Cognitive neuroscience of dyscalculia and math learning disabilities.

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Abstract

Dyscalculia and mathematical learning disability (MD) are neurodevelopmental disorders characterized by difficulties in reasoning about numbers. Children with MD lag behind their typically developing peers in a broad range of numerical tasks, including magnitude judgement, quantity manipulation, arithmetic fact retrieval, and problem-solving. This chapter reviews current theories and knowledge of MD and its neurobiological basis from a systems neuroscience perspective. The chapter shows that MD involves processing deficits and aberrancies in multiple neurocognitive systems associated with non-symbolic and symbolic quantity judgment, visuo-spatial working memory, associative memory, and cognitive control. Convergent evidence from task and resting-state fMRI, along with morphometric and tractography studies, is used to demarcate distributed brain circuits disrupted in MD. The chapter examines neural mechanisms underlying intervention and remediation of deficits in MD, highlighting links between brain plasticity and response to treatment. The view that emerges is of a multi-component neurodevelopmental disorder, arising from aberrancies at one or more levels of the numerical information processing hierarchy.

Keywords : dyscalculia, math achievement, learning disabilities, arithmetic problem-solving, number sense, cognitive intervention

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Introduction

Dyscalculia or mathematical disability (MD) is a specific learning disability characterized by difficulties in processing numerical and mathematical information despite normal IQ (Butterworth, Varma et al., 2011; Kaufmann, Mazzocco et al., 2013; Price and Ansari, 2013). Developmental dyscalculia was originally described as a deficit solely limited to the understanding of quantity and numerical sets (Butterworth, 2005), but cases of pure developmental dyscalculia are relatively rare as numerical processing deficits are often accompanied by difficulties in other visuospatial and verbal domains (von Aster and Shalev, 2007; Devine, Soltész et al., 2013). More generally, children and adults who are in the bottom quartile of mathematics achievement are at risk for poor long-term outcomes in mathematics learning and in real-world endeavors that require mathematics (Parsons and Bynner, 1997; Parsons and Bynner, 2005). The definition of dyscalculia has therefore been revised to include a broader group of individuals with MD, and increasingly the focus is on characterization of multicomponent deficits and impairments of functional circuits that impact acquisition of numerosity and performance on numerical problem-solving skills. Individuals with MD show poor performance on a broad range of basic numerical tasks including magnitude judgment (Geary, Hamson et al., 2000; Ashkenazi, Rubinsten et al., 2009; Mussolin, Mejias et al., 2010) and enumeration (Geary and Brown 1991; Geary, Bow-Thomas et al.,1992; Knootz and Berch 1996; Landerl, Bevan et al., 2004; Schleifer and Landerl, 2011). They also lag behind their typically developing (TD) peers in basic arithmetic problem-solving skills (Geary, Bow-Thomas et al., 1992; Shalev, Auerbach et al., 2000; Shalev, Manor et al., 2005). This review thus necessarily takes a systems neuroscience approach to the investigation of MD.

This chapter summarizes current knowledge about the neurocognitive basis of MD. We also discuss how recent advances in functional and structural neuroimaging provide a more comprehensive understanding of neurocognitive impairments in affected individuals. Considerable progress has been made over the past several decades in identifying the cognitive deficits that contribute to MD (Geary, Hoard et al., 2007; De Smedt, Noël et al., 2013; De Visscher and Noël, 2014; Attout and Majerus, 2015), and in recent years, the identification of the underlying brain systems (De Smedt, Holloway et al., 2011; Kucian, Loenneker et al., 2011; Supekar, Swigart et al., 2013; Demir, Prado et al., 2014; Attout, Salmon et al., 2015; Rosenberg-Lee, Ashkenazi et al., 2015; McCaskey, von Aster et al., 2017; McCaskey, von Aster et al., 2018; Schwartz, Epinat-Duclos et al., 2018). We first provide an overview of central cognitive theories and models of MD, including impairments in non-symbolic and symbolic representations of quantity and impairments in key "domain-general" cognitive processes including memory and cognitive control. We then describe key aspects of brain areas and functional circuits that are impacted by the disability, focusing on basic number sense and arithmetic problem-solving—the two domains of numerical cognition most widely investigated in children and adults with MD. Next, we consider the specific role of brain systems underlying working memory (WM) and cognitive control deficits in MD. Finally, we review evidence for deficits in intrinsic structural and functional circuits, which provide a convergent view of neural systems that underlie MD.

Diagnosis and prevalence of MD

The revised Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5) defines MD as a specific learning disorder with persistent difficulties in acquiring academically relevant mathematical skills, which cannot be attributed to intellectual disabilities or neurological disorders (American Psychiatric Association, 2013). MD is typically manifested in the early school years and is characterized by deficits that persist over at least six months (Chu, Vanmarle et al. 2013; Kaufmann, Mazzocco et al., 2013). Children with MD typically perform one to two years below grade level and show difficulties in one or more of the four domains identified in DSM-5: number sense, memorization of arithmetic facts, accurate and fluent calculation, and mathematical reasoning. However, the DSM-5 is limited in definition and scope of MD and does not provide specific diagnostic measures to assess individual domains of information processing deficits in affected individuals.

A number of standardized neuropsychological assessments have been developed over the past decades to overcome limitations of DSM-based criteria for defining MD. The Woodcock-Johnson (Woodcock, 1977), Wechsler Individual Achievement Test (Wechsler, 1992), and the Wide Range Achievement Test (Wilkinson and Robertson, 2006) are among the more widely used measures of mathematical skills and academic achievement in children and adults in the United States and similar measures have been developed for use in other countries, such as the Zareki (von Aster, Weinhold Zulauf et al., 2006). Behavioral and neurocognitive studies tend to vary considerably in the specific criteria used to define MD, with diagnostic cut offs on standardized neuropsychological assessments ranging typically from the 3rd percentile to the 25th percentile (Devine, Soltész et al., 2013). Discrepancy between standard math scores and IQ have also been used in many previous studies but the validity of this approach has been questioned (Mazzocco and Myers, 2003; Alloway and Alloway, 2010). Accordingly, IQ-discrepancy criteria are now neither included in the DSM-5 (2013) as a defining characteristic of MD nor are they widely used in the cognitive neuroscience literature.

In the past decade, developmental and behavioral studies have converged on more precise cutoff criteria and distinctions between subtypes of children with MD at or below the bottom quartile of mathematics achievement. Children who score at or below the 10th percentile on standardized mathematics achievement tests for at least two consecutive academic years are typically categorized as having a core math learning disorder or developmental dyscalculia and those scoring between the 11th and the 25th percentiles at any time point are characterized as low achieving (Geary, Hoard et al., 2007; Murphy, Mazzocco et al., 2007). Even though children composing these two groups represent different cut-offs on a normally distributed continuum of mathematical abilities, they often differ in their underlying cognitive strengths and weaknesses and profiles of comorbid deficits (De Smedt and Gilmore, 2011; Geary, Hoard et al., 2012). Children with MD, as a group, tend to score low average in intelligence tests and often have co-occurring deficits in reading and WM (Murphy, Mazzocco et al., 2007; Geary, Hoard et al., 2012). It is important to note here that the use of different diagnostic criteria to classify MD can impact the consistency of findings across studies, and their neurocognitive interpretations, because of variation in the precise profile of cognitive deficits in study participants, a view that has been increasingly noted in recent years (Rubinsten and Henik, 2009; Fias, Menon et al., 2013; Kaufmann, Mazzocco et al., 2013; Henik and Fias, 2018).

Neurocognitive theories and a multicomponent view of MD

In this section we present an overview of multicomponent cognitive models of MD that have emerged from cognitive and neuroscience studies of numerical cognition in MD and TD individuals. There are two major “domain-specific” aspects of information processing deficits in MD: (i) number sense and quantity manipulation, and (ii) arithmetic fact retrieval and problem-solving (Figures 1, 2).

The first is a core deficit in number sense, the ability to make judgments about quantity, and to reason with symbolic representations of quantity (Wilson and Dehaene, 2007; Piazza, Facoetti et al., 2010; Butterworth, Varma et al., 2011). Consistent with this hypothesis, it has been demonstrated that, compared to TD children, children with MD have lower than expected abilities in quantity estimation (Piazza, Facoetti et al., 2010; Mazzocco, Feigenson et al., 2011a) and abnormal magnitude representations (Ashkenazi, Mark-Zigdon et al., 2009; Mussolin, Mejias et al., 2010). Deficits in number sense also arise from weakness in automatically mapping symbols to their internal magnitude representations, reflecting a relatively greater impairment in symbolic, compared to non-symbolic processing (Rubinsten and Henik, 2005; Rousselle and Noel, 2007). A second essential aspect of MD relates to weakness in arithmetic problem-solving abilities and difficulties in committing arithmetic facts to memory. Importantly, difficulties in these core building blocks manifest in the earliest years of elementary schooling and, if not remediated, can have a lifelong impact on mathematical learning and skill acquisition in subsequent stages where more complex mathematical procedures need to be learnt. Unsurprisingly, therefore, these two categories of deficits constitute the most widely investigated neurocognitive domains in MD.

