results of the numerical Stroop task. Controls showed both facilitation (response to congruent trials faster than to neutral trials) and interference (response to neutral trials faster than to incongruent trials), whereas DD subjects showed a pattern similar to children at the end of first grade [61], that is, a lack of facilitation and a smaller overall effect [17]. **(f)** TMS to the right IPS (RIPS) but not to left IPS (LIPS) or other brain locations (Sham) produce a DD-like pattern of reaction time (RT). Error bars depict one standard error of the mean. * < 0.05, ** < 0.005. Part (c) reproduced, with permission from Ref. [5]. Part (f) reproduced, with permission, from Ref. [6].

Framework 1: a unique cognitive deficit because of a unique pathophysiology

It has been argued that dyscalculia is the result of specific disabilities in basic numerical processing [14,15], for example, a deficit in quantity processing [16–19] rather than in general cognitive abilities such as working memory [20] (Figure 2a and Box 1). Studies of distance, size congruity effects (Figure 1) and counting (Box 2) support the

Box 1. Innate core numerical processes

Research indicates that the numerical core system can be characterized as a set of intuitions for quantities (i.e. a mental representation of quantities or magnitudes) that is innately available to humans [62] and animals [63]. For example, many animal species can discriminate stimuli that differ only in numerosity (i.e. number of items in a set), and possess greater knowledge of numbers than could have been induced by training alone [64]. In addition, research indicates that even in the first week of life, human infants seem to discriminate visual displays on the basis of numerosity (for a review see Ref. [15]).

Infant research uses the classical method of habituation-recovery looking time, which is based on the fact that infants look longer at an impossible outcome or event. These habituation-recovery studies indicate that infants are able to represent the numerosity of sets of objects and to detect a change in numerosity when new items are added or taken away from a set [65]. However, some researchers argue that increased looking time in infants signifies violation of expectations and error detection rather than understanding of basic arithmetic [66]. Moreover, recent evidence showed that infants respond to numbers, time and area in a similar way, which can raise questions about the fundamental nature of numerical quantity processing. Specifically, Brannon, Lutz and Cordes [62] showed that the area discriminations of six-month-old infants match their number discriminations, and VanMarle [67] demonstrated the same pattern for six-month-olds' discrimination of temporal duration. Nonetheless, these findings still indicate that very young infants use the suggested system to represent numerosity and respond to changes in numerosity.

Box 2. Counting

Enumeration develops during the first few years of life and has been suggested as essential for the proper development of numerical cognition [68]. Discussions of enumeration distinguish between three processes: estimation, subitizing and counting. In adults, estimations relate to the strategy employed when a stimulus display has a large number of items and is presented briefly. Infants are not only capable of discriminating small object sets (as mentioned in Box 1) but are also able to discriminate large set sizes (i.e. estimation system [69]). Accordingly, it was suggested that estimation involves a separate, approximate processing system. In infants, the estimation system depends on visual-spatial processing capacities and, thus, might be linked to manifestation of MLD [Figure 2b (iii)].

Subitizing is the more accurate, automatic, effortless process of reporting the number of items in a small group. In recent years, it has been agreed that the subitizing range is between three and four items. A characteristic of DD is an impairment of the ability to subitize, which could be an example for a deficient core numerical system [70]. Counting, by contrast, is an effortful and sequential process, in which RT increases and accuracy decreases as the number of presented items increases.

It has been suggested that finger gnosis or use is related to learning to count and calculate [15]. rTMS to the left angular gyrus disrupted both finger movements and number magnitude judgments [55]. Hence, it is possible that DD is associated with deficiencies in finger use.

