CHAPTER

Neurocognitive accounts of developmental dyscalculia and its remediation

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Abstract

Numbers are one of the most pervasive stimulus categories in our environment and an integral foundation of modern society. Yet, up to 20% of individuals fail to understand, represent, and manipulate numbers and form the basis of arithmetic, a condition termed developmental dyscalculia (DD). Multiple cognitive and neural systems including those that serve numerical, mnemonic, visuospatial, and cognitive control functions have independently been implicated in the *etiology* of DD, yet most studies have not taken a comprehensive or dynamic view of the disorder. This chapter supports the view of DD as a multifaceted neurodevelopmental disorder that is the result of multiple aberrancies at one or multiple levels of the information processing hierarchy, which supports successful arithmetic learning, and suggests that interventions should target all these systems to achieve successful outcomes, at the behavioral and neural levels.

Keywords

Developmental dyscalculia, Neurocognitive systems, Systems neuroscience, Development, Brain plasticity, Learning, Education

1 INTRODUCTION

Developmental dyscalculia (DD) is a specific developmental learning disability characterized by difficulties in acquiring adequate arithmetical skills in the context of otherwise normal intelligence and age-appropriate school education (American Psychiatric Association, 2013; Butterworth et al., 2011). DD was originally described as a "core deficit" in understanding and manipulating the quantity of sets and their numerosities (Butterworth, 2005). However, other accounts have proposed DD as the result of more general cognitive impairments including short-term and working memory (WM), language abilities, attention, and executive functions

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(Donlan et al., 2007; Geary and Hoard, 2005; Geary et al., 2007; Le Corre and Carey, 2007; McLean and Hitch, 1999; Szucs et al., 2014). In parallel, at the neural level, data from neuropsychological studies of patients with acquired acalculia have linked DD with abnormalities in the intraparietal sulcus (IPS), in the posterior parietal cortex (PPC) (Cipolotti and van Harskamp, 2001). Recently, however, neuroimaging studies have posited DD as a disorder of brain plasticity in multiple functional systems that include the PPC, important for representing and processing quantity information, but also regions in the prefrontal cortex necessary for task/rule switching, and error monitoring. Moreover, aberrancies in the functional interaction between prefrontal and parietal regions, important for maintaining and manipulating information in WM, have also been described in DD (Fias et al., 2014; Iuculano et al., 2015). Mnemonic regions implicated in the retrieval of math facts and anchored in the medial temporal lobe (MTL) have also been postulated to be aberrant in DD (Cho et al., 2011; Fias et al., 2014), as well as higher level visual areas implicated in visual form judgements, and symbols' decoding (Fias et al., 2014; Iuculano et al., 2015). This chapter reviews emerging findings on the cognitive and brain correlates of DD and proposes that DD can be described as a heterogeneous learning disorder that is the result of multifaceted disturbances in one or multiple neurocognitive systems, which are implicated in the hierarchical cascade of mental computations required to perform even simple arithmetic operations. Moreover, this chapter will discuss the emerging literature on intervention studies of DD both in children and adults and assess the issue of individual differences in response to intervention. Finally, it will reflect on outstanding questions and future directions for the field.

2 MULTIPLE COGNITIVE FACTORS INVOLVED IN DD

Multiple cognitive functions come into play even when a child is asked to solve a simple arithmetic operation, such as "3+4." First, it is essential to be able to grasp the property of numbers (ie, "the number sense" of *threeness* and *fourness*), but it is also important for the learner to make the correct association between the concept of *threeness* and the culturally defined symbol that denotes it (ie, the Arabic digit 3). Moreover, this symbol needs to be visually decoded and distinguished from other symbols that denote different numerosities but might have a similar percept (ie, 3 rather than 8). Additionally, it is important to be able to decode and interpret the symbol that describes the arithmetical operation to be performed (ie, +). These represent only the cognitive scaffolds preceding the actual arithmetical computation to be performed. At the computational stage, additional cognitive functions are needed to support successful arithmetic learning and performance. These include attentional resources, language, WM, and other executive functions such as, error monitoring and rule switching. It follows that a deficit at any given stage of this hierarchical cascade of cognitive functions might be responsible for the difficulties acquiring arithmetic that characterize the cognitive phenotype of DD.

2.1 NUMBER SENSE DEFICITS

According to a growing consensus in the field of mathematical cognition, humans and also other species are endowed with a core capacity to understand numerosities (Butterworth, 1999; Carey, 2004; Dehaene, 1997). This core capacity seems to be present within the first year of life. Infants can discriminate between displays of small numerosities—eg, they respond when the display changes from 2 to 3 objects or from 3 objects to 2 (first demonstrated by Starkey and Cooper, 1980; see also Starkey et al., 1990; van Loosbroek and Smitsman, 1990). Beyond the ontogenetic evidence, the hypothesis of an endowed capacity for numbers is grounded in evidence that such capacity has an evolutionary value. Indeed, numerical discrimination abilities have been found in rats (Church and Meck, 1984; Mechner, 1958; Meck and Church, 1983), orangutans (Shumaker et al., 2001), monkeys (Brannon and Terrace, 1998), birds (Emmerton et al., 1997; Koehler, 1951), fish (Agrillo et al., 2007, 2008; Piffer et al., 2012), and also bees (Dacke and Srinivasan, 2008). Moreover, field studies have shown numerical processing abilities in animals independent of training (Mccomb et al., 1994; Wilson et al., 2001). Recently, it has been demonstrated that the visual perception of numerosity is susceptible to adaptation (Burr and Ross, 2008; see also Anobile et al., 2016) and it can, therefore, be considered a primary visual property of a scene to the same extent as color is. Together, this evidence supports the idea of a phylogenetically specified mechanism for the representation and processing of numerical quantity (ie, "the number sense"), which constitutes the scaffold to successfully learn arithmetic. One of the major theories of DD postulates that difficulties in acquiring appropriate arithmetic skills might be rooted within a specific deficit in this innate ability to process and manipulate numerosities (ie, the *core deficit hypothesis*) (Butterworth, 2005, 2010).