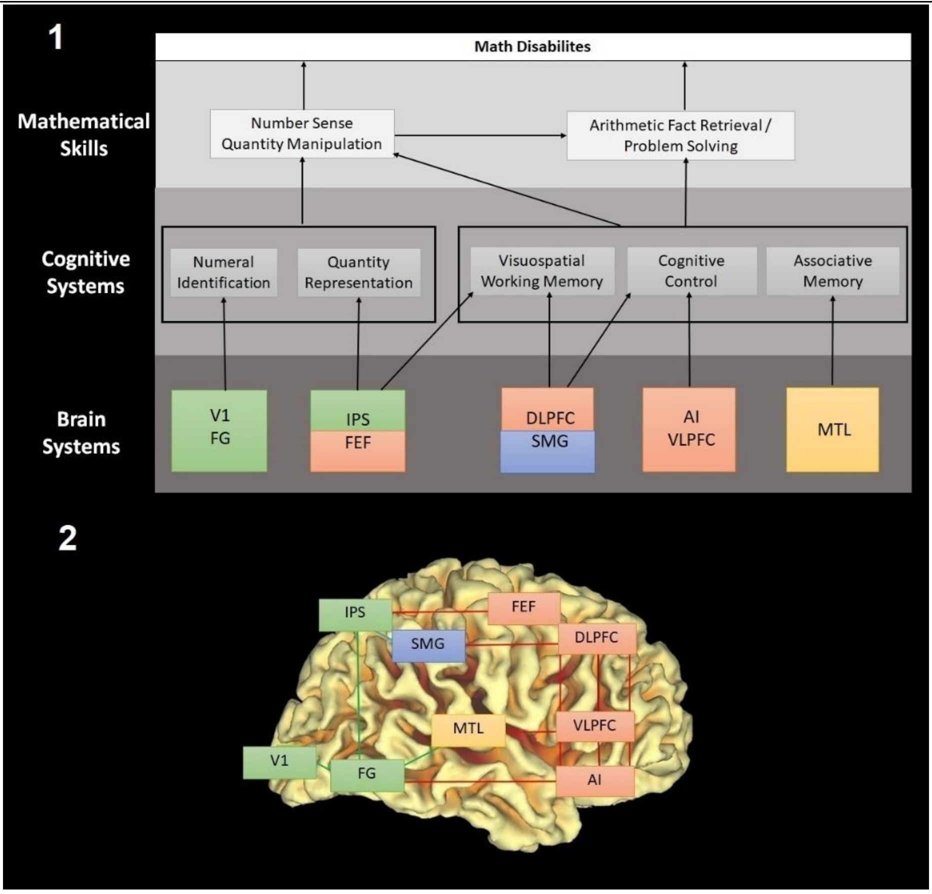

Figure 1 (1) Cognitive and brain systems that underpin MD. Mathematical difficulties arise from impairments in two core domains of mathematical cognition: (i) number sense and quantity manipulation, and (ii) arithmetic fact retrieval and problem-solving. Impairments in number sense and quantity manipulation arise from weak symbolic and non-symbolic representations of quantity as well as "domain-general" deficits in visuospatial working memory capacity and cognitive control. Impairments in arithmetic fact retrieval and problem-solving arise from deficits in the ability to manipulate internal representations of quantity as well as "domain-general" deficits in visuospatial working memory, cognitive control, and associative memory encoding and retrieval. Impairments in any of these components can compromise efficiency of numerical problem-solving skills and constitute risk factors for MD**. (2) Schematic diagram of number, arithmetic, memory, and cognitive control circuits impaired in MD.** The fusiform gyrus (FG) in the inferior temporal cortex decodes number form and together with the intra-parietal sulcus (IPS) in the parietal cortex which helps builds visuo-spatial representations of numerical quantity (shown in green boxes and links). Distinct parietal-frontal circuits differentially link the IPS and supramarginal gyrus (SMG) with the frontal eye field (FEF) and dorsolateral prefrontal cortex (DLPFC), respectively. These circuits facilitate visuospatial working memory for objects in space and create a hierarchy of short-term representations that allow manipulation of multiple discrete quantities over several seconds. The declarative memory system anchored in the medial temporal cortex (MTL)—the hippocampus, specifically, plays an important role in long-term memory formation and generalization beyond individual problem attributes. Finally, prefrontal control circuits (shown in red) anchored in the anterior insula (AI), ventrolateral prefrontal cortex (VLPFC) and DLPFC serve as flexible hubs for integrating information across attentional and memory systems, thereby facilitating goal-specific problem-solving and decision making

Source: Part 2: Reprinted from *Trends in Neuroscience and Education*, *2*(2): 43–47, Wim Fias, Vinod Menon, and Denes Szucs, Multiple Components of Developmental Dyscalculia. https://doi.org/10.1016/j.tine.2013.06.006.

In recent years, researchers have also identified “domain-general” cognitive factors underlying information processing deficits in MD. The two most well studied of these factors are WM and cognitive control. Individuals with MD show prominent deficits in the use of developmentally appropriate arithmetic procedures, and these impairments have been attributed to weaknesses in manipulation of quantity in WM independent of “domain-specific” deficits in number sense. Meta-analyses of behavioral studies in children with MD have pointed to a consistent pattern of visuo-spatial and verbal WM deficits in affected children (Swanson, Howard et al., 2006). Deficits in cognitive control, including interference resolution, also influence problem-solving and decision making across multiple domains of mathematics, including comparison of numerical magnitude (Gilmore, Attridge et al., 2013; Bugden and Ansari, 2016), arithmetic problem-solving (De Visscher and Noël, 2014; De Visscher, Szmalec et al., 2015), and logical reasoning (Morsanyi, Devine et al., 2013). Finally, difficulties with word-based reasoning problems (Jordan, Hanich et al., 2003) are an important source of vulnerability and a significant number of children with MD have comorbid reading disability including dyslexia (Lewis, Hitch et al., 1994; Knopik, Alarcon et al., 1997; Willcutt, Petrill et al., 2013; Wilson, Andrewes et al., 2015). MD arises from a complex interplay between “domain-specific” and “domain-general” deficits. In this view, number processing and mathematical problem-solving are built on multiple neurocognitive components that are implemented by distinct and overlapping brain systems. Impairments in any of these components can compromise efficiency of numerical problem-solving skills and constitute risk factors for MD (Figures 1, 2).

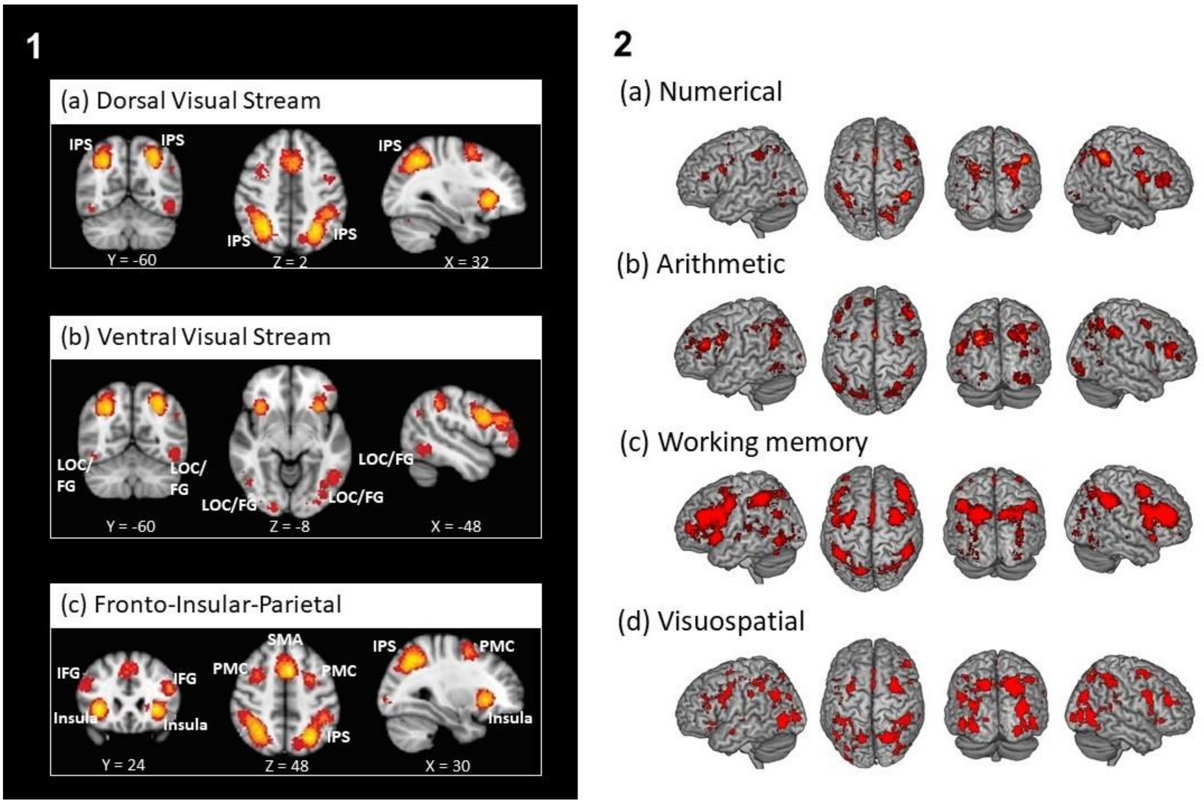

Figure 2 **(1) Canonical brain areas involved in arithmetic problem-solving.** (a) Dorsal visual stream anchored in the intraparietal sulcus within the posterior parietal cortex. (b) Ventral visual stream anchored in the lateral occipital cortex (LOC) and FG. (c) Prefrontal cortex control system anchored in the anterior insula, inferior frontal gyrus (IFG) and premotor cortex (PMC). Maps are based on a meta-analysis of "arithmetic" studies in neurosynth.org (Yarkoni et al., 2011). **(2) Common patterns of fronto-parietal network activations elicited by numerical, arithmetic, working memory and visuospatial processing tasks.** Results from a meta-analysis conducted using Neurosynth (www.neurosynth.org) with the corresponding search terms

Number sense deficits in MD

Behavioral findings

Humans, as well as other species, are endowed with a core capacity to discriminate between sets of objects that differ on numerosity (Dehaene, 1997; Butterworth, 1999; Carey, 2004). This core capacity is present in infants (Izard, Dehaene-Lambertz et al., 2008; Izard, Sann et al., 2009). Infants can discriminate between displays of small numerosity—e.g., they respond when the display changes from two to three objects, or from three objects to two (Starkey and Cooper, 1980; Starkey, Spelke et al., 1990; van Loosbroek, 1990). An evolutionarily endowed capacity for numerosity is grounded in evidence that such capacity has adaptive value, but importantly also serves as the foundation for number sense and manipulating numerical quantity. Weaknesses in representing, accessing, and manipulating numerical quantity—number sense—have been hypothesized to be a core deficit in MD (Butterworth, Varma et al., 2011). Children with MD show deficits in magnitude judgment in both symbolic (e.g., Arabic numerals, number words) (Rousselle and Noel, 2007; Mussolin, Mejias et al., 2010) and non-symbolic formats (e.g., dots patterns and random sticks patterns) (Price, Holloway et al., 2007).

