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VISUOSPATIAL AND NUMERICAL COGNITIVE DEFICITS IN CHILDREN WITH CHROMOSOME 22Q11.2 DELETION SYNDROME

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Abstract

This article presents some of the earliest evidence of visuospatial and numerical cognitive deficits in children with the chromosome 22q11.2 deletion syndrome; a common but ill-understood genetic disorder resulting in medical complications, cognitive impairment, and brain morphologic changes. Relative to a group of typically developing controls, deleted children performed more poorly on tests of visual attentional orienting, visual enumeration and relative numerical magnitude judgment. Results showed that performance deficits in children with the deletion could not be explained by a global deficit in psychomotor speed. Instead, our findings are supportive of the hypothesis that visuospatial and numerical deficits in children with the chromosome 22q11.2 deletion are due, at least in part, to posterior parietal dysfunction.

Keywords

child; chromosome 22q11.2; VCFS; parietal lobe; attention; enumeration; magnitude; judgment

Introduction

With the emergence of the field of developmental cognitive neuroscience there has been a dramatic increase in the study of the neurocognitive implications of genetic disorders such as Down syndrome, Williams-Beuren syndrome and Fragile X syndrome. Much of the initial focus was on developing a clear understanding of the genetic effects on brain and cognitive function that produce the characteristic deficits in these syndromes so that management and intervention programs could be created. However, these syndromes have allowed researchers to explore the relationship between genetics and cognitive function. Thus, these disorders also provide considerable insight into how normal neurocognitive development occurs and how disturbances in that process generate functional deficits (Karmiloff-Smith, 1998; Oliver, Johnson et al., 2000).

There are now quite sophisticated levels of understanding of the neurocognitive bases of intellectual and communicative deficits in Williams syndrome (Bellugi et al., 1999, 2000;

Mervis et al., 1999), Down syndrome (Chapman and Hesketh, 2000; Paterson, 2001), Fragile X syndrome (Bennetto and Pennington, 1996; Freund and Reiss, 1991) and Turner syndrome (Reiss et al., 1995; Ross et al., 2000). In stark contrast, little is known at this level of analysis about individuals with another disorder, which is the most common genetic deletion syndrome and also one of the most common genetic sources of mental retardation or developmental disability (McDonald-McGinn et al., 1999). This syndrome results from a submicroscopic deletion of approximately 3 mb on the long (q) arm of chromosome 22 (Dunham et al., 1999) and is thus referred to as the chromosome 22q11.2 deletion syndrome (hereafter 22q). It encompasses the DiGeorge (DGS) (DiGeorge, 1965) and Velocardiofacial (VCFS) (Shprintzen et al., 1978) syndromes.

The lag in understanding about the neurocognitive implications of 22q is partially due to fairly recent developments in cardiac surgery (e.g. Bellinger et al., 1995), which allow repair in infancy of the once fatal congenital heart defects that are estimated to affect around 70-75% of 22q11.2 deleted individuals (McDonald-McGinn et al., 1999). More significant were the observations of common deletions in multiple patients with DGS and VCFS (Driscoll et al., 1992; Driscoll et al., 1992) and the development of a diagnostic test for the chromosome 22q11.2 deletion that made it possible to determine that the large and variable set of symptoms which had been associated with DGS and VCFS all originated from the same genetic source. The use of that test set the prevalence of the deletion at around one in 4000-5000 live births (Driscoll et al., 1993) and focused attention on the now large and growing population of affected individuals. Though fewer than 10% of deletions reported to date have been familial (McDonald-McGinn et al., 1999), the fact that VCFS has a 50% recurrence risk means that the population is likely to enlarge even further as some members of the current cohort of children and adolescents reach maturity. Therefore it is crucial that advances be made in understanding the characteristics and biological bases of the cognitive and behavioral deficits in this population so that interventions and treatments can be sought. This paper represents a very early contribution to that process.

