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Mathematical Skills in Williams Syndrome: Insight into the Importance of Underlying Representations

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Williams syndrome (WS) is a developmental disorder characterized by relatively spared verbal skills and severe visuospatial deficits. Serious impairments in mathematics have also been reported. This article reviews the evidence on mathematical ability in WS, focusing on the integrity and developmental path of two fundamental representations, namely those that support judgments of "how much" (i.e., magnitude) and "how many" (i.e., number of objects). Studies on magnitude or "number line" representation in WS suggest that this core aspect of mathematical ability, is atypical in WS throughout development, causing differences on some but not all aspects of math. Studies on the representation of small numbers of objects in WS are also reviewed, given the proposed links between this type of representation and early number skills such as counting. In WS, representation appears to be relatively typical in infancy but limitations become evident by maturity, suggesting a truncated developmental trajectory. The math deficits in WS are consistent with neurological data indicating decreased gray matter and hypoactivation in parietal areas in WS, as these areas are implicated in mathematical processing as well as visuospatial abilities and visual attention. In spite of their deficits in core mathematical representations, people with WS can learn many mathematical skills and show some strengths, such as reading numbers. Thus individuals with WS may be able to take advantage of their relatively strong verbal skills when learning some mathematical tasks. The uneven mathematical abilities found in persons with WS provide insight into not only appropriate remediation for this developmental disorder but also into the precursors of mathematical ability, their neural substrates, and their developmental importance. © 2009 Wiley-Liss, Inc. Dev Disabil Res Rev 2009;15:11–20.

Key Words: Williams syndrome; mathematics; number; magnitude representation; developmental disorder

Mathematical skills do not consist of a single process but instead utilize multiple cognitive components including verbal skills, rote memorization, and the manipulation of abstract representations, to name a few [McCloskey, 1992; Geary, 1993; Dehaene et al., 1999]. In adulthood, acquired brain injuries can affect distinct components of math skills producing, for example, a dissociation between facts (i.e., rote memory) and procedures [McNeil and Burgess, 2002], or between approximate (i.e., number estimation) and exact calculation [Dehaene and Cohen, 1991]. The study of developmental disorders such as Williams syndrome (WS), which is associated with atypical patterns of cognitive deficits and brain function, provides evidence on whether such dissociations can occur over development [see also Geary, 1993]. Importantly, this research approach also provides insight into (1) the effect of core impairments to number representation (e.g., magnitude) or more general cognitive issues (e.g., visuospatial attention, low IQ) on learning math knowledge over development and, (2) whether there are multiple pathways to math knowledge.

What makes this population of particular interest to the study of mathematics is the opportunity to assess how the reported uneven cognitive profile—most strikingly, poor visuospatial ability and strong verbal skills—affects the development and function of math skills. One possibility is that learning math skills requires the early development of core psychological representations thought to be available to typically developing infants. One such core representation is a representation of magnitude ("how much"); another is the representation of a small number of objects ("how many?") [Ansari and Karmiloff-Smith, 2002; Feigenson et al., 2004]. Magnitude representations allow the infant to discriminate two quantities (i.e., 8 from 16) without representing exact number; later in development, this spatial/magnitude representation may support the use of an orderly, sensitive number line in a wide range of math tasks (see [Halberda et al., 2008; Holloway and Ansari, 2008] for the link between magnitude representation and math skills). Object representations (e.g., object indexes) may allow infants to track and individuate a small number of objects, and possibly form sets, and this skill may later support early number skills such as counting, 1:1 correspondence and cardinality ([Carey, 1998; Ansari and Karmiloff-Smith, 2002; Feigenson et al., 2004]; but see Gelman and Butterworth, [2005]). If these core representations develop abnormally in developmental disorders such as WS, math skills may never be acquired; on the other hand, alternate representation may be used to support math knowledge in WS, leading to atypical developmental paths to mathematical knowledge [Karmiloff-Smith, 1998]. Following a brief overview of WS, we review math skills in WS. We then

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discuss whether the brain anomalies associated with this disorder lead to overall or uneven impairment, how math skills may be related to parietal lobe functions in WS, and the possible developmental pathways of these two core representations in WS. This research provides insight into the role of these early representations in the development of math skills.

WILLIAMS SYNDROME: PHYSICAL AND NEUROCOGNITIVE PHENOTYPE

WS is associated with a distinct physical and behavioral phenotype [Mervis and Morris, 2007], and recent reports suggest it occurs in 1:7,500 live births [Meyer-Lindenberg et al., 2006]. The syndrome generally causes mild to moderate retardation as well as physical anomalies such as a distinctive facial morphology, small stature, and heart defects ([Ewart et al., 1993; Mervis et al., 2000; Bellugi et al., 2001; Meyer-Lindenberg et al., 2006]). In addition, there is a reported psychosocial profile/phenotype marked by high levels of both sociability and anxiety [Klein-Tasman and Mervis, 2003; Meyer-Lindenberg et al., 2006]. In view of the general intellectual disability associated with the syndrome, individuals with WS perform on most tasks—including math tasks—at a level lower than that expected on the basis of chronological age.

The uneven cognitive profile in WS was initially documented by the pioneering work of Ursula Bellugi and her colleagues [Bellugi et al., 1990, 1992]. Although this profile appears to be more nuanced than originally reported, evidence continues to support the pattern of relatively spared language together with severely delayed visuospatial abilities [Mervis et al., 2000; Bellugi et al., 2001; Meyer-Lindenberg et al., 2006]. Language, especially vocabulary, is a strength for individuals with WS, as are some aspects of syntax and semantics ([Karmiloff-Smith et al., 1998; Landau and Zukowski, 2003; Zukowski, 2005; Musolino et al., 2006] but see Karmiloff-Smith et al. [1998]). Relatedly, verbal short-term memory is also relatively strong [Mervis et al., 2000]. In contrast, visuospatial abilities such as block construction and drawing are significantly deficient, with adolescents and adults with WS performing at the level of typically developing 3- and 4-year-olds (Fig. 1: [Bertrand and Mervis, 1996; Farran et al., 2001; Hoffman et al., 2003; Georgopoulos et al.,

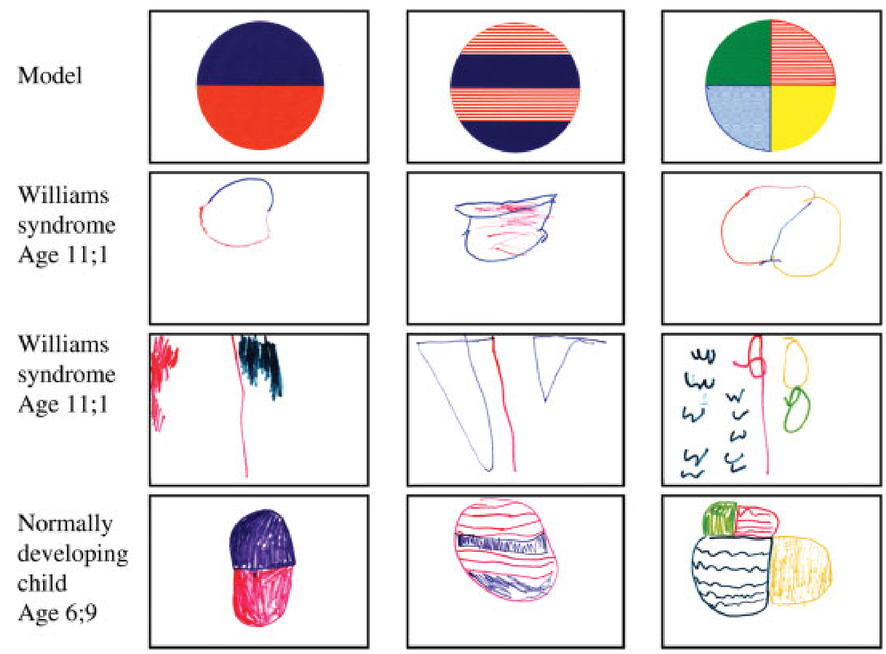

Fig. 1. Copies of models (row 1) made by children with Williams syndrome (rows 2 and 3) and by one mental age-matched normally developing child (row 4). The models remain visible while the child is copying them.

