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Children With Chromosome 22q11.2 Deletion Syndrome Exhibit Impaired Spatial Working Memory

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Abstract

Individuals with chromosome 22q11.2 deletion syndrome (22q11.2DS) have been shown to have impairments in processing spatiotemporal information. The authors examined whether children with 22q11.2DS exhibit impairments in spatial working memory performance due to these weaknesses, even when controlling for maintenance of attention. Children with 22q11.2DS ($n = 47$) and typically developing controls ($n = 49$) ages 6–15 years saw images within a grid and after a delay, then indicated the positions of the images in the correct temporal order. Children with 22q11.2DS made more spatial and temporal errors than controls. Females with 22q11.2DS made more spatial and temporal errors than males. These results extend findings of impaired spatiotemporal processing into the memory domain in 22q11.2DS by documenting their influence on working memory performance.

Key Words: *22q11.2DS; spatial working memory; visuospatial attention; proactive interference*

Chromosome 22q11.2 deletion syndrome (22q11.2DS) is caused by a 1.5–3 Mb microdeletion on the long arm of chromosome 22 (Driscoll et al., 1992). It is estimated to occur in 1:4,000 live births (Bassett et al., 1998; Burn & Goodship, 1996), and is the underlying genetic cause of several disorders, including DiGeorge syndrome (Cooper, Peterson, & Good, 1965) and velocardiofacial syndrome (Shprintzen et al., 1978). In 22q11.2DS, there is an increased prevalence of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, specific and social phobias, generalized anxiety disorder, separation anxiety disorder, obsessive compulsive disorder, and autism spectrum disorder in children and adolescents, and 25%–30% of adult cases develop schizophrenia (Antshel et al., 2007; Baker, Baldeweg, Sivagnanasundaram, Scambler, & Skuse, 2005; Fine et al., 2005; Gothelf et al., 2004; Karayiorgou & Gogos, 2004; Papolos et al., 1996).

Despite considerable variability, the majority of individuals with 22q11.2DS exhibit a cognitive profile in which full scale IQ (FSIQ) is reduced, often into the borderline range, but where functioning in the verbal domain (VIQ or VCI) is at a higher level than that in the nonverbal/performance domain (PIQ or PRI). Similarly, several studies report relative strengths in reading and spelling compared to math skills (De Smedt et al., 2007; Jacobson et al., 2010; Moss et al., 1999; Oskarsdóttir, Belfrage, Sandstedt, Viggedal, & Uvebrant, 2005; Swillen et al., 1997; Swillen et al., 1999) and atypical recruitment of brain regions during mathematical reasoning (Eliez et al., 2001). However, some children exhibit the opposite profile, so this is not a defining feature of the phenotype (Wang, Woodin, Kreps-Falk, & Moss, 2000). Magnetic resonance imaging (MRI) studies reveal that children with 22q11.2DS exhibit atypical connective patterns (Simon et al., 2008), volume reductions (Campbell et al., 2006), and cortical thinning in regions critical for visuospatial processing, while cortical thinning also occurs in regions important in language development (Bearden et al., 2006; Bearden et al., 2008). Thus, it is likely that developmental changes in the pattern of brain maturation lead to specific cognitive profiles.

Reduced scores in the nonverbal domain are reflected in impairments in a range of abilities,

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of which one of the most prevalent is visual spatiotemporal processing, which is perception and representation of space and time in the visual domain. Differences in visual spatiotemporal processing may affect other cognitive abilities, such as memory. For example, children with 22q11.2DS had lower scores than expected (with respect to their FSIQ score) on visual but not verbal memory (Campbell et al., 2010), and performance in visuospatial working memory (WM), which is memory for items presented visually across space, is worse compared to verbal WM in children with 22q11.2DS using the Kaufman assessment battery for children (Wang et al., 2000). This was replicated in a study comparing verbal memory, using the Wide Range Assessment of Memory and Learning and California Verbal Learning Test (CVLT), to visuospatial memory using the Children's Memory Scale, which found that the children with 22q11.2DS were impaired only in the visuospatial memory task. The finding is particularly noteworthy given that impaired visuospatial memory was accompanied by impaired arithmetic achievement (Bearden et al., 2001), and arithmetic impairments were accompanied by superior verbal memory. This suggests a double dissociation between verbal skills and visuospatial processing, which provides the foundation for numerical thinking and arithmetic performance (Simon, 2008), and verbal skills. Moreover, these impairments persist even in individuals without intellectual disability (Vicari et al., 2012), and there is reason to suspect these impairments are long lasting and will persist throughout life, as impairments are observed in adults on tasks assessing visuoperceptual ability, problem solving, and planning, as well as abstract and social thinking (Henry et al., 2002). Together, these studies suggest that some aspect of atypical visual spatiotemporal processing might lead to subsequent impairments in visuospatial memory.