The most systematically observed manifestations of the 22q11.2 deletion syndrome include cleft palate, conotruncal heart defects, T-cell abnormalities, and neonatal hypocalcemia. Commonly observed also are neurologic signs and brain morphologic (Bingham et al., 1997) and volumetric changes (e.g. Eliez et al., 2000; Kates et al., 2001), facial dysmorphisms including prominent nasal bridge, ear abnormalities, velopharyngeal insufficiency, hypernasal speech, and mild to moderate cognitive deficit. This mild retardation has been characterized to date primarily in terms of standardized neuropsychological measurement. As a result, there is now good evidence (Gerdes et al., 1999; Moss et al., 1999; Swillen et al., 2000; Wang et al., 2000) that a typical set of observable cognitive deficits exists in this population, even though there is some degree of variance in phenotypic expression. Along with an overall delay in early cognitive, psychomotor and language development and an overall IQ in the range of 70-85, a subset of deficits are evident in the areas of visuospatial and arithmetical performance (Bearden et al., 2001).

Despite their early language delays, children with 22q still score higher on standardized tests of verbal abilities than tests of visuospatial abilities. To be more specific, "analysis of the IQ test subtest scores suggest relative strengths in the area of rote verbal knowledge and great

weaknesses in the areas of visual-perceptual-spatial abilities and nonverbal reasoning” (Swillen et al., 2000). This pattern has been further characterized by a study (Woodin et al., 2001) of 81 22q children (40 female, 41 male) ranging in age from 6-17 years, 50 of whom were school aged (mean = 10.3 years). This group showed the characteristic pattern of IQ scores with a Full Scale IQ mean of 76 (sd = 12.7) but Verbal IQ mean of 88.3 (sd = 14.1), which was significantly higher than Performance IQ where the mean was 73 (sd = 12.4). Broad reading scores were significantly higher than for broad math on the Wechsler Individual Achievement Test, and while word reading scores were significantly higher than reading comprehension, both pencil and paper arithmetic and mathematical reasoning produced similarly low scores. With respect to memory, the difference between verbal and visuospatial domains is most clear from a different report on an overlapping group of individuals. Bearden et al (Bearden et al., 2001) report significantly higher scores on a test of rote verbal memory (Wide Range Assessment of Memory and Learning -verbal learning) than on test of visuospatial memory (Children's Memory Scale – dot locations). Overall, these results consolidate the picture of individuals with 22q exhibiting relative strengths in some verbal domains while visuospatial and numerical performance tends to be generally depressed.

The purpose of this current paper is to report on some early findings from a large-scale investigation of the visuospatial and numerical cognitive deficits at Children's Hospital of Philadelphia. We take the neuropsychological profile described above as our starting point, and are investigating the hypothesis that a major cause of both the visuospatial and numerical cognitive deficits is a dysfunction in the posterior parietal lobes (PPL) of deleted individuals. Based on this reasoning we have undertaken an analysis of visuospatial and numerical processing in children with VCFS and controls using three cognitive tasks whose required processes are known to depend upon this substrate. The tasks are: attentional orienting, visual enumeration and numerical magnitude comparison.

The tasks were chosen because of evidence indicating the role of posterior parietal function in successful performance. The posterior parietal cortex (PPC) contains areas 5 and 7, and 39 and 40 (superior parietal lobule, and posterior parietal lobule comprising the angular and supramarginal gyri, and the intraparietal sulcus). As Kolb and Whishaw (1996) state, “the polymodal region of posterior parietal cortex is [...] important in various aspects of ‘mental space’, which range from arithmetic and reading to the mental rotation and manipulation of visual images” (p. 271). A further motivation for our hypothesis is that the volumetric imaging studies mentioned earlier (Eliez et al., 2000; Kates et al., 2001) reported reductions in parietal gray and white matter, indicating that this brain region may be subject to anomalous development and thus more likely to exhibit dysfunction.

Recent studies have linked areas in PPL to visuospatial cognitive function (Culham and Kanwisher, 2001), including its importance to shifting spatial attention within a visual scene (Corbetta et al., 1993; Corbetta, 1998), to object detection (Corbetta et al., 2000), and also to the temporal dynamics (di Pellegrino et al., 1998; Duncan et al., 1994) and resource limitations (Marois et al., 2000) of those processes. Considerable evidence also exists linking these visuospatial processes to basic functions of numerical cognition.

Trick and Pylyshyn (1994) showed that subitizing and counting depend on different visual attentional processes. Subitizing was only possible in pop-out displays, which depend on so-called “preattentive” disjunctive visual search, while counting was called into play whenever targets needed to be effortfully discriminated from distracters, no matter how few targets were present. Sathian et al. (1999) reported similar activations in extrastriate occipital cortex (BA 18/19) for subitizing and pop-out. In contrast, counting activated widespread areas including bilateral involvement of similar intraparietal areas to those implicated in studies of enumeration and arithmetic (e.g. Dehaene et al., 1999; Menon et al., 2000) and attentional orienting and target detection (Corbetta, 1998; Corbetta et al., 2000).

