CHAPTER

15

Systems Neuroscience of Mathematical Cognition and Learning: Basic Organization and Neural Sources of Heterogeneity in Typical and Atypical Development

Teresa Iuculano, Aarthi Padmanabhan, Vinod Menon

Stanford University, Stanford, CA, United States

OUTLINE

Heterogeneity of Function in Numerical Cognition
https://doi.org/10.1016/B978-0-12-811529-9.00015-7

INTRODUCTION

Mathematical skill acquisition is hierarchical in nature, and each iteration of increased proficiency builds on knowledge of a lower-level *primitive*. For example, learning to solve arithmetical operations such as "3+4" requires first an understanding of what numbers mean and represent (e.g., the symbol "3" refers to the quantity of three items, which derives from the ability to attend to discrete items in the environment). Thus, all forms of mathematical cognition, from basic to complex, require proficiency in a fundamental system of "*number sense*," including elemental properties of numbers, principles of cardinality, numerosity as abstract representations of sets, and the axiomatic rules by which numerical quantity is manipulated (Dantzig, 1930; Dehaene, 1997). The brain systems supporting mathematical cognition parallel these behavioral constructs and function as a set of (partly) hierarchically organized and dynamically interacting systems. Each brain system subserves specific perceptual and cognitive processes, including visual and auditory processing, quantity processing, working memory, declarative memory, attention, and cognitive control (Fig. 15.1). Importantly, the topology of brain systems engaged during mathematical cognition varies considerably not only across individuals but also with learning and development, as individuals gain proficiency in mathematical skills.

The basic building blocks of mathematical cognition, which are learned early in a child's development, include understanding numerical magnitude and the ability to manipulate symbolic and nonsymbolic quantity ("*number sense*"). Human imaging studies using electroencephalography

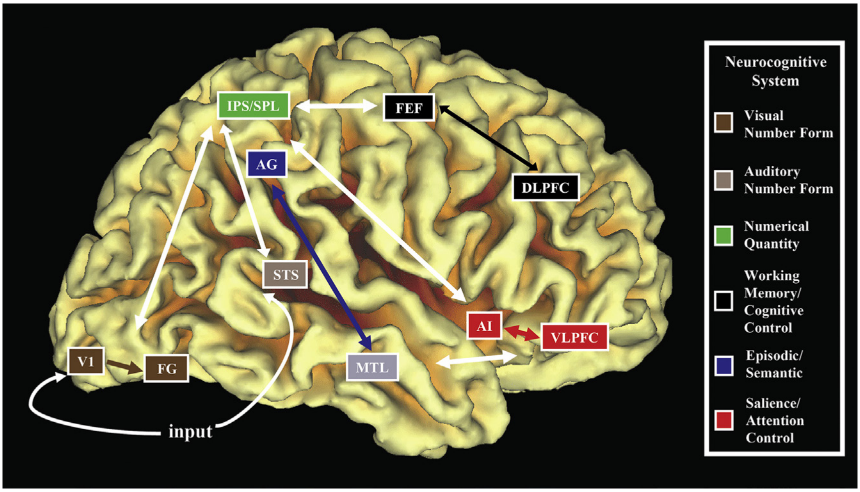


FIGURE 15.1 **Schematic circuit diagram of brain regions involved in mathematical learning and cognition.** The fusiform gyrus (FG) in the ventral temporal-occipital cortex decodes visual number form and together with the intraparietal sulcus (IPS) in the posterior parietal cortex (PPC)—which helps build visuospatial representations of numerical quantity (shown in *green boxes*)—forms the building blocks of mathematical cognition. The superior temporal sulcus (STS) aids in decoding auditory number words. Multiple parietal-frontal circuits link the IPS with working memory and cognitive control systems that include the frontal eye field (FEF), and the dorsolateral prefrontal cortex (DLPFC). 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 short periods (i.e., several seconds). The declarative memory system anchored in the medial temporal lobe (MTL)—and particularly the hippocampus—plays an important role in long-term memory formation and generalization beyond individual problem attributes. Finally, ventral prefrontal control circuits (shown in red) anchored in the anterior insula (AI) and ventrolateral prefrontal cortex (VLPFC) serve as flexible *hubs* for integrating information across attentional and memory systems, thereby facilitating goal-directed problem-solving and decision-making during mathematical cognition. Relative transparency for MTL indicates subsurface cortical structure. *Adapted from: Fias et al., 2013*, Trends in Neuroscience and Education © *2013 by Elsevier.*

and functional magnetic resonance imaging (fMRI) have shown that these building blocks are subserved by specific and interacting brain systems (Fig. 15.1). First, visual and auditory association cortices decode the visual form (e.g., visual shape of the symbol "3") or phonological feature (e.g., the word "three") of numerical stimuli. Next, the fusiform gyrus (FG) in the higher-level visual cortex (i.e., ventral temporal–occipital cortex) plays an important role in visual object recognition and in forming relevant representations of symbolic stimuli. As the child begins to learn the use of orthographic symbols (i.e., written symbols and number words), new representations for these visual stimuli are developed in the FG (Allison, McCarthy, Nobre, Puce, & Belger, 1994; Ansari, 2008; Dehaene, Molko, Cohen, & Wilson, 2004; Park, Hebrank, Polk, & Park, 2012; Shum et al., 2013). Simultaneously, the superior temporal sulcus (STS) and middle temporal gyrus (MTG) are involved in forming representations of number words (Thompson, Abbott, Wheaton, Syngeniotis, & Puce, 2004). The parietal attention system helps build semantic representations of quantity (Ansari, 2008) from multiple low-level *primitives* (Box 15.1), including the ability to attend to and individuate individual objects in space, and the ability to perceive the numerosity of such objects (i.e., "oneness," "threeness"). These low-level *primitives* are processed in the posterior parietal cortex (PPC), particularly in its intraparietal sulcus (IPS) subdivision and are established many years before a child learns to process numerical symbols and number words (Hyde, Boas, Blair, & Carey, 2010). Taken together, the perceptual and cognitive brain systems that underlie "*number sense*" come on line early in development, providing a critical foundation for the acquisition of later mathematical skills.

BOX 15.1

GLOSSARY

Systems Neuroscience: refers to a subdiscipline of neuroscience and systems biology, which studies the function of brain circuits and systems. It concerns the study of brain regions and their function during a task and their interaction with other—proximal and distal—brain regions and the derived neural systems/networks.

Primitives: refer to a core set of cognitive capacities—pertinent to the intended domain—that can be utilized and integrated to develop higher-order cognitive capacities.

Schema of knowledge: refers to a cognitive construct that helps to organize categories of information and the relationship between them.

Hub: refers to a central structure within a network.

Distance effect: refers to the measurable behavior—assessed by accuracy and reaction time—which instantiates that it is harder to discriminate two sets of items as their distance decreases. It is more difficult to compare 8 versus 9—i.e., distance of 1 unit—than it is to compare 8 versus 5—i.e., distance of 3 units.

Neural distance effect: refers to the neural correlate of the *distance effect*, such that functional activation in dedicated brain regions is greater when the numerosities to be compared have a smaller distance (i.e., 8 vs. 9), compared to a larger distance (i.e., 8 vs. 5).

Proficiency in mathematics includes learning not only how to perceive and process (i.e., represent) numerical information but also to manipulate it, which requires engagement of multiple neurocognitive networks in the brain (Fig. 15.1). First, frontoposterior parietal brain circuits underlying working memory processes support the online manipulation of discrete quantities (e.g., individual objects) by creating short-term representations of such quantities and to help solve more complex problems (Metcalfe, Ashkenazi, Rosenberg-Lee, & Menon, 2013). Second, the prefrontal cortex (PFC) helps guide and maintain attention in the service of goal-directed problem-solving and cognitive control. Third, the medial temporal lobe (MTL) memory system, anchored in the hippocampus, plays an important role in long-term memory formation, and consolidation of mathematical concepts (i.e., arithmetical facts) and generalizations beyond individual problem attributes within a broader *schema of knowledge* (Box 15.1) (Davachi, 2006; Davachi, Mitchell, & Wagner, 2003). Together, these systems provide necessary cognitive scaffolding and play varying roles in mathematical skill acquisition throughout learning and development.

Considerable heterogeneity of mathematical proficiency in both children and adults is well documented, with some individuals demonstrating remarkable abilities (Cowan & Carney, 2006; Cowan & Frith, 2009; Cowan, O'Connor, & Samella, 2003; Iuculano et al., 2014; Pesenti, Seron, Samson, & Duroux, 1999; Pesenti et al., 2001) and others showing marked deficits (Butterworth, 2005, pp. 455–467; Butterworth & Kovas, 2013; Butterworth & Reigosa-Crespo, 2007, pp. 65–81; Butterworth, Varma, & Laurillard, 2011; Iuculano, Tang, Hall, & Butterworth, 2008; Kucian & von Aster, 2015; Landerl, Bevan, & Butterworth, 2004; Rousselle & Noel, 2007). This heterogeneity in mathematical abilities is likely due, in part, to variability in learning and brain plasticity throughout development. Importantly, aberrant plasticity of the brain systems described above (Fig. 15.1) is thought to underlie the pathogenesis of learning disabilities specific to mathematics or otherwise referred to as mathematical learning disabilities (MLD) (DSM-V Association, 2013). Thus, the study of typical and atypical neurocognitive development and plasticity provides a unique opportunity to help characterize sources of heterogeneity in mathematical learning.

This chapter synthesizes the extant literature on functional brain circuits underlying "*number sense*" and scaffolding of mathematical cognition and learning in children and adults, with a focus on sources of heterogeneity in typical and atypical development. We take a *systems neuroscience approach* (Box 15.1) to elucidate sources of heterogeneity arising from multiple distributed neural circuits critical for number form identification, magnitude and quantity representations, working memory, declarative memory, attention, and cognitive control (Fig. 15.1) (Arsalidou & Taylor, 2011; Fias, Menon, & Szucs, 2013; Qin et al., 2014). We conclude by highlighting directions for future research.

VENTRAL AND DORSAL VISUAL STREAMS: NEURAL BUILDING BLOCKS OF MATHEMATICAL COGNITION

Basic Organization

The cognitive building blocks of "*number sense*" are constructed from local and global functional circuits anchored in the FG and the IPS, which are considered *hub* (Box 15.1) regions within the ventral and dorsal visual streams, respectively (Figs. 15.1 and 15.2A,a,b). Specifically, these *hub* regions code perceptual and semantic representations of nonsymbolic and symbolic quantities and facilitate their dynamic manipulation in a context-dependent manner (Ansari, 2008).

The FG, which is located in the ventral temporal–occipital cortex, plays an essential role in high-level visual object recognition (Gauthier, Skudlarski, Gore, & Anderson, 2000; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Goodale & Milner, 1992; Grotheer, Herrmann, & Kovacs, 2016; Holloway, Battista, Vogel, & Ansari, 2012; Shum et al., 2013; Wimmer, Ludersdorfer, Richlan, & Kronbichler, 2016) and in forming an automated representation of number forms. The IPS, which is located within the dorsal aspects of the PPC, is thought to synthesize incoming information from both visual and auditory modalities (Vogel et al., 2017). With the support of these two key neurocognitive systems, the human brain builds more complex mathematical problem-solving skills. In the following section, we describe the neurocognitive functions of IPS and FG systems and their relative roles in basic number processing.

FG regions, which are proximal to the visual word form area of the ventral temporal–occipital cortex (McCandliss, Cohen, & Dehaene, 2003; Saygin et al., 2016), show strong responses to numerical symbols in both adults and children (Ansari, 2008; Cantlon et al., 2009; Grotheer et al., 2016; Holloway et al., 2012; Shum et al., 2013) (Fig. 15.2A,b). Furthermore, intracranial electrophysiological recordings suggest that distinct subdivisions of the FG may be differentially sensitive to number stimuli compared with perceptually similar letters and nonword stimuli (Shum et al., 2013) (Fig. 15.2A,b), suggesting a unique role of the FG in perceptual decoding of numerical digits. Involvement of the FG in numerical judgment and manipulation of quantity, not just perception, is also supported by the fact that the FG, like the IPS, also exhibits *neural distance effects* (Box 15.1) during symbolic comparisons of numerical digits (Fig. 15.2A,c) (Vogel et al., 2017).

The IPS plays a crucial role in numerical quantity judgments in both adults and children (Cantlon et al., 2009; Cutini, Scatturin, Basso Moro, & Zorzi, 2014; Heine, Tamm, Wissmann, & Jacobs, 2011; Hyde & Spelke, 2009; Kucian, von Aster, Loenneker, Dietrich, & Martin, 2008; Piazza, Mechelli,

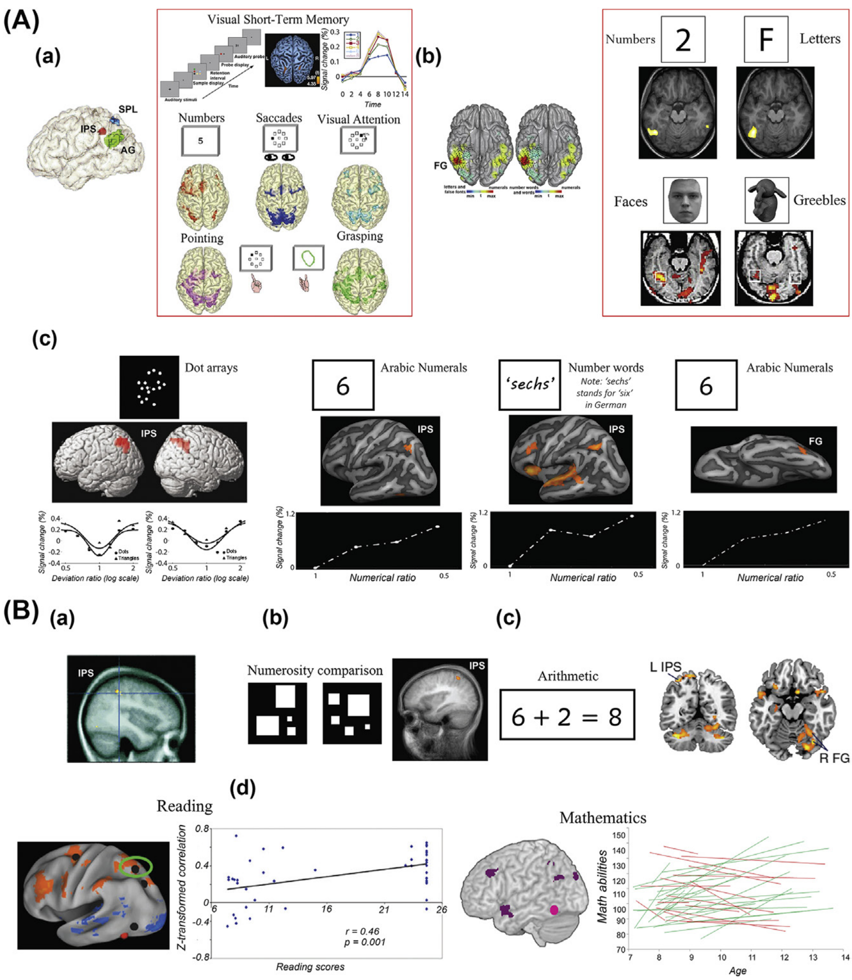


FIGURE 15.2 **Neural building blocks of mathematical cognition and learning. (A)** Basic organization. **(a)** Posterior parietal cortex. Regions of the intraparietal sulcus (IPS), superior parietal lobe (SPL), and angular gyrus (AG) implicated in numerical representations and arithmetic overlap anatomically with (***Square-top***) regions of the visual short-term memory (vSTM) system during a probe-matching (i.e., color and position) short-term memory; (***Square-bottom***) regions of the IPS that show significant functional activation for several cognitive tasks, including number comparisons, visual saccades and visual attention, pointing, and grasping; **(b)** Ventral temporal–occipital cortex. The fusiform gyrus (FG) shows preferential gamma-band responses to numerals; the FG shows significant functional activation for several stimulus categories, including numbers and letters (***Square-top***), as well as faces and complex shapes (***Square-bottom***); **(c)** Symbolic *distance effects* in the IPS and FG. **IPS**: distance/ratio effects in the bilateral parietal IPS for nonsymbolic numerical stimuli (i.e., dot arrays) (***Left***); symbolic numerical stimuli (i.e., Arabic digits) (***Middle***); "sechs" is German for "six" (***Right***). **FG**: distance/ratio effects in the FG for symbolic numerical stimuli (i.e., Arabic digits). **(B)** Heterogeneity of skills. **(a)** Reduced gray matter volume in the IPS of adolescents of low birth weight and with mathematical learning disabilities (MLD); **(b)**

Butterworth, & Price, 2002). Specifically, the IPS is engaged when a child or an adult is asked to select stimuli based on their numerosity (e.g., select the largest between two sets of stimuli—one containing 4, the other containing 5 items). Within the context of such cognitive computations, the IPS has been shown to be sensitive to the numerical distance between the nonsymbolic quantities to be compared, either when they are presented as discrete (Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004) (Fig. 15.2A,c) or analog forms (Vogel, Grabner, Schneider, Siegler, & Ansari, 2013) (i.e., the *neural distance effect*—see Box 15.1). The IPS is also strongly modulated by the numerical distance of symbolic representations and number words (Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007; Hinton, Dymond, von Hecker, & Evans, 2010; Naccache & Dehaene, 2001) (Fig. 15.2A,c) (i.e., the *neural distance effect*—see Box 15.1). Although the IPS was initially considered solely a "*number module*" in the brain (Butterworth, 1999, 2010; Dehaene, 2003; Dehaene & Cohen, 1995), it is now widely accepted that the IPS is also critical for a broad class of related processes, including spatial attention, individuation, pointing of objects in extrapersonal space (Schaffelhofer & Scherberger, 2016; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002), and encoding object locations into visual short-term memory (vSTM) storage (Knops, Piazza, Sengupta, Eger, & Melcher, 2014; Luck & Vogel, 2013; Todd & Marois, 2004) (Fig. 15.2A,a). This is likely due to its widespread connectivity (Vogel, Miezin, Petersen, & Schlaggar, 2012) with multiple prefrontal and parietal systems (Fig. 15.3A,a,b). Taken together, these

functional aberrancies in the IPS of 10- to 12-year-old children with MLD during a nonsymbolic numerosity comparison task; **(c)** functional aberrancies in the IPS and FG of 7- to 9-year-old children with MLD during an arithmetic task; **(d)** ventral and dorsal stream intrinsic connectivity strengthens the link between orthographic symbols and semantic representations in reading (***Left***) and math (***Right***). ***Left***: significant relationship between reading scores and FG to left anterior IPS connectivity during resting. Dorsal stream regions in orange and ventral stream regions in blue. Regions of interest in black. ***Right***: Functional connectivity patterns with the FG predict gains in mathematical skills over development. FG seed region in pink and functional connectivity maps in purple (including the dorsal IPS). ***(A,a)*** *Modified from:* *Dehaene et al., 2003*, Cognitive Neuropsychology *© 2003 by Taylor & Francis; Adapted from:* *Todd & Marois, 2004*, Nature *© 2004 by NPG; Adapted from:* *Simon et al., 2002*, Neuron *© 2002 by Cell Press.* ***(A,b)*** *Adapted from:* *Shum et al., 2013*, Journal of Neuroscience *© 2013 by SfN; Adapted from:* *Grotheer et al., 2016*, Journal of Neuroscience *© 2016 by SfN; Adapted from:* *Gauthier et al., 1999*, Nature Neuroscience *© 1999 by NPG.* ***(A,c)*** **Left**: *Adapted from:* *Piazza et al., 2004*, Neuron *© 2004 by Elsevier; Adapted from:* *Vogel et al., 2017*, Neuroimage *© 2017 by Elsevier;* **Far right**: *Adapted from:* *Vogel et al., 2017*, Neuroimage *© 2017 by Elsevier.* ***(B,a)*** *Modified from:* *Isaacs et al., 2001*, Brain *© 2001 by Oxford University Press;* ***(B,b)*** *Based on:* *Price et al., 2007*, Current Biology *© 2001 by Cell Press;* ***(B,c)*** *Based on:* *Iuculano et al., 2015*, Nature Communications *© 2015 by NPG.* ***(B,d)*** **Left**: *Modified from:* *Vogel et al., 2012*, Cerebral Cortex *© 2015 by NPG;* **Right**: *Modified from:* *Evans et al., 2015*, Journal of Neuroscience *© 2015 by SfN.*

findings suggest that the IPS builds a modal representations of quantity through neural substrates that overlap with those that serve other cognitive functions such as vSTM and attention.

