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# Clues to the Foundations of Numerical Cognitive Impairments: Evidence From Genetic Disorders

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## Abstract

Several neurodevelopmental disorders of known genetic etiology generate phenotypes that share the characteristic of numerical and mathematical cognitive impairments. This article reviews some of the main findings that suggest a possible key role that spatial and temporal information processing impairments may play in the atypical development of numerical cognitive competence. The question of what neural substrate might underlie these impairments is also addressed, as are the challenges for interpreting neural structure/cognitive function mapping in atypically developing populations.

One strategy that has been employed by cognitive scientists attempting to understand typical functioning in a specific domain has been to examine cases where a known biological anomaly exists in order to see how that functioning has been affected. Initially, such an approach was focused on healthy adults who had developed typical mature functioning in the domain of interest and then had suffered brain damage or injury. The resulting dysfunctions were assumed to have directly arisen from the lesion, thereby pointing to the neural substrate for the functional domain of interest. In this vein, considerable study in clinical neuropsychology and cognitive neurology has focused on the spatial, temporal and numerical sequelae of brain damage, particularly that arising from parietal lobe lesions that result from stroke and related brain damage (Halligan, 2003; Marshall & Fink, 2001; Mesulam, 1981; Zorzi, Priftis, & Umilta, 2002).

More recently, those interested in typical and atypical numerical development in humans have investigated several neurodevelopment disorders (NDDs) with identifiable genetic basis because of consistent reports that affected individuals experience significant impairments in the numerical cognitive domain. These disorders include chromosome 22q11.2 deletion (22q11.2DS), also known as Velocardiofacial or DiGeorge, syndrome (De Smedt, Swillen, Verschaffel, & Ghesquière, 2009; Simon, 2008; Simon, Bearden, McDonald-McGinn, & Zackai, 2005). Turner syndrome (TS) (Bruandet, Molko, Cohen, & Dehaene, 2004; Kesler, Menon, & Reiss, 2006; M. M. Mazzocco, 1998; Molko et al., 2004; Simon et al., 2008; Temple & Carney, 1995), fragile X syndrome (FXS) (Mazzocco, 2000; Rivera, Menon, White, Glaser, & Reiss, 2002), Williams syndrome (WS) (Mervis, Morris, Bertrand, & Robinson, 1999; Paterson, Girelli, Butterworth, & Karmiloff-Smith, 2006; Van Herwegen, Ansari, Xu, & Karmiloff-Smith, 2008) and, to a much lesser extent, Prader-Willi syndrome (PWS) (Bertella et al., 2005). However, important interpretive differences exist between studying the neurobiological bases of numerical processing in brain damaged typical adults and atypically developing children.



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The clearest difference between impairments arising from the damaged mature typical case and the congenitally atypical case is what might be termed the *epigenetic developmental trajectory* of those affected by genetically based NDDs versus otherwise healthy individuals. As stated so clearly by Dennis and colleagues (2009), "[n]eurodevelopmental disorders are different from adult acquired disorders [and from childhood acquired disorders involving traumatic brain injury (TBI), strokes, or tumors] in an important way: they involve no period of normal development" (p. 331). As Karmiloff-Smith and colleagues have pointed out (Ansari & Karmiloff-Smith, 2002; Johnson, 2000; Karmiloff-Smith, 1998; Scerif & Karmiloff-Smith, 2005), one cannot understand the implications of atypical behaviors for neurocognitive accounts of functional domains without explicitly studying the changes in those domains over an extended developmental trajectory from infancy to, at least, middle childhood. Furthermore, it is critical to not mistakenly assume that atypical behavioral profiles can provide unequivocal information about the neural substrates of that function based on structure/function mappings observed in typical individuals. If individuals experience no period of typical brain development then our default assumption should probably be that the brain regions that underlie the mature state in typical populations do *not* implement impaired versions of the same function in atypically developing populations (Johnson, Halit, Grice, & Karmiloff-Smith, 2002). Since the minds and brains of those with NDDs of genetic etiology develop in a different environment to healthy individuals, it is quite possible that the neural solutions that they generate may be significantly different from those seen in typical adults. They might develop identically structured but differently functioning brains or they might, as the data seem to suggest, develop quite differently structured and connected brains. Either way, we should not expect such individuals to be operating with the typical brain network that is in some way "broken." Therefore we will proceed to examine, with some caution, the atypical development of numerical competence in several populations with identifiable genetic anomalies in order to examine what might be learned about how they come to represent, process and understand numerical information and what we might be able to learn from this about the same process in typically developing individuals.