Dehaene's “Triple Code” theory (Dehaene, 1992; Dehaene and Cohen, 1995; Dehaene et al., 1999) proposes that three kinds of representations come to support numerical processing. An advanced verbal system of numerical facts supporting arithmetical computations is to be found in left frontal language regions. A visual form (number word or Arabic numeral) representation, which supports stimulus identification and interpretation, is associated bilaterally with the occipital-temporal, or “what”, pathway. The major quantitative processing unit of the system, in bilateral posterior parietal lobes, implements an approximate analog quantity representation, used to make magnitude comparison. Pinel et al. (1999) generally provided support for this model with fMRI data showing activations in a magnitude comparison task for “near” numbers (close to 5) in left inferior temporo-parietal junction and for “far” numbers in the right intraparietal area. Göbel and colleagues (Göbel et al., 2001) also linked the functions of visuospatial orienting and magnitude comparison by showing that deactivating the angular gyrus with repetitive Transcranial Magnetic Stimulation (rTMS) produced deficits in both functions. These findings are consistent with clinical data from adult lesion studies. For example, deficits resulting from left inferior parietal damage include left-right confusion, agraphia, finger agnosia (inability to identify or name touched fingers) and acalculia. This is known as Gerstmann's Syndrome (Benton, 1987; Cipolotti et al., 1991). A recent study by Levy, Reis and Grafman (1999) of a developmental dyscalculic reported that the patient showed extremely good academic performance except in reading, spelling and numeracy, most particularly in arithmetical computation. Magnetic Resonance Spectroscopy showed a significant drop in metabolites in the patient's left angular gyrus region, suggesting that a focal change in cellular structure or energetics may have caused the observed deficit.

Thus, each of our tasks is motivated by a direct link between PPL function and the demands of some or all of the conditions involved. Specific predictions based on those mappings are presented in the next section, following descriptions of the tasks. Other components of this project include a battery of neuropsychological tests and an array of structural and functional magnetic resonance imaging (MRI) techniques. However, in the current report we shall focus only on cognitive performance data. For the sake of early dissemination of some key cognitive process deficits, we present the results of a small study of 12 children with the chromosome 22q11.2 deletion and 15 typically developing controls.

Materials and methods

Subjects

We report here on 12 children with the chromosome 22q11.2 deletion and 15 comparison children from whom a full set of scores on our three cognitive tasks as well as basic IQ and processing speed measures was collected. Of the 15 controls, 7 were siblings of 22q children (though not all were siblings of the 22q children in this study) and 8 were typically developing children who were recruited through newspaper advertisements and were unrelated to the 22q children. Table I depicts the demographic information for children in each group. This includes age, Verbal IQ (VIQ), Performance IQ (PIQ), Full Scale IQ (FSIQ) and a measure of processing speed (PS) computed from the Wechsler Intelligence Scale for Children (see Procedures for details).

Procedures

The *Cueing* task was included in order to measure the function of the orienting attention system, which has been shown to be dependent on PPL (e.g. Posner et al., 1984). The task is also able to determine whether any PPL dysfunction is lateralized since orienting is measured separately in each visual hemifield. For our experiment we adapted Goldberg et al.'s design (2001) where children saw a central fixation stimulus (a solid black diamond 5.6° high and wide when viewed at a distance of 36cm) on either side of which was a square box (7.6° in diameter, formed from solid lines 0.8° thick and beginning 5° above and below the center of the diamond). Targets were 2 × 2 black and white diamond checkerboards appearing inside the boxes (see Figure 1). Valid and invalid cues were solid white triangles 2.8° wide by 1.4° high pointing left or right while neutral cues were diamonds (2° high and wide) that filled the whole central stimulus and provided no location information about the target. The child's task was to press one key (the leftmost on a button box) for a target on the left and another (the rightmost) for a target on the right. After being given instructions and 12 demonstration trials the full experiment contained 160 trials (104 valid, 20 invalid, 20 neutral and 24 catch) with a 400 msec ISI between cue and target. Catch trials were those where a cue was provided but no target appeared, thus requiring the withholding of a response. These were included to check for contingent rather than reflexive responding. We predicted that 22q children would show increased difficulty in orienting attention in the absence of facilitatory information, thereby supporting the hypothesis of parietal dysfunction involving directing and engagement processes. That performance deficit would be evident in increased reaction times and/or error rates to invalid, and perhaps also, neutral trials. Also, lateralization of parietal dysfunction would be identifiable since, if performance proved to be significantly worse in one visual hemifield, it would indicate the contralateral hemisphere as the likely site of the dysfunction.

