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Impaired acuity of the approximate number system in 22q11.2 microdeletion syndrome

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Abstract

A magnitude comparison deficit has been frequently observed in velocardiofacial syndrome (Del22q11.2). We hypothesized that this deficit extends to impairments in the acuity of the approximate number system (ANS). Three groups of children aged 8-14 years were investigated: Del22q11.2 children (n = 12), low cognitive ability children (LCA; n = 12), and matched typically developing children (TD; n = 28). All children were assessed with a simple reaction time task and symbolic and nonsymbolic number comparison tasks. To estimate the acuity of the ANS, the Weber fraction (w) was calculated from the nonsymbolic comparison task. The Del22q11.2 group exhibited a significantly higher w compared with the other groups. Importantly, no significant differences were found in w between the TD and LCA groups. The performance pattern of the Del22q11.2 group was similar to the TD group in the symbolic comparison task, and both of these groups had better performance than the LCA group. The impairment of ANS acuity observed in individuals with Del22q11.2 cannot be explained by deficits in general processing speed because no significant group differences were found in the simple reaction time task. These results suggest that lower acuity of the ANS should be added to the behavioral phenotype of Del22q11.2. The absence of impaired ANS acuity in the LCA group is consistent with the hypothesis that number sense is a relatively specific and autonomous domain. Investigations of low ANS acuity in mathematics learning difficulties and Del22q11.2 should be intensified.
Keywords: Del22q11.2 syndrome, velocardiofacial syndrome, math learning disability, approximate number system, number acuity, neuropsychology.

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Introduction

Neurodevelopmental disorders with both environmental and genetic etiology may include developmental dyscalculia and severe math learning disability (MLD) as an important phenotypic trait. In this report, we focus on 22q11.2 microdeletion (Del22q11.2; i.e., velocardiofacial syndrome; De Smedt, Swillen, Devriendt, Fryns, Verschaffel, & Ghesquière et al., 2007b; De Smedt et al., 2008; De Smedt, Reynvoet, Swillen, Verschaffel, Boets, & Ghesquière, 2009). Del22q11.2 syndrome is one of the most frequent genetic disorders of medical, psychological, and social importance (Óskarsdóttir, Belfrage, Sandstedt, Viggedal, & Uvebrant, 2005).

Del22q11.2 is associated with more than 180 different phenotypic traits including velopharyngeal insufficiency, minor facial dysmorphic features, cardiac malformations, social-cognitive impairments, and risk of psychiatric disorders (Shprintzen, 2008). Important in this context are intellectual disability (present in 40-45% of individuals; De Smedt, Devriendt, Fryns,

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Vogels, Gewillig, & Swillen, 2007a) and math learning disability (De Smedt et al., 2007b, 2008; Simon, Bearden, Mc-Ginn, & Zackai, 2005; Simon, 2008).

Elucidation of the cognitive mechanisms that underlie MLD in Del22q.11.2 can potentially contribute to a better understanding of MLD in general and help to more precisely define the endophenotypes of MLD and their genetic-phenotypic correlations (De Smedt et al., 2007b, 2008, 2009; Simon et al., 2005).

Math learning disability is a notably heterogeneous condition that presents comorbidities with other disorders such as developmental dyslexia and attention-deficit/hyperactivity disorder (Henik, Rubistein, & Ashkenazi, 2011; Rubinsten & Henik, 2009). Accordingly, several mechanisms may contribute to the genesis of MLD. General cognitive factors such as deficits in visuospatial and phonological processing and working memory impairments, have been shown to influence mathematical performance (Geary, 2011; Wilson & Dehaene, 2007). Evidence is accumulating that a significant proportion (approximately 3%) of school-age children may present a relatively pure form of MLD that is associated with basic deficits in number processing (Reigosa-Crespo et al., 2011) such as number sense or acuity of the approximate number system (ANS).

The term "number sense" refers to the ability of human infants and adults and other animals to rapidly and approximately discriminate the numerosity of sets of objects without resources of counting (Dehaene, 1997). The nature of the ANS has been investigated by means of experiments conducted with animals, human infants, and human adults, demonstrating that discrete numerical processing obeys traditional psychophysical laws, such as the ones described by Weber and Fechner (Dehaene, 2003). For example, Moyer and Landauer (1967) observed that the response of comparing the magnitudes of two Arabic numerals was slower and more error prone when the numerical distance between the compared numbers was less (i.e., a distance effect; see Sekuler & Mierkiewicz, 1977, for a description of the distance effect in children). Because the ANS is already present in newborns (Izard, Sann, Spelke, & Streri, 2009) and interacts with culturally derived symbolic representations during development (Dehaene, 1992), it is considered an important start-up tool for the acquisition of mathematical knowledge (Piazza et al., 2010).