However, other factors such as impaired visuospatial attention, which is the ability to maintain and shift attention in space and time, may underlie observed impairments in visuospatial WM and PIQ. For example, impairments in 22q11.2DS have been reported on both visuospatial WM tasks and tasks involving visual attention (Sobin et al., 2005), attentive tracking (Cabaral, Beaton, Stoddard, & Simon, 2012), endogenous cueing (Shapiro, Takarae, Harvey, Cabaral, & Simon, 2012), and executive attention (Sobin et al., 2004; Stoddard, Beckett, & Simon, 2011). The latter finding is consistent with previous research using a variety of paradigms showing that children with 22q11.2DS exhibit poorer control over visual attentional orienting (Simon et al., 2005) and that attentional orienting to spatial locations is impaired relative to object based attention (Bish, Chiodo, Mattei, & Simon, 2007). Finally, gray matter volume in several key brain regions is associated with impaired working memory and sustained attention, and gray matter volume in those regions is reduced in children with 22q11.2DS (Shashi et al., 2010). Thus, it is possible that atypical development of brain regions subserving shifts in attention may mediate visuospatial WM performance.

Other studies suggest that processing of temporal information is a key problem in 22q11.2DS that may underlie visuospatial WM performance. For example, children with 22q11.2DS exhibit impaired judgment of temporal duration, as well as frontal hypoactivation during an N-back WM task, which requires maintenance of temporal order of items (Debbané, Glaser, Gex-Fabry, & Eliez, 2005; Gabriel Mounir, Debbané, Schaer, Glaser, & Eliez, 2011; Kates et al., 2007). In serial order memory paradigms, participants must remember items in the temporal order in which they are presented. More children with 22q11.2DS showed impairments in serial order recall than in serial order recognition, when compared to age-matched controls (Majerus, Glaser, Van Der Linden, & Eliez, 2006), and in serial order WM compared to vocabulary- and age-matched controls (Majerus, Van der Linden, Braissand, & Eliez, 2007). In a directed forgetting and continuous recognition paradigm, which requires attention to the temporal order and context in which stimuli are presented, children with 22q11.2DS were more likely to make false recognitions and commission errors, which may be due to an inability to retrieve correct temporal context (Debbané, Glaser, & Eliez, 2008). Thus, these studies suggest that children with 22q11.2DS have difficulty parsing information presented across time, a process necessary for successful memory performance.

Finally, although there have been many studies investigating neuropsychological functioning in 22q11.2DS, very few studies address whether there are gender differences in cognitive functioning or development. Despite this, the question is of great interest because gender effects on brain development in typical children likely

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drive differences in cognitive functioning, and gender effects on brain development and cognitive functioning could be further altered in populations with neurodevelopmental disorders (Giedd et al., 1999). One study found that in children with 22q11.2DS, boys have larger frontal lobes than girls (Antshel, Abdulsabur, Roizen, Fremont, & Kates, 2005). Another found that whole brain volume and frontal lobe volume is preserved in girls but reduced in boys with 22q11.2DS, relative to age-matched controls (Kates et al., 2005). In a small number of studies, it has been reported that boys with 22q11.2DS have lower FSIQ and PIQ than girls with 22q11.2DS (Antshel et al., 2005), or that boys have lower VIQ as well (Niklasson & Gillberg, 2010), but another found no gender difference (Woodin et al., 2001). Thus, there is conflicting evidence for an effect of gender in 22q11.2DS.

In the present study, we accomplished several goals. First, we replicated the finding of relative strength in verbal memory and relative weakness in visuospatial memory in children with 22q11.2DS. To do this, we compared performance between diagnostic groups on the CVLT and a visuospatial WM task, respectively. Second, we studied a relatively large sample to facilitate examination of the effect of gender and age on visuospatial WM performance. Third, we examined performance in a visuospatial WM task while varying task demand, delay, and memory load. We extended the finding of visuospatial WM impairment in children with 22q11.2DS by specifying the types of errors children make and characterizing the pattern of performance. Fourth, we tested whether temporal processing might be a key underlying impairment in 22q11.2DS, and found that children with 22q11.2DS are more susceptible to temporal (proactive) interference. Using this approach we provide a detailed description of factors influencing visuospatial WM performance, which will contribute to current understanding of the cognitive phenotype in 22q11.2DS with greater knowledge about memory processes.

Method

Participants

Participants, ages 6–15 years, were 47 children with 22q11.2DS and 49 age- and gender-matched typically developing (TD) children (Table 1). Children with 22q11.2DS were recruited through the University of California, Davis MIND Institute. Diagnosis of 22q11.2DS was defined as a positive result from the standard fluorescence in situ hybridization (FISH) test. Parental consent and child assent were obtained prior to behavioral testing for all participants in accordance with the requirements of the Institutional Review Board of the University of California, Davis. The behavioral task and neuropsychological test battery were administered as part of a larger NIH-funded study. Participants were compensated with a $60 gift card for one day of participation in the larger study. While most participants completed testing at the MIND Institute, several participants completed testing at a conference. Thus, data from all measures were not available from all participants due to time constraints or conference testing.