Although the construct of a core "number sense" has been well established, there is still disagreement about the precise nature of this capacity and how it developmentally supports the trajectory of successful arithmetic learning. Some have described "number sense" as the capacity to represent the exact numerosity of a set (Butterworth, 1999; Butterworth and Reigosa-Crespo, 2007; Zorzi et al., 2005); while others have referred to it as the ability to represent approximate numerosities (Barth et al., 2005; Feigenson et al., 2004; Halberda et al., 2008; Piazza et al., 2010). These competing proposals have led to variations in characterizing the nature of the underlying impairments in DD.

Both theories acknowledge that DD can be highly selective. Sufferers can be average or even excellent at all school subjects apart from mathematics; normal or superior IQ does not protect one against it (Landerl et al., 2004) and the common DD symptom of poor memory for arithmetical facts does not need to be part of a wider impairment in either long-term memory or working memory. Yet, one proposal posits that DD is the result of a deficit in the representation of exact numerosities, which in turn, leads to deficits in performing arithmetical computations on them (Butterworth, 1999, 2010; Butterworth and Reigosa-Crespo, 2007). This is supported by data showing that DD children are not only poor on school arithmetic and on

standardized tests of arithmetic, they are slower and less efficient at very basic numerical tasks, such as recognizing the numerosities of displays of objects (typically dots), and at comparing numerosities in a variety of number comparison tasks with nonsymbolic (ie, arrays of dots) and symbolic (ie, Arabic numerals) material (Butterworth, 2005; Iuculano et al., 2008; Landerl and Kolle, 2009; Landerl et al., 2004; see also Butterworth, 2010 for a review).

The competing proposal postulates that DD is the result of an inability to form approximate representations of numerical magnitude (Feigenson et al., 2004; Halberda et al., 2008; Piazza et al., 2010). Indeed, recent studies have argued in favor of the foundational role of the approximate number system for the development of higher level numerical abilities by reporting a significant link between DD and an impaired approximate number sense (Mazzocco et al., 2011; Piazza et al., 2010). However, these studies found that performance on an approximate comparison task was predictive of performance on symbolic comparison tasks but it did not correlate with children's math achievement (Mazzocco et al., 2011; Piazza et al., 2010). Hence, in order to get from approximate numerosities to the exact numerosities needed to perform arithmetical computations, a "mediation model" has been proposed in which knowledge of the counting words is required to "bootstrap" from approximate to exact representations (Carey, 2004). Within this account, DD starts to delineate as a multifaceted disorder that could be the result of multiple cognitive deficits, not just a weak "number sense."

2.2 MEMORY DEFICITS

Behavioral studies in typical and atypical developmental populations have shown that a shift from counting-based to memory-based problem-solving strategies is a hallmark of adequate cognitive development within arithmetic and other academic domains (Geary, 1994; Menon, 2014; Siegler, 1996). Within this framework, a seminal account of DD describes it as a deficit in retrieving arithmetical facts from long-term semantic memory (Geary, 2011a,b, 2012; McCloskey et al., 1991).

During successful learning, the representation of addition facts in long-term memory is aided by the repeated use of counting and other updating procedures (Ashcraft, 1982; Groen and Parkman, 1972; Siegler and Shrager, 1984; Siegler et al., 1995). For example, when counting on from 3 to 7 to solve the problem "3 +4 = ?" an association is dynamically formed between the correct solution (seven) and the addends (three and four). After many repetitions, children begin to directly retrieve the answer when presented with the solution (Siegler and Shrager, 1984). In this way, knowledge of counting properties and principles, language, and WM supports encoding of information into long-term semantic memory.

Poor short-term and WM abilities have also been proposed as a cause for DD (Geary, 1993; Geary and Hoard, 2005; Geary et al., 1999, 2012; Hitch and Mcauley, 1991; Koontz and Berch, 1996; McLean and Hitch, 1999), and all three distinct subcomponents of WM (Baddeley and Hitch, 1974, 1977) have been associated with DD. Some studies report deficits in tasks that rely primarily on the verbal

component of WM, such as immediate serial recall (eg, digit span) (Hecht, 2002; Hetch et al., 2001; Hitch and Mcauley, 1991; Swanson and Sachse-Lee, 2001). Others have reported deficits in tasks tapping the central executive (CE) (Iuculano et al., 2011; McLean and Hitch, 1999; Noel et al., 2004; Passolunghi and Siegel, 2004; Siegel and Ryan, 1989; Swanson and Sachse-Lee, 2001) or the visuospatial components (Ashkenazi et al., 2012; Mammarella et al., 2015; Moll et al., 2014) of WM. Visuospatial WM and attentional resources have often been linked to subitizing abilities (ie, the rapid apprehension of small quantities) (Vetter et al., 2011), and deficits in subitizing have been reported in DD (Landerl et al., 2004), and more generally, in atypical development of mathematical skills (Reeve et al., 2012). Recently, Bugden and Ansari (2015) have proposed that visuospatial WM, and its interaction with attentional resources, is essential to extract relevant numerosity information in a nonsymbolic comparison task (ie, comparing the numerosities of distinct arrays of dots). Sustained attention has also recently been shown to predict measures of number comparison, but not arithmetic measures, thereby acting as a mediator in the acquisition of mathematics (Szucs et al., 2014). Distinct processes coordinated by the CE component of WM (Miyake et al., 2000) have also been shown to differentially modulate math performance in DD. Specifically, the ability to successfully update relevant information has been shown to be related to children's arithmetical performance, and inhibition processes have also been shown to differ between DD and typically developing (TD) children (Iuculano et al., 2011). Recently, impairments in inhibitory functions (ie, interference suppression) have been hypothesized to be at the core of arithmetical impairments in DD, as well as contribute to their visuospatial and attentional processing deficits (Szucs et al., 2013).