An important feature of mathematical development is that symbolic problem-solving skills are built upon, and activate, non-symbolic quantity representations (Gilmore, McCarthy et al., 2007). When children learn to count and acquire a symbolic system for representing numbers, they map these symbols onto a preexisting system involving approximate visuo-spatial representations of quantity (Mundy and Gilmore, 2009). Children with MD have difficulties with both non-symbolic quantity representation, as assessed using the approximate number system (ANS) (Halberda, Mazzocco et al., 2008; Mazzocco, Feigenson et al., 2011), and symbolic quantity representation, as assessed by standard achievement tests and cognitive tasks involving Arabic numerals (Geary, 1993; Jordan, Hanich et al., 2003; Rousselle and Noel, 2007; Butterworth, Varma et al., 2011; Mazzocco, Feigenson et al., 2011; Geary, Hoard et al., 2012). Moreover, they are particularly impaired at mapping between symbolic and non-symbolic representations.

Although MD is typically identified after the first years of formal schooling, there are hints that number sense deficits may be apparent early in development in individuals who later go on to develop MD (Butterworth, 2005; Butterworth, 2010). Number sense involves two distinct processes: one for subitizing for smaller numbers and the other an ANS for larger numbers and both processes have early developmental origins. Subitizing, the ability to spontaneously recognize small numbers up to three or four develops as early as 6-months of age (Wynn, 1992). ANS involves the ability to discriminate between relatively large numerosities without counting. Performance of the ANS follows Fechner's psychophysical principles (Fechner, 1966) and is a function of the ratio between two sets of objects. This skill is also evident as early as 6-months of age (Libertus, Brannon et al., 2011) and continues to develop until late childhood (Mazzocco, Feigenson et al., 2011). An intermediate stage of number sense development relates to knowledge of the cardinal properties of numbers, for example, *threeness* and *fourness* of sets of objects, and their mapping to visual symbols such as “3” and “4” (Carey, 2004).

Lower subitizing performance has been reported in MD as compared to TD (Landerl, Bevan et al., 2004; Schleifer and Landerl, 2011), and spontaneous discrimination of large numerical magnitudes is also more difficult for individuals with MD (Price, Holloway et al., 2007; Piazza, Facoetti et al., 2010; Mazzocco, Feigenson et al., 2011). Lastly, there is evidence that individuals with MD might have difficulties with the mapping of exact numerical quantities onto their symbol, which might delay refinement of the ANS in later childhood (Noël and Rousselle, 2011). There has been considerable debate regarding the relative contributions of symbolic and non-symbolic magnitude judgement to overall math abilities in TD children and adults (De Smedt, Noël et al., 2013). While some studies have pointed to the primacy of non-symbolic capacities (Halberda, Mazzocco et al., 2008), others have suggested a stronger relation between symbolic skills and math abilities (Rousselle and Noel, 2007; Holloway and Ansari, 2009; Kolkman, Kroesbergen et al., 2013). The emerging consensus is that symbolic skills may be a more robust predictor of math skills (Lyons, Price et al., 2014). Crucially, among symbolic skills, counting (the ability to correctly sequence numbers orally) is a good predictor of the subsequent development of arithmetic skills (Geary, 1993) and an early source of vulnerability in children who subsequently go on to develop MD (Geary, 2004).

Neurobiological correlates

Neuroimaging investigations of number sense deficits in MD have used symbolic number and non-symbolic dot comparison tasks with different types of control tasks. While some functional neuroimaging studies use fine-grained manipulations involving small and large distance between pairs of numbers to investigate neural distance effects similar to the behavioral distance effect (Ashkenazi, Mark-Zigdon et al., 2009), others have used non-numerical control tasks with the goal of elucidating number-specific differences in brain activation. The design of these tasks is based on the landmark behavioral research of Moyer and Landauer demonstrating a numerical distance effect: adults are significantly slower and more error prone when they compare numbers with a smaller distance (e.g., 1 and 2) compared to a larger distance (e.g., 1 and 7) (Moyer and Landauer, 1967). Notably, the type of control task used (e.g., numerical distance effect vs. non numerical) can influence the pattern of aberrancies reported in MD. We first focus on studies of the neural distance effect because they provide greater specificity arising from closely matched perceptual, cognitive, and response factors.

Studies of number sense deficits in MD have focused on the intra-parietal sulcus (IPS), a brain region important for numerical magnitude judgement at all stages of development including infancy (Hyde, Boas et al., 2010), pre-school children (Cantlon, Brannon et al., 2006) as well as older children and adults (Pinel, Dehaene et al., 2001). Specifically, in neurotypical individuals, the IPS is modulated by numerical distance (Dehaene, Piazza et al., 2003). Using a non-symbolic quantity comparison task, Price and colleagues demonstrated weak modulation of IPS activity in a group of 12-year-old children with MD (Figure 3.1) (Price, Holloway et al., 2007). Aberrant activation of the IPS and adjoining posterior parietal cortex has also been reported in younger children for both symbolic (Mussolin, De Volder et al., 2010) and non-symbolic number comparison tasks (Kucian, Loenneker et al., 2006; Kaufmann, Vogel et al., 2009; Kucian, Loenneker et al., 2011). Lastly, reduced modulation of the left IPS by numerical distance has also been reported in children with MD for symbolic tasks (Figure 3.2) (Mussolin, De Volder et al., 2010).

More generally, the causal role of the right parietal cortex in numerical processing is supported by brain stimulation studies in adults, who showed that transcranial magnetic stimulation (TMS) over the right parietal lobe, which likely encompassed the IPS, disrupted numerical magnitude judgement and discrimination in healthy adults (Cohen Kadosh, Cohen Kadosh et al., 2007). Convergent on these findings, children with MD also show structural anomalies in the right IPS as discussed in a later section of this chapter. Taken together, these results suggest that atypical activity of the IPS may be a proximal cause of impairments in processing numerical magnitudes in MD.

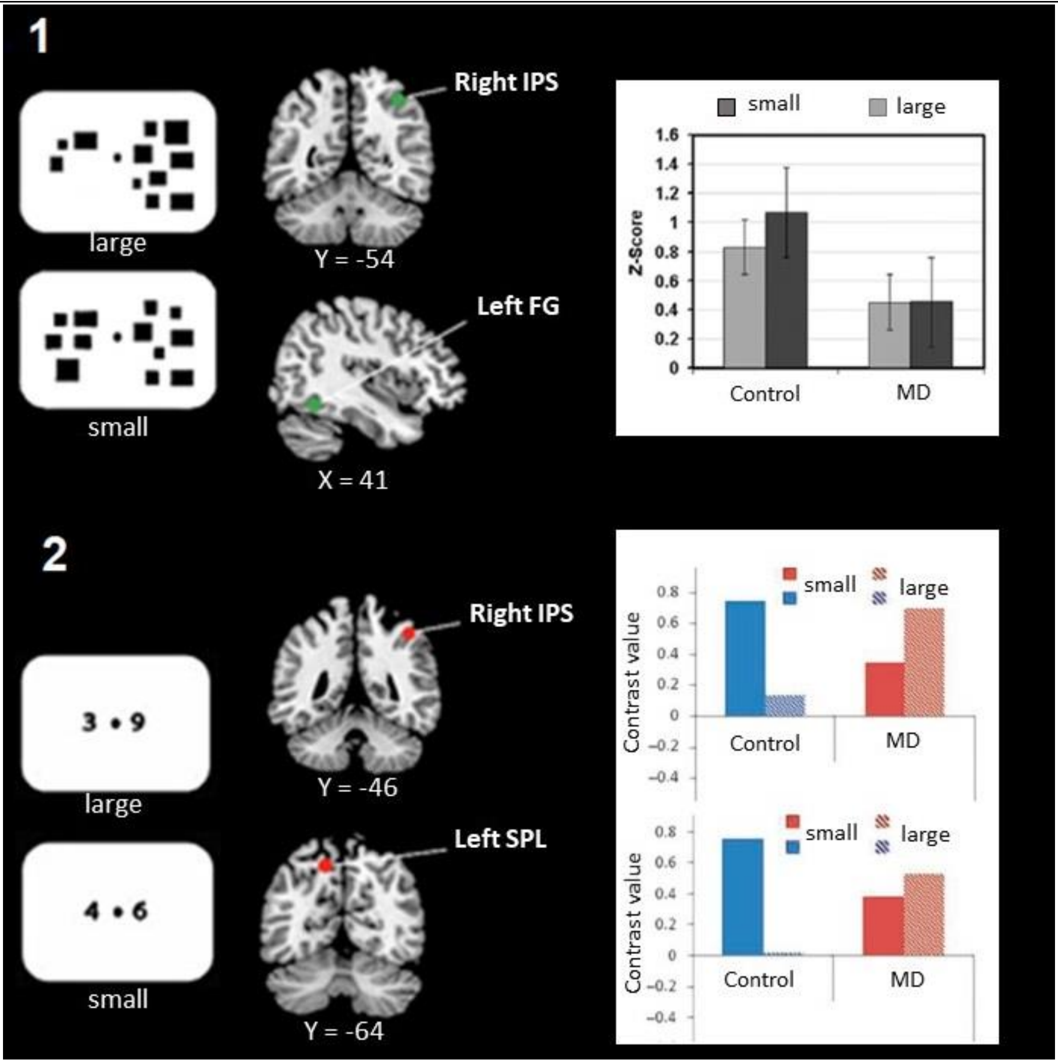

Figure 3. Aberrant parietal and ventro-temporal cortex responses during magnitude judgement. **(1) Reduced modulation of brain responses by numerical distance during non-symbolic quantity comparison in children with MD, relative to control children.** Results from an interaction analysis of group (MD, Control) x distance (small, large) in the right intraparietal sulcus (IPS) and left FG. The left panel shows stimuli used in the large and small distance conditions. The middle panel depicts brain areas that showed a neural distance effect. The right panel shows signal levels in each condition by group. **(2) Reduced modulation by numerical distance during symbolic quantity comparison in children with MD relative to Control.** Results from an interaction analysis of group x distance in the right IPS and left superior parietal lobule (SPL)

Source: Part 1: Adapted from *Current Biology*, 17 (24), Gavin R. Price, Ian Holloway, Pekka Räsänen, Manu Vesterinen, and Daniel Ansari, Impaired parietal magnitude processing in developmental dyscalculia, PR1042–R1043, https://doi.org/10.1016/j.cub.2007.10.013. Copyright © 2007 Elsevier Ltd. All rights reserved. Part 2: adapted from Christophe Mussolin, Anne De Volder, Cécile Grandin, Xavier Schlögel, Marie-Cécile Nassogne, and Marie-Pascale Noël (2010). Neural correlates of symbolic number comparison in developmental dyscalculia. *Journal of Cognitive Neuroscience*, *22*(5): 860–874. © 2010 by the Massachusetts Institute of Technology.