Importantly, the IPS and FG do not function independently, with evidence suggesting that functional connections between dorsal and ventral streams are important for making links between visual-orthographic items and their semantic representations (Jeong & Xu, 2016; Vogel et al., 2012). Together this body of evidence suggests that both the FG and IPS and their interactions help create neural representations for symbolic form and the quantities they represent.

Heterogeneity in Typical and Atypical Development

As described in the section above, although the basic roles of the IPS and FG in "*number sense*" are well characterized in both children and adults (Ansari, 2008; Cantlon, Brannon, Carter, & Pelphrey, 2006), considerable heterogeneity exists within and across developmental groups in the function and interaction of these brain systems. With learning and development there are increased and more refined interactions between these brain systems, which gradually support proficiency and automatization of mapping between Arabic digits and quantity representations (Fan, Anderson, Davis, & Cutting, 2014; Vogel et al., 2012, 2013).

Marked heterogeneity in mathematical cognition and learning is apparent in the widespread prevalence and persistence of domain-specific learning disabilities (Butterworth et al., 2011; Shalev, Auerbach, Manor, & Gross-Tsur, 2000; Shalev, Manor, & Gross-Tsur, 2005; Szucs & Goswami, 2013) and in genetic developmental syndromes, such as Turner syndrome (TS) and Fragile X syndrome, which present significant difficulties in numerical problem-solving. Early research has consistently pointed to the IPS as a locus of dysfunction in these populations (Isaacs, Edmonds, Lucas, & Gadian, 2001; Molko et al., 2003; Price, Holloway, Rasanen, Vesterinen, & Ansari, 2007) (Fig. 15.2B,a,b,c). Specifically, lack of functional modulation during numerical judgment tasks (Price et al., 2007) and decreased gray matter density in the IPS have been reported in individuals with TS (Molko et al., 2003, 2004), Fragile X (Rivera, Menon, White, Glaser, & Reiss, 2002), as well as children (Price et al., 2007; Rotzer et al., 2008) and adolescents with MLD (Isaacs et al., 2001) (Fig. 15.2B,a,b). Furthermore, Cohen Kadosh et al. were able to induce MLD-like symptoms (i.e., reduced automaticity for processing numerical information) in a group of neurotypical adults by applying fMRI-guided transcranial magnetic stimulation over the right PPC adjoining the IPS (Kadosh et al., 2007). Functional aberrancies in the activity of the IPS and the FG have also been reported during arithmetic problem-solving tasks in MLD (Iuculano et al., 2015; Rosenberg-Lee et al., 2014) (Fig. 15.2B,c). Moreover, it has been shown that intrinsic connectivity between the FG and IPS is positively associated with mathematical skills over development (Evans et al., 2015) (Fig. 15.2B,d). This is consistent with the notion that ventral to dorsal stream connectivity is essential for the successful mapping between orthographic symbols and their semantic representations. This is a key milestone for efficient development of mathematical skills, as well as other complex and uniquely human cognitive tasks, such as reading (Vogel et al., 2012) (Fig. 15.2B,d).

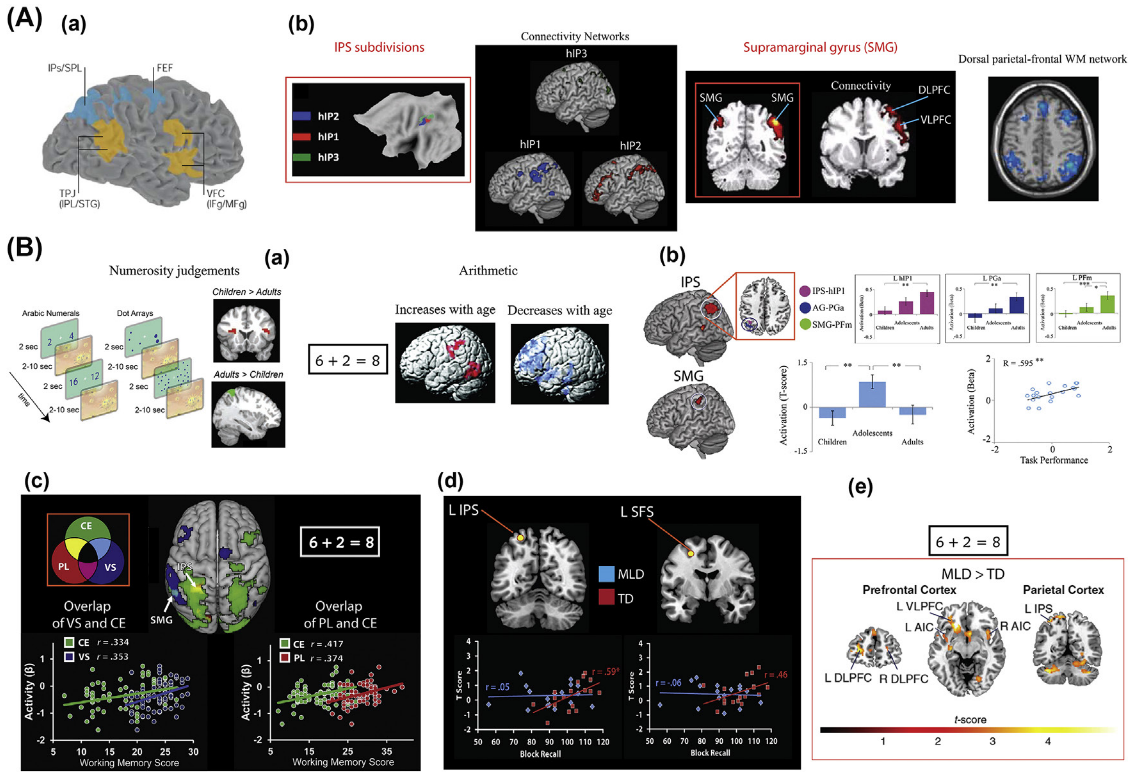
As reviewed in the subsequent sections, it is increasingly clear that some forms of MLD may arise from aberrant circuits encompassing the PFC, parietal, and MTL along with the FG and IPS (Fig. 15.1). A *systems neuroscience approach* naturally leads to the proposal that heterogeneous development and outcomes in mathematical learning and cognition are the result of differences in the functional and structural architecture of these multiple functional brain systems (Fias et al., 2013; Menon, 2014).

PARIETAL-FRONTAL SYSTEMS: SHORT-TERM AND WORKING MEMORY

Basic Organization

In the previous section, we synthesized converging evidence that the IPS plays a central role in representing and manipulating numerical quantities. We also highlighted evidence that the IPS is involved in a broader class of cognitive processes that support such quantity judgments and numerical representations. These include spatial attention (Simon et al., 2002) and encoding object locations into vSTM storage (Knops et al., 2014; Luck & Vogel, 2013; Todd & Marois, 2004). For example, IPS activity is enhanced during vSTM tasks during which participants are asked to remember the spatial location of objects (Todd & Marois, 2004) (Fig. 15.2A,a). Moreover, IPS regions that are engaged during vSTM tasks overlap with regions that are activated during enumeration tasks (Knops et al., 2014), highlighting the close correspondence between these two cognitive functions. Critically, the IPS is part of an intrinsically connected dorsal frontoparietal system that includes the superior parietal lobe (SPL) and frontal eye fields (FEFs) (Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008) (Fig. 15.3A,a) for online tracking of items in space.

Other cytoarchitectonic subdivisions of the parietal cortex, including the supramarginal gyrus (SMG), are more intrinsically connected



(A) (a)
IPs/SPL
FEF
TPJ (IPL/STG)
VFC (IFg/MFg)
(b)
IPS subdivisions
hIP2
hIP1
hIP3
Connectivity Networks
hIP3
hIP1
hIP2
Supramarginal gyrus (SMG)
SMG
SMG
Connectivity
DLPFC
VLPFC
Dorsal parietal-frontal WM network
(B)
Numerosity judgements
(a)
Arabic Numerals
Dot Arrays
2 sec
2-10 sec
time
Children > Adults
Adults > Children
6 + 2 = 8
Arithmetic
Increases with age
Decreases with age
(b)
IPS
SMG
IPS-hIP1
AG-PGa
SMG-PFm
L hIP1
L PGa
L PFm
Children
Adolescents
Adults
Activation (T-score)
Activation (Beta)
R = .595 **
Task Performance
(c)
CE
PL
VS
Overlap of VS and CE
IPS
SMG
6 + 2 = 8
Overlap of PL and CE
CE r = .334
VS r = .353
CE r = .417
PL r = .374
Activity (β)
Working Memory Score
(d)
L IPS
L SFS
MLD
TD
r = .05
r = .59*
r = -.06
r = .46
T Score
Block Recall
(e)
6 + 2 = 8
MLD > TD
Prefrontal Cortex
Parietal Cortex
L VLPFC
L AIC
R AIC
L IPS
L DLPFC
R DLPFC
t-score

FIGURE 15.3 **Parietal-frontal working memory systems for mathematical cognition and learning. (A)** Basic organization. **(a)** Schematic model of dorsal and ventral frontoparietal networks. Areas in blue indicate the dorsal frontoparietal network encompassing the intraparietal sulcus (IPS), superior parietal lobe (SPL), and the frontal eye field (FEF). Areas in orange indicate the ventral frontoparietal network encompassing the temporoparietal junction (TPJ), inferior parietal lobe (IPL), and superior temporal gyrus (STG), as well as ventral frontal cortex (VFC), inferior frontal gyrus (IFG), and middle frontal gyrus (MFG). The IPS–FEF network is involved in top-down control of visual processing. The TPJ–VFC network is involved in stimulus-driven control; **(b)** Parietal-circuits connectivity. ***Left***: Functional connectivity of horizontal segments of the IPS subdivisions. Seed Regions of Interest (ROIs) derived from cytoarchitectonic maps for hIP1 (blue), hIP2 (red), and hIP3 (green). Colors on brain rendering surface represent voxels correlated with each seed-ROI. ***Right***: Supramarginal gyrus (SMG) connectivity with dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC)—obtained by independent component analysis—forms the dorsal–parietal–frontal working memory (WM) network (***Far right***). **(B)** Heterogeneity of skills. **(a)** Frontoparietal shift. ***Left***: Statistical comparison of 6- to 7-year-olds and adults during numerosity tasks with symbolic and nonsymbolic stimuli. Children show greater prefrontal cortex (PFC) activation compared with adults (shown in red); whereas adults show greater activation in the intraparietal sulcus (IPS) compared with children (shown in green). ***Right***: Brain areas where activity during arithmetic problem-solving increases or decreases with age. Increases are evident in the supramarginal gyrus (SMG) and in the ventral temporal–occipital cortex (VTOC) (shown in red); whereas decreases are seen in the lateral PFC and superior and middle temporal gyri (shown in blue); (b) Developmental trajectories of parietal circuits. ***Top***: Cytoarchitectonic probabilistic labeling indicates that functional activations during arithmetic problem-solving in ventral lateral subdivisions of the IPS (hIP1), anterior angular gyrus-PGa (AG-PGa), and the posterior subdivision of the supramarginal gyrus (SMG-PFm) show linear increases from childhood to adulthood. ***Bottom***: Activation in the left anterior SMG showed an inverted U-shaped profile across age groups. Greater SMG-PF activation was correlated with task performance in adolescents only; **(c)** Neural overlap between the central executive (CE) and visuospatial (VS) components of WM was observed only in the left SMG, whereas overlap between the CE and phonological loop (PL) components was observed only in the left IPS; no overlap was observed between VS and PL WM components. *Scatterplots*. ROIs characterized by overlap in correlations of activity and individual WM components show significant correlations with WM scores; **(d)** Relation between functional brain activity during arithmetic problem-solving and visuospatial working memory abilities in *a-priori*-defined frontoparietal ROIs: the IPS and the superior frontal sulcus (SFS). Typically developing (TD) children show a significant relationship between visual WM abilities and activity in these brain regions, whereas children with mathematical learning disabilities (MLD) do not; **(e)** Children with MLD show significantly greater activation than TD children in regions of the parietal-frontal network, including the bilateral DLPFC, left VLPFC, left insular cortex, and right IPS during an arithmetic problem-solving task. ***(A,a)** Modified from:* *Corbetta & Shulman, 2002*, Nature Reviews Neuroscience *© 2002 by NPG.* ***(A,b)*** **Left***: Modified from:* *Uddin et al., 2010*, Cerebral Cortex *© 2010 by Oxford University Press;* **Right***: Adapted from:* *Sridharan et al., 2008*, PNAS *© 2008 by The National Academy of Sciences of the USA.* ***(B,a)*** **Left***: Modified from:* *Cantlon et al., 2009*, Journal of Cognitive Neuroscience *© 2009 by MIT Press and the Cognitive Neuroscience Institute;* **Right***: Modified from:* *Rivera et al., 2005*, Cerebral Cortex *© 2005 by the Oxford University Press.* ***(B,b)** Adapted from:* *Chang et al., 2015*, Neuroimage *© 2015 by Elsevier.* ***(B,c)** Modified from:* *Metcalfe et al., 2013*, Developmental Cognitive Neuroscience *© 2013 by John Wiley & Sons, Inc.* ***(B,d)** Modified from:* *Ashkenazi, Rosenberg-Lee et al. (2013)*, Neuropsychologia *© 2013 by Elsevier.* ***(B,e)** Modified from:* *Iuculano et al., 2015*, Nature Communications *© 2015 by NPG.*

to the supplementary motor area, anterior insula, and dorsolateral PFC (DLPFC) (Bressler & Menon, 2010; Sridharan, Levitin, & Menon, 2008; Uddin et al., 2010) (Fig. 15.3A,b), and support active storage and manipulation of contents in working memory (Menon, 2016). During successful mathematical learning, updating procedures such as repeated counting aid the encoding of arithmetic facts in long-term memory (Ashcraft, 1982; Groen & Parkman, 1972; Siegler & Shrager, 1984, pp. 229–293). For example, when counting on from 5 to 7 to solve the problem "5 + 2," an association is dynamically formed between the correct solution (i.e., "7") and its addends ("5" and "2"). After many repetitions, children are able to directly retrieve the answer from memory when presented with the problem (Siegler & Shrager, 1984, pp. 229–293). In this way, working memory processes support the successful encoding of information of numerical content into long-term memory. Two distinct working memory circuits, anchored in the IPS and SMG, support this process by tracking and manipulating numerical information over multiple time scales (Menon, 2016).

Heterogeneity in Typical and Atypical Development

Heterogeneity in the function of parietal–frontal working memory systems is the most apparent and insightful in the context of development (Menon, 2014). In childhood, even the most basic numerical computations require high working memory resources because mathematical problems and numerical computations need to be broken down into elemental components. It is important to note that working memory resources are still necessary in adulthood, especially when learning new concepts, or when mathematical computations become more complex (e.g., arithmetic operations with multidigits, which involve carrying and borrowing) (DeStefano & LeFevre, 2004; Imbo, Vandierendonck, & Vergauwe, 2007). Here, we focus on developmental changes at the brain level that are related to arithmetic learning during early schooling as this has been more extensively studied in the context of mathematical skill acquisition. We anticipate that this framework might translate to more complex arithmetical operations that occur later during development (see, for example, Stocco & Anderson, 2008 on the role of the prefrontal working memory system in the online manipulation of arithmetic facts during algebraic equations).

Developmentally, an anterior-to-posterior neural shift occurs as specialized regions of the PPC overtake the cognitive processes that were required by the PFC during childhood. A seminal study reported that relative to adults, children tend to engage the PPC less and the PFC more, when solving simple arithmetic problems—such as 3 + 4—reflecting higher demands on working memory processes (Rivera, Reiss, Eckert, & Menon, 2005) (Fig. 15.3B,a). This pattern of age-related engagement of the PFC extends to more elemental, nonsymbolic processing as well; while 6- and 7-year-old children engaged the bilateral inferior frontal gyrus (IFG) and adjoining insular cortex during a nonsymbolic magnitude discrimination task, young adults (24-years-olds) engage the PPC (Fig. 15.3B,a) (Cantlon et al., 2009). Other evidence suggests that children (9–11 years) show modulation of brain activity as a function of problem complexity (i.e., the *neural distance effect*) (see Box 15.1) in the PFC, including the DLPFC, precentral gyrus, and the inferior frontal gyrus, whereas young adults (19–21 years) exhibit this *neural distance effect* only in the IPS (Ansari & Dhital, 2006; Ansari et al., 2005). Taken together, these findings suggest that with learning and development, more precise representations are built within the PPC, thus "freeing up" prefrontal working memory resources.