The *Enumeration* task was included in order to relate modes of visual attention to modes of enumeration (Sathian et al., 1999; Trick and Pylyshyn, 1994). The task required the child to sit in front of a computer screen and complete trials where 1-8 objects were displayed on the screen. The child's task was to respond by speaking into a microphone, as quickly as possible, the number of objects that were presented. Target stimuli were bright green bars, measuring 0.25° × 0.14° on a red background square of side 2° visual angle when viewed

from a distance of 60cm. For each numerosity there were 20 different stimuli (where the requisite number of targets is placed randomly within an invisible 8×8 grid). The experiment began with instructions followed by 16 practice trials (2 for each numerosity). There were then 20 blocks each with 8 trials (for numerosities 1-8) randomly distributed within them, for a total of 160 trials. There was a rest period whose length was determined by the child after every 4 blocks. We predicted similar performance in the subitizing range between 22q children and controls due to a lack of dependence on posterior parietal cortex and a counting deficit for 22q children due to the heavy involvement of that neural region, as indicated by Sathian et al. (1999).

The *Distance Effect* task (e.g. Pinel et al., 1999; Temple and Posner, 1998) was included to test whether problems in navigating the visuospatial environment within the context of enumeration tasks disturbs the normal formation of spatially coded representations of relative numerical magnitudes. We replicated the task that Temple and Posner (1998) used successfully with young children. The use of both analog (dots) and symbolic (numerals) forms of numerical representation also allowed us to compare the function of two neural circuits for which we can generate different predictions. The task involves making a judgment about whether the value of a stimulus is “greater than” or “less than” 5. The stimuli had the values “one”, “four”, “six” and “nine” and each was presented within a 5cm square at a viewing distance of 60cm thus subtending a visual angle of 4.75° . Each of the four stimuli were presented in each of five colors and in both Arabic numeral and dot pattern form for a total 20 instances of each or 80 trials presented in two blocks of 40 each.

Following instructions and 8 practice trials, each experimental block was initiated by the child when s/he was ready. Numerals were presented in Helvetica font 5cm high. Dot patterns were a single large dot, two columns of two smaller dots, two columns of three dots and three columns of three dots, where the individual dots were adjusted for size so that each array occupied approximately the same space within the 5cm square. Our main prediction was that the normal distance effect, where judgments of relative magnitude with respect to a reference (here 5) take longer with “near” numbers (4 and 6) than with “far” numbers (1 and 9), would be disturbed in the 22q children. This is because we hypothesize that, if there is dysfunction of the posterior parietal lobes, they may not be able to establish the same kinds of associations between quantity and space as those without disturbance to this neural substrate. We also predicted, based on Dehaene and Cohen's (1995) Triple Code Theory, some effect of notation since the quantitative information carried by numerals is thought to be identified by ventral stream, temporal lobe circuits with their relative magnitude being compared parietally, while dot stimuli would have to be processed entirely in parietal cortex.

Every child in this study completed sufficient neuropsychological testing to provide us with measures of Full Scale, Verbal and Performance IQ as well as the “processing speed” index (computed from the Coding and Symbol Search tests on the Wechsler Intelligence Scale for Children, or WISC-3). All 22q children and siblings completed the WISC-3 as part of a larger neuropsychological battery while the unrelated controls completed the Wechsler Abbreviated Scale of Intelligence (WASI) and the two processing speed measures from the WISC-3. We decided to use this processing speed index as a covariate in our statistical analysis to attempt to control for global differences in our two populations on a

psychologically relevant dimension. By definition, the two groups would be expected to differ on primary IQ scores because one group is defined by their borderline mental retardation and the other by being essentially “normal”. The processing speed index is derived directly from the Symbol Search and Coding subtests of the WISC-3, and is a measure of speeded visuomotor processing. Numerous authors (e.g. Sternberg, 1985; Kail, 2000) have linked processing speed to efficiency of processing, increases in mental capacity and overall intellectual function. Therefore, we felt that this measure would be a good way to control for global cognitive differences between the groups, as well as general information-processing speed, and thus allow us to assess the direct effects of the hypothesized differences in posterior parietal dysfunction.