How typical development of numerical representations and processes takes place is still far from clear, although some converging models are extensively reviewed by Ansari (2008). At this point, though, a growing body of evidence appears to indicate that one of the foundational competencies from which numerical cognitive processes and their associated representations are either constructed or to which they are strongly related is spatial information processing (Ansari et al., 2003; Hartje, 1987; Simon, 1997, 1999). There is also growing evidence of similar relationships between mental representations of space and time (Casasanto & Boroditsky, 2008; Coull, Frith, Buchel, & Nobre, 2000; Simon, 2008; Walsh, 2003). Some recent neuroimaging studies also indicate overlapping neural activations for comparative processing in general, and spatial and size comparisons in particular (Cohen Kadosh et al., 2005). Indeed, one of the few attempts to computationally model the transition from early, mainly perceptual, non-symbolic magnitude processing to the formation of numerical symbols (and their meanings) states that "individuation and enumeration of elements in a visual display depends on spatial processing" (Verguts & Fias, 2004).

It is somewhat better established that typical adults who suffer brain damage that engenders spatial neglect also experience the onset of impairments in broad magnitude or numerical processing (Cipolotti, Butterworth, & Denes, 1991; Vuilleumier, Ortigue, & Brugger, 2004; Zorzi, Priftis, Meneghello, Marenzi, & Umilta, 2005; Zorzi, Priftis, & Umilta, 2002). Furthermore, the same effect can be induced by transiently interrupting neural processing in areas typically associated with spatial functioning (Gobel, Calabria, Farne, & Rossetti, 2006). Similarly, several studies show that numerical cues appear to affect spatial attention

(Fischer, Castel, Dodd, & Pratt, 2003), temporal attention (Casarotti, Michielin, Zorzi, & Umilta, 2007), as well as manual aiming (Ishihara et al., 2006). Finally, an extensive review of phenomenon of damaged-induced spatial neglect in previously healthy adults makes a strong link to spatial attention (Chatterjee, 2002).

Therefore, one hypothesis that has been explored is whether basic spatial attentional processing is impaired across these NDD populations and, if so, whether any relationship to numerical processing can be found. It is now quite well established (Piazza, Mechelli, Butterworth, & Price, 2002; Sathian et al., 1999; Simon, 1997, 1998, 1999; Simon & Vaishnavi, 1996; Trick & Pylyshyn, 1993, 1994) that attentional processing is intricately linked with different modes of enumeration. Based on these findings, I have proposed (Simon 1997, 1998, 1999, 2008) that spatial and temporal attentional functions serve as the basic capabilities upon which numerical competencies are constructed, and that impairments in these may help to explain the prevalence of numerical and mathematical learning difficulties in several neurodevelopmental disorders. Thus, several converging lines of evidence appear to support hypothesis that those who show numerical impairments are likely to also show more basic attentional impairments. I will review findings from studies of several genetic NDDs below and then examine further relationships between these and very basic but procedural enumerative and then arithmetical computational tasks before addressing possible neural substrates of the reported atypicalities.

## ATTENTION AND SPATIAL PROCESSING

Spatial attention, particularly when operating in the volitional mode that requires internally generated search, as opposed to reflexive shifts of attention in response to environmental location cues, appears to be impaired in several NDDs. Children with 22q11.2DS had much greater difficulty than typical controls in response to invalid spatial cues, that is, when attention was initially misleadingly cued by a central arrow that pointed to the wrong one of two locations where targets could subsequently appear (Simon, Bearden, et al., 2005). They were less impaired in response to invalid cues in an experiment where, instead of a central spatial cue that pointed to a potential location, peripheral spatial cues were used in the form of a flashing of the box at one of the two actual locations in which targets could appear. Children with 22q11.2DS did still respond significantly more slowly than typical children in this experiment (Bish, Ferrante, McDonald-McGinn, Zackai, & Simon, 2005). These results both indicate attentional search impairment because, on a simple reaction time task, speeded responses of children with 22q11.2DS were not different to that of the controls (Simon et al., 2008). Children with 22q11.2DS also showed significant impairments relative to TD children when invalid spatial cues required them to shift attention between discrete objects in a stimulus display (Bish, Chiodo, Mattei, & Simon, 2007). However, they showed a relative advantage compared to typicals when required to reorient attention within these objects. Together, these findings indicate that children with 22q11.2DS are impaired in the ability to volitionally navigate visual space in a goal directed fashion and that this impairment is slightly reduced in the presence of helpful environmental cues.

Scerif, Cornish, Wilding, Driver, and Karmiloff-Smith (2004) reported related attentional impairments in two other NDDs. She compared the performance of 3- to 4-year-old boys with FXS, similarly aged boys and girls with WS and chronological or mental age-matched typical controls on a visual search task. Both of the NDD groups where more impaired than controls and differed from each other only in error types not amounts. Toddlers with WS searched incorrect distractor locations more often while those with FXS more often revisited locations where they had previously revealed non-target items. In each case the evidence points to impaired visual attentional search in children with either FXS or WS, though the effect on behavior is slightly different in nature. Munir, Cornish, and Wilding (2000) found

similar results in 8–15 year old boys with FXS on a similar visuospatial search task. They produced significantly fewer correct target identifications, slower responses and more incorrect identifications of distractors as targets than age matched typical controls, even those selected on the basis of having poor attentional capabilities. So, it does appear that some commonalities in spatial attentional limitations occur in childhood in several genetic NDD groups.