As noted in basic organization section, the IPS and SMG are associated with distinct working memory circuits. Notably, these circuits show heterogeneous age- and ability-related patterns in their functional organization. A recent cross-sectional study with three age-cohorts (children, adolescents, and adults) found that, while engagement of the bilateral ventral IPS increased linearly with age (Fig. 15.3B,b***; top part***), a left anterior subdivision of the SMG (SMG-PF) showed an inverted U-shaped age-related profile, such that adolescents exhibited greater activation than children and young adults (Fig. 15.3B,b***; bottom part***). Furthermore, greater SMG-PF activation was associated with task performance only in adolescents (Fig. 15.3B,b***, bottom part***) and adolescents also showed greater task-related functional connectivity of the SMG-PF with ventro-temporal, anterior temporal, and prefrontal cortical regions, relative to children and adults (Chang, Metcalfe, Padmanabhan, Chen, & Menon, 2016). These results suggest that nonlinear upregulation of the SMG and its interconnected functional circuits facilitates adult-level performance in adolescents. Importantly, this study provides fine-grained evidence for the changing role of distinct working memory circuits with development.

A different view of heterogeneity in neurocognitive function comes from characterization of individual working memory components as defined by Baddeley's original model (Baddeley & Hitch, 1974). Critically, the relative roles of these individual working memory components depend on problem complexity, individual differences in learning, and stage of skill development. Recent evidence demonstrates fractionation of neurofunctional systems associated with distinct working memory components during arithmetic problem-solving in 7- to 9-year-old children.

Specifically, visuospatial working memory and the central executive components of working memory are associated with distinct patterns of brain responses (Metcalfe, Rosenberg-Lee, Ashkenazi, & Menon, 2013)

(Fig. 15.3B,c). Furthermore, visuospatial working memory is the strongest predictor of mathematical ability, compared with the other working memory components (i.e., central executive and phonological loop) (Metcalfe et al., 2013). Visuospatial working memory is also uniquely associated with increased arithmetic complexity–related responses in DLPFC and ventrolateral PFC (VLPFC) and the bilateral IPS and SMG in children (Menon, 2016). Taken together, there is evidence that distinct working memory components play unique roles in mathematical learning and are important to consider when examining developmental trajectories and sources of heterogeneity within this domain.

Atypical working memory is strongly associated with aberrancies in mathematical learning and cognition in children with MLD (Ashkenazi, Rosenberg-Lee, Metcalfe, Swigart, & Menon, 2013; Geary, Hoard, Byrd-Craven, Nugent, & Numtee, 2007). Importantly, a number of studies have reported that individuals with MLD show aberrant recruitment of prefrontal and parietal working memory systems during mathematical tasks, including arithmetic problem-solving and numerosity judgments (Butterworth et al., 2011; Davis et al., 2009; Iuculano et al., 2015; Kaufmann, Vogel, Starke, Kremser, & Schocke, 2009; Kucian & von Aster, 2015; Kucian et al., 2006, 2011; Menon, 2014; Price et al., 2007; Rosenberg-Lee et al., 2014). Evidence to date further suggests that visuospatial working memory is a specific source of vulnerability in numerical calculation deficits in children with MLD. For example, Ashkenazi, Rosenberg-Lee, et al. (2013) reported deficits in visuospatial working memory skills, in addition to deficits in arithmetic task performance in children with MLD, compared with a group of IQ- and verbal abilities-matched typically developing (TD) children (Fig. 15.3B,d). Furthermore, activation of the IPS and DLPFC and VLPFC were positively correlated with visuospatial working memory in TD children, but no such association was seen in children with MLD (Fig. 15.3B,d). Iuculano et al. (2015) also showed aberrant engagement of frontoparietal regions, including DLPFC and VLPFC, IPS, and the left insular cortex in children with MLD (Fig. 15.3B,e). These results suggest that children with MLD fail to appropriately exploit working memory resources during arithmetic problem-solving. Taken together, there is evidence to suggest that individual working memory components are engaged differently in children with MLD, further highlighting sources of heterogeneity in atypical development.

In summary, a large body of research shows that multiple working memory components and distinct frontoparietal circuits play a central and dynamic role in mathematical cognition, and that the differential engagement of these components and their associated circuits contributes to heterogeneity in both typical and atypical development.

LATERAL FRONTOTEMPORAL CORTICES: LANGUAGE-MEDIATED SYSTEMS

Basic Organization

Phonological skills are essential for successful mathematical skill acquisition, particularly during the early stages of learning (Carey, 2004). Even before formal schooling, children are introduced to number words during language acquisition. Specifically, phonological processing plays a pivotal role in learning to count and in the perceptual-to-semantic mapping from number words (i.e., "one," "two," "three," "four") to numerosities (Carey, 2004). There is evidence that phonological awareness (i.e., the ability to recognize and manipulate different word sounds) and arithmetic skills are associated with one another (De Smedt, Taylor, Archibald, & Ansari, 2010). Moreover, several behavioral studies have demonstrated a link between the ability to process linguistic information and arithmetic word problems (e.g., "John has 9 pennies. He spent 3 pennies at the store. How many pennies does he have left?"), and arithmetic computations (Fuchs, Fuchs et al, 2008; Fuchs, Powell et al, 2008; Jordan, Levine, & Huttenlocher, 1995). There is also evidence that arithmetic facts are represented as a "verbal code" in the cortex (Dehaene, Piazza, Pinel, & Cohen, 2003; Grabner et al., 2009; Prado et al., 2011). Moreover, processing of arithmetic facts engages verbal information processing regions in the STS, the MTG, and the IFG (Andres, Michaux, & Pesenti, 2012; Andres, Pelgrims, Michaux, Olivier, & Pesenti, 2011; Lee, 2000; Prado, Mutreja, & Booth, 2014; Prado et al., 2011) (Fig. 15.4A,a,b).

Heterogeneity in Typical and Atypical Development

Mathematical proficiency is dependent on successful early learning about numerical quantity, including binding of individual numbers to their names, which requires engagement and parallel development of language-related processing (Gobel, Watson, Lervag, & Hulme, 2014). Indeed, several neuroimaging studies have reported engagement of language-related brain systems during mathematical tasks in children (Evans, Flowers, Napoliello, Olulade, & Eden, 2014; Prado et al., 2011, 2014; Rosenberg-Lee et al., 2014; Zarnhofer et al., 2012). The degree of this engagement is often based on problem type (e.g., the arithmetic operation to be performed) and strategy use, highlighting a source of heterogeneity in the role of language processing on mathematical cognition. For example, Prado et al. report age-related activation increases in left lateral temporal cortex, a region typically associated with language comprehension, for multiplication, but not for subtraction (Fig. 15.4B,a). Conversely, subtraction problems showed increased activity in regions of the PPC involved in numerosity and visuospatial processing as a function of age and skills (Prado et al., 2011, 2014). These findings are in line with previous results demonstrating that multiplication relies more on verbal strategies, whereas subtraction is often solved through visuospatial strategies as reflected by the differential neural substrates engaged (Dagenbach & McCloskey, 1992; Dehaene & Cohen, 1995; Ischebeck et al., 2006). Paralleling these findings, similar results have emerged in a heterogeneous population of elementary school children, involving children with MLD. In their study, Rosenberg-Lee et al. (2014) found greater activity for addition relative to subtraction problems in the bilateral STS, middle temporal gyri (MTG), and the hippocampus, regions involved in language processing, and memory, respectively. Conversely, subtraction problems were supported by a network of posterior parietal and frontal regions (Rosenberg-Lee et al., 2014)—see also Evans et al. (2014) for a similar result.

Moreover, there is evidence that variability in strategy use modulates activation in verbal brain systems during mathematical problem-solving. Zarnhofer et al. reported that individuals who verbalize multiplication and addition operations show stronger activation in regions associated with auditory processing—in the Heschl's gyrus and Rolandic operculum—compared with individuals who simply visualize the numbers, independent of whether problems were presented as Arabic numerals or written number words (Zarnhofer et al., 2012) (Fig. 15.4B,b).

With respect to heterogeneity in mathematical abilities, children with MLD show aberrant activation in verbal information processing regions of the STS, MTG, and IFG—identified via an independent phonological localizer task (Berteletti, Prado, & Booth, 2014; Prado et al., 2011)—suggesting difficulties in verbal retrieval of problem solutions (Fig. 15.4B,c).

Furthermore, the integration of phonological and orthographic codes, anchored in the STS, MTG, and FG, respectively, might also play an important role in individual differences in the acquisition of mathematical skills, similarly to reading skills. A previous study in 7- to 9-year-olds, found that subtraction problems activated a network of posterior parietal regions, including the IPS and SMG, whereas addition problems activated a network of language-related regions in the STS and MTG (Evans et al., 2014). This same network of language-mediated areas was also active during a reading task, suggesting that verbally mediated systems underlie both arithmetic problem-solving and reading. The integration of phonological and orthographic codes has not been formally explored in mathematical cognition, however, it is plausible to predict that, at least for certain arithmetical operations (i.e., addition and multiplication), successful neural integration of these two codes at the early stages of development might predict later learning and proficiency.

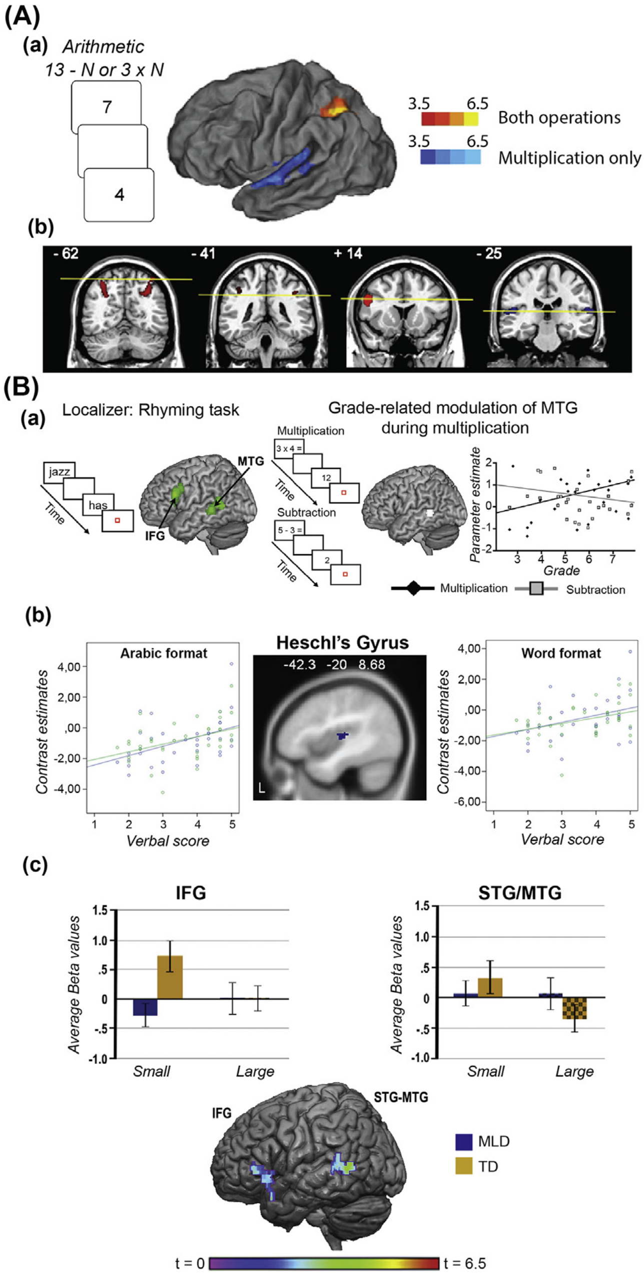

(A)
(a) Arithmetic
13 - N or 3 x N
7
4
3.5 6.5 Both operations
3.5 6.5 Multiplication only
(b)
- 62
- 41
+ 14
- 25
(B)
(a) Localizer: Rhyming task
jazz
has
Time
MTG
IFG
Grade-related modulation of MTG during multiplication
Multiplication
3 x 4 =
12
Time
Subtraction
5 - 3 =
2
Time
Parameter estimate
Grade
Multiplication
Subtraction
(b)
Arabic format
Heschl's Gyrus
-42.3 -20 8.68
Word format
Contrast estimates
Verbal score
(c)
IFG
STG/MTG
Average Beta values
Small
Large
IFG
STG-MTG
MLD
TD
t = 0
t = 6.5

FIGURE 15.4 **Language systems for mathematical knowledge. (A)** Basic organization. **(a)** Brain areas showing increased activity during mental arithmetic tasks compared to letter reading. ***Left***: Schematic of the arithmetic task during which participants had to multiply the Arabic digit displayed on the screen by 3 or 4, or subtract it from 11 or 13. ***Right***: brain regions of the middle temporal gyrus (MTG) and superior temporal sulcus (STS) (in blue) were more active for multiplication tasks, whereas posterior parietal regions (in orange) showed significant activation for both multiplication and subtraction tasks; **(b)** CORONAL views of brain regions showing increased functional activity during the same mental arithmetic task as **(A,a)**. Red clusters (first three from the ***left***) show the parietal and frontal areas involved in subtraction and multiplication. These include the posterior superior parietal lobe (pSPL), the horizontal segment of the intraparietal sulcus (hIPS), and the inferior frontal gyrus (IFG). Blue clusters (last panel on the ***right***) include perisylvian areas of the STS and MTG that showed greater activation for multiplication than subtraction. **(B)** Heterogeneity of skills. **(a)** Functional activity modulation of the MTG during multiplication, but not subtraction, in children. ***Left***: Localizer task—participants decided whether two visually presented words rhymed or not. ***Middle***: Arithmetic tasks—participants were asked to evaluate multiplication (***top***) or subtraction (***bottom***) math problems containing single-digit operands. ***Right***: Activity in the left MTG region of interest (ROI) as a function of operation (multiplication and subtraction) and school grade; **(b)** significant correlations between peak activations in the Heschl's gyrus in the temporal lobe during mental arithmetic (multiplication and subtraction) and self-reported use of verbalization strategies for different stimulus presentation (i.e., Arabic digits and number words). *Note*: Heschl's gyrus ROI defined based on the automated anatomical labeling atlas; **(c)** Group differences in functional activation during multiplication in ROIs identified using the same rhyming task as **(B,a)**. IFG and STG–MTG clusters showed greater activation for small compared with large problems for typically developing (TD) children, but not for children with mathematical learning disabilities (MLD). ***(A,a)*** *Modified from: Andres et al., 2012*, NeuroImage *© 2012 by Elsevier.* ***(A,b)*** *Modified from: Andres et al., 2011*, NeuroImage *© 2011 by Elsevier.* ***(B,a)*** *Modified from: Prado et al., 2014*, Developmental Science *© 2014 by John Wiley & Sons, Inc.* ***(B,b)*** *Modified from: Zarnhofer et al., 2012*, Behavioral and Brain Functions *© 2012 by BioMed Central Ltd.* ***(B,c)*** *Modified from: Berteletti et al., 2014*, Cortex *© 2011 by Elsevier.*

This framework could also be useful for assessing the known associations of math and reading skills and comorbidity of disabilities in these two cognitive domains (Ashkenazi, Black, Abrams, Hoeft, & Menon, 2013). Indeed, a recent study demonstrated that compared with TD controls, children with developmental dyslexia and mild impairments in fact retrieval displayed greater activity in the SMG for both addition and subtraction problems (Evans et al., 2014). Conversely, the TD group engaged the SMG only for subtraction and not addition problems, suggesting that children with developmental dyslexia might use alternate nonverbal strategies for both operations to compensate for neural aberrancies in language-related areas.

Together these findings highlight the importance of these—often overlooked—verbally mediated systems in the development of mathematical cognition. The extant literature also demonstrates that it is important to consider multiple variables (i.e., type of task, type of strategy, age, comorbidity of skills) when assessing neurocognitive correlates of heterogeneity of outcomes in mathematical learning.

THE MEDIAL TEMPORAL LOBE: DECLARATIVE MEMORY

Basic Organization

The hierarchical nature of mathematical skill acquisition requires building-up associations between basic numerical concepts to more complex numerical attributes, binding old and new concepts, and accessing information about numerical attributes from long-term memory. Thus, declarative memory and associated neural circuits play a critical role in mathematical learning and cognition. These processes depend on the function of subcortical structures important for learning and memory consolidation within the MTL (Davachi, 2006; Davachi et al., 2003; Diana, Yonelinas, & Ranganath, 2007; Eichenbaum, Yonelinas, & Ranganath, 2007; Squire, 1992; Squire, Genzel, Wixted, & Morris, 2015, pp. 1–21; Squire, Stark, & Clark, 2004; Tulving, 1983) (Fig. 15.5A,a,b). Despite its critical role in learning and memory formation, the role of the hippocampus in mathematical learning has received little attention. This is likely because the critical role of this system decreases over development. For almost two decades, neuroimaging studies of mathematical cognition only assessed samples of already proficient adult participants who often do not rely on this system during simple arithmetic tasks. Here, by providing a developmental and learning perspective, we are able to shed light on the critical and unique role of the MTL memory system in the successful acquisition of mathematical skills.