Moreover, it has also been suggested that there are domain-specific coding processes that occur within the WM system. In particular, number representations may be maintained in WM differently than words (Butterworth et al., 1996). Notably, various studies have reported WM processing deficits that are semantically specific to numerical content. For example, McLean and Hitch (1999) showed that verbal memory deficits in children with DD were selective for the digit span task, while no differences were seen in a nonword repetition task. Iuculano et al. (2011) also report a domain-specific deficit in a semantic number-updating task, but not in a word-updating task. Children with DD have also been shown to perform poorer when asked to memorize order-related information, while no deficits were reported in storage capacity (ie, number of items to be retained regardless of order) (Attout and Majerus, 2015).

2.3 ORDINALITY AND OTHER NUMERICAL MAPPING DEFICITS

Recent efforts have also implicated rank, another fundamental property of numbers (ie, 3 5 7 is an ordered ascending sequence while 5 3 7 is not) to arithmetic skills (for a review, see Lyons and Ansari, 2015). Ordinal numbers are not ordered by magnitude though they correspond to the cardinality that denotes them (ie, the next number on

the counting list is always greater than the previous one). Counting a set of objects involves mapping each object one-by-one to the corresponding counting words (eg, "one, two, three, four") and such counting procedures can result both in a numerosity outcome (ie, the number of objects in the set is four) and an ordinal outcome (ie, this is the fourth object). Children often confuse the ordinal and cardinal meanings of numbers (Gelman and Gallistel, 1978), which raises the question of whether and how these two scaffolds of numerical cognition are related. Do ordinality and cardinality share overlapping cognitive functions that could be accounted for by the metaphorical construct of the mental number line (Dehaene, 1992; Dehaene et al., 1993)? Or does ordinality represent an independent component of mathematical skills, that is more related to domain-general abilities, such as language, attention, or WM? A recent study has shown that in a large sample of 6th graders numerical-ordering performance was a better predictor of mental arithmetic than other numerical tasks, and remained so even when controlling for nonnumerical factors such as reading abilities, visuospatial intelligence, or inhibitory control (Lyons et al., 2014). Yet, both ordinality and cardinality components predicted variance in a mathematical achievement task at earlier grades (Lyons et al., 2014), suggesting dissociations as well as associations between the cognitive processes that support these skills as a function of development. Integration between cardinality and ordinality has been proposed to be related to knowledge of counting words, which might mediate the estimation of ordinal information (Rubinsten and Sury, 2011). Interestingly, verbal processes involved in learning the labels of Arabic numerals, and the ability to translate between Arabic numerals and verbal codes, have also been related to arithmetic achievement (Gobel et al., 2014).

DD has also been described as a deficit in mapping number symbols onto otherwise intact representations of numerical quantity. This proposal was initially put forward by Rousselle and Noel (2007) who compared a group of TD children in grade 2 with a group of age and education matched DD children. The DD group was slower—yet equally accurate—than the control group in comparing quantities presented as Arabic digits (eg, 5 vs 6), but showed no impairment when comparing the same quantities presented as sets of items (eg 5 lines vs 6 lines). For a similar result, see also Iuculano et al. (2008).

2.4 OTHER DOMAIN-GENERAL PROCESSING DEFICITS

Other domain-general cognitive functions have been reported to be atypical in DD. These include processing speed and temporal processing (Moll et al., 2014; but see Reeve et al., 2012). Again, these impairments seem to be restricted to semantic-specific (ie, numerical) information. For example, Willburger et al. (2008) reported that children with DD presented a specific deficit in naming quantities. In a study on adults with persistent DD, Cappelletti et al. (2011) showed that time perception was not impaired in DD when numbers were not included in the task. Finally, language processes (Donlan et al., 2007), as well as general intelligence (ie, *g* factor) (Spearman, 1904) have also been associated with individual differences in arithmetic

achievement (Kovas et al., 2005; O'Connor et al., 2000; Szucs et al., 2014; but see Reeve et al., 2012).

2.5 MATH ANXIETY

Mathematics seems particularly vulnerable to any kind of stress on learning, perhaps because of the cumulative structure of its content: failing to understand one concept can mean that the learner will fail to understand concepts that depend on it. Notably, math anxiety, a negative emotional reaction to situations involving math problem solving, can impair performance on a wide range of mathematical tasks (Hembree, 1990; Ma, 1999). Moreover, math anxiety has been postulated as a prominent cause of math difficulties in children (Ashcraft and Krause, 2007), and it has formally been linked with DD (Passolunghi, 2011; Rubinsten and Tannock, 2010). Yet, there is a fundamental causality issue in the directionality of the correlation: is it the underlying deficit in mathematics that creates anxiety when having to solve a math problem, or is it the opposite? Indeed, longitudinal studies support the idea that an underlying deficit in mathematics is responsible for higher anxiety levels (Ma and Xu, 2004). However, studies manipulating anxiety levels (ie, timed tests) and inducing stereotype threat (ie, females are worse than males in math) observe changes in mathematics performance (Galdi et al., 2014; Marx et al., 2013). A recent account has proposed a dynamic bidirectional relationship between these two constructs (Carey et al., 2016), yet unpacking such causality remains an outstanding question in DD, and in the field of mathematical cognition more broadly.

Altogether, the evidence presented here suggests that DD, a neurodevelopmental learning disorder, might be the result of multiple cognitive disturbances at any level of the hierarchical cascade of domain-specific as well as domain-general cognitive skills, which are involved in learning and performing arithmetic throughout a child's development.

3 MULTIPLE NEUROCOGNITIVE SYSTEMS INVOLVED IN DD

Deficits in brain plasticity are thought to subtend the pathogenesis of specific learning disabilities in children (Butterworth and Kovas, 2013), and multiple brain areas have been reported to show functional, structural, and connectivity abnormalities in DD. This section reviews emerging findings on the brain correlates of DD, that together give support to a multisystems level deficit.