Halberda, Mazzocco, and Feigenson (2008) demonstrated an association between ANS acuity, indexed by the internal Weber fraction (w) and standardized math performance in typically developing (TD) children. More recent research has suggested that ANS acuity may be impaired in children with MLD (Mazzocco, Feigenson, & Halberda, 2011; Piazza et al., 2010). Nonsymbolic number acuity is reduced in 10-year-old MLD children, with an estimated $w = 0.35$, which is comparable to typically developing 5-year-olds, whereas 10-year-old TD children exhibit a mean $w = 0.25$ (Piazza et al., 2010).

The Del22q11.2 represents a very interesting model to investigate the role of the ANS in MLD. Compared with TD controls, children with Del22q11.2 are slower in comparing both symbolic (De Smedt et al., 2007b, 2009; Simon et al., 2005) and nonsymbolic (Simon et al., 2005) magnitudes, but the results are not always statistically significant (De Smedt et al., 2007b; Simon et al., 2005). Moreover, general cognitive factors do not appear to be the decisive factor in explaining math difficulties in Del22q11.1 individuals. Compared with TD controls, group differences in distinct working memory tasks disappear when age and Intelligence Quotient (IQ) are statistically controlled (De Smedt et al., 2008).

The present study tested the hypothesis that ANS acuity is impaired in Del22q11.2 syndrome. More specifically, we calculated w in Del22q11.2 children and compared it with two reference groups: TD controls and children with multifactorial low cognitive abilities (LCA). If ANS acuity plays a role in difficulties with mathematics in children with Del22q11.2, then a significantly lower w should be found in these children compared with TD controls. If ANS acuity impairments in Del22q11.2 are specific, then these impairments should be greater than in individuals with LCA with comparable or even lower general cognitive abilities.

Methods

Participants

Three groups of children participated in the study: children with Del22q11.2, TD children, and children with LCA (Table 1). Additionally, data from one girl with an atypical distal mutation in the 22q11.2 region was added to the Del22q11.2 group. Patients with Del22q11.2 were recruited from two specialized clinics for the treatment of craniofacial malformations: the Hospital for Rehabilitation of Craniofacial Anomalies (CENTRINHO), University of São Paulo (USP), Bauru, Brazil, and the Center for Treatment and Rehabilitation of Cleft Lip-Palate and Craniofacial Anomalies (CENTRARE), Pontificial University of Minas Gerais (PUC Minas), Belo Horizonte, Brazil. All patients had clinical manifestations that were compatible with Del22q11.2 syndrome. The diagnosis was confirmed by fluorescent *in situ* hybridization (Klinger et al., 1992) in 11 cases and multiplex ligation dependent probe amplification (MLPA; Stachon et al., 2007) in three cases. Data from three children in the Del22q11.2 group were excluded because the R^2 of the fitting procedure to calculate w was <0.20, reflecting a lack of adjustment of psychophysical function (according to Dehaene, Izard, & Piazza, 2005; Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004). This group was then reduced to 12 individuals, 11 with the full mutation and one with the atypical mutation.

The child with atypical microdeletion was an 11-year-old girl selected from population screening in Belo Horizonte of more than 1,800 children that sought to identify individuals with normal general cognitive ability with MLD (Carvalho, Vianna, Oliveira, Aguiar, Zen, & Haase, 2014). The atypical deletion was detected by MLPA and spans from probes HIC2 to TOP3B, corresponding to the LCR22-D to LCR22-E interval. The probes LZTR1 (proximally) and RTDR1 (distally) showed normal MLPA profiles. Consequently, this deletion has a minimum size of 0.67 Mb and maximum size of 2 Mb. The clinical profile of the individual with the atypical deletion was not compatible with velocardiofacial syndrome. She presented no dysmorphic anomalies. Cognitive ability, assessed by Raven's Coloured Progressive Matrices (CPM; Angelini, Alves, Custódio, Duarte, & Duarte, 1999), was in the 50th percentile.Math achievement was below the 25th percentile, and she presented mild social phobia symptoms.