It has been debated whether subitizing and counting constitute separate mechanisms or different ends of a continuum. A recent patient study has indicated that there might be a dissociation between these two processes [16], but recent imaging studies have presented somewhat contradictory results. A functional magnetic resonance imaging (fMRI) study [71] found that counting intensely activated bilateral fronto-parietal regions that were activated to a much lesser extent during subitizing. Furthermore, these regions showed no increase in activation within the subitizing range (1–3), and a sudden linear increase within the counting range (4–7). The processes involved in subitizing and counting are of importance to the development of normal arithmetic abilities [14]. Previous research indicated that deficiency in these processes might be detrimental to such development. Hence, this might also prove to be a core numerical deficit in DD.

suggestion of damaged numerical but not size-magnitude processing. Yet, some contradictory results exist. For example, Rousselle and Noel [19] found that mathematically disabled children showed deficiency with symbolic rather than non-symbolic comparisons. By contrast, Price and colleagues [5] found deficiencies in non-symbolic comparisons (Figure 1c). Results that point to difficulty with non-symbolic but not with symbolic processing challenge the notion that non-symbolic number processing might be a building block for (symbolic) arithmetic skills. More research is needed to gain a better understanding of the mapping process between symbolic and non-symbolic number representations and symbolic and non-symbolic arithmetic before a firm conclusion can be reached.

Moreover, it has been suggested that a specific part of the parietal brain region (horizontal IPS) is amodal [21] (but see Ref. [22]), language-independent and has a central role in basic representation of numerical quantity (i.e. core numerical knowledge). Assuming that a core numerical system is the basis for developing all higher mathematical abilities [23], the current framework indicates that individuals with DD have a deficiency in the neural tissue that supports this core system, namely the IPS (Figure 1).

Point of consideration: heterogeneity is most common, not the exception

The examples given earlier indicate that DD is a pure and very specific disorder. However, as in the case with many other developmental disorders [24], multiple problems are the most common and pure disorders apply to a minority of cases only.

Research reporting IPS alterations in cases of mathematical difficulties shows that additional parts of the brain might be involved. For instance, Molko and colleagues [4] showed changes in the IPS in cases of Turner Syndrome (TS), a genetic disorder characterized by deficits in visual-spatial functions, number processing, working memory, executive function and social cognition [25]. However, a closer look at this research indicates that the right fusiform gyrus, which is considered to be involved with perceiving written numbers [21], was significantly reduced in grey matter in those with TS compared to controls. Moreover, Kucian and colleagues [26] showed weaker activation during approximate calculation not only in the left and right IPS but also in the inferior and middle frontal gyri (IFG, MFG) bilaterally in children with Mathematical Difficulties (MD). Studies of typically developing children [27], adults [21] and primates [28] support this suggestion. This might indicate a general rather than a specific deficit in recruiting neural resources in children with MD when processing analogue magnitudes.

It has been suggested that genes tend to be expressed throughout most brain regions [13]. Hence, in the case of developmental abnormalities such as DD, the deletion, reduplication or mis-positioning of genes would be expected to change the course of general development, with stronger effects on some behavioural aspects (like