During the early school years, when a child learns to perform mathematical operations, such as 3+4, their brain undergoes dramatic transformations, hereafter defined as neural plasticity. Changes are widespread in terms of neuroanatomical structure, functional specialization, and connectivity patterns among brain regions supporting a variety of cognitive functions. More precisely, the brain of a child needs to learn to repurpose some of its domain-general resources (ie, visual recognition, attention, memory) to tasks that are very specific and evolutionarily recent

(eg, counting, learning symbols, remembering arithmetic facts). What are the brain mechanisms that support such transformations, and how are they aberrant in DD? Is there a specific system, or are there multiple systems that go awry at any level of the hierarchical cascade of plasticity mechanisms necessary to learn arithmetic?

3.1 DORSAL AND VENTRAL STREAMS' DEFICITS

DD was initially conceptualized as a disorder of a single brain region characterized by a localized deficit in the intraparietal sulcus (IPS), in the posterior parietal cortex (PPC) (Cipolotti and van Harskamp, 2001; Cohen Kadosh et al., 2007; Isaacs et al., 2001; Price et al., 2007). Yet, more recently, prominent neurocognitive models of DD have posited that the disorder stems from more extensive functional aberrations in a distributed network of brain areas. These include not only posterior parietal, but also prefrontal, ventral temporal-occipital, as well lateral and medial temporal cortices that are known to serve multiple cognitive functions necessary for successful arithmetical computations (Butterworth et al., 2011; Fias et al., 2014).

The first neuroimaging studies to investigate atypical math processing tested populations with numerical and visuospatial impairments occurring in the context of genetic developmental syndromes, such as Turner syndrome (TS) and Fragile X syndrome. Using both functional and structural magnetic resonance imaging (fMRI, sMRI) methods, Molko and colleagues compared TS patients to TD controls during an exact calculation task (Molko et al., 2003). While healthy participants showed increased activation in the bilateral IPS as problem difficulty increased, TS subjects failed to show the same modulation. Moreover, lack of modulation was coupled with less accurate performance in the TS group. In parallel, structural analyses revealed decreased gray matter density of the right IPS in TS subjects compared to TD controls (Molko et al., 2003, 2004; see also Rivera et al., 2002, for similar results in a group of patients with Fragile X).

Using a nonsymbolic quantity comparison task, Price et al. (2007) were the first to demonstrate weak modulation of IPS activity in a population of 12 year olds with DD. Thenceforth, activation aberrancies of the PPC have consistently been reported in even younger cohorts for symbolic (Mussolin et al., 2010), as well as nonsymbolic number comparison tasks (Kaufmann et al., 2009). These results suggest that adequate activity within the PPC, and particularly of the IPS, is crucial for successful representation and comparison of numerical quantities. These findings are further supported by studies using event-related potentials. In a recent study Soltesz and colleagues showed that at an early time window during a symbolic number comparison task, no differences were evident between DD and TD children. Yet, at a later time window (between 400 and 440 ms), compared to the TD group, the DD group showed weak modulation over right parietal areas (Soltesz et al., 2007). These results suggest that quantity judgment processes supported by the parietal lobes might arise at a slightly later stage of the task. This in turn might indicate that the deficits seen, at least in this DD group, might be semantic, rather than perceptual. Yet, aberrancies in functional activity of the fusiform gyrus in the ventral temporal-occipital cortex, a

brain region that has been implicated in the perceptual processing of high level visual stimuli (Holloway et al., 2013), have been reported in DD (Iuculano et al., 2015; Rosenberg-Lee et al., 2014). This does not necessarily suggest a deficit in this specific brain region per se, as aberrancies in the IPS and other brain regions were also reported in the same studies (Iuculano et al., 2015; Rosenberg-Lee et al., 2014). It could, however, mean that age-related activity increases that characterize the functional specialization of the fusiform gyrus over development (Cantlon et al., 2011) have failed to take place in DD (Ansari, 2008).

Structural aberrancies in the PPC have also been reported in DD. In a seminal study by Isaacs and colleagues (2001), it was found that adolescents of very low birth weight, who showed deficits in math as determined by standardized tasks, had reduced gray matter volume in the left IPS. In a later investigation, Rotzer and colleagues also demonstrated reduced gray matter density in the right IPS in younger subjects—9 to 10 year olds—(Rotzer et al., 2008).

Furthermore, in a recent study, Cohen Kadosh and colleagues were able to induce DD-like symptoms (ie, reduced automaticity for processing numerical information) in a population of neurotypical adult subjects by applying fMRI-guided transcranial magnetic stimulation over the right parietal lobe (Kadosh et al., 2007).

Together, these studies suggest that the parietal lobes represent a crucial hub that modulates the representation and processing of numerical quantities and their arithmetical computations. However, other areas, especially during development and learning, are essential during math cognition and might support the gradual functional specialization of the IPS during numerical problem solving.

3.2 FRONTOPARIETAL DEFICITS

In a pioneering study of individuals between the ages of 8 and 19, Rivera and colleagues demonstrated age-related increases in the recruitment of the left inferior parietal cortex, encompassing the left supramarginal gyrus (SMG), during an arithmetic verification task (ie, $3+4=7$?) (Rivera et al., 2005). Interestingly, increased activity in posterior parietal regions was coupled with reduced activity in regions of the prefrontal cortex, suggesting increased functional specialization over development. Menon and colleagues (2000) also reported a frontoparietal shift, extending laterally to the left angular gyrus (AG), as a function of age as well as arithmetic proficiency. Increased activity in the AG suggests that there is an age-related increase in the specialization of these regions that is associated with the refinement of representations and strategies for numerical problem solving (see also Ansari, 2008). Indeed, studies in neurotypical adults have identified the SMG, together with the AG, as critical regions supporting successful arithmetic fact retrieval (Grabner et al., 2009). Moreover, the decrease in frontal activity that occurs with increasing age has been interpreted as reduced reliance on cognitive processes such as attention and WM, as well as executive functions over development (Ansari, 2008; Menon, 2015).