The group of TD children was also selected from the aforementioned population screening. The inclusion criteria in the TD group included performance on Raven's CPM (Angelini et al., 1999) that was higher than the 15th percentile and performance on the Arithmetic and Spelling subtests of the Brazilian School Achievement Test (TDE; Stein, 1994) that was higher than the 25th percentile (for more details, see Costa et al., 2011; Ferreira et al., 2012; Moura et al., 2013; Oliveira-Ferreira, Costa, Micheli, Oliveira, Pinheiro-Chagas, & Haase, 2012).

The LCA group was composed of 12 children who were also identified in the population screening. Their performance on Raven's CPM (Angelini et al., 1999) was below the 15th percentile. These children participated as a reference group with LCA, most likely reflecting the left end of the distribution of this ability in the population.

Table 1 summarizes the sociodemographic data of the participants. The three groups did not differ in age ($F = 0.96$, $df = 2{,}49$, $p = 0.38$) or gender ($\chi^2 = 4.54$, $df = 2$, $p = 0.10$).

Table 1. Participants' sociodemographic data.

	Del22q11.2 (n=12)	LCA (n=12)	TD (n=28)
Sex (% female)	25	58.3	60.7
	mean (SD)	mean (SD)	mean (SD)
Age (years)	11.25 (1.81)	10.5 (1.00)	10.64 (1.44)

LCA, low cognitive abilities; TD, typically developing controls.

Instruments

Brazilian School Achievement Test (Teste de Desempenho Escolar; Stein, 1994; see also Ferreira et al., 2012; Oliveira-Ferreira et al., 2012). The TDE is the most widely used standardized test of school achievement in Brazil and comprises three subtests: Arithmetic, single-word Spelling, and single-word Reading. In the screening phase we used the Arithmetic and Spelling subtests, which can be applied in groups. Norms are provided for school-aged children between the second and seventh grades. The Arithmetic subtest is composed of three simple verbally presented word problems and 45 written arithmetic calculations of increasing complexity. Specific norms for each school grade were used to characterize the children's individual performance. The Spelling subtest consists of 34 dictations of words of increasing syllabic complexity. Reliability coefficients (Cronbach's α) for the TDE subtests are ≥ 0.87. Evidence of construct and criterion validity for the TDE with regard to numerical cognition and mathematical learning difficulties has been described in several previous publications by our research group (Costa et al., 2011; Ferreira et al., 2012; Haase, Júlio-Costa, Pinheiro-Chagas, Oliveira, Micheli, & Wood, 2012; Júlio-Costa et al., 2013; Moura et al., 2013; Wood et al., 2012). The children are instructed to work on the problems to the best of their ability without time limits. TD controls had Arithmetic scores above the 25th percentile on the TDE.

Raven's Coloured Progressive Matrices. General cognitive ability was assessed with the age-appropriate Brazilian-validated version of Raven's CPM (Angelini et al., 1999). According to Raven (2000), cognitive abilities assessed by the CPM comprise two main aspects: eductive ("ability to generate high-level, usually nonverbal, schemata which make it easy to handle complexity"; p. 2) and reproductive ("ability to absorb, recall, and reproduce information that has been made explicit and communicated from one person to another"; p. 2). The CPM was chosen because it is a well-validated and widely used measure of general cognitive ability that can be applied in groups. The CPM was then suited for the population screening procedures required by the present study.

Simple Reaction Time Task. This is a non-numerical computerized visual detection task that is used to control for possible differences in basic processing speed that are unrelated to numerical tasks. In this task, a picture of a wolf (9.31 cm height, 11.59 cm length) is displayed in the center of a black screen for a maximum of 3,000 ms.The participant is instructed to press the spacebar on the keyboard as fast as possible when the wolf appears. Each trial was terminated with the first key press. The task has 30 experimental trials, with an intertrial interval that varies between 2,000 ms and 8,000 ms in 1,500 ms steps. The Simple Reaction Time Task has been used in previous studies (Costa et al., 2011; Ferreira et al., 2012).