One implication of these impairments in visuospatial selective attention is that they are likely to challenge some aspects of individuation process because spatial attention appears to be required for counting. Working serially through set of items for uncounted "targets" and counted "distractors" is essentially a volitional spatial attention search with a spatial working memory load added. Therefore, if search is impaired to the extent that selection of target items fails and/or non-target items (such as those not to be included in the enumerative total or those that have already been processed and are "revisited") are included, then the set of items on which conceptual or procedural enumerative processes is applied will be inappropriate. Accordingly, the resulting quantity produced by the child will be wrong, no matter how well the higher-level knowledge and processes, such as the application of a counting string, have been developed or were applied. For example, accurate application of a learned counting procedure to a sub- or superset of the to-be-counted items will produce the wrong cardinal value. This will be discussed in more detailed in the "*Numerical and Arithmetical Procedures"* section below.

Patterns of impairment in visuospatial processing and their implications for the development of higher-level abilities are not just limited to visual search. Several experiments show that mental manipulation of the spatial characteristics of objects is also impaired in children with genetic disorders. In girls with Turner syndrome, behavioral data from functional magnetic resonance imaging (fMRI) experiments indicate impairments in matching a target line to one of a set of differently oriented comparison lines (Kesler et al., 2004) and in visuospatial working memory (Haberecht et al., 2001). Children with Williams syndrome have been shown to have significant impairments in visuomotor and visuoconstructive processing. Landau, Hoffman, and Kurz (2006) found that children with WS performed similarly to typical controls on non-spatial object recognition tasks but showed significant impairment when mental rotation of those objects was required. Similarly, on a spatiotemporal attention tasks, children with WS were less able than controls to track moving objects but not to recall the location of targets in a static display (O'Hearn, Landau, & Hoffman, 2005). Similar results have been reported in adults with WS, who showed a spatial impairment in their ability to determine whether pairs of geometric shapes could or could not be combined to complete a square yet they could detect matches between similar items without impairment (Meyer-Lindenberg et al., 2004). The results suggest that children (and adults) with these NDDs suffer from impairments in the ability to process a range of spatial information from search to the mental manipulation of spatial relationships within and between objects.

Despite the strong relationships that exist between spatial and temporal information processing, few studies of temporal cognition in individuals with genetic NDDs have been carried out. Debanné, Glaser, Gex-Fabry, and Eliez (2005) tested 6- to 39-year-old individuals with 22q11.2DS and typical age matched controls on two temporal judgment tasks. Those with 22q11.2DS showed an impaired ability to maintain the correct cadence in a finger-tapping task and, in a temporal judgment task, they required larger intervals between two durations than controls before they could as accurately tell them apart. This finding resembles the "distance effect" results commonly found in non-temporal magnitude comparison tasks discussed below. Silbert's (Silbert, Wolff, & Lilienthal, 1977) study of girls and young women with Turner syndrome did not show significantly poorer performance on similar tapping tasks, but the TS group were significantly less able to

distinguish between pairs of different rhythmic patterns presented at 92 beats per minute each. Thus, there is a little evidence that suggests similar impairments in at least two genetic NDD populations for retaining, analyzing and comparing temporal information.

Several theorists (Ansari, 2008; Ansari et al., 2003; Ansari & Karmiloff-Smith, 2002; Simon, 1997; Simon, Bearden, McDonald-McGinn, & Zackai, 2005; Walsh, 2003) have contended that spatial, and more recently temporal, processing abilities, and thus impairments in them, are strongly related to competence in the higher-level cognitive domain of numerical processing. This is because a range of basic functions in visuospatial attention has been implicated in several numerical subdomains. This is especially true of counting visually presented objects and reasoning about the relationships between different quantities. For example, quantities acquire ordinal relations that are mentally represented in linear spatial terms (e.g., two comes before three, 300 is far beyond 30). Therefore, spatial attention and associated representations are likely to be quite important to the development of simple numerical abilities like counting and magnitude comparison. My contention is that this apparently broad range of spatial and temporal processing impairments will serve to impair the development a range of estimation, enumerative and computational skills in children with these disorders.

## MAGNITUDE COMPARISON

Comparing quantities, whether analog or symbolic, appears to be a particular challenge for children with one of several NDDs. Commonly, this is found by examination of the "distance effect," where comparisons between more similar quantities produce poorer performance than when the quantities differ by much larger amounts. Children with 22q11.2DS showed impairments when comparing dot patterns or Arabic numerals (Simon, Bearden, et al., 2005) as well when they were asked to choose the larger of two stimuli in analog (block length) and symbolic (Arabic number) form (Simon et al., 2008). This latter study found an almost identical pattern of performance in girls with monsomy X (i.e., 45,X) Turner syndrome. Similar impairments were found in children and adults with WS whose mental age averaged 6.9 (Paterson et al., 2006). To date it does not appear that similar experiments have been carried out with children or adults with the other disorders discussed here.