Results

Siblings and unrelated healthy comparison subjects did not differ on measures of general cognitive ability (main effects for group: $[F(1, 13) = .89; p = .36; F(1, 13) = .00; p = .98; F(1, 13) = .33; p = .57; F(1, 13) = 2.67; p = .13]$ for VIQ, PIQ, FSIQ and PS respectively. Nor did they differ on any of the task conditions (main effects for group: $[F(1, 13) = .20; p = .7; F(1, 13) = .50; p = .49; F(1, 13) = .69; p = .42]$ for Enumeration, Cueing, and Distance, respectively. Therefore, we combined the 2 control samples for all analyses (see Table I for more detail). Comparisons between the 22q children and the combined control group showed significant differences on all measures of general cognitive ability. Main effects for group were $[F(1, 25) = 32.51; p < .001; F(1, 25) = 61.61; p < .001; F(1, 25) = 60.29; p < .001; F(1, 25) = 13.09; p = .001]$, for VIQ, PIQ, FSIQ and PS respectively.

Cueing

Figure 2 depicts reaction time as a function of target location (left or right) and cue type (*valid*, e.g. left cue, left target, *neutral*, or *invalid*, e.g. right cue, left target). As can be seen, there was indeed a deficit in performance in both fields for 22q children in the absence of valid cues, though the magnitude is somewhat reduced in the right visual field. A $3(\text{cue type}) \times 2(\text{hemifield}) \times 2(\text{group})$ ANOVA was performed on mean reaction times after removing error and catch trials and then outliers with the moving criterion based on number of trials per condition as suggested by Van Selst and Jolicoeur (1994). Cue type (*valid*, *neutral*, *invalid*) and visual field (*left*, *right*) were within-subjects factors and group (22q children, controls) was a between-subjects factor. There were significant overall effects of cue type $[F(2, 50) = 60.9; p < .001]$, a trend toward a main effect of group $[F(1, 25) = 3.29; p = .08]$, and a trend toward a cue type $\times$ group interaction $[F(2, 50) = 2.57; p = .09]$. There was no main effect of visual field, nor group $\times$ hemifield interaction. Individual contrasts revealed that both 22q children and controls were significantly slower on neutral (83.0 msec slower and 63.7 msec slower, respectively) and invalid trials (125.7 msec slower and 82.0 msec slower, respectively) than on valid trials; however, 22q children were significantly slower on invalid than neutral trials (42.7 msec slower; $p = .02$) while RTs did not significantly differ for invalid and neutral trials in controls.

The 22q children made approximately three times as many errors as normal controls overall (2.6% vs. 7.9%) (Mann-Whitney $U = 53, p = .07$), accounted for primarily by elevated error

rates on invalid trials in the right visual field (2.7% vs. 16.7%) (Mann-Whitney $U = 51$, $p = .05$). After covarying for Processing Speed the main effects of group and cue type were not significant [$F(1, 24) = .93$; $p = .3$; $F(2, 48) = 1.63$; $p = .2$, respectively].

Enumeration

After removing error trials and reaction times over 2.5 standard deviations from the mean, a repeated measures within-subjects ANOVA for reaction time with group (22q children vs. controls) as a between-subjects factor indicated a significant effect of number of objects [$F(7, 175) = 253.4$, $p < .001$], a main effect of group [$F(1, 25) = 14.4$, $p = .001$] and a significant number $\times$ group interaction [$F(7, 175) = 9.7$, $p < .001$]. Subitizing range was determined in the standard fashion by looking for the emergence of a quadratic trend in RT as responses first to 1-3 then 1-4 etc are examined. Separate 1-way ANOVA's were carried out on aggregated RT data for each group. For controls, a significant quadratic trend appeared in 1-4 range, indicating a subitizing range of 1-3 (see Figure 3). For 22q children, a quadratic component appeared in 1-3 range, indicating subitizing range of 1-2 only. Linear regressions were run on subitizing and counting range (for 22q children 1-2 vs. 3-8; controls 1-3 vs. 3-8). The 22q children's slopes were 58.9 ms/item for subitizing, and 632.8 ms/item for counting range. For controls the slopes were 53.9 ms/item for subitizing (1-3), and 524.8 ms/item for counting. The significant number $\times$ group interaction [$F(5, 21) = 4.66$, $p = .001$] for the 22q children's counting range (3-8) indicates a significant difference in slope between the 2 groups in this range. However, slopes did not differ in the subitizing range (1-2) [$F(1, 25) = .60$, n.s.].