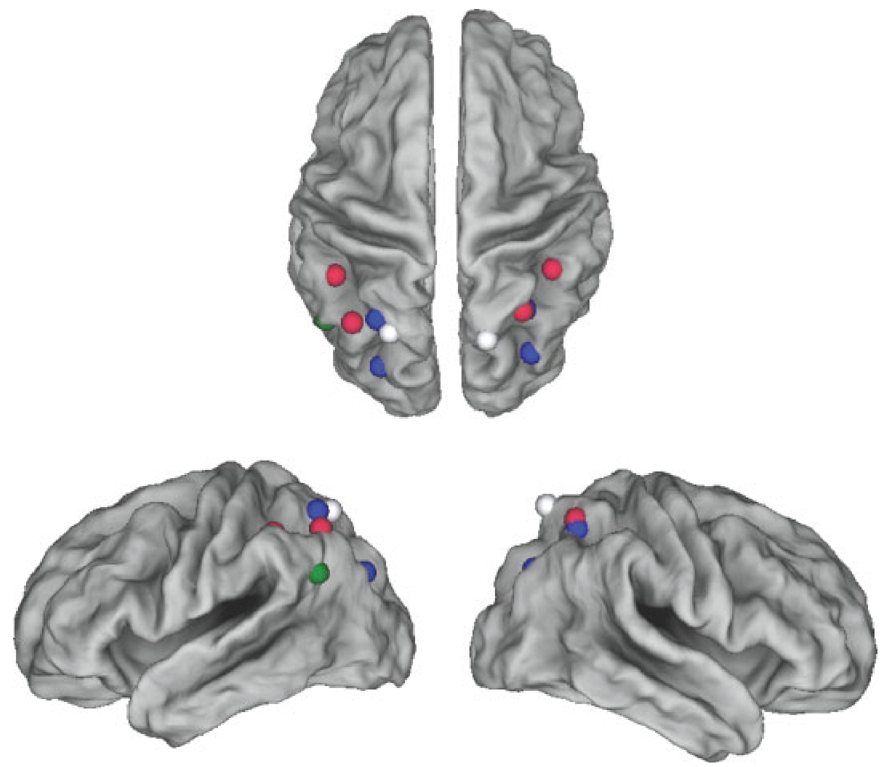

Fig. 3. Figure of brain regions discussed in the review, with spheres placed around the talaraich coordinates reported in several different papers; thus the spheres do not reflect the size of the region (brain software by Caret; [Van Essen et al., 2001]). Blue regions are where abnormalities in WS are reported in Meyer-Lindenberg et al. [2004]. Posterior blue regions are those with structural differences (−29, −79, 32; 32, −75, 29), and superior regions are those that displayed decreased functional activation (−27, −60, 56; 23, −53, 48). Crimson regions are areas implicated in magnitude representation in Piazza et al. [2004] (more posterior regions −36, −60, 52; 28, −56, 52) and a composite from a review by Dehaene et al. [2003] (more lateral superior regions; −48, −41, 43; 41, −42, 49). In addition, two other regions suggested in the review by Dehaene et al. [2003] are represented: dark green represents linguistically mediated, exact number representation (L −48, −59, 30) and white represents attentional resources (−26, −69, 61; 12, −69, 61) important for number representation in the parietal lobe.

2004]). Even within the realm of visual processing, ability levels in older children and adults with WS are uneven. Although visuospatial processes are particularly impaired, other visual abilities such as perception of biological motion, motion coherence, and face or object recognition are relatively stronger, often above the level expected on the basis of mental age [Jordan et al., 2002; Tager-Flusberg et al., 2003; Reiss et al., 2005; Landau et al., 2006].

This behavioral pattern is broadly consistent with the proposal that WS is associated with abberant development of the dorsal stream, which would particularly impact visuospatial processing [Mesulam, 1981; Ungerleider and Mishkin, 1982] and may be evident in other genetic disorders. Ventral stream/temporal lobe areas appear to follow a more typical pattern of development, leaving face recognition, biological motion, and language processes at a level often above that expected on the basis of mental age [Jordan et al., 2002; Paul et al., 2002; Tager-Flusberg et al., 2003; Reiss et al., 2005]. Brain volume is smaller overall in people with WS, and many areas might be subtly different due to atypical neural development [Reiss et al., 2004; Meyer-Lindenberg et al., 2005]. However, evidence indicates that the parietal and dorsal regions are particularly atypical in WS. Studies have reported decreased gray matter volume [Reiss et al., 2000; Meyer-Lindenberg et al., 2004; Eckert et al., 2005; Chiang et al., 2007], sulcal depth [Kippenhan et al., 2005; Van Essen et al., 2006], and functional activation [Meyer-Lindenberg et al., 2004; Mobbs et al., 2004]. For instance, a neuroimaging study of WS [Meyer-Lindenberg et al., 2004] directly compared dorsal and ventral stream function using a face/place task in a functional MRI study in adults with WS who had IQs in the normal range and controls individually matched on both age and IQ. Participants reported whether two sequential stimuli were at the same vertical position (i.e., location task) or were the same object (i.e., identity task). No behavioral differences were found on either task, unlike previous reports using similar behavioral tasks with an intellectually disabled sample [Paul et al., 2002]. However, there were differences in the level of functional activation during the location task. The group with WS displayed decreased activation in bilateral parietal lobes, compared with controls when encoding location (location > identity contrast). However, the level of activation in ventral stream areas during object recognition (identity > location contrast) did not differ between groups. A path analysis associated the decreased functional activation in the parietal lobe in WS with decreased gray matter volume in the intraparietal sulcus (IPS) in WS, when compared with controls (See Fig. 3 for the representation of these areas in blue). That this sample of individuals with WS were able to perform the task despite less parietal activation suggests that a different circuitry may be used to compensate for limitations in functions typically subserved by the parietal lobe.

MATHEMATICAL SKILLS IN WS

The evidence for atypical parietal development and function in persons

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with WS, combined with demonstrated links between mathematical processing and parietal lobe activation, suggests that the study of this developmental disorder may provide insight into the specific contributions of parietal cortex on the development of mathematical skills. Although the developmental mechanisms underlying these parietal lobe abnormalities are unclear, relatively decreased gray matter in these areas is evident in persons with WS, even in childhood [Boddaert et al., 2005]. Two alternatives have been proposed regarding math abilities in WS. One possibility is that spatial deficits and possible damage to a core system of magnitude representation in the parietal lobe, in combination with overall mental retardation in people with WS, leads to global mathematical impairment [Paterson et al., 2006]. Another possibility is that math skills subserved by the parietal lobe, namely the magnitude representation/number line often considered a necessary "core" component of math abilities [Dehaene et al., 1998; Feigenson et al., 2004], may be particularly affected, whereas math skills relying on verbal ability may be relatively strong owing to the strengths in language and short-term verbal memory associated with the WS cognitive phenotype [Paterson et al., 2006; Ansari et al., 2007; O'Hearn and Landau, 2008].