One possible explanation of these findings comes from the view that the relationships between numerical magnitudes are represented in spatial terms on a putative "mental number line" (Dehaene, Bossini, & Giraux, 1993; Dehaene & Cohen, 1995). Therefore, impairments in spatial processing might result in increased overlap in spatial representations of similar magnitudes thereby decreasing their discriminability (Simon, 2008). For example, children with 22q11.2DS, appear to be less impaired on number reading and number fact recall tasks, which are strongly verbal, but more impaired on arithmetic problems involving carrying across columns where visuospatial processing is required (De Smedt et al., 2009). An alternative account of magnitude comparison processing (Van Opstal, Gevers, De Moor, & Verguts, 2008) is based on the Verguts and Fias model mentioned earlier. It generates the association between a comparison and response not in terms of representational overlap, such as spatial position on a mental number line, but as a learned association between comparative terms (e.g., larger quantity on the left) and specific learned responses (e.g., a left hand response). While it is possible that this explanation could account for the impairments discussed here, the accrued evidence of spatial impairments in several NDD populations suggests that the overlapping spatial representation account is currently the more convincing hypothesis to disprove when trying to explain the impairments under discussion here.

## NUMERICAL AND ARITHMETICAL PROCEDURES

If spatial and temporal information processing do indeed form an important foundation for the implementation and construction of procedures for generating exact quantitative values (such as counting or arithmetical computation), then it is reasonable to hypothesize that impairments in the former will contribute to atypical development of the latter. In other words, spatial cognition impairments and associated representational degradations relationships might “cascade” into development of exact arithmetical computation and other number processing tasks. A similar argument is made by Rubenstein and Henik (2009) in their discussion of the neurodevelopmental progression toward dyscalculia or mathematical learning disability (MLD). They state that, “instead of being genetically pre-specified, the specific brain areas that eventually serve a particular cognitive function (e.g., IPS) seem to emerge developmentally through interactions with the environment and to be interconnected with each other. Behavioural symptomatology consistent with MLD could be the result of atypical ‘interactive specialization”’ (p. 96). In other words, they argue that math learning, and the related disability, emerges from a gradual specialization of brain areas to the representation and processing of numerical information rather than being biologically prespecified. My claim is that the initial cognitive processes involved in that specialization process are those that are involved the spatial and temporal attention.

We (Simon, Bearden, et al., 2005) have shown that impaired visuospatial attentional search in children with 22q11.2DS likely contributed to poorer performance when counting items randomly arranged in visual displays. Unlike counting, subitizing, which is the enumeration of around 1–3 items, appears to depend minimally on the spatial attention system (Ansari, Lyons, van Eimeren, & Xu, 2007; Piazza, Giacomini, Le Bihan, & Dehaene, 2003; Piazza et al., 2002; Sathian et al., 1999). So, as predicted, children with 22q11.2DS were only impaired when using the attentionally dependent counting process. They subitized fewer items than controls and, consistent with reduced resolution that increased representational overlap of spatial representations, and/or poor implementation of attentional search, they made significantly more undercount than overcount errors (around 73% vs. 27%) compared to the TD children (Simon, 2008). Using the same task to study girls with 45,X Turner syndrome we (Simon et al., 2008) found that, although the counting slope for these girls was not significantly different from that of typical children (or those with 22q11.2DS) the intercept of their slope was almost twice as great (i.e., −1016 msec vs. −578 msec) indicating a considerable slowing in their ability to count accurately. A similar pattern also appears to be evident in girls with fragile X syndrome (manuscript in preparation).

Others have also made the link between spatial and arithmetical processing in both Turner and fragile X syndromes. For example, Mazzocco, Singh Bhatia, and Lesniak-Karpiak (2006) reported a correlation between the performance of girls with either fragile X or Turner syndrome on a standardized measure of spatial orientation judgment and on performance on a standardized counting task. Similarly a study of girls with TS (Rovet, Szekely, & Hockenberry, 1994) found significant impairments on arithmetical calculation, reduced arithmetical knowledge and a tendency to rely on verbal rather than visuospatial skills in arithmetic processing. An earlier study (Rovet & Netley, 1980) had found that females with TS were impaired on the visuospatial mental rotation of objects tasks. Other studies (Temple & Carney, 1993; Temple & Marriott, 1998) have also reported impairments in spatial and arithmetical performance in girls with TS. Children with Williams syndrome appear to show a similar profile to those with Turner syndrome described by Rovet et al. (1994). When asked to give an experimenter a specific number of marbles from a bowl, they performed as well as controls but while the performance of controls was accounted for by visuospatial competence, performance of children with WS was accounted for by language competence (Ansari et al., 2003).