Although 22q children made no more errors than controls in the subitizing range (1.17%-controls, vs. 1.25% – 22q) (M-W U test: n.s. – $p = .49$), they made approximately twice as many errors as controls in the counting range (4.6% vs. 10.4%). (M-W U test: n.s. – $p = .10$). After covarying for PS, the main effect of number of objects remained significant [$F(7, 168) = 7.68$, $p < .001$], and the main effect of group remained significant [$F(1, 24) = 7.11$, $p = .013$]. There was still a significant number $\times$ group interaction [$F(7, 168) = 5.21$, $p < .001$].

Distance Effect

As can be seen from Figure 4, our predictions about the distance effect were borne out in an interesting way. After removing error trials and reaction times greater than 2.5 SDs above the mean, reaction times for each group were subjected to a within-subjects repeated-measures ANOVA with notation (digit vs. dot), distance (close to 5 vs. far from 5) and magnitude (smaller than 5 vs. larger than 5) as within-subjects factors and group (22q children vs. controls) as a between-subjects factor. Reaction time analyses revealed a significant main effect of distance [$F(1, 25) = 4.73$, $p < .001$], and a magnitude $\times$ distance $\times$ group interaction [$F(1, 25) = 6.23$, $p = .02$], as well as a significant 4-way interaction between magnitude $\times$ distance $\times$ notation $\times$ group [$F(1, 25) = 6.72$, $p = .02$]. There was no main effect of notation, magnitude, or group. Analysis of the patient data revealed significant overall main effects for distance [$F(1, 11) = 18.01$; $p = .001$] (close numbers 64.3 msec slower). Although there were no main effects of magnitude or notation, there was a significant 3-way interaction between notation, magnitude and distance [$F(1, 11) = 7.14$, p

= .02]. 22q children did not show the expected distance effect for 1 vs. 4 dots or digits, or 6 vs. 9 digits, but had significantly faster RTs for 9 dots than for 6 dots ($t = 4.16$; $p = .002$).

For controls there were also significant main effects for distance [$F(1, 14) = 21.2$; $p < .001$] (close numbers 91.0 msec slower) but no effects of magnitude or notation. Pairwise contrasts revealed that controls had significantly faster RTs for 1 vs. 4 dots ($t = 4.83$; $p < .001$) and digits ($t = 3.50$; $p = .004$), as well as 9 vs. 6 digits ($t = 2.96$; $p = .02$), and a trend toward faster RTs for 9 vs. 6 dots ($t = 1.9$; $p = .08$). 22q children made significantly more errors than controls overall (12.0% vs. 2.3%), with highest error rates occurring for 4 dots (13.8%) and 4 digits (15%) (Mann-Whitney $U = 25.5$, $p = .001$). After covarying for PS, the previously significant main effect of distance was no longer significant [$F(1, 24) = .03$; $p = .9$], although the 4-way distance $\times$ magnitude $\times$ notation $\times$ group interaction remained significant [$F(1, 24) = 5.54$, $p = .03$]. There was also a significant interaction between magnitude, notation and processing speed [$F(1, 24) = 5.2$; $p = .03$].

Discussion

The data that we have collected appear to provide support for our hypothesis that deficits in visuospatial and numerical cognitive processes that are exhibited by children with the chromosome 22q11.2 deletion are, to some considerable degree, the result of dysfunction of the posterior parietal lobe (PPL). That conclusion is drawn from the pattern of performance we predicted based on the existing literature. Specifically, we expected that performance would be worse in 22q children for tasks or conditions more heavily dependent on PPL function than in those less heavily dependent, when compared to controls. To review, the findings of Posner et al. (1984) would predict that parietal dysfunction would produce the worst performance in the invalidly cued condition of the cueing task than in the other conditions. While all participants produced longer reaction times for the neutral than valid cue conditions, as expected, only the 22q children produced significantly longer reaction times for invalid than for neutral trials. They also produced most of their errors in that condition also.