In addition to weak modulation of the IPS, individuals with MD also show reduced activity in the ventral temporal occipital cortex (VTOC) and multiple areas of the prefrontal cortex (PFC) during basic number comparison tasks. Decreased activation in relation to numerical distance has been detected in the dorsolateral PFC during symbolic (Mussolin, De Volder et al., 2010) and non-symbolic number comparison tasks (Price, Holloway et al., 2007), but the laterality of PFC findings has not been consistent across these studies. Aberrant engagement of the fusiform gyrus (FG) within the VTOC in MD has also been reported in both symbolic and non-symbolic tasks with evidence of deficits (Price, Holloway et al., 2007) as well as over-compensation (Kucian, Loenneker et al., 2011). Another study that parametrically varied the numerical distance during a non-symbolic comparison task found evidence for compensatory engagement of bilateral supplementary motor area and the right FG in children with MD (Kucian, Loenneker et al., 2011).

Studies using low-level non-numerical control tasks have provided further insights into the neurocognitive basis of MD. A careful examination of the differential contrasts reported in various studies suggests that when activation during magnitude judgment are compared against low-level non-numerical control tasks, children with MD often show hyper-activation when compared to TD children, relative to hypo-activation during magnitude comparison as described previously. A conflicting pattern of hypo- and hyper-activation in MD reported in studies to date may therefore be directly related to the control task used. For example, in the study by Mussolin and colleagues, despite weak modulation by numerical distance, when activations were compared to passive fixation, children with MD showed greater activation than TD children in several brain regions, including right supramarginal gyrus and right postcentral gyrus (Mussolin, De Volder et al., 2010). Similarly, when magnitude judgment was contrasted against judgment of palm rotation, children with MD showed greater activation in left and right IPS, supramarginal gyrus, paracentral lobule and right superior frontal gyrus (Kaufmann, Vogel et al., 2009). Similar to children, adults with MD have also been reported to show compensatory hyper-activation in multiple PFC regions, including right superior frontal gyrus and left inferior frontal gyrus (IFG) (Cappelletti and Price, 2014). These findings suggest that individuals with MD can engage compensatory mechanisms in task-relevant brain regions during numerical information processing.

Despite the lack of consistency in the use of control conditions between studies, the general pattern that emerges from these studies is one of abnormal activity in distributed brain areas that extend beyond the IPS into multiple regions of the PFC, posterior parietal cortex (PPC) and VTOC regions bilaterally. Comparisons with low level baseline tasks reveal compensatory engagement of PPC, PFC, and VTOC in ways that may allow individuals with MD to achieve similar levels of performance as their TD peers on simpler numerical quantity processing tasks. At the same time, evidence from well controlled tasks involving the numerical distance effects suggests weaker magnitude comparison-related modulation of brain responses in children with MD.

Arithmetic problem-solving deficits in MD

Behavioral findings

Weak arithmetic problem-solving abilities, including poor fluency in retrieval of math facts, are a major area of difficulty in MD (Geary, 2004), even with solving simple arithmetic problems (Svenson and Broquist, 1975; Geary, 1990; Geary and Brown, 1991; Gross-Tsur, Manor et al., 1996; Barrouillet, Fayol et al., 1997; Jordan and Montani, 1997; Ostad, 1997; Ostad, 1998; Hanich, Jordan et al., 2001; Jordan, Hanich et al., 2003). In fact, poor fluency in retrieval of math facts in children with MD are typically the domain in which the math difficulties are first noticed (Geary, 2004). Most of the behavioral research on children with MD has focused on the strategies they use to solve single- or double-digit arithmetic problems (Geary, 1990; Jordan, Levine et al., 1995; Hanich, Jordan et al., 2001). A shift from immature to mature problem-solving strategies, such as counting to numerical fact retrieval, is a cardinal feature of mathematical development in children (Geary, 1994; Siegler, 1996). Children with MD use immature procedures and, unlike their TD peers, they do not show a developmental shift from calculation to efficient memory-based problem-solving (Jordan and

Montani, 1997; Geary, Hamson et al., 2000), suggesting difficulties in storing and accessing facts from long-term memory (Garnett and Fleischner, 1983; Geary and Brown, 1991; Jordan and Montani, 1997; Ostad, 1997; Ostad, 1998). Moreover, the speed and accuracy with which individual strategies are executed improves with development and experience. Children with MD continue to use less mature strategies such as finger counting, to solve arithmetic problems (Geary, 1993; Shalev, Auerbach et al., 2000), commit more counting-procedure errors than do their TD peers (Jordan and Montani, 1997; Geary, Hamson et al., 2000), and rely on finger counting and use the sum procedure for many more years than TD children do (Geary and Brown, 1991; Geary, Hamson et al., 2000; Ostad, 2000).

Neurobiological correlates

Most neuroimaging studies of aberrant brain response and representations during arithmetic problem-solving in MD have focused on addition operations, drawing on an extensive body of behavioral research. These studies have found evidence for atypical functional activation in the IPS as well as multiple PFC regions during problem-solving tasks involving mental addition. Crucially, differences in multiple functional systems can be found even when TD and MD groups are matched on performance. However, the direction of effects between MD and TD has not always been consistent with individuals with MD showing both hyper- and hypo-activation of relevant brain regions relative to TD individuals. For example, Kucian and colleagues (2006) using a task that measured approximate and exact addition problem-solving as well as magnitude estimation, found reduced brain activity in the right IPS, ventrolateral and dorsolateral PFC in children with MD (3rd to 6th graders), but only for addition problems that participants were asked to solve approximately (Kucian, Loenneker et al., 2006). In contrast, Davis and colleagues (2009), using a similar addition task, found hyper-activation in many regions of the PPC and PFC during both exact and approximate addition trials in 3rd grade children with MD (Davis, Cannistraci et al., 2009). These discrepancies in hyper- vs. hypo activation in MD might be related to differences in the criteria used to define MD, the age ranges studied, and developmental changes that occur during key periods of skill acquisition between grades 3 and 6.

Moreover, more targeted studies of 7–9-year-old (grades 2 and 3) children with MD, who were matched on intelligence, WM, and reading with their TD peers, suggest that profiles of activation differences between MD and TD also depends crucially on control tasks used (Ashkenazi, Rosenberg-Lee et al., 2012; Rosenberg-Lee, Ashkenazi et al., 2015). When compared to passive fixation baseline, children with MD typically engage regions of the PPC and PFC at similar, or even higher, levels than those seen in their well-matched TD peers (Rosenberg-Lee, Ashkenazi et al., 2015). However, when “complex” “x + y” problems are used relative to a “simple” “x + 1” control task (Barrouillet and Lépine, 2005), children with MD fail to show appropriate increases in brain responses with increasing arithmetic complexity (Figure 4.1) in the IPS but also the adjoining superior parietal lobule in the dorsal PPC, supramarginal gyrus in the ventral PPC, and bilateral dorsolateral PFC.

There is also evidence of weak modulation of neural representations for distinct arithmetic problems in children with MD, which has been probed using multivariate pattern analyses (MVPA) (Ashkenazi, Rosenberg-Lee et al., 2012). MVPA examines the spatial pattern of multi-voxel brain activity in a specific region of interest between task conditions, which are independent of overall differences in signal level (Formisano and Kriegeskorte, 2012). While TD children showed high differentiation between complex and simple problems in the bilateral IPS, children with MD showed less differentiated activation patterns independent of overall differences in signal level (Figure 4.2) (Ashkenazi, Rosenberg-Lee et al., 2012). Taken together, these results suggest that children with MD not only have weak modulation of response in key brain regions but also fail to generate distinct neural representations for distinct arithmetic problems.