The above review appears to indicate that, while the pattern and degree of relationship among the domains of function is variable in different disorders, there appears to be considerable evidence consistent with the hypothesis that impairments in spatial attention and related processing cascade into problems acquiring even basic numerical and arithmetical abilities. Where verbal processing is relatively strong, it appears to be adopted as an alternative foundation for that development, or at least an alternative computational strategy. These data suggest that impairment in or facility with numerically related cognition can be constructed on a range of foundations and with a variety of resulting performance profiles. The hypothesis I wish to advance here is that the later states of these trajectories relate strongly to the characteristics of spatial and temporal processing that are apparent earlier in development.

## INDICATIONS OF NEURAL BASIS

There is growing evidence that individuals with neurogenetic disorders associated with a range of numerically relevant cognitive impairments also show differences in several brain regions often associated with numerical functioning in healthy individuals. However, this does not mean that we should assume that such neural anomalies are the cause of or the explanation for these cognitive impairments (see also Rubenstein & Henik, 2009). One reason, as discussed earlier, is that those with NDDs have almost certainly followed an atypical trajectory shaped by an environment unlike that experienced by the brains of typically developing individuals. This makes interpretation of neural findings much more complex than in the typical population. If, for example, activation of a region correlated with a particular cognitive function in typical individuals is not evident in those with genetic disorders, it should not be assumed that the affected individuals are not carrying out the same neurocognitive computations. They may be doing so with alternate neural circuits hitherto unrecognized as being related to that specific cognitive function and that difference may partially explain their inability to function as optimally as typical individuals. There is already some evidence that, in individuals with the disorders discussed here, there are differences in neuroconnective patterns in brain regions often associated with numerical and magnitude processing and that they correlate with performance on tasks in that domain (Barnea-Goraly, Eliez, Menon, Bammer, & Reiss, 2005; Molko et al., 2004). I will discuss those findings shortly. These different circuits *may* be the cause of the observed functional differences. However, they are more likely the *result* of an altered developmental process perhaps shaped by atypical neurocognitive algorithms for computing numerical functions (for a detailed discussion of the typical case see Ansari, 2008). If this is the case, then what might be the underlying cause or start of that process? Some clues are beginning to emerge from research on at least two disorders: 22q11.2DS and FMR1 gene mutations along the fragile X spectrum of disorders.

I (Simon, 2008) have proposed that, at least in the case of 22q11.2DS, there are strong associations between the basal ganglia, posterior thalamus and cerebellum and basic spatial and temporal information processing systems in typical animals and humans. These are early developing neural systems and are situated in the most heavily affected region of the body and brain of those affected by neurogenetic disorders (i.e., the midline). Furthermore, anomalies in these brain regions have been reported in affected children (Bish, Nguyen, Ding, Ferrante, & Simon, 2004; Bish et al., 2006; Campbell, 2006; Eliez, Barnea-Goraly, Schmitt, Liu, & Reiss, 2002; Eliez, Schmitt, White, Wellis, & Reiss, 2001; Kates et al., 2004; Sugama, 2000) although no systematic developmental studies of these systems appear to exist as yet. In particular, I (Simon, 2008) focused on the pulvinar region of the posterior thalamus, which is critical to basis attentional functions in animals and humans (Karnath, Himmelbach, & Rorden, 2002; Petersen, Robinson, & Morris, 1987; Robinson & Petersen, 1992; Ward, Danziger, Owen, & Rafal, 2002). Not only does the pulvinar appear to be much

smaller in those with 22q11.2DS but its volume also strongly correlates with spatial attentional functioning (Bish, Nguyen, Ding, Ferrante, & Simon, 2004; Shapiro, Zhang, Gee, Amaral, & Simon, 2008). Finally the fact that the pulvinar's connectivity to primate parietal regions locate implicate it in the early stages of the dorsal visual processing system (Kaas & Lyon, 2007).