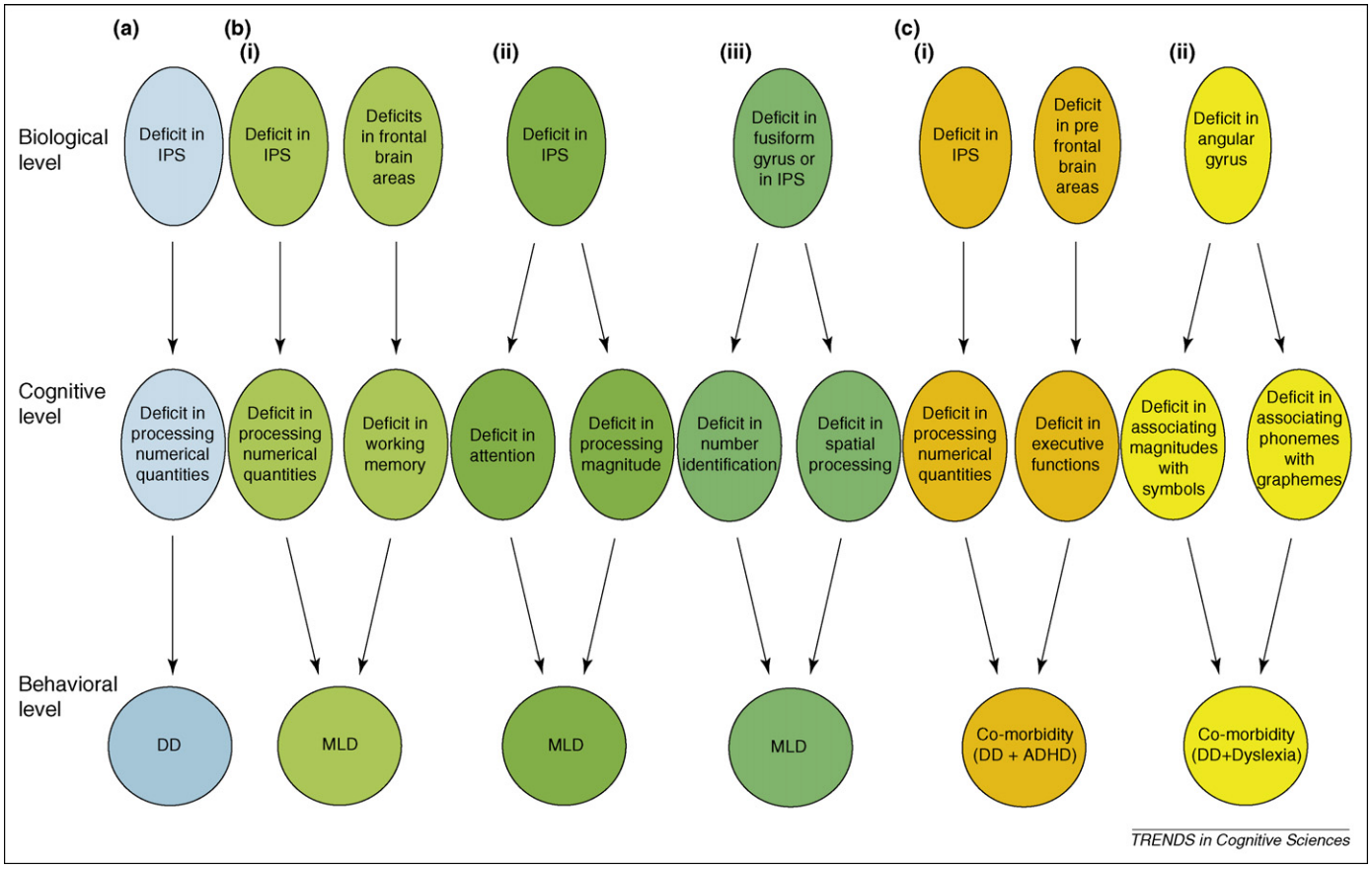

Figure 2. Three alternative frameworks for the origin of mathematical deficits and their underlying neurocognitive deficits. **(a)** DD as a unique pathophysiology. The flat arrow represents the direction of causal relationship [used also in **(b)** and **(c)**]. A hypothesized single origin at the biological level gives rise to a specific cognitive deficit, which is solely responsible for the behavioural signs of DD. Because very little is yet known about the molecular biological origins of DD, here, we emphasize brain dysfunction as the possible origin, but it could possibly be genetic or both. (b) Multiple cognitive deficits in MLD. (i) Multiple brain dysfunctions responsible for MLD. A variety of initial deficits at the biological level are possible. Each deficit is related to a different cognitive ability and, hence, is responsible for different aspects of the behavioural manifestations of MLD. (ii,iii) A single pathophysiology produces MLD. The biological level in this sub-framework (IPS) represents a summary across the full range of the disorder. That is, the biological deficit might give rise to different cognitive deficits so that children might differ in cognitive deficits and in the behavioural manifestation of the arithmetic difficulty. An alternative is that one damaged biological origin is involved with several identifiable cognitive functions. (c) Co-morbidity. Specific examples for (i) multiple pathophysiologies with multiple deficits resulting in co-morbidity and (ii) a unique pathophysiology with multiple deficits resulting in co-morbidity.

numerical processing) and weaker effects on others [13,29,30].