Neuropsychological Measures

Intelligence. Intelligence was assessed using the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV; Wechsler, 2003). IQ data were available for 33 TD children and 34 children with 22q11.2DS.

Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD status was diagnosed in accordance with the parent-rated Swanson, Nolan, and Pelham IV Rating Scale (SNAP-IV; Swanson, 1992). If the individual was above the SNAP-IV parent cut-off for symptoms of ADHD on any of the three subscales, they were considered to have ADHD. The questionnaire was not administered to parents of TD children. Because not all parents completed the assessment forms, ADHD data were available for 36 children with 22q11.2DS.

Verbal working memory. Verbal working memory was assessed using the California Verbal Learning Test—Children's Version (CVLT; Delis, 1994). In this test, a shopping list of 16 items comprised of four categories was read to the child, who was asked to recall the items. There were five trials, and the total score was the number of items recalled across all trials. CVLT data were available for 14 TD children and 24 children with 22q11.2DS.

Visuospatial Working Memory Task

Participants viewed a 3 × 3 grid of squares on a computer screen at a distance of 60 cm. A stimulus image of a frog appeared sequentially in two, three, four, or five random locations

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Table 1
Participant Characteristics and Neuropsychological Scores (mean ± SD)

		TD	22q11.2DS	*p* value
Age (years)	*N* =	49	47	
	Total	10.1 ± 2.4	10.6 ± 1.8	.91
	Male	10.6 ± 2.4	10.1 ± 2.1	.49
	Female	9.7 ± 2.3	10.3 ± 1.6	.28
	N =	26	26	
	TS	10.3 ± 2.2	9.8 ± 1.7	.41
	N =	23	23	
	NT	10.1 ± 2.6	10.8 ± 1.9	.22
IQ	*N* =	33	34	
	FIQ	113.1 ± 10.8	77.8 ± 13.3	< .0001
	VIQ	112.8 ± 13.1	82.6 ± 12.6	< .0001
	PIQ	113.1 ± 10.3	80.4 ± 14.8	< .0001
SNAP-IV	*N* =	—	36	
	Inattention	1.65 ± .66	—	
	Hyperactivity/Impulsivity	1.13 ± .71	—	
	Combined	1.40 ± .59	—	
CVLT	*N* =	14	24	
	List A	46.9 ± 9.7	43.1 ± 16.9	.38

Note. TD = typically developing; TS = touchscreen; NT = nontouchscreen; FIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ; CVLT = California Verbal Learning Test.

within the grid. Participants were instructed to remember the grid locations into which the frog jumped, as well as the correct order of locations. Within each trial, no location was repeated. Each stimulus was presented for 1000 ms. After either a short (500 ms) or long (5000 ms) delay, a question mark appeared (for 500 ms), indicating the response period (lasting up to 15 s) had begun. After successfully completing several practice trials, participants completed 48 trials of this task, with 12 trials of each memory load (two, three, four, or five items). All participants completed an identical set of trials, in randomized order. An outline of a sample trial is shown in Figure 1.

Task demand was manipulated across two different task versions. In the nontouchscreen (NT) version, participants responded by pointing to a blank grid, and the experimenter recorded the child's responses by manual transcription. After our lab purchased a touchscreen monitor, we were able to remove this complexity and add to our data by having the computer record the location, as well as latency, of each response as the child touched the recalled locations, in order, on a blank grid on the computer screen. This latter version was the touchscreen (TS) version. Participants performed either the NT or TS version. Accuracy (both versions) and reaction time (RT; TS version) were the primary dependent measures.

In both versions, the experimenter was seated behind the participant during the encoding and maintenance periods. Notably, in the TS version, the experimenter remained present but did not interact with the participant after the practice period. Thus, manipulation of task demand, via manipulation of task version, was not initially part of our experimental design. However, we reasoned that the TS version might be more difficult than the NT version, because the child must interact directly with a computer. This removed unintentional performance cues (e.g., indication of when the correct number of responses have been made, thus precluding additional responses) or positive feedback from the experimenter in the TS relative to NT version.