A similar story has emerged from studies of indviduals with either full mutation fragile X syndrome (FXS) or premutation carriers. Kogan (2003) has shown that the lack of the FMR1 protein (FMRP) that results from silencing of the FMR1 gene in full mutation fragile X creates structural anomalies in magnocellular neurons in the lateral geniculate nucleus of the thalamus, adjacent to the pulvinar. Kogan also showed that adult males with FXS showed impairments on spatiotemporal functions thought to directly tap the magnocellular, such as motion perception, but not parvocellular, such as the perception of form from high spatial frequency information, visual pathway. A similar pattern of performance has recently been reported in adult female premutation carrieers, that is, those with shorter expansions than the ≥200 CGG repeats required to meet criteria for FXS (Kéri & Benedek, 2009). Like those with 22q11.2DS, children with FXS have also been shown to have larger caudate volumes than typical children while girls with FXS also had larger thalamic volumes than typical children. Like children with 22q11.2DS, those with FXS also had enlarged volumes in another midline structure, the lateral ventricles (Campbell, 2006; Eliez, Blasey, Freund, Hastie, & Reiss, 2001; Simon et al., 2005). Also like those with 22q11.2DS, children with FXS have been shown to have reduced size of the medial cerebellum (Mostofsky et al., 1998). At least one report (Murphy et al., 1993) notes a similar pattern in a study of 18 women with TS who had reductions in basal ganglia, thalamic nuclei, and hippocampal volumes (as well as in the parieto-occipital region) and increased CSF volume in the midline third ventricle. This study found no cerebellar differences and another (Brown et al., 2002) found increased cerebellar volume in their TS group but neither reported values for just the medial region. Williams syndrome appears to generate a rather different pattern. While overall brain volume and lateral ventricle volumes are somewhat reduced, the cerebellar vermis appears to be enlarged (Jernigan & Bellugi, 1990; Reiss et al., 2000; Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001) and this might create an unusal pattern in anatomically connected thalamic and frontal volumes. Thus, one possible common developmental anomaly could be early disruption to key components of the magnocellular visual processing pathway. On the basis of the currently limited evidence base, however, this remains something of a speculative proposal for a common neurobiological basis for the phenotypic commonalities discussed here.

Several functional imaging studies show that individuals with these neurodevelopmental disorders produce unusual patterns of neural activation in areas associated, in typical individuals, with numerical and quantitative processing. In general, the findings are that primarily parietal, along with other, regions activated by typical, healthy participants are activated by those with neurogenetic disorders but to a different, predominantly lesser, degree. There is evidence that brain regions commonly associated with spatial attention activate when adults and children carry out a magnitude comparison task (Dehaene, Piazza, Pinel, & Cohen, 2003; Temple & Posner, 1998). However, one should be cautious about assuming that inferior parietal and intraparietal regions instantiate even a developmentally acquired brain region (or "module") for numerical processing. This is because several experiments have shown evidence for both specific and common functional activations in these areas for numerical tasks as well as other comparative tasks involving color, size, brightness, angular degree, line length, object matching, and feature similarity (Cohen Kadosh et al., 2007; Cohen Kadosh et al., 2005; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Shuman & Kanwisher, 2004; Wojciulik & Kanwisher, 1999). The relationship

does, however, further strengthen the relationship between attentional, spatial, and some aspects of quantitative cognition.

Using a simple functional imaging task where participants decide whether the answer presented for an easy (2-operand) or slightly harder (3-operand) arithmetic problem is correct, several studies have reported a similar pattern of neural activation and arithmetical impairment. Despite comparable accuracy, Rivera (Rivera et al., 2002) found that girls and young female adults with full mutation fragile X syndrome did not recruit the prefrontal-parietal-cerebellar network that they (Rivera, Reiss, Eckert, & Menon, 2005) reported finding in typical 9- to 18-year-old children when moving from 2 to 3 operand problems. In a small study of individuals with 22q11.2DS and age-matched typical controls where performance was not balanced, Eliez and colleagues (2001) found that, for 3-operand problems, the 22q11.2DS group performed more poorly and produced greater activation than controls in bilateral inferior parietal lobe (mainly in the supramarginal gyrus region), the right intraparietal sulcus, left precentral gyrus and the right insular gyrus and parietal operculum regions. In girls and women with Turner syndrome and age-matched typical controls, aged 7 to 24 years who performed with similar accuracy and activated typical frontoparietal regions, Kesler and colleagues (2006) found that the TS group also activated anterior cingulate, left precentral to medial frontal, left postcentral and supramarginal gyrus and left superior to middle temporal gyrus extending into inferior frontal regions more than the TD group on easier tasks only. For the harder problems the TD group activated left inferior, superior and intraparietal regions along with fusiform, medial temporal gyrus, anterior cingulate to superior frontal, bilateral medial and inferior frontal, caudate and cuneus regions more than the TS group. Further studies have characterized neural differences in TS. Molko and colleagues (2003) examined exact and approximate arithmetical processing and letter matching in 14 women with TS and matched typical controls. For calculation, the TS group activated essentially the same brain networks as typical controls except for a relative reduction in anterior cingulate activation. However, the effect of numerical size-dependent difficulty was seen in more right IPS activation for the TD than the TS group for exact calculation TD. For approximate calculation the TD group showed greater bilateral IPS and caudate and left precuneus activations. In a series of fMRI experiments with school-aged and teenaged girls with Turner syndrome discussed earlier, Kesler et al., Haberecht et al., and Hart et al. all reported reduced activation in parietal lobe areas that are typically associated with spatial processing. Using a multiple object tracking task to examine spatiotemporal attention, Beaton and colleagues (2010) found that, despite similar performance, girls with TS activated the typical network for this task, which includes medial and intraparietal regions as was as prefrontal regions (Culham, Cavanagh, & Kanwisher, 2001) less strongly than typical controls. They also activated atypical regions including bilateral precentral gyri extending into middle and inferior frontal gyri, bilateral putamen, left medial dorsal and ventral posterior thalamic nuclei, left cingulate gyrus, left postcentral gyrus and left superior and middle temporal gyri much more than the typical controls. A study of spatial shape processing in adults with WS (Meyer-Lindenberg et al., 2004) also found reduced activation in parietal cortex associated with the cognitive impairment. So, like the findings from cognitive studies of attention, enumeration and calculation, there is both overlap and heterogeneity in the genetic NDD groups. Almost all show some activation in the NDD groups of the brain areas observed in typical participants but rarely is the activation pattern of the same strength or limited to the same regions. There is also a rather wide variety of different patterns that do not just vary with the task used. This finding seems to support the view that spatial, temporal, and attentional processing impairments are associated with numerical ones but have not yet been able to produce a clear characterization of the nature, extent, or dynamics of the neural network(s) that are developed in these groups for these cognitive functions.