Symbolic Magnitude Comparison Task. In the symbolic magnitude comparison task, Arabic numerals from 1 to 9 were presented on the computer screen (2.12 cm height, 2.12 cm length). The visual angle of the stimuli was 2.43° in both the vertical and horizontal dimensions. The children were instructed to compare the stimuli with the reference number 5. The numerals were presented in white on a black background. If the presented number was less than 5, then the child had to press a predefined key on the left side of the keyboard with the left hand. If the stimulus was greater than 5, then the key to be pressed was located on the right side and was pressed with the right hand. The number 5 was never presented on the computer screen. Numerical distances between stimuli and the reference number (5) varied from 1 to 4. Each numerical distance was presented the same number of times. Between trials, a fixation point of the same size and color as the stimuli was presented on the screen. The task was composed of 80 experimental trials. The maximum stimulus presentation time was 4,000 ms, and the intertrial interval was 700 ms.

Nonsymbolic Magnitude Comparison Task. A nonsymbolic magnitude comparison task was used, which has also been employed in previous studies (Costa et al., 2011; Ferreira et al., 2012; Júlio-Costa et al., 2013). The participants were instructed to compare two simultaneously presented sets of dots, indicating which one contained the larger number of dots. Black dots were presented on a white circle over a black background. In each trial, one of the two white circles contained 32 dots (reference numerosity), and the other one contained 20, 23, 26, 29, 35, 38, 41, or 44 dots (ratios: 0.63, 0.72, 0.81, 0.91, 1.09, 1.19, 1.28, 1.38). Each magnitude of dot sets was presented eight times. The task was composed of eight learning trials and 64 experimental trials. Perceptual variables were randomly varied such that in half of the trials the individual dot size was held constant. In the other half of the trials, the size of the area occupied by the dots was held constant. The control of possibly intervening perceptual variables followed procedures described by Dehaeneet al. (2005). The maximum stimulus presentation time was 4,000 ms, and the intertrial interval was 700 ms. Between each trial, a fixation point (i.e., a cross, printed in white, with 30 mm in each line) appeared on the screen. If the child judged that the right circle contained more dots, then a predefined key located on the right side of the keyboard would be pressed with the right hand. Conversely, if the child judged that the left circle contained more dots, then a predefined key on the left side of the keyboard had to be pressed with the left hand. To analyze ANS acuity, the internal Weber fraction (w) was calculated for each child (Dehaene, 2007; Halberda et al., 2008; Izard & Dehaene, 2008; Mazzocco et al., 2011; Piazza et al., 2004; Piazza et al., 2010). The calculation of w was based on the methods described by Piazza et al. (2004).

Procedures

LCA and TD children were individually assessed in quiet facilities provided by their schools as part of a larger project on MLD. Participants with Del22q11.2 were assessed at regular visits to the clinical services. The procedures and written informed consent form were approved by the Research Ethics Committees from the involved institutions.

Analyses

Response time data were trimmed, eliminating in two steps all responses that were more extreme than three standard deviations from the individual means and those with reaction times faster than 200 ms. This procedure discarded 4% of reaction times for the symbolic and nonsymbolic magnitude comparison tasks. Error data for the symbolic and nonsymbolic magnitude comparison tasks were arcsine-transformed to correct for skewness before subjecting them to statistical analysis.

Analyses of variance (ANOVAs) were used to assess group differences in reaction times and accuracy in both the simple reaction time task and symbolic and nonsymbolic magnitude comparison tasks. *Posthoc* pairwise group comparisons were performed with *t*-tests using Holm's (1979) correction for multiple comparisons. Group distributions of w were analyzed by means of a frequency histogram.

Results

We first looked for differences in the group distributions in the simple reaction time task and reaction times and accuracy data in the symbolic and nonsymbolic number comparison tasks. We then compared the distributions of the w estimations. No group differences were found in the simple reaction time task (Table 2).

Symbolic magnitude comparison task

Performance in the three groups significantly differed in both reactions times and accuracy in the symbolic magnitude comparison task (Table 2). Pairwise *posthoc* comparisons with the *t*-test revealed significant differences in the comparisons between the LCA group and two other groups, with worse performance in the LCA group (Table 3). The Del22q11.2 group exhibited slightly lower reactions times than the TD group in the symbolic magnitude comparison task, but no statistically significant differences were observed in performance in the Del22q11.2 and TD groups with regard to reaction times and accuracy.

Nonsymbolic magnitude comparison task

In the nonsymbolic magnitude comparison task, no significant group differences were found in reaction times (Table 2). Accuracy in the nonsymbolic magnitude comparison task differed between groups (Table 2), in which the Del22q11.2 group presented a higher error rate than both the TD and LCA groups (Tables 2 and 3). No group difference was observed in accuracy in the nonsymbolic magnitude comparison task for the TD *vs.* LCA comparison.