MATH SKILLS IN WS: OVERALL IMPAIRMENT?

Although there have long been anecdotal reports of particularly poor performance on math skills in individuals with WS, systematic studies were sparse until the last few years. Even currently, interpretation of many studies is hampered by small samples and variation in intellectual disability within a sample. Ansari and Karmiloff-Smith [2002] suggested that people with WS have specific problems with mathematics in addition to, and possibly related to, visuospatial deficits and parietal lobe abnormalities, but this notion was not strongly supported at the time they proposed it. They cite an early study by Udwin and colleagues [Udwin et al., 1996] who found that scores on standardized arithmetic tests did not improve in 23 individuals with WS, between childhood (10–15 years old) and adulthood (approximately 8.5 years later), in contrast to improvements in general IQ scores during the same time period. However, Udwin and colleagues urged caution in interpreting the results on arithmetic, as different assessments were used at different time points, and many of the arithmetic problems were beyond the skill level of most persons with WS. Later, these researchers found that only 16 of the 47 adults with WS who were given the arithmetic subtest of the IQ test (the Wechsler Intelligence Scale for Children—Third Edition UK edition; WISC-III UK) scored at or above the basal level equivalent to an age-level score of 6.2 years [Howlin et al., 1998]. Of these 16 adults who scored above the basal level, performance level was at the eight-year-old equivalent, roughly comparable to the level achieved on reading and spelling subtests. However, 46 of the 47 participant performed above the basal level on the reading and

Table 1. Demographic Information and KBIT-1, TEMA-2, and DAS Performance in WS

Demographic			KBIT-1			TEMA-2		DAS Block
Subj #	Age	Gender	IQ	Verbal Age Equivalent[a]	Matrices Age Equivalent[a]	Raw Score	Age Equivalent[a]	Age Equivalent
Williams syndrome								
106	10;5	M	69	5;10	6;4	30	6;1	3;7
115	10;9	F	90	10;4	8;0	42	7;9	5;10
103	12;7	F	86	9;0	9;6	50	8;6	5;10
102	13;0	M	88	9;0	13;1	59	>8;11[b]	9;3
107	13;2	F	74	8;9	7;1	31	6;2	3;1
101	14;1	F	46	6;4	6;4	24	5;6	4;4
111	15;9	M	62	10;6	7;1	39	7;5	5;1
113	17;3	F	51	9;10	6;0	34	6;10	4;7
114	18;11	F	59	10;1	7;6	39	7;5	4;7
110	19;4	M	40	7;10	6;0	35	7;0	5;10
105	20;4	M	51	7;10	8;4	35	7;0	4;7
104	21;0	M	78	12;1	11;4	43	7;10	
112	22;9	M	57	8;3	8;0	31	6;2	5;10
109	38;10	F	53	8;3	4;7	34	6;10	3;10

[a]These age equivalents were estimated by finding the approximate age at which the raw score fell at the 50th percentile or at an IQ of 100.
[b]The TEMA-2 was not normed at this raw score.

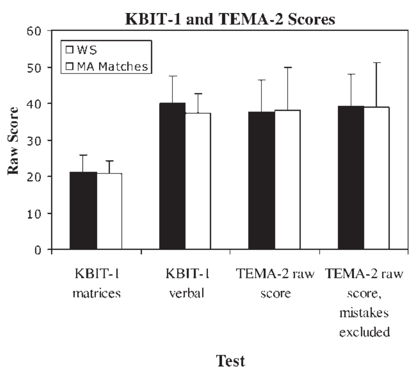

Fig. 2. Bar graphs showing raw scores on the KBIT-1 verbal and matrices subtest, and the TEMA-2 scores (both the official Tema-2 score and an alternate scoring excluding mistakes) in participants with WS and MA-matched controls. Error bars are the standard error of the mean. Adapted from O'Hearn and Landau, [2007].

spelling subtests, suggesting that the development of math skills is more specifically affected by WS than are reading and spelling.

These early studies highlighted the difficulties in testing math skills in a population in which developmental disorder leads to intellectual disability, such as WS. People with WS might appear particularly impaired on math, when they are actually just performing at a level appropriate for their mental age. To address this confound in our own research, we used a math test designed specifically for younger children, the Test of Early Mathematical Abilities, second edition (TEMA-2; [Ginsburg and Baroody, 1990]), to test 14 individuals with WS and 14 mental-age matched peers [O'Hearn and Landau, 2007]. Although less sensitive than experimental tasks, the TEMA-2 is useful for examining the level of mathematical abilities in WS because it is a standardized for use with children from 2- to 8-years of age, consistent with the mental age of most older children and adults with WS; and because it can be used to test a number of basic mathematical abilities. Also, the TEMA-2 has been used effectively to examine math deficits in people with developmental disorders and mathematics learning disability [Mazzocco, 2001; Murphy et al., 2006]. In our study of WS, the TEMA-2 indicated that overall math ability in WS matched mental age expectations, as measured by the raw score on both the verbal and matrices subtests of the Kaufman Brief Intelligence Test (KBIT, [Kaufman and Kaufman, 1990]; Fig. 2). Like their mental-age matched peers, the participants with WS did well on the broad range of basic mathematics questions that appear early in the TEMA-2, a somewhat surprising finding given speculation that people with WS are particularly poor at mathematics [Paterson et al., 2006]. Overall, mathematical skills in WS were at the level of children 6–8 years of age (Table 1), better than age-equivalents for their block construction ability [Mervis et al., 2000; Hoffman et al., 2003] and other visuospatial tasks such as drawing [Bertrand et al., 1997] and multiple object tracking [O'Hearn et al., 2005]. Although most of the participants in either group could not complete the more complex problems at the very end of the TEMA-2, two participants from each group completed the entire battery (i.e., never reached a ceiling). The two participants with WS who had the highest TEMA-2 scores accurately completed the mental number line problems (i.e., selecting which of two numbers is closer to a target), some word problems, and skip counting (by fours); the highest scoring participant with WS correctly solved symbolic 3-digit addition and speeded multiplication facts. These results support the proposal that overall math abilities in WS are associated with intellectual ability, and not specifically damaged due to parietal abnormalities.

Similarly, Ansari and colleagues [Ansari et al., 2003] reported that an understanding of cardinality—that the last number counted equals the total number of items in a set—in a group of 6–11-year-olds with WS (mean age 7, $n = 14$) was on par with mental-age matches (mostly 3- and 4-year-olds). However, they found some evidence that this ability may rely more on verbal skills in WS than it does in typical children. Verbal mental age, but not block construction scores, accounted for the variability in cardinality judgments in children with WS, whereas the opposite pattern held in typically developing children, indicating that this relatively even skill across matched groups might emerge from distinct sources.