Evidence for a frontoparietal shift has also been reported for symbolic (Ansari et al., 2005; Kaufmann et al., 2006), but not nonsymbolic (Ansari and Dhital,

2006) numerical comparisons. Numerosity comparisons become increasingly difficult as the *numerical distance* between the two stimuli decreases (ie, comparing 1 vs 9 is easier and less error prone than 8 vs 9). Ansari et al. (2005) found a reliable *neural distance effect* (ie, decreasing activation with increasing distance between the two numbers) in the bilateral IPS in a population of neurotypical adults (Ansari et al., 2005). On the other hand, 10 year olds showed a reliable *neural distance effect* in a network of prefrontal areas, including the inferior frontal gyrus (IFG), but failed to show the *neural distance effect* in the IPS. Similar to nonhuman primates (Diester and Nieder, 2007), children seem to rely more on prefrontal areas when dealing with numerical stimuli, which suggests a less specialized neural organization that supports numerosity processes at early stages of development.

To date, there are no cross-sectional nor longitudinal studies that examine the *frontoparietal shift effects* in DD, yet aberrancies in multiple regions of the prefrontal cortex have been reported in this population during number comparison (Kucian et al., 2011b) and arithmetic tasks (Davis et al., 2009; Iuculano et al., 2015; Rosenberg-Lee et al., 2014), suggesting greater reliance on effortful cognitive resources, such as executive functioning and WM in DD. Similar to children, adults with DD have also been reported to show compensatory overactivation in multiple prefrontal regions, including right superior frontal gyrus and left inferior frontal sulcus (Cappelletti and Price, 2013).

3.3 MEDIAL TEMPORAL LOBE DEFICITS

The hippocampus, in the Medial Temporal Lobe (MTL), has been proposed to mediate the shift from effortful mental processes to rapid arithmetic fact retrieval constituting an essential hub during math learning (Cho et al., 2011, 2012; De Smedt et al., 2011; Qin et al., 2014). Notably, recent studies have reported increased activation in the MTL coupled with decreased activation in frontal areas as a function of strategy refinement—ie, the more children relied on retrieval rather than counting strategies, the higher the MTL activation—(Cho et al., 2011, 2012). Yet, learning studies in adults have shown a more selective involvement and increased specialization of the PPC along with reduced activation in frontal regions as a function of refinement of strategies for math problem solving (Grabner et al., 2009; Ischebeck et al., 2007).

A recent study helps to consolidate these findings by framing them within the context of development. Using a combined cross-sectional and longitudinal design, Qin and colleagues assessed a sample of 7–9-year-old children during an arithmetic task at Time 1 and Time 2—*circa* 1 year later. The authors also tested separate samples of adolescents and adults during a single time point. Within the sample of children, the use of retrieval strategies during arithmetic problem solving increased significantly from Time 1 to Time 2 and it was accompanied by increases in hippocampal activity (Qin et al., 2014). Moreover, individual differences in fact retrieval strategy—use, over the course of 1 year, were significantly related to increased connectivity from the hippocampus to prefrontal and parietal cortices. In adolescents and

adults, retrieval rates continued to increase, but hippocampal activity returned to baseline, pointing to a developmentally specific role of the MTL in the acquisition of arithmetical facts (Qin et al., 2014). Notably, De Smedt et al. (2011) showed that, in a group of 10–12 year olds, hippocampal activity during an arithmetic task was evident in TD but not in DD children (De Smedt et al., 2011), suggesting that one of the possible developmental deficits in DD might derive from lack of hippocampal recruitment during crucial phases of arithmetic learning.

Within the MTL, other structures have been implicated in mathematical learning, yet they have not been experimentally linked to DD. A recent study has reported increased levels of amygdala activity, a brain region important for processing negative emotions and negatively valenced stimuli (Phelps and LeDoux, 2005; Young et al., 2012), in highly math-anxious adults (Lyons and Beilock, 2012b). Similarly, Young and colleagues have showed hyperactive amygdala responses and increased connectivity of the amygdala with brain regions of the ventromedial prefrontal cortex important for emotion regulation (Etkin and Wager, 2007; Etkin et al., 2010) in a group of 7–9 year olds with high levels of math anxiety (Young et al., 2012; see also Supekar et al., 2015). Given that in none of these studies math performance was significantly impaired to a DD-type level, the authors converged to suggest that increased connectivity of the amygdala with prefrontal regions—responsible for cognitive control and reappraisal of negative emotions—might support compensatory mechanisms that could help mitigate the effects of math anxiety on performance. The question that follows is what happens if these control mechanisms fail to take place? Would that lead to some form of DD? This remains an experimental question. Nevertheless, this emerging body of research adds another layer of complexity to the theoretical framework of neurocognitive systems implicated in math learning and suggests that affective mechanisms, which might operate at the preprocessing level (Lyons and Beilock, 2012a,b), could also be mediating heterogeneity of outcomes in the acquisition of mathematical knowledge.

3.4 NETWORK-LEVEL DEFICITS

The body of evidence presented suggests that successful arithmetic learning is engendered through dynamic interactions occurring in a distributed network of brain regions in parietal, ventral temporal-occipital, prefrontal, and medial temporal cortices (Fias et al., 2014; Menon, 2014). The extent to which this network is recruited to learn and solve arithmetic problems is modulated by age, performance, and emotional factors. Within this framework, and given that DD is formally described as a specific *developmental* and *learning* disorder (American Psychiatric Association, 2013; Butterworth and Kovas, 2013), it is reasonable to conceptualize it as a multilevel dynamic disorder wherein any of these neurocognitive systems, or their interactions, could go aberrant, impacting different stages of the information processing hierarchy of mental computations necessary for adequate arithmetic learning. Notably, recent network-level analyses of integrity of structural and functional circuits seem to corroborate this hypothesis. For instance, Rykhlevskaia and

colleagues report reduced white matter volume in tracts passing through the temporo-parietal cortices in a population of 7–9 year olds with DD (Rykhlevskaia et al., 2009). Furthermore, in the first study of its kind, Jolles and colleagues investigated intrinsic functional connectivity (ie, resting state task-free hemodynamic fluctuations across brain regions) of the IPS-network and reported significant hyperconnectivity of the IPS with a bilateral frontoparietal network in DD compared to TD children. Moreover, children with DD exhibited greater levels of low-frequency fluctuations within the frontoparietal network, which led the authors to propose that intrinsic hyperconnectivity and enhanced low-frequency fluctuations may limit flexible resource allocation in DD and could, in turn, contribute to aberrant recruitment of functional neurocognitive systems during arithmetic problem solving (Jolles et al., 2016).