Internal Weber fraction (w)

Visual inspection of Figure 1 reveals that the w distributions were more symmetrical in the TD and LCA groups and displayed a heavy right tail in the Del22q11.2 group (Figure 1).

Table 2. Group comparisons in the simple reaction time task and symbolic and nonsymbolic magnitude comparison tasks.

	Del22q11.2	LCA	TD	ANOVA results			
	Mean (SD)	Mean (SD)	Mean (SD)	*F*	*df*	*p*	Eta²
Simple reaction time task	525.52 (413.89)	535.41 (383.46)	388.09 (58.51)	1.80	2.48	0.17	0.07
Symbolic comparison task – RT	869.45 (212.34)	1201.13 (205.31)	905.66 (246.69)	7.58	2.47	0.001	0.24
Symbolic comparison task – arcsine error	0.26 (0.13)	0.40 (0.16)	0.26 (0.07)	6.58	2.47	0.003	0.21
Nonsymbolic comparison task – RT	1398.87 (401.48)	1366.42 (289.12)	1281.48 (306.99)	0.64	2.49	0.52	0.02
Nonsymbolic comparison task – arcsine error	0.51 (0.10)	0.45 (0.06)	0.44 (0.07)	3.66	2.49	0.03	0.13
Weber fraction (*w*)	0.34 (0.15)	0.23 (0.07)	0.24 (0.07)	4.63	2.49	0.01	0.16

LCA, low cognitive abilities; TD, typically developing controls; RT, reaction time.

Table 3. *Posthoc* pairwise comparisons with the *t*-test.

	Del22q11.2 × LCA				Del22q11.2 × TD				LCA × TD			
	t	*df*	*p**	*d*	*t*	*df*	*p**	*d*	*t*	*df*	*p**	*d*
Symbolic comparison task – RT	-3.72	20	<0.001	-1.59	-0.42	37	0.67	-0.16	3.51	37	<0.001	1.30
Symbolic comparison task – arcsine error	-2.25	21	0.001	-0.96	0.01	14.22	0.98	0.00	2.69	11.65	0.01	1.13
Nonsymbolic comparison task – arcsine error	1.89	22	0.03	0.73	2.51	38	0.003	0.81	0.34	38	0.73	0.15
Weber fraction (*w*)	2.06	22	0.01	0.94	2.03	13.07	0.03	0.85	-0.29	38	0.77	-0.14

LCA, low cognitive abilities; TD, typically developing controls.*Holm's correction.

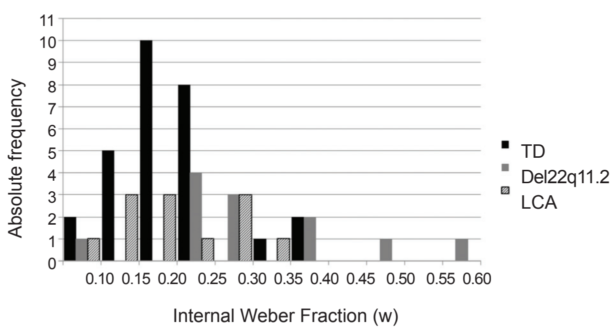

Figure 1. Distribution of the internal Weber fraction (*w*) in the three groups (Del22q11.2, typically developing controls [TD], low cognitive abilities [LCA]).

The variances for *w* significantly differed between groups (Table 2). *Posthoc* analyses were conducted using pairwise *t*-tests (Table 3). The *w* values were larger for the Del22q11.2 group compared with both the TD and LCA groups. The effect sizes were all >0.8 for the Del22q11.2 *vs*. TD and Del22q11.2 *vs*. LCA comparisons. No significant difference in *w* emerged for the LCA *vs*. TD comparison (*d* = -0.14). These results indicate comparable ANS accuracy in the TD and LCA groups and lower ANS acuity in the Del22q11.2 group.

Discussion

In the present study we investigated the functional integrity of ANS acuity in Del22q11.2 children. We measured ANS acuity by determining *w* in the nonsymbolic comparison task in a group of children with Del22q11.2 and compared these results with TD controls. To test the degree of specificity of the potential impairment of ANS acuity in children with Del22q11.2, we included an additional group of children who presented LCA. Significant impairment in ANS acuity was found in children with Del22q11.2 compared with TD controls. Importantly, this impairment was not attributable to general processing speed difficulties because children with Del22q11.2 showed normal performance in a simple reaction time task. Interestingly, this impairment appeared to be at least partially specific to the syndrome because children with LCA exhibited preserved ANS acuity.