In contrast to the relative skill reported in these studies, Paterson et al. [2006] found that the group with WS did not perform particularly well on their mathematical battery, including the verbal portions, when compared with typically developing individuals and people with Down syndrome matched for nonverbal ability. This latter group provides a general control for intellectual disability, as well differences that may be related to special education. The mathematical battery included a counting task (counting forwards from 1 to 20 or from 25 to 35, and counting 1–20 backwards); serial order for dots and numbers (1–3 digit) presented on cards; determining what comes before or after a spoken number; matching numbers to quantities of dots presented visually on cards; reading 1-, 2-, and 3-digit numerals; and verbally answering single-digit addition, subtraction, and multiplication problems presented on cards. Significant differences between the WS group and the Down syndrome group were evident on two tasks: seriation (arranging numbers and dots in sequential order; mental-age matches also did poorly on the numbers) and the "what comes before/after" question.[1] Although it provides an interesting comparison, differences between WS and another special population such as Down syndrome are difficult to interpret because—like other developmental disorders [Murphy et al., 2006]—their abilities may not be evenly impaired and their pattern of impairment is likely to differ from that of people with WS. Additional limitations of this study included a relatively small sample[2], common in this rare disorder, and a mathematical battery that was not standardized. Another factor that could potentially account for the difference in results between this study and O'Hearn and Landau [2007] was that the mental-age matches in this study were slightly older than the matched participants in O'Hearn and Landau [2007]. In summary, while two recent studies [O'Hearn and Landau, 2007; Ansari et al., 2003] report that people with WS perform as expected on the basis of mental age, Patterson et al. [2006] hint that some samples of individuals with WS may be particularly impaired on math skills generally.

[1]The "what comes before/after" question would appear to require a strong verbal component; it is unclear what type of knowledge the seriation task might use (with numbers, it might reflect the verbal component; with dots, possibly use of the mental number line).

[2]Paterson et al. [2006] included 8 individuals with WS and 9 with Down syndrome but 2 with Down syndrome did not do the math battery and some others could not complete all items on the battery.

MATH SKILLS IN WS: RELATIVELY POOR MAGNITUDE REPRESENTATION AND STRONG VERBAL SKILLS?

What makes the study of math in WS particularly interesting is the potential for an uneven profile of math skills despite the fact that these skills inform each other and are typically learned very gradually over many years. The most frequently proposed WS profile includes impaired representation of magnitudes and approximate number, and relatively strong memory for math facts. Extensive evidence from studies of typical adults and those with brain damage suggest that there are distinct psychological and neural representations for the magnitude/quantity components of numerical reasoning involved in approximate arithmetic and for the verbal/linguistic components involved in exact arithmetic [Cipolotti et al., 1991; Dehaene et al., 1999, 2003, 2004]. An approximate nonsymbolic magnitude representation may support reasoning about quantity (i.e., a mental number line). This representation is not sensitive to the language in which it was learned, is available to infants and nonhuman animals, and appears to utilize bilateral dorsal areas in the parietal lobe [see Dehaene et al., 1999, 2003, 2004] specifically the horizontal segment of IPS, according to Dehaene et al. [2003; seen in lateral red areas in Fig. 3]. These areas appear sensitive to numerical magnitude, in that increases in number lead to parametric increases in activation [Piazza et al., 2003]. In contrast, linguistic or verbal knowledge relies on number words as symbols to refer to exact quantities; as such, it is associated with linguistic processing and is sensitive to the language in which it was encoded. This knowledge may support species-specific reasoning about number, and may be represented near language association areas of the left hemisphere (L angular gyrus, represented in green in Figure 3: [Dehaene et al., 2003; Grabner et al., 2008]).

It is unclear how parietal areas develop abnormally in WS, or how this atypical development impacts the representation of magnitude and the ability to learn math skills. Dehaene and colleagues posit that similar parietal areas support magnitude representation throughout development typically, [Temple and Posner, 1998; Cantlon et al., 2006; Cantlon et al., 2008]; thus, genetic disorders like WS that impact this region may affect judgments of magnitude throughout development. In typical development, activation in the L IPS may become more sensitive to differences in magnitude [Ansari and Dhital, 2006], and reliance on the inferior frontal regions may diminish with age [Cantlon et al., 2008]. In childhood, the use of symbolic number—even in magnitude judgments—seem to rely on frontal regions [Kaufmann et al., 2006; Cantlon et al., 2008]. Number operations may involve more posterior function with age, especially symbolic operations, relying more on parietal areas in adulthood than in childhood [Rivera et al., 2005]. Therefore, a second way that WS may result in atypical math skills is that these individuals may not undergo these later developmental changes, such as involvement of parietal areas in a wider range of math skills, with increased sensitivity to number increments.

There has been some evidence of uneven math skills in WS. Although math skills in general in WS were on par with mental age in the study of O'Hearn and Landau [2007], analyses of the individual items on the TEMA-2 provided evidence that the uneven cognitive profile generally found in WS might also be evident in math skills. Participants with WS performed more poorly than MA matches when asked to choose the number that was quantitatively closer to the target number (e.g., "is five or nine closer to six?"). This type of "informal" mathematical knowledge is thought to require the use of a magnitude representation subserved by the parietal lobe [Dehaene et al., 1999]. On the other hand, despite relatively similar scores on the verbal subtest of the KBIT, the WS group performed better than controls at reading numbers. They were more accurate than the mental-age matched comparison group at reading 3-digit numerals, and tended to be better at counting out 19 manipulatives, reading 2-digit numerals in both the teens and above, and writing 2-digit numerals. These results suggest that people with WS have particular difficulty on tasks requiring a well-articulated number line, likely to reflect the abnormalities in parietal areas, but that verbal aspects of mathematical skills are a relative strength that may provide another path to math knowledge.

Recent work by Krajcsi and colleagues also found a pattern of strengths and weaknesses in WS, consistent with the results from O'Hearn and Landau [Krajcsi et al., 2008]. Their study examined addition, multiplication, and number comparison in eight older children and young adults with WS [Krajcsi et al., 2008]. Addition and multiplication both presumably rely more heavily on rote memorization, playing to the WS strengths in verbal recall, whereas number comparison is thought to tap the mental number line or magnitude representation, which should be more challenging for persons with WS. Individuals with WS were compared with second graders (8-year-olds), third graders (9-year-olds), and fourth graders (10-year-olds). Participants judged whether addition/multiplication problems were correct, and which of two single-digit symbolic numbers was larger. Error rates were generally low, indicating that all groups could do the tasks. Findings were consistent with predictions: Individuals with WS were as fast as third graders at judging whether solutions to addition problems were correct or incorrect, and were almost as fast as fourth graders at judging solutions to multiplication problems, but were slower than all typically developing groups at judging which of two numbers was larger.

Several other studies suggest that magnitude representation may be impaired in persons with WS, including young children. Van Herwegen and colleagues [Van Herwegen et al., 2008] found that nine children with WS from 15 to 53 months did not appear to discriminate eight dots from 16, a distinction typically developing infants can make under similar circumstances at 6 months of age [Xu and Spelke, 2000]. Ansari et al. [2008] found that the ability of 18 children with WS (mean age 9.7 years) to estimate a small number of dots (up to 11) displayed briefly was comparable to 4–5-year-old typically developing children. The 13 adults with WS (mean age 28.9 years) performed like typically developing 6–7-year-olds, suggesting some albeit limited developmental improvement. Paterson et al. [2006] examined the symbolic distance effect (SDE) in WS. A magnitude representation is thought to be responsible for the SDE, in which participants are faster to discriminate numbers that are farther apart than those that are close together, presumably due to greater overlap in the representations of numbers that are close together [Moyer and Landauer, 1967; Sekuler and Mierkiewiez, 1977]. Paterson and colleagues found that a group of eight individuals with WS (10–32 years old) displayed no SDE (i.e., significant difference in RT to close versus far apart numbers), unlike participants with Down syndrome ($n = 7$, 11–35 years old) and mental-age matches ($n = 8$; 5–8 years old), both matched on mental age to the WS, and chronological age matches ($n = 8$, 9–29). However, the SDE in WS did become significant when overall differences in RT were controlled for, and Krajski et al. [2008] report a normal SDE in their number comparison task. So, people with WS appear to display a SDE, but it may not be as notable as in typically developing children and individuals with Down syndrome. Unlike the previously discussed studies which suggest a relative limitation in magnitude representation [O'Hearn

So, in these studies, it is impossible to determine whether there is overall impairment or an uneven pattern of math skills in WS. Either outcome could result from an impaired magnitude representation since, if this representation is truly 'core' to number understanding, it may be required to form the knowledge structure from which verbal number skills are learned.

et al., 2007; Krajcsi et al., 2008], these studies do not present a contrasting areas of strength [Ansari et al., 2008], or verbal skills are similarly damaged [Paterson et al., 2006]. So, in these studies, it is impossible to determine whether there is overall impairment or an uneven pattern of math skills in WS. Either outcome could result from an impaired magnitude representation because, if this representation is truly "core" to number understanding, it may be required to form the knowledge structure from which verbal number skills are learned.