More generally, the body of results discussed here is in line with the *interactive specialization framework* of postnatal brain development (Johnson et al., 2002; Schlaggar and McCandliss, 2007), which suggests that developmental disorders follow a different developmental trajectory from typical development and thus are characterized by subtle, but diffuse, rather than gross and focal, functional (and structural) abnormalities.

To be able to fully characterize what goes awry during learning and development in DD, especially in terms of neural activation, connectivity, representation, and structural integrity, represents the next challenge in advancing the field and being able to develop efficient, ad-hoc strategies for diagnosis and intervention in this population.

4 REMEDIATING DD

DD has profound negative consequences on educational and professional outcomes. Low mathematical abilities have been shown to highly correlate with poorer academic and professional achievement (Duncan et al., 2007), use of health resources (Nelson and Reyna, 2007; Peters et al., 2006; Reyna and Brainerd, 2007), as well as socioeconomic status (SES) (Parsons and Bynner, 2005), even more so than reading abilities (Butterworth et al., 2011). Interventions for remediating poor math skills in children, and even adults with DD have, therefore, taken on great significance.

4.1 PEDAGOGICAL AND COGNITIVE STUDIES

Pedagogically, remediation approaches to DD have capitalized on the use of concrete material and informational feedback to the learner. Specifically, the use of Cuisenaire rods, number tracks, and number cards has been incentivized in educational settings to help the learner discover from direct manipulations of concrete objects (Butterworth and Yeo, 2004). Moreover, classroom-based interventions designed to strengthen mathematical problem-solving skills have successfully combined

conceptual activities with speeded practice to promote efficient retrieval of arithmetical facts (Fuchs et al., 2008, 2009; Powell et al., 2009).

Capitalizing on cognitive theories of DD, two recent studies have looked at the effects of software-based learning programs on remediating DD. One study used *The Number Race* (Wilson et al., 2006), a software specifically designed to train "number sense." The other study tested the efficacy of *The Graphogame-Math* (Rasanen et al., 2009), a software aimed at strengthening the mapping between numerosities and their symbolic representations (ie, Arabic numerals). Both programs improved children's numerical understanding, as measured by a number comparison task, but gains were minimal and transfer effects to arithmetic tasks were rather weak.

Together, this body of evidence suggests that a comprehensive intervention that builds upon educational principles, but also cognitive models of DD, might represent the best approach to remediate performance in children with DD.

4.2 NEUROIMAGING STUDIES

Even when an intervention is successful at a behavioral level, the extent to which it can alter aberrant functional and structural activity and connectivity in different neurocognitive systems is still unknown. Specifically, it is not known whether a successful behavioral intervention that is informed by cognitive and pedagogical principles can effectively normalize brain features, or whether compensatory mechanisms might take place in children with DD. This represents a great limitation of the current literature as there is evidence to suggest that DD is a disorder of brain plasticity (Butterworth and Kovas, 2013) across multiple functional systems (Fias et al., 2014). Critically, gaining a comprehensive understanding of how these systems are affected by intervention may provide important insights into the neurocognitive mechanisms by which poor math problem-solving skills are strengthened in DD as a result of intervention.

Initial studies that have informed on brain plasticity during math skill acquisition are learning studies in neurotypical adults. In these experiments, adults are asked to practice solving arithmetic problems that are not normally memorized in school. Soon thereafter, they are tested with trained vs untrained lists of problems. At post-training, participants are usually faster and less error prone on the trained problems. Notably, the effects of practice on trained problems have been shown to map onto functional systems implicated in efficient arithmetic problem solving (Dehaene et al., 2003; Menon, 2014). In a very influential study, Delazer and colleagues had healthy subjects practice a set of complex multiplication problems and reported that trained problems activated the left AG, a region implicated in memory retrieval (Grabner et al., 2009). Conversely, untrained problems activated a more distributed network of regions that included the bilateral IPS and the bilateral IFG. These regions are commonly associated with more demanding and less efficient computational processes during arithmetic problem solving (Delazer et al., 2003, 2005).

The first study that investigated the effects of intervention from a behavioral as well as neuroimaging perspective in DD used a custom-made computerized program

that focused on strengthening number representations through spatial associations (ie, mental number line training) (Kucian et al., 2011a). After 5 weeks of training, there was a general learning effect: both dyscalculic and typical learners showed improved performance on the mental number line task, and minimal transfer to arithmetic problems. However, performance gains in the DD group were modest after training, and children with DD did not normalize their behavioral nor brain responses to the level of typical peers. Specifically, after training, the DD group still showed greater engagement of prefrontal cortex regions, compared to the TD group. Prefrontal cortex activation is associated with effortful cognitive resources, and is a hallmark of less mature, inefficient processing (Rivera et al., 2005). Hence, these results seem to support a *compensatory model* of brain plasticity in DD. However, in this case, DD's improvement in performance was minimal after training, suggesting that plasticity effects might not have entirely occurred in this group.