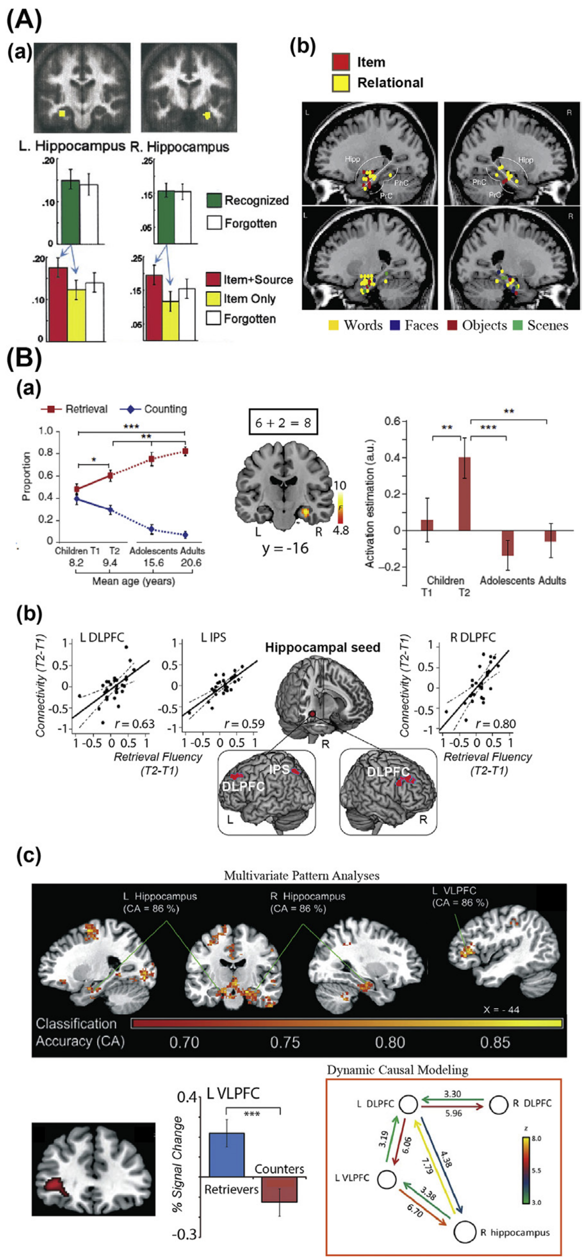
Heterogeneity in Typical and Atypical Development

It is well established that during mathematical learning, inefficient procedural strategies in childhood (e.g., counting) are gradually replaced with direct retrieval of mathematical facts (Cho, Ryali, Geary, & Menon, 2011; Geary, 2011; Geary & Brown, 1991; Geary & Hoard, 2003, pp. 93–115; Qin et al., 2014). Importantly, the key role of the hippocampus in learning decreases as skills are acquired, and retrieval of numerical information is processed by neocortical systems important for mathematical cognition (Qin et al., 2014). Indeed, previous studies have demonstrated that children show increased engagement of the hippocampus relative to adolescents and adults during mathematical problem-solving (De Smedt, Holloway, & Ansari, 2011; Rivera et al., 2005). In a seminal study, Qin et al. (2014) demonstrated that children's transition from counting to memory-based retrieval strategies over a 1.2-year interval was mediated by increased hippocampal activation and increased hippocampal-neocortical connectivity (Fig. 15.5B,a,b). Critically, following an initial increase in hippocampal engagement from early to middle childhood (i.e., from 8.2 to 9.4 years), hippocampal activation decreased during adolescence and adulthood, despite further improvements in memory-based problem-solving skills. This pattern of initial increases and subsequent decreases in activation provides support for models of long-term memory consolidation, which posit that the hippocampus plays a time-limited, yet pivotal role in the early phase of knowledge acquisition (e.g., learning to associate the addend pairs 3 and 4, to the answer 7) (McClelland, McNaughton, & O'Reilly, 1995; Tse et al., 2007). Moreover, consistent with this model of developmental change, previous studies in adults have not reported reliable hippocampal engagement during basic arithmetic tasks (Dehaene et al., 2003). There is also evidence for a causal interaction between the hippocampus and the VLPFC during arithmetic problem-solving (Fig. 15.5B,c) as a function of cognitive strategy. Specifically, children with higher retrieval fluency rates show greater functional responses in the hippocampus, parahippocampal gyrus, and VLPFC (Fig. 15.5B,c). Moreover, there is evidence of a significant direct causal influence from the left VLPFC to the right hippocampus during arithmetic fact retrieval (Cho et al., 2012). Finally, differential functional activity patterns of the hippocampus are observed in 7- to 9-year-olds during arithmetic problem-solving as a function of retrieval and counting strategies (Cho et al., 2011) (Fig. 15.5B,c). Together this body of evidence suggests that the hippocampus and the PFC are engaged differently as a function of strategy in young children.

Taken together, converging evidence points to the hippocampal system and its interactions with the PFC as critical to children's early learning of arithmetic facts (Cho et al., 2011, 2012; De Smedt, Holloway, & Ansari, 2011; Qin et al., 2014), while retrieval in adolescents and adults relies predominantly on the neocortex (Dehaene, Piazza, Pinel, & Cohen, 2003; Menon, 2014).

These heterogeneous patterns of hippocampal involvement as a function of development, skill acquisition, and strategy use are consistent with the developmental cognitive model of "overlapping waves" whereby acquisition of cognitive skills is characterized by changes in the distributions of strategies over development (Siegler, 1996). In the case of mathematics, children's immature problem-solving abilities, which require breaking down numerical problems into more basic components, are slowly replaced by efficient retrieval of arithmetical facts (Cowan et al., 2011). These findings highlight the dynamic role of the hippocampus in the maturation of memory-based problem-solving strategies. Moreover, these findings demonstrate greater engagement of the hippocampus in childhood followed by decreased involvement during adolescence and adulthood.

Critically, consolidation of efficient strategy use and progressive engagement of the hippocampus during learning and development is accompanied by decreases in parietal–frontal engagement and concurrent increases in functional connectivity between hippocampal and neocortical circuits. Increases in hippocampal–PFC connectivity are significantly


(A)
(a)
L. Hippocampus
R. Hippocampus
Recognized
Forgotten
Item+Source
Item Only
Forgotten
(b)
Item
Relational
Hipp
PhC
PrC
Words
Faces
Objects
Scenes
(B)
(a)
Retrieval
Counting
Proportion
Children T1
T2
Adolescents
Adults
8.2
9.4
15.6
20.6
Mean age (years)
6 + 2 = 8
y = -16
Activation estimation (a.u.)
(b)
L DLPFC
L IPS
Hippocampal seed
R DLPFC
Connectivity (T2-T1)
Retrieval Fluency (T2-T1)
r = 0.63
r = 0.59
r = 0.80
DLPFC
IPS
(c)
Multivariate Pattern Analyses
L Hippocampus (CA = 86 %)
R Hippocampus (CA = 86 %)
L VLPFC (CA = 86 %)
X = - 44
Classification Accuracy (CA)
0.70
0.75
0.80
0.85
L VLPFC
% Signal Change
Retrievers
Counters
Dynamic Causal Modeling
L DLPFC
R DLPFC
L VLPFC
R hippocampus
3.30
5.96
3.19
6.06
7.79
4.38
3.38
6.70

related to longitudinal improvements in retrieval fluency in early to middle childhood (Qin et al., 2014) (Fig. 15.5B,b). Together, these findings suggest that hippocampal-neocortical circuit reorganization plays a crucial role in children's shift from effortful counting to more efficient memory-based problem-solving during development. Consistent with this, children with MLD do not show hippocampal engagement during arithmetic problem-solving, suggesting that MLD, at least partially, derives from lack of hippocampal recruitment during crucial phases of mathematical learning and skill development (De Smedt et al., 2011).

Taken together, research is beginning to highlight the role of the hippocampus and its associated prefrontal-parietal circuits in consolidating basic arithmetic facts into long-term memory in children. Moreover, this body of research points to another key neurocognitive component underlying heterogeneous trajectories of typical and atypical skill development.

FIGURE 15.5 **Medial temporal lobe memory systems for mathematical knowledge.** **(A)** Basic organization. **(a)** Peak signal change during image encoding in bilateral hippocampi. Encoding activation is sorted according to whether the item was later recognized (*green bars*) or forgotten (*white bars*). For recognized items, both left and right hippocampi are sensitive to source memory outcome recollection (i.e., item + source > item only), suggesting that the hippocampus plays a crucial role in recollecting specific contextual details about a prior encounter (i.e., source recollection). *Red bars*: item + source; *Yellow bars*: item only; **(b)** ***Top***: Metaanalysis of studies reporting medial temporal lobe (MTL) peaks for item-specific effects versus relational memory effects. Relational memory effects are predominantly seen in the bilateral hippocampus (Hipp) and the parahippocampal cortex (PhC), whereas item-specific effects are evident in the perirhinal cortex (PrC). ***Bottom***: MTL peaks plotted as a function of stimulus type (i.e., words, faces, objects, scenes). **(B)** Heterogeneity of skills. **(a)** Developmental differences in hippocampal engagement. ***Left***: Gradual increases in memory-based strategies and decreases in counting strategies. ***Middle and Right***: Right hippocampal response during arithmetic problem-solving showing a main effect of age-group across children at different time points (Time 1 and Time 2, ~1.2 years apart), adolescents, and adults; **(b)** Hippocampal-neocortical connectivity. Longitudinal changes in hippocampal-neocortical connectivity (Y-axes) plotted against individual improvements in children's use of memory-based problem-solving strategies (X-axes); *DLPFC*, dorsolateral prefrontal cortex; *IPS*, intra parietal sulcus. **(c)** Hippocampal-prefrontal retrieval network. ***Top***: Multivariate pattern analyses showing significant differences in spatial activation patterns between retrievers and counters in the bilateral hippocampus, adjoining parahippocampal gyrus, and in the left ventrolateral prefrontal cortex (VLPFC). Peak classification accuracies are shown in parentheses. ***Bottom left***: The left VLPFC displays greater functional activation in 7- to 9-year-old retrievers (blue) compared with counters (red). ***Bottom right***: Multivariate dynamical systems modeling of the hippocampal-prefrontal retrieval network. The left ventral and dorsal lateral aspects of the prefrontal cortex (VLPFC and DLPFC) show direct causal influence to the right hippocampus in 7- to 9-year-olds. ***(A,a)*** *Modified from:* *Davachi et al., 2003*, PNAS *© 2002 by The National Academy of Sciences of the USA.* ***(A,b)*** *Modified from:* *Davachi, 2006*, Current Opinion in Neurobiology *© 2006 by Elsevier.* ***(B,a)*** *Modified from:* *Qin et al., 2014*, Nature Neuroscience *© 2014 by NPG.* ***(B,b)*** *Modified from:* *Qin et al., 2014*, Nature Neuroscience *© 2014 by NPG.* ***(B,c)*** **Top**: *Modified from:* *Cho et al., 2011*, Developmental Science *© 2011 by John Wiley & Sons, Inc.;* **Bottom left**: *Modified from:* *Cho et al., 2011*, Developmental Science *© 2011 by John Wiley & Sons, Inc.;* **Bottom right**: *From:* *Cho et al., 2012*, Journal of Cognitive Neuroscience *© 2012 by MIT Press and the Cognitive Neuroscience Institute.*

THE CIRCUIT VIEW: ATTENTION AND CONTROL PROCESSES AND DYNAMIC CIRCUITS ORCHESTRATING MATHEMATICAL LEARNING

Basic Organization

The findings reviewed above demonstrate that mathematical cognition relies on interactions within and between multiple functional brain systems and circuits, including those subserving quantity processing, declarative, semantic, and working memory (e.g., Arsalidou & Taylor, 2011; Fias et al., 2013; Fig. 15.1). As noted, connectivity between the ventral and dorsal streams, and specifically from the higher-level ventral temporal–occipital visual cortices to dorsal posterior parietal cortices, helps to strengthen the link between visual percepts and their semantic representations—a key building block of numerical cognition. Although the IPS plays a key role in building representations of numerical quantity, it is also part of an intrinsically connected dorsal frontoparietal system that includes the SPL, FEFs, supplementary motor area, insula, and DLPFC (Corbetta & Shulman, 2002; Corbetta et al., 2008; Menon & Uddin, 2010; Supekar & Menon, 2012; Uddin et al., 2010) (Fig. 15.3A,a,b). This system is thought to be important for top-down goal-driven attention, including performance monitoring and manipulation of (numerical) information in working memory (Corbetta & Shulman, 2002; Corbetta et al., 2008). Furthermore, the ventral attention system, which includes the SMG, insula, and IFG, is involved in saliency processing and attentional filtering (Corbetta & Shulman, 2002; Corbetta et al., 2008; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Menon & Uddin, 2010; Supekar & Menon, 2012) (Fig. 15.3A,a,b). Finally, memory systems anchored in the medial and anterior temporal lobe are important for encoding and retrieval of math facts (Grabner et al., 2009; Qin et al., 2014).

Critically, the flow of information within and across these multiple brain systems is regulated by flexible cognitive control systems, which facilitate the integration and manipulation of quantity and mnemonic information. These include most prominently the salience network, anchored in the anterior insula and dorsal anterior cingulate cortex, and the frontoparietal working memory network, anchored in the ventral and dorsal aspects of the lateral PFC and the SMG (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Cai et al., 2015; Cai, Ryali, Chen, Li, & Menon, 2014; Cole et al., 2013; Ham, Leff, de Boissezon, Joffe, & Sharp, 2013; Seeley et al., 2007; Sridharan et al., 2008) (Fig. 15.6A,a,b). Mechanistically, the implementation of cognitive control processes relies on both dynamic functional interactions within (Cai et al., 2014, 2015; Cole et al., 2013; Ham et al., 2013; Seeley et al., 2007; Sridharan et al., 2008) and across these brain systems (Bressler & Menon, 2010). Specifically, interactions between the salience

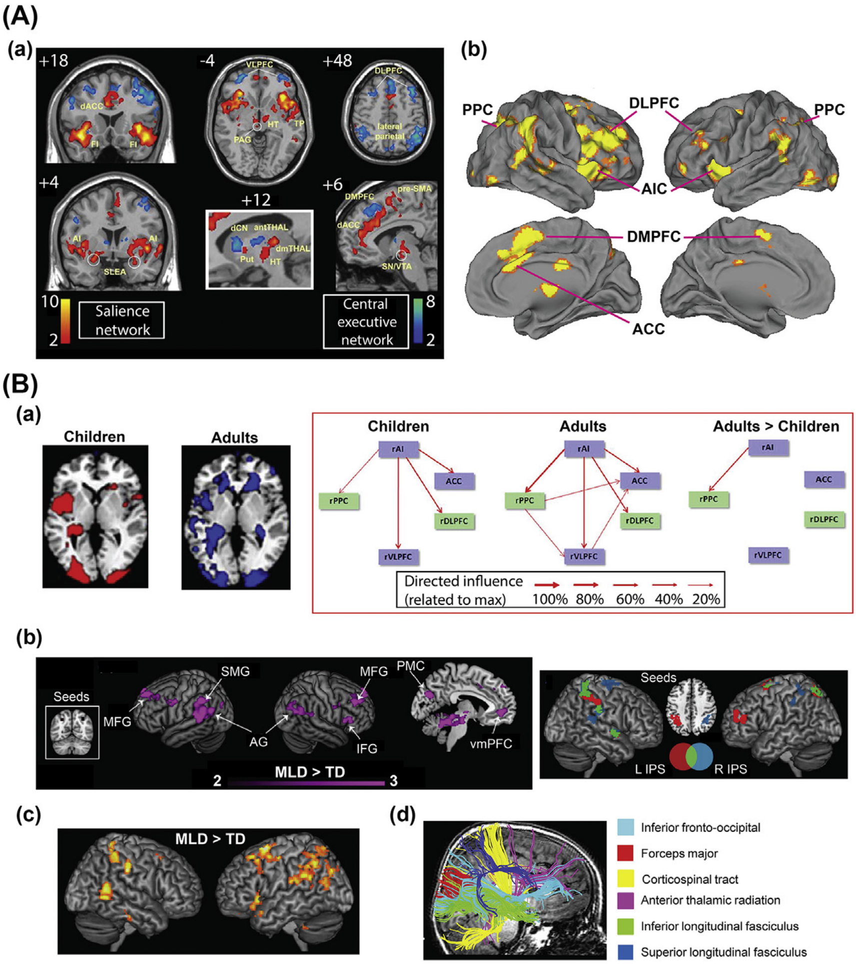


FIGURE 15.6 **Cognitive control circuits for mathematical knowledge. (A)** Basic organization. **(a)** The two core cognitive control brain networks identified using intrinsic physiological coupling during resting state fMRI. In red: the salience network (SN) important for monitoring salience of external inputs and internal brain events; in blue: the frontoparietal central executive/working memory network engaged in higher-order cognitive and attentional control tasks; **(b)** activation likelihood estimation (ALE) map of significant activated regions during an inhibitory control task. Significant clusters are evident in the anterior insular cortex (AIC), dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), anterior cingulate cortex (ACC), and posterior parietal cortex (PPC). **(B)** Heterogeneity of skills. **(a)** ***Left***: Brain activation in the SN and the frontoparietal central executive/working memory network during arithmetic problem-solving in children (***left*** and in red) and adults (***right*** and in blue). ***Right***: Weaker dynamic causal interactions between cognitive control networks in children compared to adults; **(b)** ***Left***: Hyperconnectivity of IPS circuits in children with mathematical learning disabilities (MLD), compared with typically developing (TD) children during an arithmetic task. ***Right***: Hyperconnectivity of IPS circuits in children with MLD, compared with TD children during rest;

network and the frontoparietal working memory network help maintain attention on goal-relevant numerical representations, while inhibiting irrelevant information or immature strategies. Interactions between the salience, frontoparietal, and hippocampal-frontal networks help to consolidate arithmetical representations in long-term memory.

Heterogeneity in Typical and Atypical Development

Cognitive skill acquisition during development is characterized by marked functional and structural maturation of individual brain areas (Bressler & Menon, 2010). In parallel, functional and structural brain connectivity across large-scale functional networks also undergoes significant changes with development (Bressler & Menon, 2010). Of particular interest here, connectivity between the FG and IPS increases significantly between childhood and adulthood (Vogel et al., 2012), which may underlie more efficient mapping between symbolic representations of numbers and the quantities they represent. Furthermore, intrinsic functional connectivity of the FG with the PPC and the PFC significantly predicts gains in numerical skills over development (Evans et al., 2015) (Fig. 15.2B,d). These findings illustrate how multiple functional circuits influence the development of mathematical skills and identify sources of individual differences at the brain circuit level.