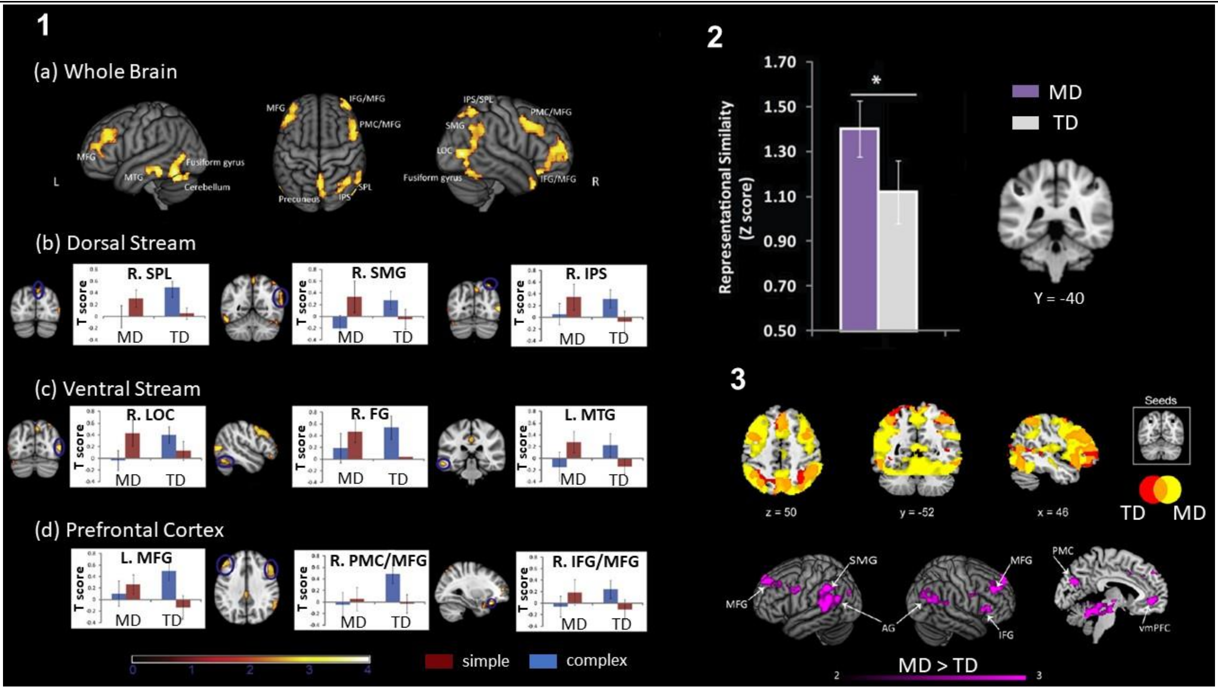

Figure 4. Aberrant parietal, ventro-temporal and prefrontal cortex responses during arithmetic problem-solving. **(1) Reduced modulation of brain responses during arithmetic problem-solving in children with MD, compared to TD children**. (*a*) Surface rendering of brain areas activated in the MD and TD groups by "complex" (x + y) vs. "simple" (x + 1) and arithmetic problems. (*b*,*c*,*d*) Signal levels elicited by each problem type. FG = fusiform gyrus; IPS = intraparietal sulcus; LOC = lateral occipital cortex; MFG= middle frontal gyrus; MTG = middle temporal gyrus; PMC= premotor cortex; SMG = supramarginal gyrus; SPL = superior parietal lobule. **(2) Representational similarity analysis** demonstrating greater similarity of multi-voxel brain responses to "complex" and "simple" problems in the anterior IPS (hIP2: −44, −40, 48) of the left and right IPS; *$p < .05$. (**3) IPS connectivity during arithmetic problem-solving in the MD (shown in yellow) and TD (shown in red) groups.** Note the more extensive connectivity in the MD group. Brain regions that showed greater IPS connectivity in the MD group included multiple frontal, parietal and occipital regions: bilateral angular gyrus (AG), left supramarginal gyrus (SMG), right middle frontal gyrus (MFG), right inferior frontal gyrus (IFG), posterior-medial cortex (PMC) and ventral medial prefrontal cortex (vmPFC)

Sources: Parts 1 and 2: Reprinted from *Developmental Cognitive Neuroscience*, 2 (Supplement 1), Sarit Ashkenazi, Miriam Rosenberg-Lee, Caitlin Tenison, and Vinod Menon, Weak task-related modulation and stimulus representations during arithmetic problem solving in children with developmental dyscalculia, S152–S166, https://doi.org/10.1016/j.dcn.2011.09.006 Copyright © 2011 Elsevier Ltd. Published by Elsevier Ltd. All rights reserved. Part 3: Adapted from *Developmental Science*, *18*(3), Miriam Rosenberg-Lee, Sarit Ashkenazi, Tianwen Chen, Christina B. Young, David C. Geary, and Vinod Menon, Brain hyper-connectivity and operation-specific deficits during arithmetic problem solving in children with developmental dyscalculia, 351–372, https://doi.org/10.1111/desc.12216. Copyright © 2014 John Wiley and Sons Ltd.

Operation-specific deficits and functional hyper-connectivity in MD

Although most behavioral studies of children with MD have focused on addition problems, there is also evidence of impairments in subtraction (Ostad, 2000; Jordan, Hanich et al., 2003). Children with MD are particularly impaired at solving subtraction, relative to addition problems and one report has suggested that they continue to rely extensively on finger counting to solve subtraction problems even in the 7th grade (Ostad, 1999). Despite their surface similarity, subtraction problems rely more on quantity-based calculation procedures and are less well rehearsed using memory retrieval strategies relative to addition (Campbell and Xue, 2001; Barrouillet, Mignon et al., 2008). Contrasting brain responses to these two distinct but related operations has provided further insights into problem-solving deficits arising from weaknesses in executing calculation procedures in MD.

Relative to TD children, children with MD demonstrate aberrant brain responses during the solving of subtraction problems (Rosenberg-Lee, Ashkenazi et al., 2015). Remarkably, despite poorer performance on subtraction problems, children with MD show hyper-activation in multiple IPS and superior parietal lobule subdivisions in the dorsal PPC as well as the FG in VTOC. They also engage the right anterior insula and dorsolateral PFC, right supplementary motor area and bilateral superior frontal gyrus, and PFC regions involved in cognitive and motor control more than TD children (Figure 4.3). Together, these results suggest that children with MD show more extensive dysfunction in multiple PPC, VTOC, and PFC areas while solving subtraction problems. Critically, hyper-activation of multiple brain areas may reflect the need for more processing resources during calculation-based problem-solving, such as subtraction, rather than an inability to activate task-relevant brain areas. Furthermore, effective connectivity analyses revealed hyper-connectivity, rather than hypo-connectivity, between the IPS and multiple brain systems including regions within the lateral fronto-parietal and default mode networks in children with MD during both addition and subtraction (Rosenberg-Lee, Ashkenazi et al., 2015) (Figure 4.3). These findings suggest the IPS and its functional circuits are a major locus of dysfunction during both addition and subtraction problem-solving in MD. Moreover, recent findings suggest that inappropriate task modulation and hyper-connectivity, rather than under-engagement and under-connectivity, are also key neural mechanisms underlying problem-solving difficulties in children with MD.

WM deficits in MD

Behavioral findings

WM deficits also contribute to weak math problem-solving skills in MD (Geary, Hoard et al., 2007). There is growing evidence that WM deficits contribute to multiple aspects of MD, encompassing not only complex arithmetic problem-solving, which requires online manipulation of information in WM, but also basic quantity representation (Chu, Vanmarle et al., 2013; Fias, Menon et al., 2013), number ordering (Attout and Majerus, 2017) and word problem-solving (Fung and Swanson, 2017). Among the three main components of the Baddeley WM model—the central executive, visuo-spatial sketchpad, and phonological loop (Baddeley, 1996; Baddeley, Emslie et al., 1998), visuospatial WM is a particular source of numerical problem-solving deficits in MD (Wilson and Swanson, 2001; Swanson, Howard et al. 2006; Rotzer, Loenneker et al. 2009; Ashkenazi, Rosenberg-Lee et al., 2013; Szucs, Devine et al., 2013; Attout and Majerus, 2015). Furthermore, visuospatial WM is a specific deficit in children with MD when they are compared to children with reading disabilities (Swanson, Howard et al., 2006) and is also a strong predictor of math learning over development (Geary, 2011).

Neurobiological findings

The importance of visuospatial WM and associated fronto-parietal processing during arithmetic problem-solving is further highlighted by neuroimaging studies of children with MD. Rotzer and colleagues (2009) found that children with MD had lower scores on a Corsi Block Tapping test, a standard measure of visuospatial WM ability, than TD children. This study also found that children with MD had lower activity levels in the right IFG, right IPS, and right insula during a visuospatial WM task, and that right IPS activity was positively correlated with visuospatial WM ability.

More direct evidence for a neurocognitive link between WM deficits and MD was provided by Ashkenazi and colleagues using standardized measures of all three components of WM, central executive, visuo-spatial, and phonological loop (Ashkenazi, Rosenberg-Lee et al., 2013) and examined their role in modulating brain responses to numerical problem-solving. Children with MD demonstrated lower visuospatial WM, even with normal IQ and preserved abilities on the phonological and central executive components of WM. Crucially, activations in IPS, and dorsolateral and ventrolateral PFC were positively correlated with visuospatial WM ability in TD children, but no such relation was seen in children with MD. These results suggest that visuospatial WM is a specific source of vulnerability in MD and thus needs to be seriously considered as a key component in cognitive, neurobiological, and developmental models of the disability. Notably, extant findings point to the IPS as a common locus of visuospatial WM and arithmetic problem-solving deficits, storing and manipulating quantity representations in MD (Metcalfe, Rosenberg-Lee et al., 2013; Iuculano, Rosenberg-Lee et al., 2015; Jolles, Ashkenazi et al., 2016).

Cognitive control deficits in MD

Behavioral findings

A core deficit underlying MD and persistent low achievement in mathematics is difficulty committing basic arithmetic facts to long-term memory or retrieving them from memory (Temple, 1991; Geary, Hoard et al., 2012). This deficit is thought to arise from proactive interference, that is, confusion of related, previously learned information with current learning (De Visscher and Noël, 2013; De Visscher and Noël, 2014). Proactive control is specially required when the learning of arithmetic facts is highly prone to interference. For example, when asked to solve “6 x 3 = ?,” participants might answer “24” (6 x 4) or “12” (6 x 2) instead of “18” (Campbell and Graham, 1985). One possible reason for these relatively common errors is that arithmetic facts may be stored in memory in the form of a “network,” whose size increases over the course of development, and whose nodes consist in operands (Ashcraft, 1992). Arithmetic problem-solving (production or verification of a result) is thought to activate relevant nodes as well as adjacent nodes, leading irrelevant facts to compete with the problem to solve. For example, when asked to solve “6 x 3,” the competitors “6 x 4” and “6 x 2” can also be activated in WM and interfere with problem-solving. Proactive control is thus required to inhibit the competitors and select the correct answer. In this context, individual differences in the learning of arithmetic facts might come from differences in resisting interference in WM (Barrouillet, Fayol et al., 1997; Barrouillet and Lépine, 2005; De Visscher and Noël, 2014).