The first study that formally tested specific models of neural plasticity after successful math intervention (Fuchs et al., 2008, 2009, 2010, 2013; Powell et al., 2009) combined cognitive assessments with event-related fMRI during arithmetic problem solving, and utilized advanced multivariate pattern classification analyses in 7–9 year olds with DD (Iuculano et al., 2015). The authors showed that in parallel with performance normalization, 8 weeks of 1:1 tutoring elicited extensive functional brain changes in children with DD normalizing their aberrant functional responses to the level of neurotypical peers (ie, *normalization model*). Brain plasticity effects were evident in a distributed network of prefrontal, parietal, and ventral temporal-occipital brain areas. Remarkably, machine learning algorithms revealed that brain activity patterns in children with DD were significantly discriminable from neurotypical peers before tutoring, but statistically indistinguishable after tutoring. This is in stark contrast with a "compensatory" model of plasticity, which would posit that after tutoring, children with DD would recruit additional and distinct (compensatory) brain systems compared to neurotypical peers. Moreover, these results do not support a *persistent neural aberrancy* model, which would have predicted that children with DD would continue to show atypical responses in the same brain areas that they did before tutoring. Notably, changes in brain activity after tutoring in DD were characterized by significant reduction of widespread overactivation in multiple neurocognitive systems in prefrontal, parietal, and ventral temporal-occipital cortices. This suggests that this type of intervention can induce global changes across distributed brain systems that encompass multiple stages of the information processing hierarchy necessary for successful arithmetic problem solving. Specifically, by facilitating the development of quantity representations and the use of sophisticated counting procedures, this type of tutoring might place fewer demands on quantitative and higher order visual form processes supported by the posterior parietal and ventral temporal-occipital cortices. Concurrently, it might facilitate efficient processing by decreasing load on cognitive neural resources (eg, WM, nonverbal reasoning, attention) supported by the prefrontal cortex.

More generally, these findings suggest that a comprehensive tutoring, one which integrates conceptual as well as procedural aspects of arithmetic learning rather than

focusing on isolated components (Kucian et al., 2011a), might be more effective in remediating deficits in multiple neurocognitive systems in DD.

4.3 INDIVIDUAL DIFFERENCES IN INTERVENTION OUTCOMES

Similar to other learning disabilities (Torgesen, 2000), response to behavioral intervention varies considerably across individuals with DD (Fuchs et al., 2012). Studies of heterogenous profiles of intervention outcomes have pointed to behavioral factors, such as severity of symptoms at the beginning of treatment, or domain-general cognitive abilities (ie, IQ, WM), as potential mediators of success or failure in response to interventions. Recently, other authors have proposed that poor response to intervention may be associated with weak structural and functional brain plasticity (Gabrieli et al., 2015). Notably, retrospective and prospective studies that used prediction approaches have suggested that a potential source of individual differences in mathematical learning lies in the integrity of the neural architecture supporting numerical problem solving. Specifically, accurate quantity representations in the IPS (Price et al., 2013), as well as integrity of brain systems important for declarative and procedural memory in the hippocampus and basal ganglia (Supekar et al., 2013), have been suggested to mediate heterogeneity of math outcomes. In a recent study, Iuculano and colleagues corroborated and extended these findings by showing that, after tutoring, individual differences in behavioral gains in a group of 7–9 year olds with DD were significantly predicted by the degree of tutoring-induced functional brain plasticity (Iuculano et al., 2015). Effects were evident in multiple neurocognitive systems that support successful numerical problem solving. Critically, none of the behavioral measures (ie, IQ, WM, math scores) significantly predicted individual differences in performance gains after tutoring in DD. Together, these findings corroborate the idea that poor response to intervention may be associated with weak brain plasticity (Gabrieli et al., 2015). More generally, these findings further support the notion that systems neuroscience-based approaches can provide essential theoretical advances, and methodological tools to inform the remediation of DD.

4.4 REMEDIATION OF PERSISTENT DD

Evidence discussed here suggests that weak brain plasticity might negatively impact response to intervention in DD. If this is true, what happens in cases where early intervention does not take place and *the system* has less room for plasticity? Notably, in cases of persistent DD (Shalev et al., 2005), behavioral interventions such as the ones described here are unfeasible and likely ineffective. However, in these cases, other approaches have been explored. In a recent study, Iuculano and Kadosh (2014) capitalized on recent findings that have successfully combined training paradigms with noninvasive brain stimulation techniques commonly used for restorative (Baker et al., 2010; Brunoni et al., 2014), or cognitive facilitation (Kadosh et al., 2010) purposes. Specifically, the authors combined a numerical learning paradigm with transcranial direct current stimulation (tDCS), the most common form of noninvasive brain stimulation, in two adults with persistent DD. They aimed to assess the

potential benefits of this methodology in remediating numerical difficulties in persistent DD (Iuculano and Kadosh, 2014). Patients learned to associate arbitrary symbols (ie, the Gibson figure) (Gibson et al., 1962; Tzelgov et al., 2000) to numerical quantities within the context of a trial and error paradigm, while tDCS was applied to the PPC. During the learning phase, one of the subjects received anodal (ie, excitatory) stimulation to the right PPC and cathodal (ie, inhibitory) stimulation to the left PPC. For the other patient the montage was reversed (ie, left anodal, right cathodal). Anodal (ie, excitatory) stimulation to the left PPC improved two indices of numerical proficiency: (i) automaticity of number processing as assessed by a numerical Stroop task (Girelli et al., 2000; Rubinsten et al., 2002; Tzelgov et al., 1992) and (ii) numerical representations as assessed by a number line task (Booth and Siegler, 2008; Dehaene et al., 2008). These results differ from previous findings where anodal stimulation to the right (not left) PPC boosted numerical performance in nondyscalculic subjects. This apparent discrepancy in the directionality of the effects has been interpreted in the context of interhemispheric compensation from right to left PPC. Particularly, it has been proposed that the system to be boosted shifts hemispheres in DD. That is, from a right PPC-based system that is specialized in magnitude representation, to a left PPC system that relies more on a verbal and mnemonic code (Dehaene et al., 2003). Indeed, a signature for hemispheric reorganization has been proposed for DD children as young as 9 years old (Kaufmann et al., 2009). Thus, in DD, tDCS might affect cortical function by modulating interhemispherical interactions through upregulation of the compensatory neural populations in the left PPC and downregulation of the right PPC. Together, these initial results represent an important step informing the rehabilitation of numerical skills in cases of persistent DD, as well as in shedding light onto mechanisms of brain reorganization in these individuals.