The functional maturation of cognitive control systems also influences the development of mathematical skills. Despite greater PFC activation, there are decreased dynamic causal interactions between the anterior insula and the VLPFC and DLPFC in children, relative to adults (Supekar & Menon, 2012) (Fig. 15.6B,a). Moreover, weaker prefrontal control signals have been associated with worse performance on an arithmetic task with distinct pathways contributing differently to performance in children and adults (Supekar & Menon, 2012). Specifically, in children, the strength of causal signals from the anterior insula to the SMG and VLPFC significantly predicted faster reaction times; whereas in adults, an additional link from the insular cortex to the anterior cingulate cortex significantly predicted faster reaction times (Supekar & Menon, 2012). Thus, the interaction

(c) Frontoparietal regions showing greater fractional amplitude of low-frequency fluctuations (fALFF) in children with MLD, compared with TD children; **(d)** streamlined reconstruction of white matter pathways passing through the right temporal-parietal regions: children with MLD showed significant white matter volumetric deficits compared with TD children. ***(A,a)*** *Modified from: Seeley et al., 2007,* Journal of Neuroscience *© 2007 by SfN.* ***(A,b)*** *Modified from: Cai et al., 2014,* Journal of Neuroscience *© 2014 by SfN.* ***(B,a)*** *Modified from: Supekar & Menon, 2012,* PLoS Computational Biology *© 2012 by PLoS.* ***(B,b)*** **Left***: Modified from: Rosenberg-Lee et al., 2014,* Developmental Science *© 2014 by John Wiley & Sons, Inc.;* **Right***: Modified from: Jolles, Ashkenazi, et al. (2016),* Developmental Science *© 2016 by John Wiley & Sons, Inc.* ***(B,c)*** *Modified from: Jolles, Ashkenazi, et al. (2016),* ***(B,d)*** *Modified from: Rykhlevskaia et al., 2009,* Frontiers in Human Neuroscience *© 2009 by Frontiers Media S.A.*

between prefrontal cognitive control systems with frontoparietal systems for numerical manipulations represents a predominant source of heterogeneity in mathematical cognition across both development and levels of ability.

Similarly, the interaction between cognitive control systems in the ventral and dorsal aspects of the PFC with mnemonic systems anchored in the hippocampus may also be related to individual differences in mediating retrieval fluency during arithmetic problem-solving (Cho et al., 2012) (Fig. 15.5B,c). Specifically, dynamic causal modeling of fMRI data during arithmetic problem-solving has highlighted strong bidirectional causal interactions between these regions as a function of cognitive strategy for arithmetic problem-solving in elementary school children (Fig. 15.5B,c).

Both task-based and task-free fMRI studies demonstrate that connectivity of parietal-frontal circuits is impaired in children with MLD. Surprisingly, despite weaker performance, children with MLD show hyperconnectivity of the IPS with VLPFC and DLPFC and the SMG (Rosenberg-Lee et al., 2014) (Fig. 15.6B,b—***Left***). Hyperconnectivity of these circuits may arise from greater demands on working memory and cognitive control because of the need to inhibit problem-irrelevant information. This is consistent with behavioral studies showing greater intrusion errors of problem-irrelevant information in working memory during arithmetic fact retrieval in children with MLD (Barrouillet, Fayol, & Lathuliere, 1997; Geary, Hamson, & Hoard, 2000; Geary, Hoard, & Bailey, 2012). This pattern of hyperconnectivity is also apparent for intrinsic functional circuits, using "task-free" resting-state fMRI data. Compared with matched TD controls, children with MLD showed increased intrinsic functional connectivity between left and right IPS and between the IPS and DLPFC and VLPFC (Jolles, Ashkenazi, et al., 2016) (Fig. 15.6B,b—***Right***).

Taken together, converging evidence suggests that hyperconnectivity of intrinsic functional circuits associated with the IPS in children with MLD may underlie the commonly observed pattern of increased activation and task-based connectivity within these regions (Iuculano et al., 2015; Kaufmann et al., 2009a, 2009b; Kaufmann, Wood, Rubinsten, & Henik, 2011; Rosenberg-Lee et al., 2014). Notably, there is recent evidence that enhanced low-frequency fluctuations in the IPS are associated with individual differences in math abilities in children with MLD (Jolles, Ashkenazi, et al., 2016) (Fig. 15.6B,c—***Left***). Furthermore, the middle and superior frontal gyri, SMG, and superior parietal lobule also showed spontaneous regional hyperactivity and critically, hyperconnectivity with the IPS in children with MLD compared with TD children (Jolles, Ashkenazi, et al., 2016) (Fig. 15.6B,c—***Left***). These findings lead us to hypothesize that intrinsic hyperconnectivity and enhanced low-frequency fluctuations may limit flexible resource allocation and contribute to aberrant recruitment of task-related brain regions during mathematical cognition. Moreover, these results point to aberrant excitatory/inhibitory balance in the IPS in MLD. The neurotransmitters glutamate (Glx) and gamma-aminobutyric acid (GABA) play prominent roles in cortical excitability and in maintaining an optimal excitatory/inhibitory balance across brain systems and are thought to drive learning (Gupta et al., 2016; Naaijen et al., 2017; Pugh et al., 2014; Tatti, Haley, Swanson, Tselha, & Maffei, 2016). Elevated levels of Glx or decreased levels of GABA can lead to hyperexcitability and disruption of neural circuits in many neurodevelopmental and learning disorders, including dyslexia, autism, and attention-deficit hyperactivity disorder (Drenthen et al., 2016; Pugh et al., 2014; Tatti et al., 2016). Studies using magnetic resonance spectroscopy, which can provide a proxy for Glx and GABA concentrations in specific brain regions, are required to test this hypothesis in MLD.

In addition to atypical circuit function described above, structural aberrancies of gray matter volume have also been reported in MLD. These include multiple brain regions, including the parietal lobes, the ventral temporal–occipital cortices, and the anterior temporal cortices (Rykhlevskaia, Uddin, Kondos, & Menon, 2009). Individuals with MLD also show white matter deficits in the right inferior frontooccipital fasciculus, the right inferior and superior longitudinal fasciculi, the left longitudinal fasciculus, and the bilateral anterior thalamic radiation (Rykhlevskaia et al., 2009) (Fig. 15.6B,d—***Right***). Reduced integrity of white matter pathways within the right temporoparietal cortex has also been reported in MLD and has been associated with poorer performance on a standardized math task (Rykhlevskaia et al., 2009). Together, these results suggest that MLD might be reflected in gray matter structural abnormalities in a network of right temporoparietal areas and the white matter pathways associated with it. More generally, these results suggest that aberrant gray and white matter structure may drive functional abnormalities of intrinsic and task-based connectivity, resulting in inefficient communication between task-relevant brain regions. Together, these results highlight the importance of investigating local and large-scale circuit features underlying heterogeneity in typical and atypical development.

PLASTICITY IN MULTIPLE BRAIN SYSTEMS: RELATION TO LEARNING

Basic Organization

Brain plasticity is fundamental to any type of learning and a core characteristic of human cognition and development. Within this framework, learning studies are beginning to provide new insights into how mathematical knowledge is acquired, by more precisely linking learning to brain plasticity of relevant neurocognitive systems and circuits (Fig. 15.1). A popular paradigm for short-term arithmetic learning typically consists of multiple repetitions of a defined set of complex problems (i.e., training set), whereas another set is presented at a lower frequency (i.e., novel set). Training-contingent learning effects are rapid, and typically become significant after approximately eight repetitions of a problem, and remain stable over the course of the experiment (~1 week) (Ischebeck, Zamarian, Egger, Schocke, & Delazer, 2007). Comparison of brain responses between trained and novel problems is used to examine the effects of training-contingent learning; implicit in this design is the assumption that brain responses to untrained and trained problems are otherwise well matched prior to training. These studies typically reveal that training decreases responses in the PFC and IPS (Delazer et al., 2005; Ischebeck et al., 2006, 2007) (Fig. 15.7A,a,b,c), suggesting greater processing automaticity. In parallel, these studies report relative increases in activation in the left angular gyrus (AG) (Fig. 15.7A,a,b,c) (Delazer et al., 2003, 2005; Ischebeck et al., 2006, 2007; Zamarian & Delazer, 2014), although this result often reflects decreases in deactivation relative to baseline as the problems become more automatized (Wu et al., 2009).

Collectively, a handful of these studies have converged on similar results and suggest that mathematical learning is associated with not only major functional reorganization within the PPC but also other parietal-frontal circuits important for numerical reasoning (Delazer et al., 2005; Ischebeck et al., 2007; Zamarian, Ischebeck, & Delazer, 2009). More generally, these studies corroborate the evidence described in previous sections (from developmental and cross-sectional studies) regarding the pivotal contribution of all these systems to mathematical learning.

Heterogeneity in Typical and Atypical Development

Cognitive learning is shaped by brain plasticity through changes in local and large-scale functional circuits. Learning studies using continuous cohorts of participants that included TD children and children with MLD report an exceptional degree of functional and structural plasticity in the aforementioned systems (Fig. 15.1). Specifically, 2 months of a comprehensive training program emphasizing conceptual knowledge of number properties, arithmetical operations, and speeded practice of arithmetic facts (Fuchs et al., 2008, 2009, 2010, 2013; Powell, Fuchs, Fuchs, Cirino, & Fletcher, 2009) (Fig. 15.7B,a) shows significant functional and structural neuroplasticity-related effects in multiple functional brain networks important for mathematical cognition (Fig. 15.7B,a,b,c). Functional circuits associated with the IPS showed high levels of plasticity in their connectivity with the lateral PFC, the ventral temporal–occipital cortex, and the hippocampus (Jolles, Supekar, et al., 2016) (Fig. 15.7B,b). Furthermore, these connectivity changes were associated with performance gains (Fig. 15.7B,b). Conversely, functional circuits associated with other parietal regions such as the AG showed no training-related plasticity effects, highlighting the unique role of the IPS as a critical *hub* during active learning. This study extends previous

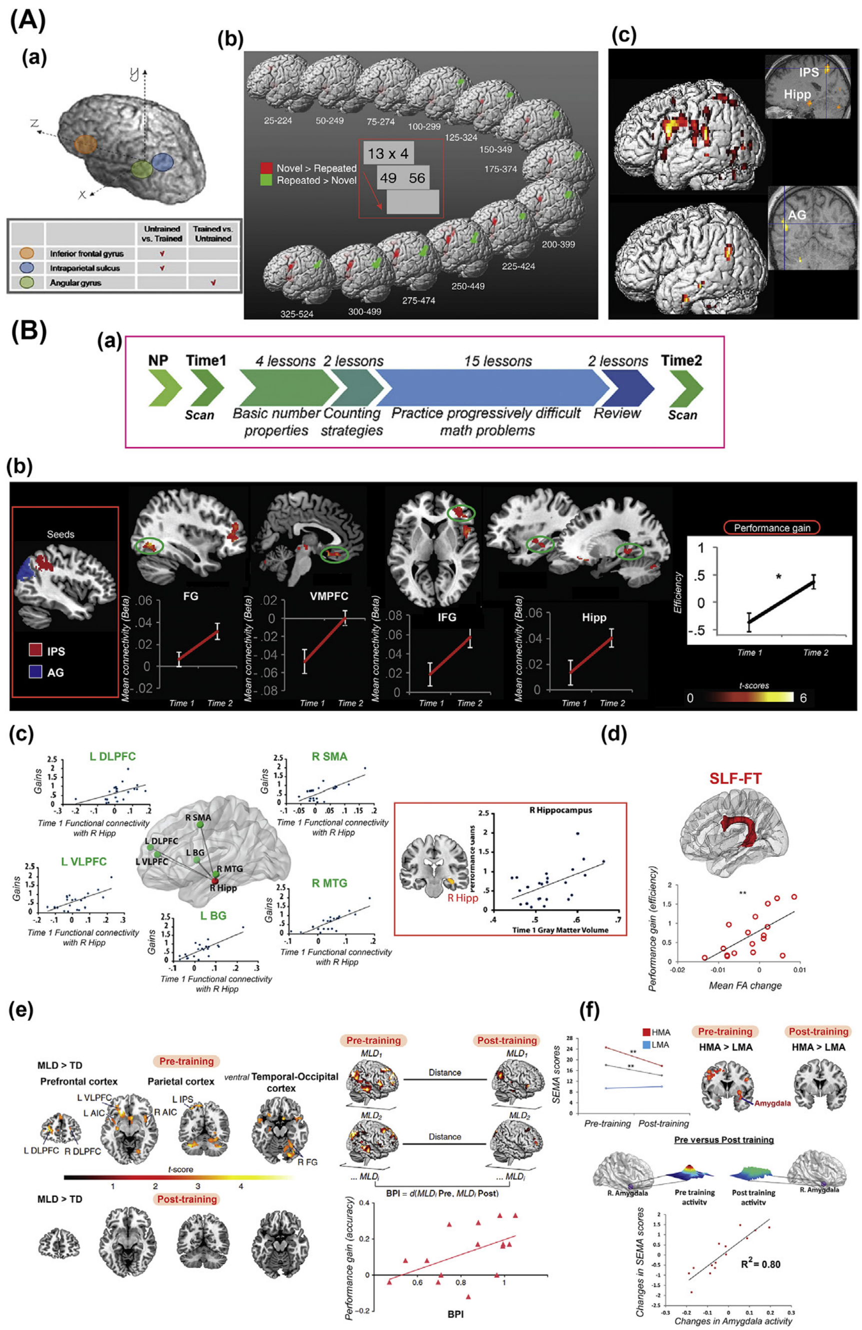

(A)
(a)
Untrained vs. Trained
Trained vs. Untrained
Inferior frontal gyrus
Intraparietal sulcus
Angular gyrus
(b)
25-224
50-249
75-274
100-299
125-324
150-349
175-374
200-399
225-424
250-449
275-474
300-499
325-524
13 x 4
49 56
Novel > Repeated
Repeated > Novel
(c)
IPS
Hipp
AG
(B)
(a)
NP
Time1
Scan
4 lessons
Basic number properties
2 lessons
Counting strategies
15 lessons
Practice progressively difficult math problems
2 lessons
Review
Time2
Scan
(b)
Seeds
IPS
AG
FG
VMPFC
IFG
Hipp
Mean connectivity (Beta)
Time 1
Time 2
Performance gain
Efficiency
t-scores
(c)
L DLPFC
R SMA
L VLPFC
L BG
R MTG
R Hipp
Gains
Time 1 Functional connectivity with R Hipp
R Hippocampus
Time 1 Gray Matter Volume
(d)
SLF-FT
Performance gain (efficiency)
Mean FA change
(e)
MLD > TD
Pre-training
Prefrontal cortex
Parietal cortex
ventral Temporal-Occipital cortex
L VLPFC
L AIC
R AIC
L IPS
L DLPFC
R DLPFC
R FG
t-score
Post-training
Distance
BPI = d(MLDi Pre, MLDi Post)
Performance gain (accuracy)
BPI
(f)
HMA
LMA
Pre-training
Post-training
HMA > LMA
SEMA scores
Amygdala
Pre versus Post training
R. Amygdala
Pre training activity
Post training activity
Changes in SEMA scores
R² = 0.80
Changes in Amygdala activity

FIGURE 15.7 **Cognitive learning and brain plasticity. (A)** Basic organization. **(a)** Schematic illustration of functional brain activation for untrained versus trained problems and the reverse (i.e., trained vs. untrained) during a short-term (~1 week) arithmetic training paradigm in adults. Extended activations in frontal and posterior parietal cortices, encompassing the intraparietal sulcus (IPS) are normally found for untrained versus trained problems (*orange and blue circles*). Higher activation in the lateral aspect of the posterior parietal cortex, particularly of the angular gyrus (AG), is often found on the contrast between trained and untrained problems in adults (*green circle*); **(b)** activation changes as a function of training: during task, participants had to choose the alternative solution that was closest to the actual solution of the presented multiplication problem. Rendering of moving window of 200 scans: training effects become significant starting at the 100- *to* 299-*scans* time-window. Green: repeated (trained) > novel (untrained) problems. Red: novel (untrained) > repeated (trained) problems; **(c)** ***Top***: Functional activation maps for untrained versus trained multiplication problems in adults. Significant effects are evident in the IPS and the Hippocampus (Hipp); ***Bottom***: Functional activation maps for trained versus untrained multiplication problems. Significant effects are seen in the AG. **(B)** Heterogeneity. **(a)** Experimental design of training studies in children. Before 2 months of cognitive training, children undergo an extensive battery of neuropsychological (NP) assessments and a scan session, which includes functional MRI (MRI), diffusion tensor imaging (DTI), resting-state fMRI (rsfMRI), and structural MRI (sMRI). 1:1 training focuses on conceptual aspects of number knowledge, effective counting strategies, and speeded practice. After training, children undergo another scanning session; **(b)** Functional IPS circuits show high level of plasticity after training. Training increased intrinsic functional connectivity between the IPS and the fusiform gyrus (FG), the ventromedial prefrontal cortex (VMPFC), the lateral prefrontal cortex encompassing the inferior frontal gyrus (IFG), the hippocampus (Hipp), and parahippocampal gyrus in a group of 7- to 9-year-old children. Intrinsic functional connectivity of the AG did not show any training-related effect except with the postcentral gyrus (not shown). Increases in IPS-functional connectivity were related to performance gains defined as efficiency gains from T1 to T2 (shown in graph); **(c)** Functional and structural hippocampal circuits show high levels of plasticity after cognitive training. ***Left***: Functional connectivity of the hippocampus was correlated with improvements in arithmetic performance (i.e., gain as a function of both accuracy and RTs—efficiency measure) in response to 2-months of the same cognitive training as in **(B,a)**. Performance gains correlated with Time 1 hippocampal connectivity to the left dorsolateral prefrontal cortex (L DLPFC), left ventrolateral prefrontal cortex (L VLPFC), right supplementary motor areas (R SMA), left basal ganglia (L BG), and right middle temporal gyrus (R MTG). ***Right***: Gray matter volume in the hippocampus was significantly correlated with improvements in arithmetic performance after 2 months of training; **(d)** White matter changes after training. Performance gains (i.e., efficiency) were associated with fractional anisotropy (FA) value changes in the left superior longitudinal fasciculus (SLF) linking frontal and temporal cortices (FT) in 7- to 9-year-old children; **(e)** Plasticity after training in different performance-level cohorts. ***Left***: Normalization of aberrant functional brain responses in children with MLD after 2 months of cognitive training. ***Top***: Before training, children with MLD showed greater functional brain activation levels compared with TD children in multiple regions of the prefrontal, parietal, and ventral temporal–occipital cortices. ***Bottom***: After 2 months of training, functional brain responses in MLD children normalized to the levels of TD children. *AIC*, anterior insular cortex; *DLPFC*, dorsolateral prefrontal cortex; *FG*, fusiform gyrus; *IPS*, intraparietal sulcus; *VLPFC*, ventrolateral prefrontal cortex. ***Right***: Brain plasticity index (BPI) calculated as a multivariate correlation between post- and prefunctional brain activation maps significantly correlated with performance gains (i.e., accuracy) in children with MLD; **(f)** Plasticity of emotional circuits after cognitive training. ***Top left***: Mathematical training decreased scores on a math anxiety questionnaire (Scale for Early Math Anxiety—SEMA) in 7- to 9-year-old children with high levels of math anxiety (HMA). ***Top right***: Mathematical

Continued

training induced functional plasticity during an arithmetic problem-solving task in children with HMA, compared to children with low levels of math anxiety (LMA). Coronal view: significant results were evident in emotional processing regions anchored in the basolateral amygdala. ***Bottom***: Connectivity changes in emotion-related circuits anchored in the basolateral amygdala were significantly related to changes in SEMA scores in 7- to 9-year-olds after training. ***(A,a)*** *Modified from: Zamarian et al., 2009*, Neuroscience and Biobehavioral Reviews *© 2009 by Elsevier.* ***(A,b)*** *Modified from: Ischebeck et al., 2007*, Neuroimage *© 2007 by Elsevier.* ***(A,c)*** *Modified from: Delazer et al., 2003*, Cognitive Brain Research *© 2003 by Elsevier.* ***(B,a)*** *Adapted from: Jolles, Supekar, et al., (2016), Jolles, Wassermann, et al. (2016)*, Cortex *© 2016 by Elsevier.* ***(B,b)*** *Modified from: Jolles, Supekar, et al., (2016)*, Cortex *© 2016 by Elsevier.* ***(B,c)*** *Modified from: Supekar et al., 2013*, PNAS *© 2013 by The National Academy of Sciences of the USA.* ***(B,d)*** *Adapted from: Jolles, Wassermann, et al. (2016)*, Brain Structure and Function*, © 2016 by Springer.* ***(B,e)*** *Modified from: Iuculano et al., 2015*, Nature Communications *© 2015 by NPG.* ***(B,f)*** *Modified from: Supekar et al., 2015*, Journal of Neuroscience *© 2015 by SfN.*

findings regarding connectivity features of the IPS in MLD (Rosenberg-Lee et al., 2014) (Fig. 15.6B,b) and points to cognitive training as a way to rectify functional circuit imbalances in children with MLD (see also Fig. 15.6B,c).