Barrouillet and Lépine (2005) found that adolescents with higher proactive control were better at retrieving arithmetic facts, while individuals who were more sensitive to interference showed lower arithmetic fluency (Barrouillet and Lépine, 2005). Similarly, adolescents with MD also show fact retrieval deficits arising from a lower ability to resist interference (generated by competitors), despite intact encoding in memory (Barrouillet, Fayol et al., 1997). Consistent with this initial finding, recent work has confirmed that difficulties with arithmetic problem-solving in MD are associated with hypersensitivity to interference (De Visscher and Noël, 2013; De Visscher and Noël, 2014; De Visscher, Szmalec et al., 2015). Thus, for example, children ages 8 to 10 with low arithmetic fluency showed poorer WM performance relative to TD children under high-interference, but not under low-interference conditions (De Visscher and Noël, 2014). Finally, adults with a history of MD, and in particular with low arithmetic fluency, showed the same type of WM impairments under high interference conditions (De Visscher, Szmalec et al., 2015). Taken together, these results suggest that hypersensitivity to high interference in WM contribute to numerical problem-solving deficits in MD.

Neurobiological correlates

Two neuroimaging studies in adults have investigated the neural correlates of the interference effects during arithmetic problem-solving. They revealed increased brain activity under high interference (as compared to low interference) in the left IFG (De Visscher, Vogel et al., 2018) and in the right IFG, bilateral insula, medial PFC, and premotor and motor cortex (De Visscher, Berens et al., 2015). Interestingly, brain activity in the left IFG during high interference was negatively correlated with arithmetic skills (De Visscher, Vogel et al., 2018), pointing to greater need for cognitive control resources in individuals with low arithmetic fluency. These findings are consistent with reports of hyperactivity and over-engagement of multiple cognitive control regions of the PFC reported in MD (Rosenberg-Lee, Ashkenazi et al., 2015), especially when neural activations are compared using low-level task baselines, as summarized previously.

Intrinsic brain connectivity in MD

As described previously, numerical cognition relies on interactions between multiple functional brain systems, including those subserving quantity processing, WM, and cognitive control (Fias, Menon et al., 2013; Arsalidou, Pawliw-Levac et al., 2018) (Figure 1). An important question is whether aberrations in brain activation and connectivity are a task / state dependent with variable profiles of differences arising from the type of numerical tasks used (e.g., non-symbolic number comparison, symbolic number comparison, addition, subtraction) and baseline ("control") conditions (e.g., fixation, mental rotation, manipulation of task complexity) used in various studies, or whether they arise from differences in task performance between MD and TD groups. Intrinsic functional connectivity using task-free resting state fMRI has the potential to address questions related to functional brain organization in MD, provide insights into impairments in functional brain circuity and how they might influence the ability of individuals with MD to perform numerical tasks, and circumvent methodological issues arising from differences in the type of numerical task and control conditions used, as well as confounding effects of task performance and strategy use (Fair, Schlaggar et al., 2007; Church, Wenger et al., 2009; Koyama, Di Martino et al., 2011; Supekar, Uddin et al., 2013; Uddin, Supekar et al., 2013; Finn, Shen et al., 2014).

Using this approach, Jolles, Ashkenazi et al. (2016) characterized intrinsic functional connectivity of the IPS in children with MD, relative to a group of TD children who were matched on age, gender, IQ, WM, and reading abilities (Jolles, Ashkenazi et al., 2016) using a multilevel analytical approach (Figure 5). First, compared to TD children, children with MD showed hyper-connectivity of the IPS with multiple prefrontal, parietal and basal ganglia regions. Hyperconnectivity of the IPS with prefrontal and parietal cortex was also associated with poorer math ability in children with MD (Figure 5.1). Furthermore, machine learning algorithms revealed that aberrant IPS connectivity patterns accurately discriminated children with MD and TD children. Lastly, children with MD showed higher levels of spontaneous low frequency fluctuations in multiple frontal and parietal areas, including IPS, superior parietal lobule, supramarginal gyrus, and hippocampus (Figure 5.2). Notably, children with MD showed higher low-frequency fluctuations in multiple fronto-parietal areas that overlapped with brain regions that exhibited hyper-connectivity with the IPS. These results suggest that intrinsic hyper-connectivity and enhanced low-frequency fluctuations may limit flexible resource allocation, and contribute to aberrant recruitment of task-related brain regions during numerical problem-solving in MD.

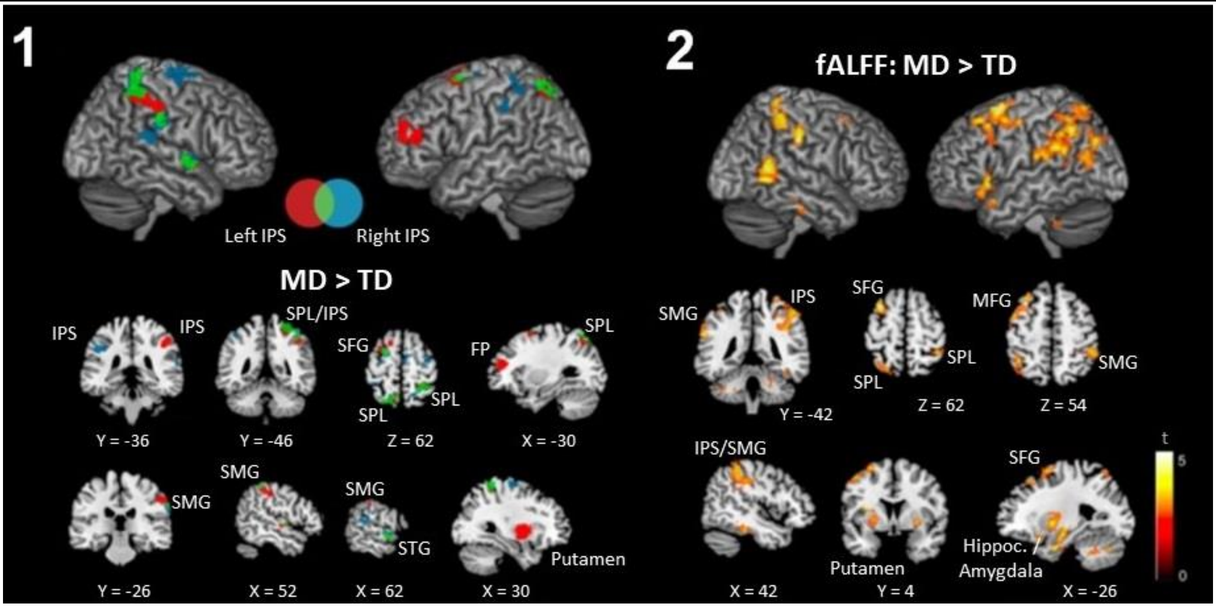

Figure 5. Aberrant intrinsic functional connectivity in MD. (1) Brain areas that showed greater IPS connectivity in children with mathematical disabilities (MD) compared to typically developing (TD) children. Children with MD showed hyper-connectivity between bilateral IPS and multiple dorsal frontal and parietal cortical regions, between bilateral IPS and right hemisphere SMG and STG, and between left IPS and right putamen. Greater connectivity for MD > TD in red (left IPS), blue (right IPS), and green (both left and right IPS). Coordinates are in MNI space. FP = frontal pole; IPS = intraparietal sulcus; SFG = superior frontal gyrus; SMG = supramarginal gyrus; SPL = superior parietal lobe; STG = superior temporal gyrus. (2) Greater fALFF in children with MD compared to TD children. fALFF = Fractional Amplitude of Low Frequency Fluctuations; MFG = middle frontal gyrus

Source: Adapted from *Developmental Science*, *19*(4): 613–631, Dietsje Jolles, Sarit Ashkenazi, John Kochalka, Tanya Evans, Jennifer Richardson, Miriam Rosenberg-Lee, Hui Zhao, Kaustubh Supekar, Tianwen Chen, and Vinod Menon, *Parietal Hyper-Connectivity, Aberrant Brain Organization, and Circuit-Based Biomarkers in Children with Mathematical Disabilities*. https://doi.org/10.1111/desc.12399.

Neuroanatomical basis of MD

A more general view of neurobiological deficits in MD, without the confounding effects of task performance, is provided by neuroanatomical investigations of gray and white matter (Rotzer, Kucian et al., 2008; Rykhlevskaia, Uddin et al., 2009; Kucian, Ashkenazi et al., 2014). As reviewed in the previous sections, the profile of aberrant functional activations varies considerably with the level of task difficulty, the type of operation performed, and the control task against which activations are compared. Gray and white matter integrity are crucial for all cognitive operations and systematic identification of anatomical deficits can provide concrete and convergent evidence for core areas of deficits in MD.

Decreased gray matter volume in multiple parietal, temporal, and occipital areas, including bilateral IPS, superior parietal lobule, FG, para hippocampal gyrus, hippocampus, and anterior temporal cortex areas that have been implicated in numerical problem-solving has been consistently reported in children and adolescents with MD (Rotzer, Kucian et al., 2008, Rykhlevskaia, Uddin et al., 2009; Ranpura, Isaacs et al., 2013) (Figure 6.1). One study reported reduced gray matter volume in superior parietal lobule, IPS, FG, para hippocampal gyrus, and right anterior temporal cortex as well as reduced structural connectivity in long-range white matter projection fibers linking the right FG with temporo-parietal cortex in children with MD (Figure 6.2) (Rykhlevskaia, Uddin et al., 2009). DTI studies also suggest a link between arithmetic skills and white matter integrity in left fronto-parietal tracts (Tsang, Dougherty et al., 2009), and in several tracts that directly pass through the IPS (Rykhlevskaia, Uddin et al., 2009; Li, Hu et al., 2013; Kucian, Ashkenazi et al., 2014). Additionally, deficits in the inferior fronto-occipital fasciculus and inferior and superior longitudinal fasciculus, tracts that link parietal and occipital cortex with the PFC have also been detected (Figure 6.3). Taken together, findings to date suggest that both gray matter reductions in posterior brain areas and weak integrity of white matter tracts linking them with the PFC are a potential locus of information processing deficits and learning in MD.