In addition to a deficit in magnitude representation, the general visuospatial deficits that are a benchmark of cognition in WS may impact math skills directly [Ansari and Karmiloff-Smith, 2002], leading to a relatively specific deficit in aspects of math that rely on visuospatial function. Dehaene et al. [2003] hypothesize that visuospatial functions used for a wide range of tasks are also important for math skills, leading to activation of dorsal bilateral parietal areas (white areas in Fig. 3) in many imaging studies examining math reasoning in adulthood as well as other visuospatial tasks [Simon et al., 2002]. These areas related to visuospatial attention appear distinct from the parietal areas supporting magnitude representation (Fig. 3). However, these two abilities may work in concert during math problem solving. Dehaene and colleagues speculate that the attentional selection subserved by this area may be applied to number representations that are spatial (such as a number line), in addition to being used generally for spatial representation. Alternately, there may be extensive overlap in the representation of magnitude and space in the parietal lobe even in children [Kaufman et al., 2008], or the areas could be close enough physically that both are affected by the atypical brain development in WS. These possibilities would also lead to the atypical development of parietal areas in WS affecting both sets of skills.

In summary, magnitude representation may differ between persons with WS and typically developing children and adults. This pattern appears continuous throughout the life span, as it is evident in infants [Van Herwegen et al., 2008], children [Ansari et al., 2008], and adolescents/young adults with WS [O'Hearn et al., 2007; Krajcsi et al., 2008]. The evidence of a SDE (though possibly decreased) in WS, and the developmental improvement as reported by Ansari et al. [2008], suggests that the magnitude representation exists but may be less finely tuned in WS than in typical development. In addition, deficits in spatial attention commonly found in WS could particularly impact math skills. In contrast, there is some evidence that mathematical abilities that rely on linguistic encoding and rote verbal memorization may be particularly strong in WS [O'Hearn et al., 2007; Krajcsi et al., 2008], and that under some circumstances, children with WS may rely more on verbal representations to help with math skills than do typically developing preschoolers [Ansari et al., 2003]. However, this strength may not generalize to all verbally mediated skills [Paterson et al., 2006]; hard word problems [O'Hearn et al., 2007], or possibly all samples of individuals with WS [Paterson et al., 2006].

Is a Deficit in Magnitude Representation Evident in Other Disorders?

One possibility is that such a core deficit in magnitude representation is evident in all populations with mathematical learning disabilities (MLD); this would suggest that this deficit does not reflect the parietal lobe abnormalities found in WS. However, several facts suggest that the profile found in WS is not observed in all math-impaired populations. First, the performance profile on the TEMA in WS differs from that found in children with poor math skills (i.e., MLD), so does not seem to be simply a reflection of low math abilities. Mazzocco and Thompson [Mazzocco and Thompson, 2005] found that 5-year-olds later identified as MLD, while impaired on the mental number line question on TEMA-2, were also impaired on a host of other questions, including reading numerals, items on which participants with WS did particularly well. Secondly, the profile of individuals with WS also differs from profiles of TEMA-2 scores reported for individuals with fragile X or Turner syndrome [Murphy et al., 2006; Murphy, this issue]. Although 6-year-old girls with fragile X syndrome showed the same difficulty on mental number line problems as observed in individuals with WS, these girls also had difficulty with the counting principles, including cardinality, which were not evident in the WS group. In this study, girls with Turner syndrome showed no item-specific performance profile on the TEMA-2. Thus, it is not the case that children with MLD or developmental disability, in general, show a particular profile on the TEMA-2. These results indicate that math abilities in WS are relatively unique and are not associated with generalized math impairment.

However, this division of labor—between aspects of mathematical reasoning that are supported primarily by verbal knowledge and those supported by a magnitude representation—may be evident in some other neurodevelopmental disorders that particularly impact parietal lobe areas. Although Murphy et al. [2006] did not find evidence of an impaired magnitude representation in third graders with Turner syndrome, Bruandet, Dehaene and colleagues reported such a deficit in women with Turner syndrome [Bruandet et al., 2004], and they suggest it could be related to differences in IPS and other parietal areas [Brown et al., 2004; Dehaene et al., 2004; Molko et al., 2008]. The difference in the results from these two studies [Bruandet et al., 2004; Murphy et al., 2006] may reflect that the disorder has several subclasses, one of which may be more similar to WS. Another possibility is that the deficit in Turner syndrome is more subtle than that found in WS, thus not identifiable on the TEMA-2 but evident on other tests, or that it emerges later in development. Thus, it is still an open question whether other neurodevelopmental disorders with parietal abnormalities might lead to similar impairments in magnitude representation [see Mazzocco, this issue].

MATH SKILLS IN WS: STRONG REPRESENTATION OF A SMALL, EXACT SET?

Another innate psychological representation that may support early number knowledge is the ability to locate and keep track of a small number of individual items (i.e., indexes; [Carey, 1998; Leslie et al., 1998; Scholl and Leslie, 1999; Feigenson et al., 2004]). This ability may provide a bootstrap for early number skills and appears related to counting [Benoit et al., 2004]. In theory, this ability to track small sets of objects (less than four) in infancy has also been related to the ability to rapidly enumerate ("subitize") objects in adulthood and to track them as they move [Leslie et al., 1998; Pylyshyn, 2000]. For adults, this ability is relatively effortless in adulthood up to 3–4 items, but accuracy and speed rapidly deteriorate with higher numbers.

At least in infancy, the ability to represent small numbers of objects may be a strength in WS. Infants and toddlers with WS (24–36 months), like typically developing mental age matches (12–20 months) and chronological age matches (24–36 months), are able to discriminate two from three objects, in contrast to chronological age matched infants and toddlers (24–36 months) with Down syndrome [Paterson et al., 1999, 2006]. In their 1999 paper, Paterson and colleagues used this finding to suggest that the development of math skill proceeds in an atypical fashion in WS, presumably from relatively strong to more delayed, because the young children with WS performed relatively normally at representing a small number of objects. This is intriguing in light of the more recent evidence from 13–53 month olds with WS [Van Herwegen et al., 2008], described previously, which suggests that infants and toddlers with WS have an intact ability to represent an exact, small number of objects (possibly using object indexes), while simultaneous showing impairment in the ability to represent higher numbers of objects (8 versus 16), which requires only an approximate magnitude representation.