Neuroplasticity effects related to training-contingent learning might also differ based on an individual's math ability prior to training. In MLD, disrupted systems (Fig. 15.6B,b,c) will need to "normalize" before more efficient connectivity features can emerge, whereas in TD, increases in connectivity—accompanied by performance increases—(Fig. 15.7B,b) might reflect better and more efficient cross talk between critical brain systems.

Connectivity and structural features of other brain systems important for mathematical cognition also demonstrate plasticity as a function of training-contingent learning. In a seminal study, using a similar mathematical training paradigm to the one described above (Jolles, Supekar, et al., 2016), Supekar et al. (2013) showed that hippocampal volume prior to training was a strong predictor of performance gains in mathematical skills (Fig. 15.7B,c). Furthermore, intrinsic functional connectivity of the hippocampus with ventral and dorsal aspects of the PFC and the basal ganglia prior to training were the strongest predictors of math performance gains after training (Fig. 15.7B,c). These findings further highlight that the hippocampus plays a critical, yet underappreciated role in children's mathematical learning (Qin et al., 2014; Supekar et al., 2013). Moreover, the results of these studies suggest that quantitative measures of brain structure and organization can provide reliable and predictive markers of learning in children, and these can be more sensitive than behavioral measures (Jolles, Supekar, et al., 2016; Supekar et al., 2013).

There is also evidence of prominent changes in structural brain features as a function of the same 2-month mathematical training described above (Jolles, Wassermann, et al., 2016). Notably, individual differences in behavioral gains in mathematical skills were predicted by plasticity of the white matter tract of the left longitudinal fasciculus linking frontal and temporal cortices in 7- to 10-year-old children (Jolles, Wassermann, et al., 2016) (Fig. 15.7B,d).

Cognitive training studies not only provide insights into mechanisms of learning and brain plasticity but also, and more pragmatically, can aid in testing the efficacy of an intervention in children with MLD. Iuculano et al. (2015) used a comprehensive training protocol (Fuchs et al., 2008, 2009, 2010, 2013; Powell et al., 2009) (Fig. 15.7B,a) to test plasticity-related effects in a selected population of 7- to 9-year-old children with MLD. Results showed that in parallel with improved performance—to the level of TD controls—2 months of training resulted in dramatic and extensive functional brain changes in children with MLD and normalized functional responses to the level of TD controls (Fig. 15.7B,e). Brain plasticity effects in MLD occurred in multiple brain systems important for mathematical learning (Fig. 15.1). These include higher-level visual areas in the ventral temporal–occipital cortex that support visual form judgment and symbol recognition, posterior parietal areas that are involved in quantity representations, and prefrontal regions that support domain-general cognitive functions critical for successful learning, including attention, rule switching, and some aspects of working memory (Fig. 15.7B,e). Critically, the degree of plasticity in all these systems was significantly related to performance gains in MLD (Fig. 15.7B,e—***Right***). Consistent with previous studies in adults (Delazer et al., 2003, 2005; Ischebeck et al., 2006, 2007; Zamarian & Delazer, 2014), children with MLD showed significant reductions in widespread activation after training. This suggests that this type of training can release the burden across distributed brain systems by placing fewer demands and concurrently decreasing load on neurocognitive resources in these children. More generally, these findings suggest that a comprehensive training, one which integrates conceptual and retrieval aspects of mathematical learning, might be highly effective in eliciting significant neuroplasticity effects in MLD.

Learning does not occur in isolation; there is the growing need to assess the contribution of other factors that are often neglected in neurocognitive models but are essential in modulating relevant brain circuits and can significantly contribute to individual differences in learning and development. These include, for example, motivational, affective, and social factors. To this end, in a recent study, Supekar et al. applied the same cognitive training paradigm (Fig. 15.7B,a) (Supekar, Iuculano, Chen, & Menon, 2015) and assessed behavioral and brain changes in a group of 7- to 9-year-old children with high levels of math anxiety (Young, Wu, & Menon, 2012). Cognitive training significantly reduced high levels of math anxiety in this cohort (Fig. 15.7B,f—***Top left***). Moreover, this training remediated aberrant functional responses and connectivity in emotion-related circuits, anchored in the basolateral amygdala (Fig. 15.7B,f—***Top right***), suggesting that focused exposure to mathematical problems can reduce negative emotional response to mathematics and highlighting a key role of the amygdala in this process (Supekar et al., 2015). Critically, changes in functional circuits related to emotion processing, anchored in the basolateral amygdala, were related to reductions in anxiety with training (Fig. 15.7B,f—***Bottom***).

Taken together, cognitive learning approaches provide well-controlled settings for examining sources of individual differences in learning and brain plasticity. Moreover, building toward explanatory learning frameworks informed by cognitive and *systems neuroscience* of cognitive and affective dimensions of learning may enable us to create paradigms to reduce the burden of mathematical difficulties at different points of development and in heterogeneous groups with varying cognitive abilities.

CONCLUSIONS AND FUTURE DIRECTIONS

In this chapter, we have taken a *systems neuroscience* approach to describe the basic organization of brain processes involved in mathematical cognition and learning, and sources of heterogeneity that underlie different aspects of information processing in this domain. The perspective taken in this review is that the multilayer complexity of neurocognitive processes involved in mathematical cognition and learning is best viewed in the context of typical and atypical development. This is because of the highly dynamic role of working memory, attention, declarative and semantic memory, and cognitive control systems at different stages of proficiency and skill acquisition.

We have reviewed the key building blocks of mathematical cognition and described how they depend on core *hubs* anchored in the IPS and the FG. These regions play an essential role in the perceptual and semantic representation of quantity and help build a-modal semantic representations of numerosity by combining perceptual inputs with visuospatial *primitives* (e.g., detecting the property of "threeness" in a set of three "scanned" and "attended" items in the environment). At their core, these processes depend on the integrity of the IPS and its interactions with the FG.

Multiple PFC circuits associated with various subdivisions of the PPC, not just the IPS, facilitate access to multiple working memory circuits for additional processing and manipulation of discrete quantity. The circuit view that emerges is that perceptual and semantic representations of quantity in the ventral temporal–occipital cortex and PPC anchor mathematical cognition (e.g., the ability to understand the meaning of "three items" in a set and to make the association between such semantics and their arbitrary symbols—to know that "3" represents "three items"); while multiple prefrontal, parietal, and MTL functional brain circuits help to scaffold learning and increase capacity for problem-solving (e.g., 3 items plus 4 items results in a total of 7 items). The manner in which these circuits are engaged changes with brain maturation, cognitive development, levels of ability, and as a function of task.

There is now growing evidence to suggest that functional circuits engaged by children are not the same as those engaged by adults, who have evolved multiple strategies and schema-like knowledge for efficient learning. A number of scaffolding systems are involved during development to support the efficient acquisition of mathematical knowledge and learning. A particularly striking example is the demonstration of hippocampal-frontal and parietal-frontal circuits that are recruited in children but not in adults. The data reviewed here converge on the idea that the precise nature of this engagement is a function of developmental stage, domain knowledge, problem complexity, and individual proficiency in use of efficient problem-solving strategies.

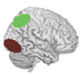
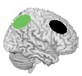
We are still in the initial stages of understanding how functional brain circuits unfold with development and how they go awry in atypical development. It is, nevertheless, clear that the exclusive focus on activity levels in a small set of brain regions identified in highly skilled adults will likely miss important changes in network-level functional organization that accompanies learning and development. Increasingly, the focus has also shifted to multivariate analyses, as it is evident that similar levels of activation across task conditions do not necessarily imply similar kinds of information processing (Blair, Rosenberg-Lee, Tsang, Schwartz, & Menon, 2012; Prado et al., 2011; Raizada et al., 2010). These types of fine-grained analyses clearly have important implications for understanding brain mechanisms mediating the formation of unique stimulus representations and how they mature with learning and development (Ashkenazi, Rosenberg-Lee, Tenison, & Menon, 2012; Chang, Rosenberg-Lee, Metcalfe, Chen, & Menon, 2015).

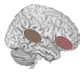
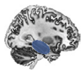
Most previous normative adult and developmental studies of mathematical cognition have mainly focused on localization of activation and age-related changes, but it is becoming increasingly clear that cognition depends on interactions within and between large-scale brain systems (Bressler & Menon, 2010). New research is beginning to highlight the significant and specific changes in anterior–posterior functional connectivity that take place during time periods important for developing core competence in mathematics (Rosenberg-Lee, Barth, & Menon, 2011). A *systems neuroscience approach*, with its emphasis on networks and connectivity, rather than a pure localization approach, is better suited to further understand how even basic mathematical skills develop and are ultimately expressed in the adult brain. Moreover, analysis of network changes with learning can further clarify dynamic processing involved in mathematical learning and better address sources of individual differences in learning profiles (Bassett et al., 2011).

In sum, mathematical learning and skill acquisition require the coordination and integration of multiple cognitive processes, which rely on the engagement of short- and long-range connectivity between distributed brain systems that undergo significant changes—in terms of recruitment and organization—as a function of development and learning (Fair et al., 2008; Supekar & Menon, 2012; Supekar et al., 2010) (Box 15.2). In the many different ways we have tried to highlight in this chapter, mathematical knowledge serves as a model domain for investigating the ontogenesis of human cognitive and problem-solving skills, and explain why some individuals excel and others struggle.

BOX 15.2

FUNCTIONAL BRAIN SYSTEMS, THEIR ASSOCIATED BRAIN REGIONS, AND COGNITIVE FUNCTIONS INVOLVED IN MATHEMATICAL LEARNING AND COGNITION

Brain System	**Brain Region**	**Cognitive Function**
Ventral–dorsal visual streams 	Posterior parietal cortex • Intraparietal sulcus	*Building blocks of mathematical cognition* Quantity representation
	Ventral temporal–occipital cortex • Fusiform gyrus	Symbols’ recognition
Parietal-frontal 	Posterior parietal cortex • Frontal eye fields • Intraparietal sulcus	*Working memory processing* Visual short-term memory and attention
	Lateral parietal cortex • Supramarginal gyrus • Dorsolateral prefrontal cortex • Supplementary motor area • Anterior insula	Quantity manipulation in working memory

Lateral frontotemporal 	Superior and middle temporal lobe • Superior temporal sulcus • Middle temporal gyrus	*Phonological awareness and processing* Auditory representation
	Lateral frontal lobe • Inferior frontal gyrus	Verbal information processing
Medial temporal 	Hippocampus	*Arithmetic facts* Memory formation
Prefrontal 	Lateral frontal lobe • Dorsolateral prefrontal cortex • Ventrolateral prefrontal cortex	*Mathematical problem-solving/reasoning* Cognitive control/executive functions
	Anterior frontal lobe • Anterior cingulate cortex • Anterior insula	Salience

References

Allison, T., McCarthy, G., Nobre, A., Puce, A., & Belger, A. (1994). Human extrastriate visual cortex and the perception of faces, words, numbers, and colors. *Cerebral Cortex*, *4*(5), 544–554. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/7833655.

American Psychiatry Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatry Publishing.

Andres, M., Michaux, N., & Pesenti, M. (2012). Common substrate for mental arithmetic and finger representation in the parietal cortex. *Neuroimage*, *62*(3), 1520–1528. https://doi.org/10.1016/j.neuroimage.2012.05.047.

Andres, M., Pelgrims, B., Michaux, N., Olivier, E., & Pesenti, M. (2011). Role of distinct parietal areas in arithmetic: An fMRI-guided TMS study. *Neuroimage*, *54*(4), 3048–3056. https://doi.org/10.1016/j.neuroimage.2010.11.009.

Ansari, D. (2008). Effects of development and enculturation on number representation in the brain. *Nature Reviews Neuroscience*, *9*(4), 278–291. https://doi.org/10.1038/nrn2334.

Ansari, D., & Dhital, B. (2006). Age-related changes in the activation of the intraparietal sulcus during nonsymbolic magnitude processing: An event-related functional magnetic resonance imaging study. *Journal of Cognitive Neuroscience*, *18*(11), 1820–1828. https://doi.org/10.1162/jocn.2006.18.11.1820.

Ansari, D., Garcia, N., Lucas, E., Hamon, K., & Dhital, B. (2005). Neural correlates of symbolic number processing in children and adults. *Neuroreport*, *16*(16), 1769–1773. https://doi.org/10.1097/01.wnr.0000183905.23396.f1.

Arsalidou, M., & Taylor, M. J. (2011). Is 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. *Neuroimage*, *54*(3), 2382–2393. https://doi.org/10.1016/j.neuroimage.2010.10.009.

Ashcraft, M. H. (1982). The development of mental arithmetic: A chronometric approach. *Developmental Review*, *2*(3), 213–236.

Ashkenazi, S., Black, J. M., Abrams, D. A., Hoeft, F., & Menon, V. (2013). Neurobiological underpinnings of math and reading learning disabilities. *Journal of Learning Disabilities*, *46*(6), 549–569. https://doi.org/10.1177/0022219413483174.

Ashkenazi, S., Rosenberg-Lee, M., Metcalfe, A. W., Swigart, A. G., & Menon, V. (2013). Visuo-spatial working memory is an important source of domain-general vulnerability in the development of arithmetic cognition. *Neuropsychologia*, *51*(11), 2305–2317. https://doi.org/10.1016/j.neuropsychologia.2013.06.031.

Ashkenazi, S., Rosenberg-Lee, M., Tenison, C., & Menon, V. (2012). Weak task-related modulation and stimulus representations during arithmetic problem solving in children with developmental dyscalculia. *Developmental Cognitive Neuroscience*, *2*, S152–S166. https://doi.org/10.1016/j.dcn.2011.09.006.

Baddeley, A. D., & Hitch, G. J. (1974). Working memory. In G. A. Bower (Ed.), *Recent advances in learning and motivation*. New York: Academic Press.

Barrouillet, P., Fayol, M., & Lathuliere, E. (1997). Selecting between competitors in multiplication tasks: An explanation of the errors produced by adolescents with learning difficulties. *International Journal of Behavioral Development*, *21*(2), 253–275.

Bassett, D. S., Wymbs, N. F., Porter, M. A., Mucha, P. J., Carlson, J. M., & Grafton, S. T. (2011). Dynamic reconfiguration of human brain networks during learning. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(18), 7641–7646. https://doi.org/10.1073/pnas.1018985108.

Berteletti, I., Prado, J., & Booth, J. R. (2014). Children with mathematical learning disability fail in recruiting verbal and numerical brain regions when solving simple multiplication problems. *Cortex*, *57*, 143–155. https://doi.org/10.1016/j.cortex.2014.04.001.

Blair, K. P., Rosenberg-Lee, M., Tsang, J. M., Schwartz, D. L., & Menon, V. (2012). Beyond natural numbers: Negative number representation in parietal cortex. *Frontiers in Human Neuroscience*, *6*, 7. https://doi.org/10.3389/fnhum.2012.00007.

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends in Cognitive Sciences*, *14*(6), 277–290. pii: S1364-6613(10)00089-6 https://doi.org/10.1016/j.tics.2010.04.004.

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. (2002). Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. *Neuron*, *33*(2), 301–311.

Butterworth, B. (1999). *The mathematical brain*. London: Macmillan.

Butterworth, B. (2005). Developmental dyscalculia. In J. I. D. Campbell (Ed.), *Handbook of mathematical cognition*. Hove: Psychology Press.

Butterworth, B. (2010). Foundational numerical capacities and the origins of dyscalculia. *Trends in Cognitive Sciences*, *14*(12), 534–541. https://doi.org/10.1016/j.tics.2010.09.007.

Butterworth, B., & Kovas, Y. (2013). Understanding neurocognitive developmental disorders can improve education for all. *Science*, *340*, 300–305.

Butterworth, B., & Reigosa-Crespo, V. (2007). Information processing deficits in dyscalculia. In D. B. Berch, & M. M. M. Mazzocco (Eds.), *Why is math so hard for some children? The nature and origins of mathematical learning difficulties and disabilities*. Baltimore, MD, USA: Paul H Brookes Publishing Co.