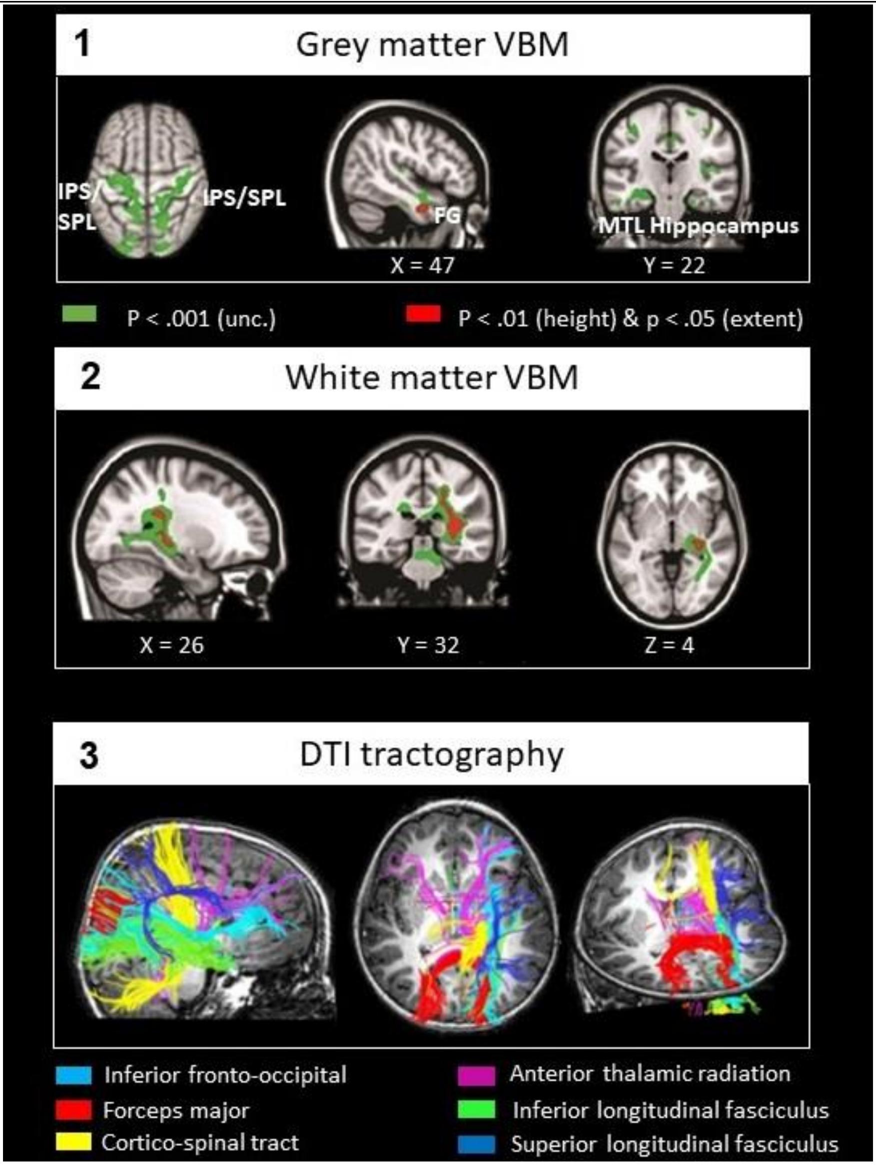

Figure 6. Gray and white matter deficits in MD. (1) Brain areas that show reduced gray matter volume in the MD group: bilateral superior parietal lobule (SPL), bilateral intra-parietal sulcus (IPS), lingual and fusiform gyri (FG), and hippocampus in the medial temporal cortex (MTL). (2) Reduced white matter volume in right temporal-parietal cortex in the MD group. (3) Lower fiber density in inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and caudal forceps major compared to typically developing children. The right panel depicts reduced connectivity in children with MD for long-range white matter projection fibers that link the right FG with temporal-parietal areas

Source: Adapted from Rykhlevskaia E, Uddin LQ, Kondos L, and Menon V (2009). Neuroanatomical correlates of developmental dyscalculia: Combined evidence from morphometry and tractography. *Frontal Human Neuroscience 3*:51. doi: 10.3389/neuro.09.051.2009. © 2009 Rykhlevskaia, Uddin, Kondos and Menon.

Interventions and remediation of cognitive deficits and math difficulties in MD

Behavioral findings

Cognitive interventions have been shown to be highly effective in improving math performance in children (Fuchs, Fuchs et al., 2013). Here, we review interventions that have targeted distinct math difficulties as well as general cognitive deficits in MD. Previous behavioral research has shown that interventions using speeded retrieval of number combinations together with conceptual number knowledge can significantly improve math skills in elementary school children (Christensen and Gerber, 1990; Okolo, 1992; Fuchs, Fuchs et al. 2002; Fuchs, Fuchs et al. 2004; Fuchs, Fuchs, Hamlet et al., 2006; Fuchs, Fuchs, Compton et al., 2006; Fuchs, Fuchs, Compton et al. 2007; Fuchs, Fuchs and Luther, 2007). Specifically, extensive research by Fuchs and colleagues have shown that interventions that directly target specific areas of math, such as the memorization of arithmetic facts (Fuchs, Powell et al., 2009; Powell, Fuchs et al., 2009), conceptual understanding of arithmetic procedures (Powell, Fuchs et al., 2009), and word problem-solving (Fuchs, Fuchs et al. 2004), can significantly improve numerical skills in children with MD. The most consistent evidence of training-related math gains comes from a series of studies using computer-assisted tutoring that taught children to recall simple math facts, with immediate feedback for improving problem-solving strategies. Training sessions typically consisted of 30 to 45 min sessions several times a week for about 3 months (Fuchs, Fuchs et al., 2013). This line of research has reported high rates of success as assessed by the number of children with MD who showed prolonged effects of intervention.

Studies focusing on improving number sense (Wilson, Revkin et al., 2006) and their spatial representation (Kucian, Grond et al., 2011) have also been shown to moderately improve math skills in MD. Children with MD who show deficits in elementary number knowledge may benefit from focused training in numerical magnitudes and mapping with number symbols during early school years, as suggested by a software-based training in 7–9-year-old children with MD (Wilson, Revkin et al., 2006). After training, children with MD also showed improvement in subtraction and symbolic as well as nonsymbolic number comparison (Wilson, Revkin et al., 2006). Similarly, in a sample of 8- to 10-year-old children with MD, programs designed to remediate immature mental number line improved spatial representation of numbers, and most importantly improved arithmetic skills (Kucian, Grond et al., 2011). Similarly, a computerized training focused on spatial number representations, arithmetic, and word problem-solving found improvement on number representations as well as arithmetic problem-solving (Rauscher, Kohn et al., 2016). These findings suggest that tapping into basic numerical and spatial skills can have generalizable effects on math performance.

Other remediation and training studies aimed at improving math learning in MD, or in TD individuals, have targeted general cognitive abilities such as attention (Ashkenazi and Henik, 2012), spatial skills (Uttal, Meadow et al., 2013), and finger representations, with mixed results. Using a video-game targeting attention orienting skills in adults with MD, Ashkenazi and Henik (2012) showed that although participants' attention improved after training, no transfer occurred on math skills. Cheng and Mix (2014) found that mental rotation training improved arithmetic problem-solving in TD children (Cheng and Mix, 2014). Another study that trained finger representation in children in 1st grade who showed poor finger gnosia resulted in improved symbolic and nonsymbolic skills (Gracia-Bafalluy and Noël, 2008), suggesting that improved finger gnosia can be a pathway for improving math skills in children with MD with visuo-motor deficits and profiles (Kinsbourne and Warrington, 1963).

Taken together, these studies also suggest that the remediation of poor math skills in children with MD might require focused training on different cognitive mechanisms. Cognitive factors influencing individual intervention gains may vary depending on overall cognitive abilities, age range targeted, the difficulty and modality of the training, and affective factors (Chodura, Kuhn et al., 2015; Powell, Cirino et al., 2017). Behavioral studies indicate that children with MD can benefit from structured interventions, but how these improvements occur and why some children are more responsive than others is not known (Fuchs, Fuchs et al. 2004; Griffin, 2007; Fuchs, Powell et al., 2008; Chodura, Kuhn et al., 2015). Neuroimaging studies might be useful to better characterize individual differences in response to intervention and tailor cognitive intervention to individual profiles of cognitive, numerical, as well as affective vulnerabilities. Interestingly, intervention studies focusing on arithmetic problem-solving in children have also reported improvement in cognitive and affective domains.

A noteworthy finding to emerge from these cognitive intervention studies is that tutoring designed to improve numerical problem-solving skills may also decrease math anxiety levels (Supekar, Swigart et al., 2013; Berkowitz, Schaeffer et al., 2015). Math anxiety involves negative emotions and stress in situations involving manipulation and reasoning about numerical problems in a wide variety of academic and life situations (Richardson and Suinn, 1972). The neural correlates of math anxiety have been investigated in adults (Lyons and Beilock, 2012a, 2012b) and in children (Young, Wu et al., 2012; Kucian, McCaskey et al., 2018). These studies point to increased activity in brain regions associated with emotion regulation in high math anxious individuals, in addition to a decrease in brain activity in fronto-parietal regions that support WM processes during problem-solving (Young, Wu et al., 2012). Moreover, right amygdala volume has been reported to be reduced in high math anxious children (Kucian, McCaskey et al., 2018). These findings suggest that affective factors contribute to problem-solving deficits in children with MD, and should be taken into account while designing interventions to remediate math skills in MD.

Neurobiological correlates

Several fMRI studies have now begun to examine the extent to which cognitive training alters aberrant functional activity and connectivity in relevant neurocognitive systems in MD. The effects of training can work either by normalizing deficits or by engagement of compensatory mechanisms to facilitate improved task performance.

Cognitive tutoring studies of speeded practice on math fact retrieval have shown that 8 weeks of 1:1 tutoring in 7–9-year-old children with MD can normalize aberrant functional brain responses to the level of TD peers (Iuculano, Rosenberg-Lee et al., 2015). Brain plasticity was evident not just in the

IPS, but in a distributed network of prefrontal, parietal, and ventral temporal-occipital brain areas important for numerical problem-solving (Figure 7.1). Remarkably, machine learning algorithms revealed that brain activity patterns in children with MD were significantly different from TD peers before tutoring, but statistically indistinguishable after tutoring (Figure 7.2). Crucially, findings did not provide evidence for a “compensatory” model of plasticity, which would posit that after training, children with MD would recruit additional and distinct brain systems compared to TD peers. Instead, these results indicate that intervention benefits were related to decreased load on prefrontal WM and dorsal attentional systems during arithmetic problem-solving.