If posterior parietal dysfunction were to account for performance on the enumeration task, the findings of Sathian et al. (1999) would predict worse performance for the 22q children only in the counting range, since subitizing was found not to activate posterior parietal cortex. Again, this is precisely what we found. The group $\times$ number interaction in that task was due to reaction time differences in the counting and not in the subitizing ranges, where the slopes of the 22q children and the controls were almost identical, even though there was a difference in the subitizing spans of the two groups. In the counting range, however, the reaction time slope of the 22q children was significantly greater than that of the controls. Our interpretation is that compromised navigation of the visuospatial environment, as indicated in the absence of facilitatory cues in the Cueing task, resulted in the inefficient search for targets to count. This produced a steeper slope as well as some increase in errors.

Finally, the entire Distance Effect task has been shown (Göbel et al., 2001; Pinel et al., 1999) to depend on posterior parietal function. These findings would predict that 22q children would have trouble producing the standard “distance effect” of longer reaction

times to quantities near the comparison value (here the number 5) than those further away from it if they were suffering from posterior parietal dysfunction. Based on Dehaene and Cohen's Triple Code theory, one might expect their performance to improve some in the "digits" condition of the task. This is because a component of the task, transcoding from the symbolic (and thus non-spatial) to the semantic representation of the quantity involved would be handled by apparently less handicapped ventral stream functions. However, this still leaves the critical magnitude comparison component to be handled by posterior parietal cortex. Although the main effect of distance was significant, children with the chromosome 22q11.2 deletion did not show a consistent distance effect in either condition, as we predicted.

Instead, there was a 4-way interaction, which arose from the control children demonstrating the predicted distance effect in both conditions while the 22q children showed a far more complex pattern. Although their performance in the digits condition approached the standard profile, they produced no significant differences in reaction time between any of the four quantities. This essentially flat response, which indicates a clear lack of any distance effect, was contrasted by a significant difference in the direction of the expected distance effect for the larger magnitudes in the dots condition (i.e. reaction time for 6 was much longer than for 9) but no significant difference for the smaller magnitudes, although the trend was in the unexpected direction (i.e. reaction time for 4 was shorter than it was for 1). The complexity of the response pattern in the 22q children indicates a rather simple conclusion, which is that they did not produce the same consistent distance effect as the control children, and that the difference was qualitative in nature and dependent on the characteristics of the different conditions.

One must be cautious, when interpreting data such as these, to consider whether some global difference between the groups is the basis for the divergent patterns of performance, rather than the hypothesized specific neurocognitive dysfunction. Given the slower performance of 22q children in most conditions of the three tasks, it might appear that a general deficit in psychomotor speed could account for the differences. Although, as we shall discuss below, the qualitative differences in performance provide good evidence for discounting that interpretation, we took the step of covarying the reaction time results with scores on the psychomotor processing speed (PS) index taken from the WISC-3 neuropsychological battery. Despite a very significant difference between 22q children and controls in average PS scores there were no systematic group differences in reaction time. This is one indication that the large differences in psychomotor processing speed between 22q children and control did not account for the observed pattern of performance differences. This leaves posterior parietal dysfunction as the more likely cause for their poorer performance. A closer inspection of some of the similarities and differences between the groups strengthens this view.

In the Cueing task, the main qualitative difference between the groups was that children with the 22q deletion produced the particular difference that we predicted based on posterior parietal dysfunction, i.e. an increased cost for invalid over neutral cues due the difficulty of disengaging and reorienting attention. Covarying for processing speed did remove the main effect of cue type in this task. It is possible that this is a side effect of our use of endogenous,

or central, cues in this task. These are known to engage more top-down, conscious, attention processes and so may be a less pure measure of posterior parietal function. We have now switched to a task measuring orienting performance (among other aspects of the attention system) with exogenous or peripheral cues. These engage more automatic orienting processes and it remains to be seen whether these processing speed has a significant effect on performance in that task.