In contrast to this strength at representing small sets in infancy, evidence from our laboratory suggests that these skills thought to be related to object indexes in adulthood, namely the ability to enumerate small numbers of objects (i.e., subitize) and track them (i.e., multiple object tracking), are impaired in WS when compared with mental age matches [O'Hearn et al., 2005; unpublished data]. Like the studies on enumeration in infancy, all these tasks are thought to require multiple object indexes being deployed in parallel. What provides insight into this apparent inconsistency is the manner in which multiple object representation is impaired in older children and adults with WS: individuals with WS performed well with one and two objects on both tasks but were much worse than mental-age matches with four objects. This suggests that people with WS have access to "object indexes" but may not be able to use or operate on them as well as typically developing children matched for mental age. Specifically, "indexing" may be intact enough to support number skills normally evident in preschool (e.g., learning small numbers, 1:1 correspondence and cardinality), but the development needed to support more advanced object-based abilities (e.g., multiple object tracking, fast enumeration) may never fully mature. If so, what might be impaired in WS is not the early emerging object representation in infancy (i.e., the ability to track two or three objects), but instead the developmental improvement that occurs during preschool and early school years that allows adults to keep track of four objects. Alternatively, there may be early deficits in this ability in WS that the studies in infancy are not sensitive enough to identify.

Possible Effects of Parietal Lobe Anomalies in WS on Representing Both Large and Small Sets of Objects

The benchmark deficit in WS—visuospatial representation and attention—is likely to reflect abnormalities in parietal areas near to those thought to underlie magnitude representation (Fig. 3). Studies of typical adults indicate that IPS and surrounding regions are utilized in both number and spatial tasks [Culham and Kanwisher, 2001; Dehaene et al., 2003]. Areas of IPS seem to be sensitive to differences in both small, exact sets and large, approximate numbers of objects or dots [Piazza et al., 2003, 2004; Todd and Marois, 2004] as well as digits per se [Piazza et al., 2007]. Parametrically increasing activation evident as quantity increases, though object-based attention and STM may activate more posterior IPS areas than those evident in number studies [Culham and Kanwisher, 2001; Dehaene et al., 2003; Piazza et al., 2003]. Nonetheless, that both these processes typically activate IPS hints that the anomalies in this region resulting from atypical development in WS [Meyer-Lindenberg et al., 2004], which may lead to a shallower and more medial IPS [Van Essen et al., 2006], could affect sensitivity to both the number of objects (how many) and the number line (how much). Research on adolescents who were born preterm demonstrates that those with dyscalculia show decreased gray matter in IPS when compared with those without dyscalculia, suggesting that early insults might lead to distinct patterns of development in this brain region [Isaacs et al., 2001].

Finally, as mentioned earlier, the theory of Dehaene et al. [2003] suggests another possibility—that, in addition to the IPS areas that may support magnitude representation, another area of parietal lobe supports performance on number studies, though its function may not be specific to number. Bilateral posterior parietal lobe underlies visuospatial attention but is activated in many number studies: these authors suggest that, to use the number line, participants must direct visuospatial attention to it, leading to activation of this area on number tasks. If true, function and/or structure of this area could develop atypically in WS, leading to impairments on both visuospatial and number tasks.

DEVELOPMENTAL PATHWAY

Ansari and Karmiloff-Smith [2002] suggested that impairment in a fundamental ability that supports mathematical reasoning, such as magnitude representation, might cascade over development, leading to particular mathematical deficits in WS and other developmental disorders. In adults, damage to the IPS area thought to support magnitude representation leads to quite disabling acquired math deficits [Cipolotti et al., 1991]. O'Hearn and Landau [2007] showed that, in spite of the damage to the parietal lobe and probably the ability to represent magnitude, performance on the TEMA-2 was similar overall between individuals with WS and mental age matches. This was in spite of potential differences in mathematics experience between groups (e.g., more practice on rote counting, or less introduction to complex concepts because of their level of intellectual functioning, in WS). Participants with WS performed at the level expected by mental age, suggesting that their mathematical instruction was comparable to children at similar levels of competence, and that many aspects of mathematical understanding had proceeded relatively normally despite their parietal abnormalities. A related but unexplored question is whether the verbal skills generally evident in individuals with WS allows them to learn math information in a different manner than typically developing children, and whether this sort of learning provides true insight into basic math concepts such as the number line. In sum, people with WS show relative strength, on math tasks despite their impairments, suggesting that a typically developing magnitude representation may not be needed for many aspects of math, and/or that there are other ways to learn these math skills in developmental disorders such as WS.

In sum, people with WS show substantial skill on math tasks despite their impairments, suggesting that a typically developing magnitude representation may not be needed for many aspects of math, and/or that there are other ways to learn these math skills in developmental disorders such as WS.

Although the evidence from our study of TEMA-2 performance indicates that math skills can be acquired over development despite possible impairment in magnitude representation, there appeared to be limitations in understanding magnitude representation that would—in theory—prevent people with WS from understanding advanced mathematics. Because individuals with WS did show some evidence of being able to understand magnitude (e.g., an SDE under some circumstances, and the ability of higher functioning individuals to do number line questions), it seems likely that these individuals are able to represent magnitude, but may do so with decreased sensitivity to increments. In other words, the number line may have decreased spatial resolution in WS than it does in typically developing children performing at a similar level. This less well-articulated number line may allow an understanding of number that provides a sufficient basis for learning some, but not all, math skills. It would be very interesting to identify the level of math understanding attained in individuals with WS who score within age-appropriate levels on IQ tests, a rare but important group who has been recruited by NIH [Meyer-Lindenberg et al., 2004].

CONCLUSIONS

Evidence on math skills in WS suggest areas of weakness (magnitude representation, spatial attention) and areas of strength (verbal skills, early representation of object indexes) that may impact the development of math abilities in individuals with WS. Evidence indicates that magnitude representation may be abnormal in WS throughout the lifespan, and that this affects many but not all math skills in WS. In contrast, object indexes may provide an important bootstrap to number skills early in development in WS, though their use may also be limited later on. Spatial attention and verbal skills are more general cognitive abilities shown to be differentially affected by WS, and both are likely important for mathematical development. This pattern of weaknesses and strengths may work together to produce a distinct pattern of performance on mathematical tasks in WS.

Although the number of studies on math in WS is increasing, there is still a dearth of such studies, with much of the current work hampered by the small sample sizes and variability common in studies of this relatively rare genetic disorder. This is unfortunate, as evidence from this population could illuminate how a genetic disorder that may cause atypical development in the core number system impacts cognitive function and math skills over time, and whether there may be an effective intervention that can circumvent these limitations. Further studies are needed to better characterize whether magnitude representation in WS is qualitatively or quantitatively different than observed in controls; which math skills are impacted and which are spared; the relationship between the differences in magnitude representation and visuospatial /object-based attention found in WS; and the atypical course of the behavioral and brain development in this disorder [Karmiloff-Smith, 1998]. Verbal skills and memorization may be particularly strong in WS, and instructional strategies that target these strengths may help individuals with WS achieve math skills appropriate to their approximate mental age. Further evidence on whether these skills are trainable in persons with developmental disorders (e.g., [Wilson et al., 2006]) might provide another instructional pathway to improve math skills.

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REFERENCES

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. J Cogn Neurosci 18: 1820–1828.

Ansari D, Donlan C, Karmiloff-Smith A. 2007. Typical and atypical development of visual estimation abilities. Cortex 43:758–768.

Ansari D, Donlan C, Thomas MSC, et al. 2003. What makes counting count? Verbal and visuo-spatial contributions to typical and atypical number development. J Exp Child Psychol 85:50–62.