Framework 2: multiple cognitive deficits because of multiple or unique pathophysiology

Most (if not all) cases of DD involve multiple cognitive deficits. These might be because of multiple brain dysfunctions or a unique pathophysiology (Figure 2). Although very little is known about the anatomy and physiology, let alone the molecular biological origins of MLD or DD, there is empirical evidence for the alternative frameworks in Figure 2b (i–iii).

Multiple cognitive deficits because of multiple brain dysfunctions [Figure 2b (i)]

Numerical calculation involves the use of working memory (i.e. keeping information highly available in the cognitive system, which is required, for example, for borrowing and carrying numbers) and attention (Box 3). Accordingly, several studies indicated that working memory has a central role in mathematical achievement [7,31–33]. This argument is supported by a recent event related potential (ERP) study [34]. The difference between individuals with DD and controls was found at 400–440 ms after onset of the numerical stimuli. At that time, the right parietal lobe of the DD subjects was no longer involved with the numerical distance effect. Because the DD subjects and controls did not differ during the initial stages of processing, the authors argued that individuals with DD have problems with the more complex and controlled processes such as executive functions or working memory rather than with simple mental operations that appear early in processing. It should be noted however, that although the contribution of working memory to arithmetic is not in question, other studies have shown that children with DD do not exhibit systematic impairment in tasks assessing components of working memory (e.g. span measures [14]).

The suggestion that several cognitive functions are involved in numerical calculation gains support from behavioural and neuroimaging studies of healthy adults. These studies indicate that humans have at least two distinct means of representing and processing numerical information that involve different neural networks [21]. One network is composed of the left inferior frontal lobe and left angular and fusiform gyri. These regions (i) are associated with linguistic representation of numerical symbols, concepts and rules; (ii) are activated during exact

Box 3. IPS

For many years, the IPS and close parietal structures were presented as part of the dorsal visual pathway. Early on, this pathway was portrayed as the 'where' system [72], designed to convey information about object relations in space, and later, it was suggested that it has a role in visually guided action [73]. Accumulated work indicates that the IPS has a role in spatial perception and in visually guided action but it is involved in other cognitive processes as well [74,75]. One important function of the IPS and the superior parietal lobe (SPL) is in orienting of attention. Corbetta and colleagues [76] have suggested that these structures are involved in top-down (endogenous) movement of attention to objects and locations [76,77]. In addition, these structures seem to convey environmental coordinates that help in guiding and remapping eye movements and exogenous attention [78]. Importantly, the IPS has a role in non-spatial attention functions as well [79]. One example is the attentional blink phenomenon. Participants are asked to detect two targets in a rapid sequential presentation of a series of visual stimuli. Commonly, responding to the second target is compromised if it appears between 100 ms and 500 ms after the first one – the attentional blink phenomenon. The IPS was found to be activated during such a task [80]. Other examples are sustained attention or the need to suppress task-irrelevant information [81]. As a result, it has been suggested that the IPS is involved in selection of the relevant dimension or response. Interestingly, it has also recently been suggested that the parietal cortex is part of a parieto-frontal network associated with better performance in intelligence and reasoning tasks [82]. In conclusion, the IPS supports numerical and non-numerical functions alike. Damage to the IPS might produce numerical and non-numerical (e.g. visual-spatial impairments, attentional deficits) dysfunctions. Moreover, this notion supports the possibility that a damaged IPS might be a sufficient neural underpinning for MLD (e.g. associated disorders of numerical and spatial processing).

calculation; (iii) subserve rote retrieval of arithmetic facts like simple addition and multiplication [35,36] and, (iv) support the management of successive arithmetic operations using working memory [21]. Note, however, that Venkatraman, Ansari and Chee [37] and Pesenti and colleagues [38] found no language-related frontal activations for symbolic exact arithmetic in simple addition problems, indicating that different strategies (other than retrieval from memory) might be in use. Another network involves a parietal brain region (horizontal IPS), which has a central role in basic representation and computation and subserves division or subtraction that requires manipulation of quantities [9,35].