Given the inconsistency of previous results with regard to the symbolic processing of numbers in children with Del22q11.2, we additionally used a symbolic comparison task. No deficits in the symbolic comparison task were observed in children with Del22q11.2 compared with TD controls. These results suggest that a deficit in the most basic form of number manipulation (i.e., the ANS) underlies the mathematical difficulties frequently found in children with Del22q11.2.

To our knowledge, only one study has investigated nonsymbolic processing in children with Del22q11.2. Simon et al. (2005) used a nonsymbolic comparison task with magnitudes that ranged from 1 to 9 and found no group differences between children with Del22q11.2 and TD controls. One possible explanation for these negative results may be related to the magnitude range of the comparisons employed. Evidence indicates that two nonsymbolic systems allow for quantification (Hyde, 2011). The "parallel individuation system" allows for the exact quantification of magnitudes up to 3 or 4 in tasks of subitizing. The other nonsymbolic system, the ANS, underlies the approximate quantification of larger magnitudes. Previous studies that focused on nonsymbolic magnitude processing impairments in MLD focused mainly on ANS acuity (Mazzocco et al., 2011; Piazza et al., 2010). Therefore, children with Del22q11.2 may only present deficits in representing large magnitudes.

No group differences were found in performance in a simple reaction time task. Therefore, impairments in magnitude comparison tasks could not be attributable to a more basic deficit in processing speed. This result is consistent with the literature. De Smedt et al. (2008) compared Del22q11.2 and TD groups in measures of mathematics achievement, working memory, reading, and processing speed. Children with Del22q11.2 presented lower math achievement scores but were not different from TD controls in other cognitive abilities. Additionally, no association was found between processing speed and math achievement.

In contrast to the present study, Brankaer, Ghesquière, and De Smedt (2011) also observed deficits in nonsymbolic number comparisons in individuals with LCA. Notably, however, the participants in the study by Brankaer et al. (2011) had lower general cognitive ability than the participants in the present study. The authors selected individuals with a level of ability lower than the 5th percentile, whereas the present study selected individuals with general cognitive ability between the 5th and 15th percentiles.

Although the patient sample was small in the present study, the results were robust, reflected by effect sizes that were greater than $d = 0.80$ for the Del22q11.2 *vs*. TD and Del22q11.2 *vs*. LCA comparisons and negligible for the TD *vs*. LCA comparison. These results suggest that ANS acuity impairment in Del22q11.2 may be relatively specific and not attributable to general cognitive factors. This is compatible with the hypothesis that ANS acuity may constitute an autonomous domain that is implemented by specific brain networks and independent of general cognitive ability (Mandelbaum, 2013).

Children with Del22q11.2 did not show any impairment in the symbolic comparison task. The literature on the symbolic processing of numbers in children with Del22q11.2 has been inconsistent. Our results are consistent with De Smedt et al. (2007b) and Simon et al. (2005), who did not find main effects of group when comparing individuals with Del22q11.2 and TD. The only study that reported a significant main effect of group in a symbolic comparison task used a much larger sample (De Smedt et al., 2009). Both reaction time and accuracy in the symbolic comparison task were significantly lower in the LCA group compared with the other two groups, which did not differ from each other. Similar to the present results, impairment in a symbolic comparison task was previously observed by Brankaer et al. (2011) in individuals with LCA.

The demonstration of a severe deficit in ANS acuity in children with Del22q11.2 has important theoretical implications for the cognitive underpinnings of MLD because difficulties in number processing and arithmetic have long been recognized as important characteristics of the Del22q11.2 phenotype (Moss et al., 1999). Evidence of the involvement of number sense in MLD was recently provided by studies that assessed ANS acuity using estimates of *w* (Mazzocco et al., 2011; Piazza et al., 2010). These studies expanded previous results with TD children, showing that ANS acuity is normally distributed in the population and correlated with math achievement. In the study by Piazza et al. (2010), the mean *w* estimate in TD 10-year-olds was 0.26. The *w* estimate for MLD children of the same age was 0.36, comparable to TD 5-year-olds. The estimates of *w* in the present study were within the same range (0.24 in the TD group, 0.23 in the LCA group, and 0.34 in the Del22q11.2 group).