Butterworth, B., Varma, S., & Laurillard, D. (2011). Dyscalculia: From brain to education. *Science*, *332*(6033), 1049–1053. https://doi.org/10.1126/science.1201536.

Cai, W., Chen, T., Ryali, S., Kochalka, J., Li, C. S., & Menon, V. (2015). Causal interactions within a frontal-cingulate-parietal network during cognitive control: Convergent evidence from a multisite-multitask investigation. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhv046.

Cai, W., Ryali, S., Chen, T., Li, C. S., & Menon, V. (2014). Dissociable roles of right inferior frontal cortex and anterior insula in inhibitory control: Evidence from intrinsic and task-related functional parcellation, connectivity, and response profile analyses across multiple datasets. *Journal of Neuroscience*, *34*(44), 14652–14667. https://doi.org/10.1523/JNEUROSCI.3048-14.2014.

Cantlon, J. F., Brannon, E. M., Carter, E. J., & Pelphrey, K. A. (2006). Functional imaging of numerical processing in adults and 4-y-old children. *PLoS Biology*, *4*(5), e125. pii: 05-PLBI-RA-1376R3. https://doi.org/10.1371/journal.pbio.0040125.

Cantlon, J. F., Libertus, M. E., Pinel, P., Dehaene, S., Brannon, E. M., & Pelphrey, K. A. (2009). The neural development of an abstract concept of number. *Journal of Cognitive Neuroscience*, *21*(11), 2217–2229. https://doi.org/10.1162/jocn.2008.21159.

Carey, S. (2004). *On the origin of concepts*. New York: Oxford University Press.
Chang, T. T., Metcalfe, A. W. S., Padmanabhan, A., Chen, T. W., & Menon, V. (2016). Heterogeneous and nonlinear development of human posterior parietal cortex function. *Neuroimage*, *126*, 184–195. https://doi.org/10.1016/j.neuroimage.2015.11.053.
Chang, T. T., Rosenberg-Lee, M., Metcalfe, A. W., Chen, T., & Menon, V. (2015). Development of common neural representations for distinct numerical problems. *Neuropsychologia*, *75*, 481–495. https://doi.org/10.1016/j.neuropsychologia.2015.07.005.
Cho, S., Metcalfe, A. W., Young, C. B., Ryali, S., Geary, D. C., & Menon, V. (2012). Hippocampal-prefrontal engagement and dynamic causal interactions in the maturation of children's fact retrieval. *Journal of Cognitive Neuroscience*, *24*(9), 1849–1866. https://doi.org/10.1162/jocn_a_00246.
Cho, S., Ryali, S., Geary, D. C., & Menon, V. (2011). How does a child solve 7 + 8? Decoding brain activity patterns associated with counting and retrieval strategies. *Developmental Science*, *14*(5), 989–1001. https://doi.org/10.1111/j.1467-7687.2011.01055.x.
Cohen Kadosh, R., Cohen Kadosh, K., Kaas, A., Henik, A., & Goebel, R. (2007). Notation-dependent and -independent representations of numbers in the parietal lobes. *Neuron*, *53*(2), 307–314. https://doi.org/10.1016/j.neuron.2006.12.025.
Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, *16*(9), 1348–1355. https://doi.org/10.1038/nn.3470.
Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: From environment to theory of mind. *Neuron*, *58*(3), 306–324. https://doi.org/10.1016/j.neuron.2008.04.017.
Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201–215. https://doi.org/10.1038/nrn755.
Cowan, R., & Carney, D. P. J. (2006). Calendrical savants: Exceptionality and practice. *Cognition*, *100*(2), B1–B9. https://doi.org/10.1016/j.cognition.2005.08.001.
Cowan, R., Donlan, C., Shepherd, D. L., Cole-Fletcher, R., Saxton, M., & Hurry, J. (2011). Basic calculation proficiency and mathematics achievement in elementary school children. *Journal of Educational Psychology*, *103*(4), 786–803. https://doi.org/10.1037/a0024556.
Cowan, R., & Frith, C. (2009). Do calendrical savants use calculation to answer date questions? A functional magnetic resonance imaging study. *Philosophical Transactions of the Royal Society B-Biological Sciences*, *364*(1522), 1417–1424. https://doi.org/10.1098/rstb.2008.0323.
Cowan, R., O'Connor, N., & Samella, K. (2003). The skills and methods of calendrical savants. *Intelligence*, *31*(1), 51–65. pii: S0160-2896(02)00119-8.
Cutini, S., Scatturin, P., Basso Moro, S., & Zorzi, M. (2014). Are the neural correlates of subitizing and estimation dissociable? An fNIRS investigation. *Neuroimage*, *85*(Pt 1), 391–399. https://doi.org/10.1016/j.neuroimage.2013.08.027.
Dagenbach, D., & McCloskey, M. (1992). The organization of arithmetic facts in memory: Evidence from a brain-damaged patient. *Brain and Cognition*, *20*(2), 345–366.

Dantzig, T. (1930). *Number: The language of science: A critical survey written for the cultured non-mathematician*. New York, NY, USA: Macmillan.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Current Opinion in Neurobiology*, *16*(6), 693–700. https://doi.org/10.1016/j.conb.2006.10.012.

Davachi, L., Mitchell, J. P., & Wagner, A. D. (2003). Multiple routes to memory: Distinct medial temporal lobe processes build item and source memories. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(4), 2157–2162. https://doi.org/10.1073/pnas.0337195100.

Davis, N., Cannistraci, C. J., Rogers, B. P., Gatenby, J. C., Fuchs, L. S., Anderson, A. W., et al. (2009). Aberrant functional activation in school age children at-risk for mathematical disability: A functional imaging study of simple arithmetic skill. *Neuropsychologia*, *47*(12), 2470–2479. https://doi.org/10.1016/j.neuropsychologia.2009.04.024.

De Smedt, B., Holloway, I. D., & Ansari, D. (2011). Effects of problem size and arithmetic operation on brain activation during calculation in children with varying levels of arithmetical fluency. *Neuroimage*, *57*(3), 771–781.

De Smedt, B., Taylor, J., Archibald, L., & Ansari, D. (2010). How is phonological processing related to individual differences in children's arithmetic skills? *Developmental Science*, *13*(3), 508–520. https://doi.org/10.1111/j.1467-7687.2009.00897.x.

Dehaene, S. (1997). *The number sense: How the mind creates mathematics*. New York: Oxford University Press.

Dehaene, S. (2003). The neural basis of the Weber-Fechner law: A logarithmic mental number line. *Trends in Cognitive Sciences*, *7*(4), 145–147. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12691758.

Dehaene, S., & Cohen, L. (1995). Towards an anatomical and functional model of number processing. *Mathematical Cognition*, *1*(1), 83–120.

Dehaene, S., Molko, N., Cohen, L., & Wilson, A. J. (2004). Arithmetic and the brain. *Current Opinion in Neurobiology*, *14*(2), 218–224. https://doi.org/10.1016/j.conb.2004.03.008.

Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. *Cognitive Neuropsychology*, *20*(3), 487–506.

Delazer, M., Domahs, F., Bartha, L., Brenneis, C., Lochy, A., Trieb, T., et al. (2003). Learning complex arithmetic–an fMRI study. *Brain Research Cognitive Brain Research*, *18*(1), 76–88.

Delazer, M., Ischebeck, A., Domahs, F., Zamarian, L., Koppelstaetter, F., Siedentopf, C. M., et al. (2005). Learning by strategies and learning by drill–evidence from an fMRI study. *Neuroimage*, *25*(3), 838–849.

DeStefano, D., & LeFevre, J. A. (2004). The role of working memory in mental arithmetic. *European Journal of Cognitive Psychology*, *16*(3), 353–386.

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: A three-component model. *Trends in Cognitive Sciences*, *11*(9), 379–386.

Drenthen, G. S., Barendse, E. M., Aldenkamp, A. P., van Veenendaal, T. M., Puts, N. A., Edden, R. A., et al. (2016). Altered neurotransmitter metabolism in adolescents with high-functioning autism. *Psychiatry Research*, *256*, 44–49.

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience*, *30*, 123–152.

Evans, T. M., Flowers, D. L., Napoliello, E. M., Olulade, O. A., & Eden, G. F. (2014). The functional anatomy of single-digit arithmetic in children with developmental dyslexia. *Neuroimage*, *101*, 644–652. https://doi.org/10.1016/j.neuroimage.2014.07.028.

Evans, T. M., Kochalka, J., Ngoon, T. J., Wu, S. S., Qin, S. Z., Battista, C., et al. (2015). Brain structural integrity and intrinsic functional connectivity forecast 6 year longitudinal growth in children's numerical abilities. *Journal of Neuroscience*, *35*(33), 11743–11750. https://doi.org/10.1523/Jneurosci.0216-15.2015.

Fair, D. A., Cohen, A. L., Dosenbach, N. U., Church, J. A., Miezin, F. M., Barch, D. M., et al. (2008). The maturing architecture of the brain's default network. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(10), 4028–4032. https://doi.org/10.1073/pnas.0800376105.

Fan, Q., Anderson, A. W., Davis, N., & Cutting, L. E. (2014). Structural connectivity patterns associated with the putative visual word form area and children's reading ability. *Brain Research*, *1586*, 118–129. https://doi.org/10.1016/j.brainres.2014.08.050.

Fias, W., Menon, V., & Szucs (2013). Multiple components of developmental dyscalculia. *Trends in Educational Neuroscience*, *2*(2), 43–47.

Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(26), 10046–10051.

Fuchs, L. S., Fuchs, D., Stuebing, K., Fletcher, J. M., Hamlett, C. L., & Lambert, W. (2008). Problem solving and computational skill: Are they shared or distinct aspects of mathematical cognition? *Journal of Educational Psychology*, *100*(1), 30–47. https://doi.org/10.1037/0022-0663.100.1.30.

Fuchs, L. S., Geary, D. C., Compton, D. L., Fuchs, D., Schatschneider, C., Hamlett, C. L., et al. (2013). Effects of first-grade number knowledge tutoring with contrasting forms of practice. *Journal of Educational Psychology*, *105*(1), 58–77.

Fuchs, L. S., Powell, S. R., Hamlett, C. L., Fuchs, D., Cirino, P. T., & Fletcher, J. M. (2008). Remediating computational deficits at third grade: A randomized field trial. *Journal of Research on Educational Effectiveness*, *1*(1), 2–32.

Fuchs, L. S., Powell, S. R., Seethaler, P. M., Cirino, P. T., Fletcher, J. M., Fuchs, D., et al. (2009). Remediating number combination and word problem deficits among students with mathematics difficulties: A randomized control trial. *Journal of Educational Psychology*, *101*(3), 561–576. https://doi.org/10.1037/a0014701.

Fuchs, L. S., Powell, S. R., Seethaler, P. M., Fuchs, D., Hamlett, C. L., Cirino, P. T., et al. (2010). A framework for remediating number combination deficits. *Exceptional Children*, *76*(2), 135–165.

Gauthier, I., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. *Nature Neuroscience*, *3*(2), 191–197. https://doi.org/10.1038/72140.

Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J. C. (1999). Activation of the middle fusiform 'face area' increases with expertise in recognizing novel objects. *Nature Neuroscience*, *2*(6), 568–573. https://doi.org/10.1038/9224.

Geary, D. C. (2011). Cognitive predictors of achievement growth in mathematics: A 5-year longitudinal study. *Developmental Psychology*, *47*(6), 1539–1552. https://doi.org/10.1037/a0025510.

Geary, D. C., & Brown, S. C. (1991). Cognitive addition: Strategy choice and speed-of-processing differences in gifted, normal, and mathematically disabled children. *Developmental Psychology*, *27*(3), 398–406.

Geary, D. C., Hamson, C. O., & Hoard, M. K. (2000). Numerical and arithmetical cognition: A longitudinal study of process and concept deficits in children with learning disability. *Journal of Experimental Child Psychology*, *77*(3), 236–263 Retrieved from View Full Text in PDF format (ECO).

Geary, D. C., & Hoard, M. K. (2003). Learning disabilities in basic mathematics: Deficits in memory and cognition. In J. M. Royer (Ed.), *Mathematical cognition*. Greenwich, CT: Information Age Publishing.

Geary, D. C., Hoard, M. K., & Bailey, D. H. (2012). Fact retrieval deficits in low achieving children and children with mathematical learning disability. *Journal of Learning Disabilities*, *45*(4), 291–307. https://doi.org/10.1177/0022219410392046.

Geary, D. C., Hoard, M. K., Byrd-Craven, J., Nugent, L., & Numtee, C. (2007). Cognitive mechanisms underlying achievement deficits in children with mathematical learning disability. *Child Development*, *78*(4), 1343–1359. https://doi.org/10.1111/j.1467-8624.2007.01069.x.

Gobel, S. M., Watson, S. E., Lervag, A., & Hulme, C. (2014). Children's arithmetic development it is number knowledge, not the approximate number sense, that counts. *Psychological Science*, *25*(3), 789–798. https://doi.org/10.1177/0956797613516471.

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*, *15*(1), 20–25.

Grabner, R. H., Ansari, D., Koschutnig, K., Reishofer, G., Ebner, F., & Neuper, C. (2009). To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. *Neuropsychologia*, *47*(2), 604–608.

Groen, G., & Parkman, J. (1972). Chronometric analysis of simple addition. *Psychological Review*, *329*.

Grotheer, M., Herrmann, K. H., & Kovacs, G. (2016). Neuroimaging evidence of a bilateral representation for visually presented numbers. *Journal of Neuroscience*, *36*(1), 88–97.

Gupta, S. C., Ravikrishnan, A., Liu, J., Mao, Z., Pavuluri, R., Hillman, B. G., et al. (2016). The NMDA receptor GluN2C subunit controls cortical excitatory-inhibitory balance, neuronal oscillations and cognitive function. *Scientific Reports*, *6*, 38321.

Ham, T., Leff, A., de Boissezon, X., Joffe, A., & Sharp, D. J. (2013). Cognitive control and the salience network: An investigation of error processing and effective connectivity. *Journal of Neuroscience*, *33*(16), 7091–7098. https://doi.org/10.1523/JNEUROSCI.4692-12.2013.

Heine, A., Tamm, S., Wissmann, J., & Jacobs, A. M. (2011). Electrophysiological correlates of non-symbolic numerical magnitude processing in children: Joining the dots. *Neuropsychologia*, *49*(12), 3238–3246. https://doi.org/10.1016/j.neuropsychologia.2011.07.028.

Hinton, E. C., Dymond, S., von Hecker, U., & Evans, C. J. (2010). Neural correlates of relational reasoning and the symbolic distance effect: Involvement of parietal cortex. *Neuroscience*, *168*(1), 138–148. https://doi.org/10.1016/j.neuroscience.2010.03.052.

Holloway, I. D., Battista, C., Vogel, S. E., & Ansari, D. (2012). Semantic and perceptual processing of number symbols: Evidence from a cross-linguistic fMRI adaptation study. *Journal of Cognitive Neuroscience*, 1–13.

Hyde, D. C., Boas, D. A., Blair, C., & Carey, S. (2010). Near-infrared spectroscopy shows right parietal specialization for number in pre-verbal infants. *Neuroimage*, *53*(2), 647–652.

Hyde, D. C., & Spelke, E. S. (2009). All numbers are not equal: An electrophysiological investigation of small and large number representations. *Journal of Cognitive Neuroscience*, *21*(6), 1039–1053. https://doi.org/10.1162/jocn.2009.21090.

Imbo, I., Vandierendonck, A., & Vergauwe, E. (2007). The role of working memory in carrying and borrowing. *Psychological Research*, *71*(4), 467–483. https://doi.org/10.1007/s00426-006-0044-8.

Isaacs, E. B., Edmonds, C. J., Lucas, A., & Gadian, D. G. (2001). Calculation difficulties in children of very low birthweight: A neural correlate. *Brain*, *124*(Pt 9), 1701–1707.

Ischebeck, A., Zamarian, L., Egger, K., Schocke, M., & Delazer, M. (2007). Imaging early practice effects in arithmetic. *Neuroimage*, *36*(3), 993–1003.

Ischebeck, A., Zamarian, L., Siedentopf, C., Koppelstatter, F., Benke, T., Felber, S., et al. (2006). How specifically do we learn? Imaging the learning of multiplication and subtraction. *Neuroimage*, *30*(4), 1365–1375. https://doi.org/10.1016/j.neuroimage.2005.11.016.

Iuculano, T., Rosenberg-Lee, M., Richardson, J., Tenison, C., Fuchs, L., Supekar, K., et al. (2015). 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.

Iuculano, T., Rosenberg-Lee, M., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., et al. (2014). Brain organization underlying superior mathematical abilities in children with autism. *Biological Psychiatry*, *75*(3), 223–230.

Iuculano, T., Tang, J., Hall, C. W., & Butterworth, B. (2008). Core information processing deficits in developmental dyscalculia and low numeracy. *Developmental Science*, *11*(5), 669–680. https://doi.org/10.1111/j.1467-7687.2008.00716.x.

Jeong, S. K., & Xu, Y. (2016). Behaviorally relevant abstract object identity representation in the human parietal cortex. *Journal of Neuroscience*, *36*(5), 1607–1619. https://doi.org/10.1523/JNEUROSCI.1016-15.2016.

Jolles, D., Ashkenazi, S., Kochalka, J., Evans, T., Richardson, J., Rosenberg-Lee, M., et al. (2016). Parietal hyper-connectivity, aberrant brain organization, and circuit-based biomarkers in children with mathematical disabilities. *Developmental Science*, *19*(4), 613–631. https://doi.org/10.1111/desc.12399.

Jolles, D., Supekar, K., Richardson, J., Tenison, C., Ashkenazi, S., Rosenberg-Lee, M., et al. (2016). Reconfiguration of parietal circuits with cognitive tutoring in elementary school children. *Cortex*, *83*, 231–245. https://doi.org/10.1016/j.cortex.2016.08.004.

Jolles, D., Wassermann, D., Chokhani, R., Richardson, J., Tenison, C., Bammer, R., et al. (2016). Plasticity of left perisylvian white-matter tracts is associated with individual differences in math learning. *Brain Structure and Function*, *221*(3), 1337–1351. https://doi.org/10.1007/s00429-014-0975-6.

Jordan, N. C., Levine, S. C., & Huttenlocher, J. (1995). Calculation abilities in young children with different patterns of cognitive functioning. *Journal of Learning Disabilities*, *28*(1), 53–64. https://doi.org/10.1177/002221949502800109.