Ansari D, Karmiloff-Smith A. 2002. Atypical trajectories of number development: a neuroconstructivist perspective. Trends Cogn Sci 6:511–516.

Bellugi U, Bihrle A, Jernigan T, et al. 1990. Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome. Am J Med Genet Suppl 6:115–25.

Bellugi U, Bihrle A, Neville H, et al. 1992. Language, cognition, and brain organization in a neurodevelopmental disorder. In Gunnar MR, Nelson CA, editors. Developmental behavioral neuroscience. Hilllsdale, NJ: Lawrence Erlbaum Associates. p 201–232.

Bellugi U, Lichtenberger L, Jones W, et al. 2001. The neurocognitive profile of Williams syndrome: a complex pattern of strengths and weaknesses. In: Bellugi U, St. George M, editors. Journey from cognition to brain to gene: perspectives from Williams syndrome. Cambridge, MA: The MIT Press. p 1–41.

Benoit L, Lehalle H, Jouen F. 2004. Do young children acquire number words through subitizing or counting? Cogn Dev 19: 291–307.

Bertrand J, Mervis CB. 1996. Longitudinal analysis of drawings by children with Williams syndrome: preliminary results. Vision Arts Res 22:19–34.

Bertrand J, Mervis CB, Eisenberg JD. 1997. Drawing by children with Williams syndrome: a developmental perspective. Dev Neuropsychol 13:41–67.

Boddaert N, Mochel F, Meresse I, et al. 2005. Parieto-occipital grey matter abnormalities in children with williams syndrome. NeuroImage 30:721–725.

Brown WE, Kesler SR, Eliez S, et al. 2004. A volumetric study of parietal lobe subregions in Turner syndrome. Dev Med Child Neurol 46:607–609.

Bruandet M, Molko N, Cohen L, et al. 2004. A cognitive characterization of dyscalculia in Turner syndrome. Neuropsychologia 42:288–298.

Cantlon JF, Brannon EM, Carter EJ, et al. 2006. Functional imaging of numerical processing in adults and 4-y-old children. PLoS Biol 4:844–854.

Cantlon JF, Libertus ME, Pinel P, et al. 2008. The neural development of an abstract concept of number. J Cogn Neurosci: Epub ahead of print.

Carey S. 1998. Knowledge of number: its evolution and ontogeny. Science 282:641–642.

Chiang MC, Reiss AL, Lee AD, et al. 2007. 3D pattern of brain abnormalities in Williams syndrome visualized using tensor-based morphometry. NeuroImage 36:1096–1109.

Cipolotti L, Butterworth B, Denes G. 1991. A specific deficit for numbers in a case of dense acalculia. Brain 114:2619–2637.

Culham JC, Cavanagh P, Kanwisher NG. 2001. Attention response functions: characterizing brain areas using fMRI activation during parametric variations of attentional load. Neuron 32:737–745.

Dehaene S, Cohen L. 1991. Two mental calculation systems: a case study of severe acalculia with preserved approximation. Neuropsychologia 29:1045–1054.

Dehaene S, Dehaene-Lambertz G, Cohen L. 1998. Abstract representations of numbers in the animal and human brain. Trend Neurosci 21:355–361.

Dehaene S, Molko N, Cohen L, et al. 2004. Arithmetic and the brain. Curr Opin Neurobiol 14:218–224.

Dehaene S, Piazza M, Pinel P, et al. 2003. Three parietal circuits for number processing. Cogn Neuropsychol 20:487–506.

Dehaene S, Spelke E, Pinel P, et al. 1999. Sources of mathematical thinking: behavioral and brain-imaging evidence. Science 284:970–974.

Eckert MA, Hu D, Eliez S, et al. 2005. Evidence for superior parietal impairment in Williams syndrome. Neurology 64:152–153.

Ewart AK, Morris CA, Atkinson D, et al. 1993. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. Nat Genet 5:11–16.

Farran EK, Jarrold C, Gathercole SE. 2001. Block design performance in the Williams syndrome phenotype: a problem with mental imagery? J Child Psychol Psychiatry 42: 719–728.

Feigenson L, Dehaene S, Spelke E. 2004. Core systems of number. Trends Cogn Sci 8:307–14.

Geary DC. 1993. Mathematical disabilities: cognitive, neuropsychological, and genetic components. Psychol Bull 114:345–362.

Gelman R, Butterworth B. 2005. Number and language: how are they related? Trends Cogn Sci 9:6–10.

Georgopoulos MA, Georgopoulos AP, Kurz N, et al. 2004. Figure copying in Williams syndrome and normal subjects. Exp Brain Res 157:137–146.

Ginsburg HP, Baroody AJ. 1990. Test of early mathematics ability, 2nd ed. Austin, TX, PRO-ED.

Grabner RH, Ansari D, Koschutnig K, et al. 2008. To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. Neuropsychologia: Epub ahead of print.

Green CS, Bavelier D. 2006. Enumeration versus multiple object tracking: the case of action video game players. Cognition 101:217–245.

Halberda J, Mazzocco MM, Feigenson L. 2008. Individual differences in non-verbal number acuity correlate with math achievement. Nature 455:665–668.

Hoffman JE, Landau B, Pagani B. 2003. Spatial breakdown in spatial construction: evidence from eye fixations in children with Williams syndrome. Cogn Psychol 46:260–301.

Holloway ID, Ansari D. 2008. Mapping numerical magnitudes onto symbols: the numerical distance effect and individual differences in children's mathematics achievement. J Exp Child Psychol: Epub ahead of print.

Howlin P, Davies M, Udwin O. 1998. Cognitive functioning in adults with Williams syndrome. J Child Psychol Psychiatry 39: 183–189.

Isaacs EB, Edmonds CJ, Lucas A, et al. 2001. Calculation difficulties in children of very low birthweight: a neural correlate. Brain 124:1701–1707.

Jordan H, Reiss JE, Hoffman JE, et al. 2002. Intact perception of biological motion in the face of profound spatial deficits: Williams syndrome. Psychol Sci 13:162–167.

Karmiloff-Smith A. 1998. Development itself is the key to understanding developmental disorders. Trends Cogn Sci 2:389–398.

Karmiloff-Smith A, Tyler LK, Voice K, et al. 1998. Linguistic dissociations in Williams syndrome: evaluating receptive syntax in on-line and off-line tasks. Neuropsychologia 36:343–351.

Kaufman AS, Kaufman NL. 1990. Kaufman brief intelligence test, 1st ed. Circle Pines, MN: American Guidance Service.

Kaufman L, Vogel SE, Wood G, et al. 2008. A developmental fMRI study of nonsymbolic numerical and spatial processing. Cortex 44:376–385.

Kaufmann L, Koppelstaetter F, Siedentopf C, et al. 2006. Neural correlates of the number-size interference task in children. Neuroreport 17:587–591.

Kippenhan JS, Olsen RK, Mervis CB, et al. 2005. Genetic contributions to human gyrification: sulcal morphometry in Williams syndrome. J Neurosci 25:7840–7846.

Klein-Tasman BP, Mervis CB. 2003. Distinctive personality characteristics of 8-, 9-, and 10-year-olds with Williams syndrome. Dev Neuropsychol 23:269–290.

Krajcsi A, Lukacs A, Igacs J, et al. 2008. Numerical abilities in Williams syndrome: dissociating the analogue magnitude system and verbal retrieval. J Clin Exp Neuropscyhol 11:1–8.