The fact that many of the neural circuits now strongly associated with numerical, comparative and arithmetical cognitive processing in typicals also appear to activate in children and adults with NDDs but in different ways and under different conditions than in typical individuals suggests that they are deploying differently structured and/or functioning neural circuits for the same task. One way to more directly examine the possible experience-dependent and/or altered genetic, effect of atypical development on the structural aspects of this circuitry is to use diffusion tensor imaging (DTI). This is a specialized form of MRI that analyzes the diffusive motion of water molecules with unrestricted regions such as ventricles as compared to more restrictive tissue such as white matter tracts. As such it allows a number of diffusion scalars to be calculated that reveal certain aspects of white matter tract organization and integrity. In this way DTI can generate results about neural connectivity at the microstructural level (Basser & Pierpaoli, 1996; Conturo et al., 1999; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996).

Three articles recently reported strikingly similar, and unexpected, results from comparisons between individuals with Williams syndrome (Hoeft et al., 2007), 22q11.2DS (Simon et al., 2008) or Turner syndrome (Holzapfel, Barnea-Goraly, Eckert, Kesler, & Reiss, 2006) and typical controls. In each study at least one result found that participants with the NDD in question were found to have higher fractional anisotropy (FA) values than typically developing controls in a region of the right hemisphere (Williams syndrome), left hemisphere (Turner syndrome), or bilateral (22q11.2DS) superior longitudinal fasciculus within the inferior parietal lobe. FA measures how much diffusion in a given location is oriented in a specific direction due to the orientation of the white matter tract in which it is constrained. In general, higher FA values are thought to indicate more clearly defined white matter tracts. However, in these cases the increased FA suggested atypical connectivity along the main axis of the anterior-posteriorly oriented connective tract, possibly at the cost of reduced (radial) connectivity to contiguous parietal cortex, which might partially explain the visuospatial cognitive impairments in each disorder. Indeed, Hoeft et al. showed that high FA in the right SLF of the WS group correlated with worse WAIS 3 Object Assembly scores and Simon et al. showed that high FA in the right SLF of the 22q11.2DS group correlated with worse spatial attention performance. No correlations with function were performance by Holzapfel. Barnea-Goraly and colleagues (2005) reported the more familiar pattern of increased FA correlating with better cognitive function by showing that increases in FA in a left parietal region including the intraparietal sulcus, angular gyrus and supramarginal gyrus in children and adolescents with 22q11.2DS correlated with better WISC/WAIS arithmetic scores FA.

Finally, several small studies report connectivity differences in similar brain regions by examining characteristics of the fiber tracts using Diffusion Tensor tract tracing. One reported a range of different DTI findings indicating atypical connectivity in individuals with WS, including tracts traversing the intraparietal sulcus (Marenco et al., 2007) while another (Molko et al., 2004) used DTI and complementary methods to show that, in 14 women with Turner syndrome, several abnormalities in brain structure and connectivity could be localized in the right intraparietal sulcus (as well as other regions). A study of girls with FXS (Barnea-Goraly et al., 2003) reported a cluster of reduced FA in the left caudate region as well as bilateral clusters of reduced FA in parietal sensorimotor areas in the FXS group compared to controls. So, again, these connectivity findings illustrate some convergence with those from cognitive experiments and functional imaging studies in that they indicate there is both overlap and heterogeneity in the genetic NDD groups. However, the relatively small number of studies and the different approaches used mean that not enough data has yet been accrued to generate a characterization of the neural circuitry developed in these NDD population for the purpose spatial, temporal and numerical information processing.