Kadosh, R. C., Kadosh, K. C., Schuhmann, T., Kaas, A., Goebel, R., Henik, A., et al. (2007). Virtual dyscalculia induced by parietal-lobe TMS impairs automatic magnitude processing. *Current Biology*, *17*(8), 689–693. https://doi.org/10.1016/j.cub.2007.02.056.

Kaufmann, L., Vogel, S. E., Starke, M., Kremser, C., & Schocke, M. (2009a). Numerical and non-numerical ordinality processing in children with and without developmental dyscalculia: Evidence from fMRI. *Cognitive Development*, *24*(4), 486–494.

Kaufmann, L., Vogel, S. E., Starke, M., Kremser, C., Schocke, M., & Wood, G. (2009b). Developmental dyscalculia: Compensatory mechanisms in left intraparietal regions in response to nonsymbolic magnitudes. *Behavioral and Brain Functions*, *5*(1), 35.

Kaufmann, L., Wood, G., Rubinsten, O., & Henik, A. (2011). Meta-analyses of developmental fMRI studies investigating typical and atypical trajectories of number processing and calculation. *Developmental Neuropsychology*, *36*(6), 763–787.

Knops, A., Piazza, M., Sengupta, R., Eger, E., & Melcher, D. (2014). A shared, flexible neural map architecture reflects capacity limits in both visual short-term memory and enumeration. *Journal of Neuroscience*, *34*(30), 9857–9866. https://doi.org/10.1523/JNEUROSCI.2758-13.2014.

Kucian, K., Grond, U., Rotzer, S., Henzi, B., Schonmann, C., Plangger, F., et al. (2011). Mental number line training in children with developmental dyscalculia. *Neuroimage*, *57*(3), 782–795. https://doi.org/10.1016/j.neuroimage.2011.01.070.

Kucian, K., Loenneker, T., Dietrich, T., Dosch, M., Martin, E., & von Aster, M. (2006). Impaired neural networks for approximate calculation in dyscalculic children: A functional MRI study. *Behavioral and Brain Functions*, *2*, 31. https://doi.org/10.1186/1744-9081-2-31.

Kucian, K., & von Aster, M. (2015). Developmental dyscalculia. *European Journal of Pediatrics*, *174*(1), 1–13. https://doi.org/10.1007/s00431-014-2455-7.

Kucian, K., von Aster, M., Loenneker, T., Dietrich, T., & Martin, E. (2008). Development of neural networks for exact and approximate calculation: A fMRI study. *Developmental Neuropsychology*, *33*(4), 447–473. https://doi.org/10.1080/87565640802101474.

Landerl, K., Bevan, A., & Butterworth, B. (2004). Developmental dyscalculia and basic numerical capacities: A study of 8-9-year-old students. *Cognition*, *93*(2), 99–125. https://doi.org/10.1016/j.cognition.2003.11.004.

Lee, K. M. (2000). Cortical areas differentially involved in multiplication and subtraction: A functional magnetic resonance imaging study and correlation with a case of selective acalculia. *Annals of Neurology*, *48*(4), 657–661.

Luck, S. J., & Vogel, E. K. (2013). Visual working memory capacity: From psychophysics and neurobiology to individual differences. *Trends in Cognitive Sciences*, *17*(8), 391–400. https://doi.org/10.1016/j.tics.2013.06.006.

McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: Expertise for reading in the fusiform gyrus. *Trends in Cognitive Sciences*, *7*(7), 293–299. https://doi.org/10.1016/S1364-6613(03)00134-7.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, *102*(3), 419–457.

Menon, V. (2014). Arithmetic in child and adult brain. In R. Cohen Kadosh, & A. Dowker (Eds.), *Handbook of mathematical cognition*. Oxford: Oxford University Press.

Menon, V. (2016). Working memory in children's math learning and its disruption in dyscalculia. *Current Opinion in Behavioral Sciences*, *10*, 125–132. https://doi.org/10.1016/j.cobeha.2016.05.014.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, *214*(5–6), 655–667.

Metcalfe, A. W., Ashkenazi, S., Rosenberg-Lee, M., & Menon, V. (2013). Fractionating the neural correlates of individual working memory components underlying arithmetic problem solving skills in children. *Developmental Cognitive Neuroscience*, *6*, 162–175. https://doi.org/10.1016/j.dcn.2013.10.001.

Molko, N., Cachia, A., Riviere, D., Mangin, J. F., Bruandet, M., Le Bihan, D., et al. (2003). Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. *Neuron*, *40*(4), 847–858. https://doi.org/10.1016/S0896-6273(03)00670-6.

Molko, N., Cachia, A., Riviere, D., Mangin, J. F., Bruandet, M., LeBihan, D., et al. (2004). Brain anatomy in Turner syndrome: Evidence for impaired social and spatial-numerical networks. *Cerebral Cortex*, *14*(8), 840–850. https://doi.org/10.1093/cercor/bhh042.

Naaijen, J., Bralten, J., Poelmans, G., Consortium, I., Glennon, J. C., Franke, B., et al. (2017). Glutamatergic and GABAergic gene sets in attention-deficit/hyperactivity disorder: Association to overlapping traits in ADHD and autism. *Translational Psychiatry*, *7*(1), e999. https://doi.org/10.1038/tp.2016.273.

Naccache, L., & Dehaene, S. (2001). The priming method: Imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. *Cerebral Cortex*, *11*(10), 966–974.

Park, J., Hebrank, A., Polk, T. A., & Park, D. C. (2012). Neural dissociation of number from letter recognition and its relationship to parietal numerical processing. *Journal of Cognitive Neuroscience*, *24*(1), 39–50. https://doi.org/10.1162/jocn_a_00085.

Pesenti, M., Seron, X., Samson, D., & Duroux, B. (1999). Basic and exceptional calculation abilities in a calculating prodigy: A case study. *Mathematical Cognition*, *5*, 97–148.

Pesenti, M., Zago, L., Crivello, F., Mellet, E., Samson, D., Duroux, B., et al. (2001). Mental calculation in a prodigy is sustained by right prefrontal and medial temporal areas. *Nature Neuroscience*, *4*(1), 103–107.

Piazza, M., Izard, V., Pinel, P., Le Bihan, D., & Dehaene, S. (2004). Tuning curves for approximate numerosity in the human intraparietal sulcus. *Neuron*, *44*(3), 547–555. https://doi.org/10.1016/j.neuron.2004.10.014.

Piazza, M., Mechelli, A., Butterworth, B., & Price, C. J. (2002). Are subitizing and counting implemented as separate or functionally overlapping processes? *Neuroimage*, *15*(2), 435–446. https://doi.org/10.1006/nimg.2001.0980.

Powell, S. R., Fuchs, L. S., Fuchs, D., Cirino, P. T., & Fletcher, J. M. (2009). Effects of fact retrieval tutoring on third-grade students with math difficulties with and without reading difficulties. *Learning Disabilities Research and Practice: A Publication of the Division for Learning Disabilities, Council of Exceptional Children*, *24*(1), 1–11.

Prado, J., Mutreja, R., & Booth, J. R. (2014). Developmental dissociation in the neural responses to simple multiplication and subtraction problems. *Developmental Science*, *17*(4), 537–552.

Prado, J., Mutreja, R., Zhang, H., Mehta, R., Desroches, A. S., Minas, J. E., et al. (2011). Distinct representations of subtraction and multiplication in the neural systems for numerosity and language. *Human Brain Mapping*, *32*(11), 1932–1947.

Price, G. R., Holloway, I., Rasanen, P., Vesterinen, M., & Ansari, D. (2007). Impaired parietal magnitude processing in developmental dyscalculia. *Current Biology*, *17*(24), R1042–R1043. https://doi.org/10.1016/j.cub.2007.10.013.

Pugh, K. R., Frost, S. J., Rothman, D. L., Hoeft, F., Del Tufo, S. N., Mason, G. F., et al. (2014). Glutamate and choline levels predict individual differences in reading ability in emergent readers. *Journal of Neuroscience*, *34*(11), 4082–4089. https://doi.org/10.1523/JNEUROSCI.3907-13.2014.

Qin, S., Cho, S., Chen, T., Rosenberg-Lee, M., Geary, D. C., & Menon, V. (2014). Hippocampal-neocortical functional reorganization underlies children's cognitive development. *Nature Neuroscience*, *17*(9), 1263–1269.

Raizada, R. D. S., Tsao, F. M., Liu, H. M., Holloway, I. D., Ansari, D., & Kuhl, P. K. (2010). Linking brain-wide multivoxel activation patterns to behaviour: Examples from language and math. *Neuroimage*, *51*(1), 462–471. https://doi.org/10.1016/j.neuroimage.2010.01.080.

Rivera, S. M., Menon, V., White, C. D., Glaser, B., & Reiss, A. L. (2002). Functional brain activation during arithmetic processing in females with fragile X Syndrome is related to FMRI protein expression. *Human Brain Mapping*, *16*(4), 206–218. https://doi.org/10.1002/hbm.10048.

Rivera, S. M., Reiss, A. L., Eckert, M. A., & Menon, V. (2005). Developmental changes in mental arithmetic: Evidence for increased functional specialization in the left inferior parietal cortex. *Cerebral Cortex*, *15*(11), 1779–1790. https://doi.org/10.1093/cercor/bhi055.

Rosenberg-Lee, M., Ashkenazi, S., Chen, T., Young, C. B., Geary, D. C., & Menon, V. (2014). Brain hyper-connectivity and operation-specific deficits during arithmetic problem solving in children with developmental dyscalculia. *Developmental Science*, *18*(3), 351–372.

Rosenberg-Lee, M., Barth, M., & Menon, V. (2011). What difference does a year of schooling make? Maturation of brain response and connectivity between 2nd and 3rd grades during arithmetic problem solving. *Neuroimage*, *57*(3), 796–808. https://doi.org/10.1016/j.neuroimage.2011.05.013.

Rotzer, S., Kucian, K., Martin, E., von Aster, M., Klaver, P., & Loenneker, T. (2008). Optimized voxel-based morphometry in children with developmental dyscalculia. *Neuroimage*, *39*(1), 417–422. https://doi.org/10.1016/j.neuroimage.2007.08.045.

Rousselle, L., & Noel, M. P. (2007). Basic numerical skills in children with mathematics learning disabilities: A comparison of symbolic vs non-symbolic number magnitude processing. *Cognition*, *102*(3), 361–395. https://doi.org/10.1016/j.cognition.2006.01.005.

Rykhlevskaia, E., Uddin, L. Q., Kondos, L., & Menon, V. (2009). Neuroanatomical correlates of developmental dyscalculia: Combined evidence from morphometry and tractography. *Frontiers in Human Neuroscience*, *3*, 51. https://doi.org/10.3389/neuro.09.051.2009.

Saygin, Z. M., Osher, D. E., Norton, E. S., Youssoufian, D. A., Beach, S. D., Feather, J., et al. (2016). Connectivity precedes function in the development of the visual word form area. *Nature Neuroscience*, *19*(9), 1250–1255. https://doi.org/10.1038/nn.4354.

Schaffelhofer, S., & Scherberger, H. (2016). Object vision to hand action in macaque parietal, premotor, and motor cortices. *Elife*, *5*. https://doi.org/10.7554/eLife.15278.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, *27*(9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007.

Shalev, R., Auerbach, J., Manor, O., & Gross-Tsur, V. (2000). Developmental dyscalculia: Prevalence and prognosis. *European Child and Adolescent Psychiatry*, *9*(0), S58–S64. https://doi.org/10.1007/s007870070009.

Shalev, R. S., Manor, O., & Gross-Tsur, V. (2005). Developmental dyscalculia: A prospective six-year follow-up. *Developmental Medicine and Child Neurology*, *47*(2), 121–125. https://doi.org/10.1017/S0012162205000216.

Shum, J., Hermes, D., Foster, B. L., Dastjerdi, M., Rangarajan, V., Winawer, J., et al. (2013). A brain area for visual numerals. *Journal of Neuroscience*, *33*(16), 6709–6715. https://doi.org/10.1523/JNEUROSCI.4558-12.2013.

Siegler, R. S. (1996). *Emerging minds: The process of change in children's thinking*. New York: Oxford University Press.

Siegler, R. S., & Shrager, J. (1984). Strategy choice in addition and subtraction: How do children know what to do? In C. Sophian (Ed.), *Origins of cognitive skills*. Hillsdale, NJ: Erlbaum.

Simon, O., Mangin, J. F., Cohen, L., Le Bihan, D., & Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron*, *33*(3), 475–487.

Squire, L. R. (1992). Memory and the hippocampus – a synthesis from findings with rats, monkeys, and humans. *Psychological Review*, *99*(2), 195–231. https://doi.org/10.1037/0033-295x.99.2.195.

Squire, L. R., Genzel, L., Wixted, J. T., & Morris, R. G. (2015). Memory consolidation. In E. Kandel, Y. Dudai, & M. Mayford (Eds.), *Perspectives in biology: Learning and memory*. Cold Spring Harbor Laboratory Press.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, *27*, 279–306.

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(34), 12569–12574. https://doi.org/10.1073/pnas.0800005105.

Stocco, A., & Anderson, J. R. (2008). Endogenous control and task representation: An fMRI study in algebraic problem-solving. *Journal of Cognitive Neuroscience*, *20*(7), 1300–1314. https://doi.org/10.1162/jocn.2008.20089.

Supekar, K., Iuculano, T., Chen, L., Menon, V., (2015). Remediation of childhood math anxiety and associated neural circuits through cognitive tutoring. *Journal of Neuroscience*, *35*(36), 12574–12583.

Supekar, K., & Menon, V. (2012). Developmental maturation of dynamic causal control signals in higher-order cognition: A neurocognitive network model. *PLoS Computational Biology*, *8*(2):e1002374.

Supekar, K., Swigart, A. G., Tenison, C., Jolles, D. D., Rosenberg-Lee, M., Fuchs, L., et al. (2013). Neural predictors of individual differences in response to math tutoring in primary-grade school children. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(20), 8230–8235. https://doi.org/10.1073/pnas.1222154110.

Supekar, K., Uddin, L. Q., Prater, K., Amin, H., Greicius, M. D., & Menon, V. (2010). Development of functional and structural connectivity within the default mode network in young children. *Neuroimage*, *52*(1), 290–301. https://doi.org/10.1016/j.neuroimage.2010.04.009.

Szucs, D., & Goswami, U. (2013). Developmental dyscalculia: Fresh perspectives. *Trends in Neuroscience and Education*, *2*(2), 33–37.

Tatti, R., Haley, M. S., Swanson, O. K., Tselha, T., & Maffei, A. (2016). Neurophysiology and regulation of the balance between excitation and inhibition in neocortical circuits. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2016.09.017.

Thompson, J. C., Abbott, D. F., Wheaton, K. J., Syngeniotis, A., & Puce, A. (2004). Digit representation is more than just hand waving. *Cognitive Brain Research*, *21*(3), 412–417. https://doi.org/10.1016/j.cogbrainres.2004.07.001.

Todd, J. J., & Marois, R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature*, *428*(6984), 751–754. https://doi.org/10.1038/nature02466.

Tse, D., Langston, R. F., Kakeyama, M., Bethus, I., Spooner, P. A., Wood, E. R., et al. (2007). Schemas and memory consolidation. *Science*, *316*(5821), 76–82. https://doi.org/10.1126/science.1135935.

Tulving, E. (1983). *Elements of episodic memory*. New York: Oxford University Press.

Uddin, L. Q., Supekar, K., Amin, H., Rykhlevskaia, E., Nguyen, D. A., Greicius, M. D., et al. (2010). Dissociable connectivity within human angular gyrus and intraparietal sulcus: Evidence from functional and structural connectivity. *Cerebral Cortex*, *20*(11), 2636–2646. pii: bhq011. https://doi.org/10.1093/cercor/bhq011.

Vogel, S. E., Goffin, C., Bohnenberger, J., Koschutnig, K., Reishofer, G., Grabner, R. H., et al. (2017). The left intraparietal sulcus adapts to symbolic number in both the visual and auditory modalities: Evidence from fMRI. *Neuroimage*, *153*, 16–27.

Vogel, S. E., Grabner, R. H., Schneider, M., Siegler, R. S., & Ansari, D. (2013). Overlapping and distinct brain regions involved in estimating the spatial position of numerical and non-numerical magnitudes: An fMRI study. *Neuropsychologia*, *51*(5), 979–989.

Vogel, A. C., Miezin, F. M., Petersen, S. E., & Schlaggar, B. L. (2012). The putative visual word form area is functionally connected to the dorsal attention network. *Cerebral Cortex*, *22*(3), 537–549. https://doi.org/10.1093/cercor/bhr100.

Wimmer, H., Ludersdorfer, P., Richlan, F., & Kronbichler, M. (2016). Visual experience shapes orthographic representations in the visual word form area. *Psychological Science*, *27*(9), 1240–1248. https://doi.org/10.1177/0956797616657319.

Wu, S., Chang, T. T., Majid, A., Caspers, S., Eickhoff, S. B., & Menon, V. (2009). Functional heterogeneity of inferior parietal cortex during mathematical cognition assessed with cytoarchitectonic probability maps. *Cerebral Cortex*, *19*(12), 2930–2945.

Young, C. B., Wu, S. S., & Menon, V. (2012). The neurodevelopmental basis of math anxiety. *Psychological Science*, *23*(5), 492–501. https://doi.org/10.1177/0956797611429134.

Zamarian, L., & Delazer, M. (2014). Arithmetic learning in adults – evidence from brain imaging. In R. Cohen Kadosh, & A. Dowker (Eds.), *The Oxford handbook of numerical cognition*. Oxford, UK: Oxford University Press.

Zamarian, L., Ischebeck, A., & Delazer, M. (2009). Neuroscience of learning arithmetic–evidence from brain imaging studies. *Neuroscience and Biobehavioral Reviews*, *33*(6), 909–925. https://doi.org/10.1016/j.neubiorev.2009.03.005.

Zarnhofer, S., Braunstein, V., Ebner, F., Koschutnig, K., Neuper, C., Reishofer, G., et al. (2012). The Influence of verbalization on the pattern of cortical activation during mental arithmetic. *Behavioral and Brain Functions*, *8*, 13. https://doi.org/10.1186/1744-9081-8-13.