4.5 EMERGENT APPROACHES: EMBODIED INTERVENTION

Finally, within the context of DD intervention, it is worth mentioning another line of research that has started to emerge, and which builds on the notion that number representations are influenced by bodily sensory experiences (ie, moving the whole body along the mental number line). For example, in a recent series of studies, Fisher and colleagues have reported that kindergarten children that were trained to solve a magnitude comparison task on a digital dance mat (ie, a step to the left, a step to the right) (Fischer et al., 2011) showed significant improvements on both a number line estimation task and a transfer task (ie, counting). Notably, their improvements were greater compared to a control group that was trained on the same magnitude comparison task but on a Personal Computer. These findings suggest that interventions designed to strengthen the relationship between visuospatial and embodied number line representations can be used as an alternative, or complimentary route to enhance numerical representations, especially in children with DD.

Altogether remediation studies of DD are still in their infancy. Yet, they seem to be producing promising results, on both behavioral as well as neuroimaging

measures, and might therefore represent encouraging cornerstones to forge well-informed educational policies to assist DD individuals in overcoming their difficulties.

5 CONCLUSIONS AND FUTURE DIRECTIONS

This chapter provides evidence for DD as a multifaceted disorder and highlights the dynamic component of this disability, both in terms of learning and development. Cognitive as well as neuroimaging studies support the notion that aberrancies can occur at different processing stages of the hierarchical cascade of neurocognitive computations that lead to successful arithmetic learning during the early school years. Notably, this is the time when the brain of a child learns to repurpose some of its domain-general resources (ie, visual recognition, attention, memory) to tasks that are very specific and evolutionarily recent (eg, learning symbols, remembering arithmetic facts). This process is known to be supported by dramatic transformations in the child's brain: widespread changes are evident in terms of neuroanatomical structure, functional specialization, and connectivity patterns among brain regions supporting a variety of cognitive functions. In the case of DD, aberrancies in the posterior parietal cortices—primarily in the horizontal segment of the IPS—in the dorsal stream could lead to deficits in semantic representation and manipulation of quantity (Dehaene and Cohen, 1995); while functional and structural alterations in ventral temporal-occipital cortices in the ventral visual stream might impact successful perceptual representation of higher order visual symbols (ie, Arabic numerals) (Ansari, 2008). The interaction between these ventral and dorsal processing streams would lead to deficits in associating the appropriate symbols to their semantic representation (Iuculano et al., 2008; Rousselle and Noel, 2007). Learning these associations, as well as learning rules and principles that characterize arithmetic as a discipline (ie, commutativity rule, "+" sign indicates addition, etc.) is orchestrated by cognitive neural resources supported by the prefrontal cortex in the form of WM, nonverbal reasoning, and attentional processes (Shallice and Evans, 1978). All of these neurocognitive systems could be affected, over development and learning, in DD. Furthermore, mnemonic processes supported by the MTL and their intact interactions with cortical regions might also be aberrant in DD. Alterations of these systems might contribute to deficits in arithmetic fact retrieval that characterize the disorder (Geary, 2011a,b, 2012). Finally, it is important to note that learning does not happen in isolation and a variety of emotional and social factors interact with the successful acquisition of mathematical skills (ie, reward, positive mindset, anxiety, type of instructions, SES, etc.), and all these factors can negatively impact learning in DD. Critically, to date, the majority of effort in characterizing DD has focused on the neurocognitive factors that might lead to the disorder, yet most often these have been examined in isolation, and only few accounts have taken a comprehensive (and dynamic) view of DD (Fias et al., 2014). Moreover, thus far, affective and social factors contributing

to DD have largely been neglected in the literature. We suggest that in order to significantly advance the understanding of this disability (and its remediation), the field needs to take a more comprehensive view in assessing the *etiology* of DD. We propose this should capitalize on systems neuroscience findings and approaches and be centered on the notion of learning and development.

Similarly, intervention studies of DD are still in their infancy but they seem to converge on the idea that comprehensive paradigms that target multiple neurocognitive systems of learning by combining conceptual knowledge, speeded practice, and efficient strategies, can be successful in remediating DD, at the behavioral as well as at the brain level. Multiple functional systems can undergo widespread changes after targeted intervention in DD and plasticity can arise even within a short-time window (ie, 2 months) (Iuculano et al., 2015). However, we do not know whether the effects are long lasting and longitudinal studies are needed to assess the prognosis of DD after different types of interventions, as well as in placebo settings. Moreover, we do not know whether certain systems might be the hub of the change. We also do not know whether the degree to which certain systems might be driving plasticity more than others could differ depending on the child. Together, this knowledge might lead to the next challenge: by knowing which systems are impaired and when, will it be possible to design an ad-hoc intervention for each individual child (ie, similar to the notion of precision medicine)? Furthermore, understanding how the brain supports the hierarchical computations necessary for math skills acquisition (ie, from symbols recognition, to magnitude associations, to rules learning) over time might reveal critical information on *dedicated periods* for optimal learning. This knowledge will, in turn, inform the design of developmentally appropriate curricula as well as targeted interventions. Moreover, understanding systems-level interactions that lead to poor learning might help to shed light onto the issue of comorbidity of learning disabilities. Finally, more research is needed to investigate additional factors that can mediate heterogeneity of treatment outcomes. These include motivational, affective, and social factors (including SES), as well as sleep and nutrition. In parallel, it is important to recognize that technology is becoming a central part of children's learning experience and more and more, teachers and schools are taking advantage of recent technological advances that use adaptive tools to foster ad-hoc learning. Some of these *software* programs build upon educational principles but often they do not capitalize on neuroscience findings. This represents another challenge and a potential advantage for the field, as well as the future of intervention. Particularly, one of the fascinating questions that arises relates to how the atypical (but also the typical) brain changes and adapts to these new ways of teaching.

To conclude, within the next decade, it will become pivotal to forge the connection between cognitive, affective, computational, technological, and pedagogical sciences by positioning recent advances in understanding how, during development, the brain learns or fails to learn, at the junction of all these disciplines. This will ultimately foster better teaching regimes and learning profiles for DD and more generally for other neurodevelopmental learning disabilities.

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