The idea of distinct neural substrates for different aspects of number processing (e.g. exact versus approximate calculation, subtraction versus addition) indicates that perturbations in one or both networks (destruction, disconnection or malfunction) might give rise to different profiles of cognitive deficits and arithmetic impairments (Figure 2; MLD). Namely, MLD is a difficulty in mathematics that can manifest in various patterns of mathematical malfunction. Indeed, studies of adults with acalculia (i.e. brain injury that produces deficits in arithmetical abilities [39]) show that almost any component of arithmetic can be selectively impaired (e.g. patients can show impairments in estimation but not calculation, in subtraction but not multiplication and in written but not oral arithmetic). However, studies have not yet separated causal and correlative relationships between possible brain damage and MLD.

The suggestion of multiple cognitive deficits because of multiple brain dysfunctions fits in with the development approach. That is, instead of being genetically pre-specified, the specific brain areas that eventually serve a particular cognitive function (e.g. IPS) seem to emerge developmentally through interactions with the environment and to be interconnected with each other. Behavioural symptomatology consistent with MLD could be the result of atypical 'interactive specialization' [40]. In addition, the developmental approach fits with arguments indicating that expression of genes in the neocortex tends to spread throughout most brain regions, and that up to now, there has not been found a region-specific gene [13]. Accordingly, deficiencies in several different cortical pathways that are functionally connected to each other might be genetically caused and/or caused through development and training.

Multiple cognitive deficits with single pathophysiology within MLD [Figure 2b (ii,iii)]

It could be suggested that a single, rather than multiple, brain malfunction might give rise to more than one cognitive deficit. For example, dysfunction in either of two brain areas, the fusiform gyrus or the IPS, could result in multiple cognitive or behavioural manifestations.

Fusiform gyrus [Figure 2b (iii)]

Recent functional imaging studies have identified a region in the middle part of the left fusiform gyrus as the visual word form area (VWFA) [41]. The VWFA is responsible for computing representations of abstract letter identities [42]. However, the existence of a cerebral area exclusively devoted to processing of abstract letter or word forms has been recently challenged [43,44]. Indeed Pinel and colleagues [45] showed that the right fusiform gyrus might be implicated in the identification of Arabic numerals. Also, research [43,44] indicates that this brain area is involved in visual-spatial abilities (see for example Refs [46,47] for the involvement of the bilateral fusiform gyri in spatial processes). It has been shown that visual-spatial processing deficits are associated with MLD and impede visual-spatial orientation on the mental number line [11]. Hence, it is not surprising that the fusiform gyrus might be involved in MLD [4].

IPS [Figure 2b (ii)]

We have reviewed literature indicating that the IPS is involved in processing of size-magnitude, numerical quantity and in DD. There is accumulated evidence for the role of the IPS in attention and related cognitive processes (Box 3). Hence, damage to the IPS can result in deficient numerical processing in addition to a deficit in attention. In this case, these two deficits are caused by a single pathophysiology [Figure 2b (ii)]. Note that the IPS is involved in visual-spatial processing and, accordingly, a third path (deficit in IPS results in deficit in spatial processing – MLD) might be added [Figure 2b (iii)].

An important consideration

The current framework focuses on heterogeneity within MLD. It indicates that future work should examine

alterations over the whole brain and not single out specific brain areas. Inclusion of both direct and indirect measures of brain structure and processing is of importance.