Enumeration was the only task in which the main effect of group on reaction time was significant., and that difference survived covarying with processing speed scores as did the number x group interaction. This indicates that the performance deficit on the part of children with the 22q11.2 deletion cannot be explained in terms of general cognitive slowing. In this task, the 22q children produced very similar performance to that of the controls in their respective subitizing ranges as we predicted, because posterior parietal cortex is not engaged in that mode of enumeration. It is notable that reaction times to the $N = 1$ displays are identical in the two groups, which would also be hard to explain from a general slowing account. The only difference in the subitizing range was that 22q children exhibited a smaller subitizing span than did control children. This may suggest that their attentional capacity is reduced, which is a factor that could affect the efficiency of visual search. The other difference in the Enumeration task is that 22q children produced significantly greater reaction time slope in the counting range than did controls. We interpret this to be the result of reduced efficiency in the orienting attention system, which is largely implemented in posterior parietal areas. In the Distance Effect task qualitative differences in performance are clear and they show no systematic relation to processing speed. Control children produced the predicted distance effects in both the dots and digits conditions. For 22q children, however, the pattern was quite different. In the digits condition any advantage that may have been conferred, perhaps by a contribution from more functional ventral stream circuits or by the non-spatial format of the quantity represented, was not great enough to distinguish the “near” from the “far” conditions. In the “dots” condition, where all numerical information is presented in a spatial format, the 22q children's performance was notably different in its organization rather than just being slower. In this condition, the 22q children's judgments differed depending on the absolute as well as the relative magnitudes of quantities and this created different response patterns on either side of the comparison quantity. Apparently, the spatially based representations of relative magnitude that are typically processed by parietal cortex appear to be disturbed in the 22q children that we studied. The very preliminary results coming from our fMRI experiments with the Distance Effect task in 22q children and typically developing controls appear to converge with that finding. Analysis of an posterior parietal Region of Interest appears to indicate considerable differences in posterior parietal activations between control children and those with the 22q deletion. These results are too preliminary to generalize from but they are at least consistent with the view that posterior parietal dysfunction is the basis for the performance deficits that we have reported in our 22q children.

One of the greatest challenges of this kind of work lies in constructing an appropriate control group to satisfactorily resolve issues of global versus specific differences because, in reality, no such entity exists. In order to fully evaluate the effects of a neurogenetic disorder such as the 22q11.2 deletion, multiple comparison groups are required. One needs to account, if

possible, for maturation (with age-matched controls), environment (with siblings), IQ or cognitive function (e.g. with IQ-matched controls) and, in the case of 22q, for cardiac status (with controls matched for congenital heart defect repair). We intend to carry out all of these comparisons in the long term, and are assembling the requisite control groups. Children with the chromosome 22q11.2 deletion will increasingly come to represent one of the largest populations of those with cognitive deficits of genetic etiology. It is crucial for developmental cognitive neuroscientists to launch an array of studies aimed at first understanding and then possibly remediating some or all of these problems. This paper represents an early effort to contribute to that process.

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Fig. 1.
Example stimulus configurations from Cueing task showing: initial configuration (top),
valid cue to left side (center), and target (bottom).

Fig. 2. Reaction time and error data from the Cueing task with responses to targets that appeared in the left visual hemifield (left) and in the right visual hemifield (right).

Fig. 3.
Reaction time and error data from the Enumeration task.

Fig. 4. Reaction time and error data from the Distance Effect task in which stimuli were presented as dot patterns and as Arabic numerals.

TABLE I

Demographic information of 22q Children, Siblings and Unrelated Normal Control children.

	22q11.2	Sibling	Unrelated
Number	12	7	8
Age – range	7:10–14:0	7:11–15:6	7:6–11:0
Age – mean (sd)	10:1 (25 Mos)	11:4 (32 Mos)	9:3 (18 Mos)
VIQ – mean (sd)	83.25 (11.51)	108.14 ^{**a} (8.51)	115.0 ^{**b} (17.36)
PIQ – mean (sd)	76.67 (8.36)	109.14 ^{**a} (11.25)	109.0 ^{**b} (13.60)
FSIQ – mean (sd)	78.17 (9.78)	109.57 ^{**a} (9.86)	113.25 ^{**b} (14.10)
PS – mean (sd)	84.58 (15.49)	113.57 ^{**a} (9.54)	100.75 ^{+b} (18.71)

22q11.2 < siblings

22q11.2 < unrelated controls

⁺
p < .05^{**}
p < .001