Del22q11.2 is relevant to the characterization of the neurocognitive mechanisms involved in MLD. Children with Del22q11.2 exhibit pronounced and widespread anatomical and functional abnormalities in parietal areas that are involved in number processing and calculation (Barnea-Goraly, Eliez, Menon, Bammer, & Reiss, 2005; Eliez,Blasey, Menon, White, Schmitt, & Reiss, 2001; Schaer et al., 2010). Children with MLD also present neuroimaging alterations in parietal areas, but the type of abnormalities found in children with MLD appears to be functional in nature (Kaufmann, Wood, Rubistein, & Henik, 2011) or consist of relatively minor structural anomalies (Rykhlevskaia, Uddin, Kondos, & Menon, 2009).

One additional factor that may explain the MLD frequently observed in children with Del22q11.2 is the bilateral nature of neurological damage. Bilateral involvement is shared with other environmental and genetic syndromes characterized by MLD as a phenotypic trait, such as fetal alcohol syndrome (Jacobson, Dodge, Burden, Klorman, & Jacobson, 2011), fragile X syndrome, Turner syndrome (Murphy & Mazzocco, 2008), velocardiofacial syndrome (De Smedt et al., 2009), and Williams syndrome (Krajcsi, Lukács, Ignács, Racsmány, & Pléh, 2009). This phenomenon is also consistent with the adult neuropsychological literature. In adults, acalculia occurs primarily after left parietal damage (Dehaene & Cohen, 1995) but is also frequently observed in diseases characterized by bilateral hemispheric impairment, such as progressive cortical atrophy (Delazer, Karner, Zamarian, Donnemiller, & Benke, 2006) and cortico-basal-ganglionic degeneration (Koss et al., 2010).

A recent meta-analysis of three functional neuroimaging studies in multifactorial MLD found that MLD children exhibit activation of a more distributed network that involves the right superior frontal gyrus and right and left supramarginal gyrus compared with TD children (Kaufmann et al., 2011). Such findings may indicate the use of compensatory strategies in MLD. Given the more widespread and bilateral functional and structural abnormalities accompanied by multiple cognitive deficits in individuals with Del22q11.2 with normal IQ, the opportunities for compensation are reduced, and the deficits are more sharply delineated.

Different studies have suggested the existence of a common magnitude representation system in the intraparietal sulcus that underlies distinct forms of quantitative estimates such as numbers, time, and space (Walsh, 2003). Interestingly, in addition to impairments in basic number processing, some studies found that children with MLD may also exhibit time processing deficits (Andersson, 2010; Vicario, Rappo, Pepi, Pavan, & Martino, 2012). Similarly, individuals with Del22q11.2 have been shown to have deficient temporal discrimination (Debbané, Glaser, Gex-Fabry, & Eliez, 2005). Moreover, Simon et al. (2005) found that visuospatial attention disorder may be associated with Del22a11.2. This finding led Simon (2008) to formulate the hypergranularity hypothesis. According to this perspective, the visuospatial, temporal, and numerical deficits observed in Del22a11.2 are attributable to common low-magnitude resolution secondary to parietal lobe abnormalities. These considerations are consistent with our results in which individuals with Del22q11.2 presented a relatively specific deficit in ANS acuity that was not present in children with LCA.

Notwithstanding the present results, several issues remain unresolved. One open question concerns the impact of basic number processing deficits on math achievement. Reigosa-Crespo et al. (2011) suggested that basic number deficits in multifactorial MLD may be somewhat compensated. Unknown is whether the same occurs in Del22q11.2. Another important issue is the phenotypic variability of Del22q11.2. The distribution of general and specific cognitive abilities in Del22q11.2 is widely dispersed (Schoch et al., 2012). Therefore, low ANS acuity may possibly play a role in MLD in some Del22q11.2 individuals but not others. Some individuals may compensate for number sense deficits, whereas math learning difficulties may be related to other mechanisms such as visuospatial or executive functioning impairments, in other individuals. Single-case cognitive-neuropsychological studies with Del22q11.2 individuals are a viable strategy for investigating these issues (Temple, 1997).

In conclusion, the results of the present study suggest that children with Del22q11.2 syndrome have an impairment in ANS acuity. This impairment appears to be relatively specific because it is not related to general cognitive abilities or processing speed.

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