Similarly, intervention studies involving mental number line training found increased recruitment of bilateral parietal areas, in parallel with decreased PFC activity, in children with MD after training as compared to before training (Kucian, Grond et al., 2011). Prefrontal and parietal activations in MD were more similar to TD peers after training. This type of training was additionally associated with normalization of brain hyperconnectivity between the IPS and other cortical areas to levels seen in TD individuals (Michels, O’Gorman et al., 2018).

Training-related studies have also demonstrated that plasticity of white-matter tracts as well as intrinsic functional circuits is associated with individual differences in math learning (Jolles, Supekar et al., 2016; Jolles, Wassermann et al., 2016). Using novel fiber tracking algorithms Jolles, Wassermann et al., 2016 identified sections of the superior longitudinal fasciculus linking frontal and parietal, parietal and temporal and frontal and temporal cortices. They found that individual differences in behavioral gains math after two months of tutoring were specifically correlated with plasticity in the left frontotemporal tract that connects posterior temporal and lateral prefrontal cortices, coursing through the PPC. This tract is well positioned to integrate symbolic, numerical, and control processing carried out by distributed brain regions (Arsalidou and Taylor, 2011). Notably, additional analyses showed that brain-behavior correlations were present for multiple behavioral measures associated with numerical cognition. Analysis of intrinsic functional connectivity data further showed that training also strengthened IPS connectivity with the lateral PFC, VTOC, and hippocampus. Crucially, increased IPS connectivity was associated with individual performance gains, highlighting the behavioral significance of plasticity in IPS circuits. Tutoring-related changes in IPS connectivity were distinct from those of the adjacent angular gyrus, which did not predict performance gains (Jolles, Supekar et al., 2016).

Overall, the results of cognitive training studies in children point to plasticity of multiple brain circuits associated with the development of more or less specialized math and cognitive skills. It is noteworthy that quantitative measures of brain function and intrinsic brain organization can provide a more sensitive endophenotypic marker of skill acquisition than behavioral measures. The development of robust brain-based biomarkers will be a significant step towards understanding children's predicted learning trajectories and may facilitate improved training and intervention programs.

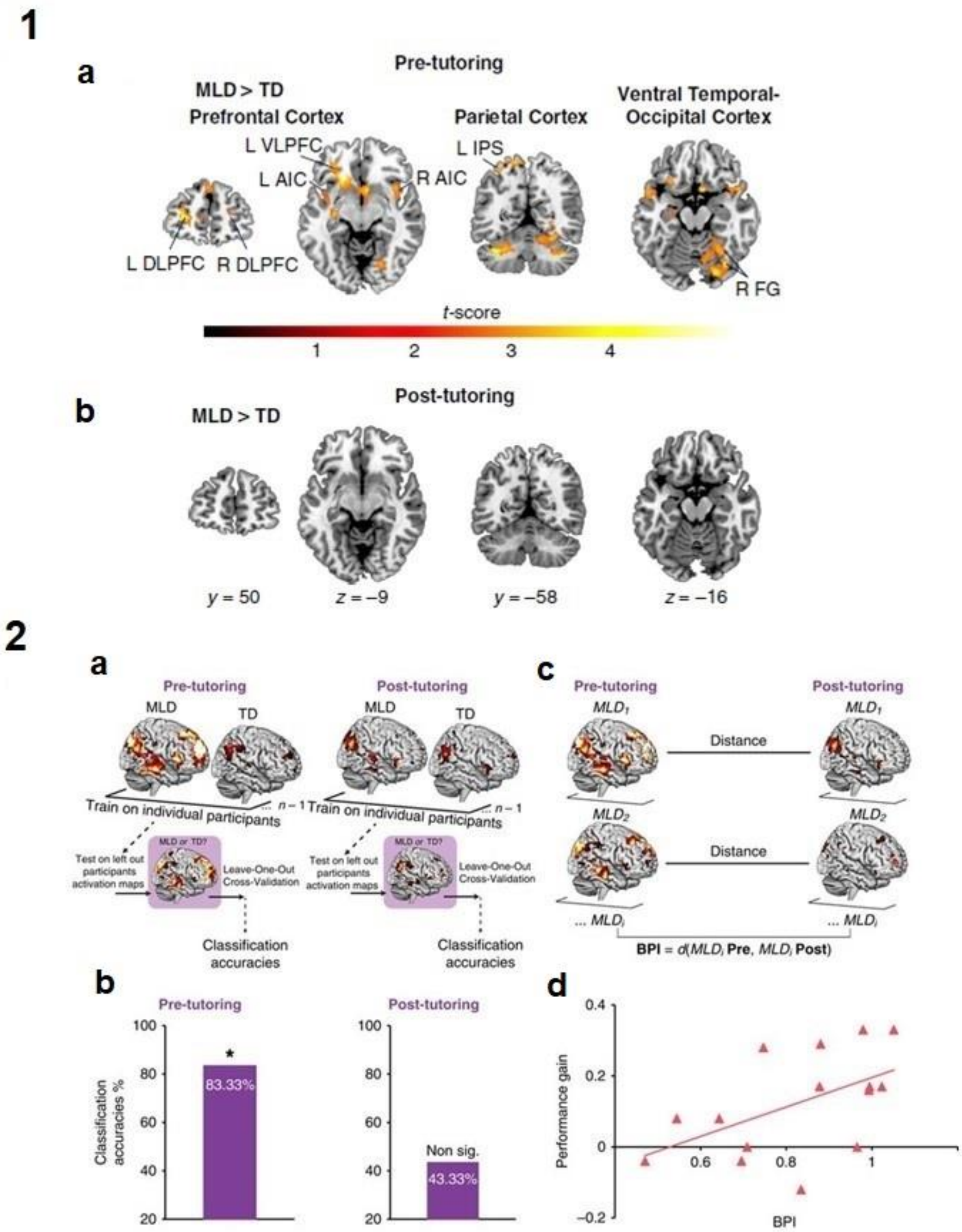

Figure 7. Cognitive training and neuroplasticity in MD. (1) Normalization of aberrant functional brain responses in children with MD after 8 weeks of math tutoring. (a) Before tutoring, children with MD showed significant differences in brain activation levels compared with TD children. Significant group differences were evident in multiple cortical areas in the Prefrontal Cortex, including the bilateral Dorsolateral Prefrontal Cortices (DLPFC), and the left Ventrolateral Prefrontal Cortex (VLPFC), as well as the bilateral Anterior Insular Cortices (AIC); in the Parietal Cortex encompassing the left Intraparietal Sulcus (IPS); and in the Ventral Temporal–Occipital Cortex including the right FG. (b) After 8 weeks of tutoring, functional brain responses in MD children (n=15) normalized to the levels of TD children. (2) Multivariate brain activity patterns-based classification of MD children and association with performance gains. (a) Classification Analysis flowchart. A linear classifier built using support vector machines (SVM) with Leave-One-Out Cross-Validation (LOOCV) was used to classify children with MD from TD children based on patterns of brain activation during arithmetic problem-solving, before and after tutoring. (b) Classification accuracies pre- and post-tutoring. Brain activation patterns

between MD and TD children during arithmetic problem-solving were significantly and highly discriminable before tutoring, while the groups were no longer discriminable by their patterns of brain activity after tutoring. (c) Brain Plasticity Index (BPI) in children with MD. A distance metric *d* was computed to quantify tutoring-induced functional brain plasticity effects pre-tutoring versus post-tutoring in children with MD. *d* was calculated individually for each MD child by computing a multivariate spatial correlation between pre- and post-tutoring patterns of brain activity, and subtracting it from 1. (d) Relation between tutoring-induced functional brain plasticity and performance gain. A significant positive correlation was observed between BPI and individual performance gains associated with tutoring in children with MD. Performance gain represents change in arithmetic problem-solving accuracy from pre- to post-tutoring

Source: Adapted from Teresa Iuculano, Miriam Rosenberg-Lee, Jennifer Richardson, Caitlin Tenison, Lynn Fuchs, Kaustubh Supekar, and Vinod Menon, Cognitive tutoring induces widespread neuroplasticity and remediates brain function in children with mathematical learning disabilities, *Nature Communications*, *6*(8453), https://doi.org/10.1038/ncomms9453, © 2015, The Authors. Licensed under CC BY 4. 0.

Conclusions and future directions

As with behavioral studies, our understanding of the neurobiology of MD is inherently constrained by criteria used to define the disorder. Despite this limitation, neurocognitive studies are revealing important new insights into brain and cognitive processes disrupted in MD.

We described multicomponent cognitive models of MD that have emerged from cognitive and neuroscience studies of numerical cognition in MD and TD individuals, emphasizing number sense and arithmetic problem-solving, the two major “domain-specific” aspects of information processing deficits in MD. This review has emphasized the role of “domain-general” deficits, most importantly visuospatial WM and cognitive control, which impact the ability to manipulate quantity, retrieve facts and resolve intrusion errors. In this view MD arises from a complex interplay between “domain-specific” and “domain-general” deficits that are implemented by overlapping brain circuits. While functional neuroimaging studies have overtly focused on the IPS as the locus of numerical information processing deficits in children with MD, it is now clear that individuals with MD show deficits in a distributed inter-connected set of brain regions that include the IPS and other parietal cortex regions, inferior temporal cortex, medial temporal lobe, and multiple PFC areas. Impairments in one or more of these brain regions and their associated brain circuits can compromise efficiency of numerical problem-solving skills and constitute risk factors for MD.

An important future research direction is the characterization of MD subtypes, including investigations of how impairments to different neurocognitive systems are related to weaknesses in math abilities. In this context, it will be crucial to investigate heterogeneity arising from co-occurring reading and attention deficits. Another important topic of ongoing research is to determine the extent to which brain networks supporting math learning are malleable, and the type of instruction that can target these networks at different developmental periods. Due to the challenges associated with neuroimaging studies of heterogeneous learning disabilities, these efforts will benefit from future multi-site studies. Finally, stronger interdisciplinary collaborations between psychology, education and neuroscience is needed to advance diagnosis and remediation of MD in affected children.

Acknowledgments

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