However, while recognizing some degree of overlap in the findings discussed above, it is also important to consider that a less commonly discussed factor may account for some of the variability. Currently, group comparisons in imaging data are carried out using a method that only reveals significantly different clusters of neural activation or tissue differences between two groups when all members of one group show a common result in a given region that distinguishes them from to all members of the other group. This method works very well in typical individuals when something like neural activation in response to two different tasks is being examined. This is because variability in major brain areas or circuits in typical individuals, while present, is not very significant. However, researchers studying neurodevelopmental disorders recognize that those affected are not only quite different from healthy age-matched controls in many ways but that they also differ on many dimensions (such as measures of brain and cognition) from one another to a much greater degree. In other words, they tend to have much higher intragroup variability. Therefore, it could be that many studies are failing to detect a range of alternate neural circuits that (suboptimally) implement the target functions in the affected group but that there is not enough overlap within that group for them to be detected with sufficient power for statistical significance. In standard analytical approaches they would, therefore, be invisible because of subthreshold statistical values. An alternative strategy might be to explore and report a range of individual participant, or subgroup, analyses to look for partial overlaps, or subsets of distinct alternative patterns of differences between the affected and typical groups and to report those rather than only paying attention to anything that meets (or more likely fails to meet) the more stringent whole group statistical threshold.

There is also a second, more technical issue to note here. In order for analysis of images from groups of participants to be accurately analyzed, each individual brain must be accurately registered, or spatially normalized, to some standard template. The reason for this is that there is a requirement that all the individuals voxels are lined up in the separate brains just as all the cells in any other data table would be aligned to ensure that values of the same tests are being compared. Usually this registration method requires complex “warping,” of adjusting the shape, of each brain to fit it to the standard template (e.g., Ashburner & Friston, 2000; Wu, Carmichael, Lopez-Garcia, Carter, & Aizenstein, 2006). This is much easier to do with typical brains because most templates are constructed using images from typical adults and, more recently, children (Evans & Group, 2006). The task becomes far more complicated, computationally intensive and often less accurate, when many individual brains have significant internal shape, volume, or other anomalies that are the hallmark of atypical brain development. Thus, some of the inconsistencies in the above results may arise from complexities that arise from the nature of neural analyses of atypically developing brains.

## CONCLUSIONS

In this article I have reviewed evidence that is consistent with the hypothesis that spatial and temporal information processing, particularly associated with attention, are critical foundational components for the construction of a range of numerical competencies including aspects of estimation, magnitude comparison, enumeration, and arithmetical computation. Increasingly, there appears to be a convergence of findings indicating that, in several neurodevelopmental disorders populations of identifiable genetic etiology there may an overlapping phenotype of numerical cognitive impairments that may be explained by dysfunction in several more basic cognitive domains. These include the ability to volitionally deploy spatial attention, estimate or compare spatial and/or temporal magnitudes, use attentional resources as part of the magnitude comparison or enumerative process, and to effectively carry out arithmetical computations. Furthermore, where language-based skills seem to be a relative strength, as in the case of Williams, chromosome

22q11.2 deletion and Turner syndromes, there is some evidence that some numerical processes are more reliant on those than is true for typically developing children. Therefore, the results reviewed here do appear to suggest that the development of spatial and temporal information processing abilities impacts the later construction of a broad swath of numerical cognitive competence. This is partly because it can be shown how impairments in the former can be related to, although not causally linked at this time, to difficulties in the latter.

It also seems apparent that atypical patterns of neural structure, function and connectivity can be found in these populations and somewhat reliably so in areas associated with spatial, attentional, comparative, and numerical processing in typical children and adults. Anomalies in these regions, particularly those associated with the dorsal visual processing stream, have been suggested as a potential explanation for these impairments (Braddick, Atkinson, & Wattam-Bell, 2003; Grinter, Maybery, & Badcock, 2010; Walter, Mazaika, & Reiss, 2009). However, I concur with Rubinstein and Henik's (2009) view that this kind of account oversimplified and insufficiently developmental in its perspective. Instead, I have presented the view here that these commonly observable cortical changes may instead be the result of an atypical developmental process that starts with changes in subcortical systems. Then, as the foundational capabilities for later numerical processing are developed during childhood in an atypical and suboptimal fashion due to dysfunctions in these suboptimal systems, different cortical circuits to support more advanced processing are constructed. Therefore, atypical spatial and temporal processing and the neural substrates that support them during childhood are proposed as an endopheno-type for the kinds of numerical cognitive impairments manifest by school aged children in the neurodevelopmental disorder populations discussed here.

Clearly, many questions remain to be resolved about the contribution of genetics to atypical, as well as typical, development of numerical cognitive function. However, the questions raised by this research may well turn out to be the very issues that clarify for us how typical development and its atypical variants in a range of cognitive domains are created. As Scerif and Karmiloff-Smith (2005) state, "genotype-phenotype mappings must operationalize the early changes in neurocomputational properties that characterize genetic disorders and their potential effects on subsequent developmental trajectories." It is for this reason that the study of neurogenetic disorders might well provide us with the clearest understanding of what is required for the typical development of cognitive competence in a range of domains, including that of numbers, and what the consequences are for that development when those neurocomputational properties are perturbed and when they are not.

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