A similar suggestion might be applicable to genetic studies that currently are very limited in number (for example, see Ref. [48]). It has been shown that MD tends to run in families [49]. Family clustering of the trait is consistent with the involvement of genetic factors but could also be accounted for by environmental influences. Therefore, it is important to map the genes involved in DD by using methods from molecular biology. However, there are no reports of DD-susceptible chromosomal regions that would sufficiently limit the genetic search to make a 'pure candidate gene' approach cost effective. Nevertheless, the current framework (i.e. multiple cognitive deficits caused by multiple or unique pathophysiology) indicates that future genetic research of DD should consider multiple phenotypes. A limited phenotype might miss much of the complexity of an individual's atypical development [24].

Framework 3: multiple behavioural disorders

Many children have both dyslexia or attention-deficit/hyperactivity disorder (ADHD) and dyscalculia. The proportions of these co-morbidities vary in different studies [2,50]. These co-morbidities could be because of several brain dysfunctions or caused by a single brain damage that causes DD or MLD together with other behavioural dysfunctions [Figure 2c (i,ii)]. We elaborate later.

Multiple pathophysiologies with multiple cognitive deficits resulting in co-morbidity [Figure 2c (i)]

Multiple abnormalities at the level of brain functioning can exist, manifesting themselves in multiple cognitive deficits. The idea of co-morbidity (i.e. multiple or different cognitive dysfunctions) falls into this category perfectly. For example, Rubinsten and colleagues [51] investigated effects of stimulant medication (methylphenidate [MPH]) on arithmetic performance in children with ADHD. They identified three groups of children with ADHD from an existing large database: one group with DD (DD+ADHD), a group with more general and less severe difficulties in arithmetic (MLD+ADHD) and a group with good arithmetic abilities (ADHD). Children with DD+ADHD exhibited both general cognitive dysfunctions and specific deficits in understanding quantities. By contrast, arithmetic difficulties in children with MD+ADHD were associated with deficits in executive function and working memory. In addition, MPH enhanced performance in arithmetic problems dependent upon working memory (involving activation in the frontal lobes) but not upon processing numerical quantity (involving activation in the parietal lobes). These findings indicate that it is important to distinguish between DD+ADHD and MD+ADHD. Very little is yet known about the anatomy, physiology and molecular biological origins of such co-morbidities. However, these findings indicate that arithmetic difficulties in these two subgroups should be attributed to different underlying cognitive problems that probably implicate dysfunction of different neural networks [Figure 2c (i)].

Box 4. Questions for further research

- How pure is pure DD in terms of neurocognitive and behavioural deficits? Specifically, what are the criteria for a distinction between DD and MLD?
- MLD versus co-morbidity – what are the neurocognitive determinants?
- How does environment (such as formal education, teaching methods and socio-economic levels) shape DD, MLD and co-morbidity, and how does it influence their neurocognitive origins?
- How do DD or MLD change during development from infancy to adulthood?

Unique pathophysiology with multiple deficits resulting in co-morbidity [Figure 2c (ii)]

Malfunctioning of a single brain area could produce different pathologies. For example, different degrees of angular gyrus dysfunction can cause both DD and dyslexia to different extents. Specifically, the angular gyrus is considered to be involved in reading and shows increased activation in response to structured phonological intervention programs [52]. It is also involved in calculation [23,53,54]. For example, repetitive transcranial magnetic stimulation (rTMS) over the left angular gyrus disrupted number magnitude processes [55]. Hence, a deficit in this structure can cause both reading impairments and calculation difficulties (DD).

Concluding remarks

This review explored and developed causal frameworks for DD and MLD. It is important to note that the frameworks themselves only indicate empirical alternatives and do not constrain the user to any one of them (Box 4). We suggest that a focus on single gene or brain-behaviour deficits could be misleading and prevent understanding the full diversity of deficits associated with DD and MLD. The use of the severity of performance on standardized tests of arithmetic computation can be a useful tool for screening for DD versus MLD (see Ref. [51]).

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