Landau B, Hoffman JE, Kurz N. 2006. Object recognition with severe spatial deficits in Williams syndrome: sparing and breakdown. Cognition 100:483–510.

Landau B, Zukowski A. 2003. Objects, motions, and paths: spatial language in children with Williams syndrome. Dev Neuropsychol 23:105–137.

Leslie AM, Fei X, Tremoulet PD, et al. 1998. Indexing and the object concept: developing 'what' and 'where' systems. Trends Cogn Sci 2:10–18.

Mazzocco MM. 2001. Math learning disability and math LD subtypes: evidence from studies of Turner syndrome, fragile X syndrome, and neurofibromatosis type 1. J Learn Disabil 34:520–533.

Mazzocco MMM. 2009. Mathematical learning disability in girls with Turner syndrome: a challenge to defining MLD and its subtypes. Dev Disabil Res Rev 15:35–44.

Mazzocco MM, Thompson RE. 2005. Kindergarten predictors of math learning disability. Learn Disabil Res Pract 20:142–155.

McCloskey M. 1992. Cognitive mechanisms in numerical processing: evidence from acquired dyscalculia. Cognition 44:107–157.

McNeil JE, Burgess PW. 2002. The selective impairment of arithmetical procedures. Cortex 38:569–587.

Mervis CB, Morris CA. 2007. Williams syndrome. In: Mazzocco MMM, Ross JL, editors. Neurogenetic developmental disorders: variation of manifestation in childhood. Cambridge, MA: MIT Press. p 199–262.

Mervis CB, Robinson BF, Bertrand J, et al. 2000. The Williams syndrome cognitive profile. Brain Cogn 44:604–628.

Mesulam MM. 1981. A cortical network for directed attention and unilateral neglect. Ann Neurol 10:309–325.

Meyer-Lindenberg A, Kohn P, Mervis CB, et al. 2004. Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. Neuron 43:623–631.

Meyer-Lindenberg A, Mervis CB, Berman KF. 2006. Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. Nat Rev Neurosci 7:380–393.

Meyer-Lindenberg A, Mervis CB, Sarpal D, et al. 2005. Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. J Clin Invest 115:1888–1895.

Mobbs D, Garrett AS, Menon V, et al. 2004. Anomalous brain activation during face and gaze processing in Williams syndrome. Neurology 62:2070–2076.

Molko N, Cachia A, Riviere D, et al. 2008. Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. Neuron 40: 847–858.

Moyer RS, Landauer TK. 1967. Time required for judgements of numerical inequality. Nature 215:1519–1520.

Murphy MM. 2009. A review of mathematical learning disabilities in children with fragile X syndrome. Dev Disabil Res Rev 15: 21–27.

Murphy MM, Mazzocoo MM, Gerner G, et al. 2006. Mathematics learning disability in girls with Turner syndrome or fragile X syndrome. Brain Cogn 61:195–210.

Musolino J, Landau B, Chunyo G. 2006. Syntax in Williams Syndrome: it's not impaired or deviant. In the 2006 Annual Boston University Conference on Language Development 2006. Boston, MA.

O'Hearn K, Landau B. 2007. Mathematical skill in individuals with Williams syndrome: evidence from a standardized mathematics battery. Brain Cogn 64:238–246.

O'Hearn K, Landau B. Mathematical abilities in Williams syndrome. J Child Psychol Psychiatry: (in press).

O'Hearn K, Landau B, Hoffman JE. 2005. Multiple object tracking in people with Williams syndrome and in normally developing children. Psychol Sci 16:905–912.

Paterson SJ, Brown JH, Gsoedl MK, et al. 1999. Cognitive modularity and genetic disorders. Science 286:2355–2358.

Paterson SJ, Girelli L, Butterworth B, et al. 2006. Are numerical impairments syndrome specific? Evidence from Williams syndrome and Down's syndrome. J Child Psychol Psychiatry 47:190–204.

Paul BM, Stiles J, Passarotti A, et al. 2002. Face and place processing in Williams syndrome: evidence for a dorsal-ventral dissociation. Neuroreport 13:1115–1119.

Piazza M, Giacomini E, Le Bihan D, et al. 2003. Single-trial classification of parallel preattentive and serial attentive processes using functional magnetic resonance imaging. Proc R Soc Lond B Biol Sci 270: 1237–1245.

Piazza M, Izard V, Pinel P, et al. 2004. Tuning curves for approximate numerosity in the human intraparietal sulcus. Neuron 44:547–555.

Piazza M, Pinel P, Le Bihan D, et al. 2007. A magnitude code common to numerosities and number symbols in human intraparietal cortex. Neuron 53:293–305.

Pylyshyn Z. 2000. Situating vision in the world. Trends Cogn Sci 4:197–207.

Reiss AL, Eckert MA, Rose FE, et al. 2004. An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. J Neurosci 24:5009–5015.

Reiss AL, Eliez S, Schmitt JE, et al. 2000. Neuroanatomy of Williams syndrome: a high-resolution MRI study. J Cogn Neurosci 12(Suppl 1):65–73.

Reiss JE, Hoffman JE, Landau B. 2005. Motion processing specialization in Williams syndrome. Vision Res 45:3379–3390.

Rivera SM, Reiss AL, Eckert MA, et al. 2005. Developmental changes in mental arithmetic: evidence for increased functional specialization in the left inferior parietal cortex. Cereb Cortex 15:1779–1790.

Scholl BJ, Leslie A. 1999. Explaining the Infant's object concept: beyond the perception/cognition dichotomy. In: Lepore E, Pylshyn ZW, editors. Rutgers Lectures on Cognitive Science. Oxford: Blackwell. p 26–73.

Sekuler R, Mierkiewiez D. 1977. Children's judgements of numerical inequality. Child Dev 48:630–633.

Simon O, Mangin JF, Cohen L, et al. 2002. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron 33:475–487.

Tager-Flusberg H, Plesa-Skwerer D, Faja S, et al. 2003. People with Williams syndrome process faces holistically. Cognition 89:11–24.

Temple E, Posner MI. 1998. Brain mechanisms of quantity are similar in 5-year-old children and adults. Proc Natl Acad Sci USA 95:7836–7841.

Todd JJ, Marois R. 2004. Capacity limit of visual short-term memory in human posterior parietal cortex. Nature 428:751–754.

Udwin O, Davies M, Howlin P. 1996. A longitudinal study of cognitive abilities and educational attainment in Williams syndrome. Dev Med Child Neurol 38:1020–1029.

Ungerleider LG, Mishkin M. 1982. Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW, editors. Analysis of visual behavior. Boston: MIT Press. p 549–586.

Van Essen DC, Dickson J, Harwell J, et al. 2001. An integrated software system for surface-based analyses of cerebral cortex. J Am Med Inform Assoc 8:443–459.

Van Essen DC, Dierker D, Snyder AZ, et al. 2006. Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses. J Neurosci 26: 5470–5483.

Van Herwegen J, Ansari D, Xu F, et al. 2008. Small and large number processing in infants and toddlers with Williams syndrome. Dev Science 11:637–643.

Wilson AJ, Revkin SK, Cohen D, et al. 2006. An open trial assessment of "The Number Race", an adaptive computer game for remediation of dyscalculia. Behav Brain Funct 30:2–20.

Xu F, Spelke ES. 2000. Large number discrimination in 6-month-old infants. Cognition 74:B1–B11.

Zukowski A. 2005. Knowledge of constraints on compounding in children and adolescents with Williams syndrome. J Speech Lang Hear Res 48:79–92.