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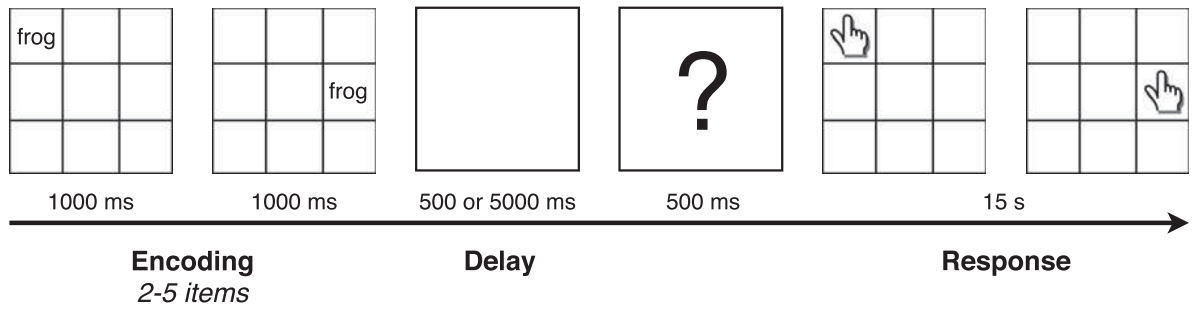

Figure 1. Schematic of a Load 2 trial. Participants viewed two, three, four, or five images of a frog appearing sequentially in different locations on the screen. After a 500- or 5000-ms delay period, a question mark appeared to indicate the beginning of the response period. The participant pointed to indicate the locations and order in which the frogs had appeared.

Analyses

Accuracy was measured in both versions, but RT was only measured in the TS version. Occasionally in the TS version, no response was given within a trial. These trials were removed from all analyses; thus accuracy reflects performance only in trials with responses. Several types of errors were identified. Span errors were trials in which the number of indicated items did not match the number of presented items, and were further divided into under- and overestimates. Once span errors were taken into account, the remaining response was examined for spatiotemporal errors. Spatiotemporal errors were trials in which an item was indicated to be in a location in which no items were actually presented (spatial error), in which the indicated sequence of items did not match the presented sequence (temporal error), or in which both spatial and temporal errors occurred.

Student's *t* tests and Wilcoxon rank-sum tests were used to determine whether there were group differences in age, IQ, CVLT score, accuracy, or RT. Chi-squared tests were used to determine whether there were group differences in gender composition or version.

For the visuospatial WM task analysis, demographic predictors were Group, Gender, and Age, and task predictors were Version, Load, and Delay. Outcome variables were accuracy, span error rate, and spatiotemporal (spatial and/or temporal) error rate. Repeated measures logistic regression and mixed model regression analyses were used to determine the effects of demographic and task predictors on outcome variables. The minimum age (84 months) was subtracted from all participant ages. The intercept was defined as performance by a TD male of minimum age who completed the TS version with a short delay and load of two. A natural logarithm transformation of the span error rate was used in the analyses to better meet the assumptions of the statistical models. For each outcome variable, a model including all six demographic and task predictors was fit. The following interaction terms were each added to the model and assessed for significance: between Version and Load or Delay; between Group and Gender, Age, Version, Load, or Delay; between Gender and Load or Delay; between Age and Load or Delay. If any of the interaction terms were significant, they were included in the final model. This process resulted in one model for each of the outcome variables.

We reasoned that to produce the correct number of responses during the response period, participants must pay attention during the encoding period. For example, if four items were presented and the child indicated four items were seen, then the child must have attended to the entire encoding sequence. Therefore, in a subanalysis we excluded trials with span errors to control post-hoc for the maintenance of attention. In this subanalysis, the pattern of results did not differ. Consequently, only results from the main analysis, utilizing all trials, are reported.

To examine the effect of temporal (proactive) interference, previous load was defined as the memory load from the previous trial. We predicted temporal interference from the previous trial would lead to an increased overestimation rate following a High load trial (4–5 items) relative to a Low load trial (2–3 items). Repeated measures logistic regression analyses were used to determine the effects of Group, Gender, Age, Version, Delay, and Previous Load on overestimation rate.

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To better fit the assumptions of the statistical models, overestimation rate was reduced to present (if the rate was greater than zero) versus absent under a particular task condition. The regression intercept was defined as performance by a TD male of minimum age who completed the TS version with a short delay and high Previous Load. As before, significant interaction terms were added to the final model.

Results

Demographics

Participant descriptive statistics are shown in Table 1. Diagnostic groups did not differ in age ($t = 0.12$, $p = .91$), gender composition ($\chi^2 = 0.67$, $p = .41$), or task version ($\chi^2 < 0.001$, $p = .99$). There were 49 children in the TD group (27 male; 22 female) and 47 children in the 22q11.2DS group (21 male; 26 female). Fifty-two participants completed the TS version (26 in each group), and 46 participants completed the NT version (23 in each group). There were no differences in age between groups within a version of the test (TS mean ± *SD*: TD = 10.3 ± 2.2, 22q11.2DS = 9.8 ± 1.7, $p = .41$; NT: TD = 10.1 ± 2.6, 22q11.2DS = 10.8 ± 1.9, $p = .22$). There were also no differences in age between genders (TD: male = 10.6 ± 2.42, female = 9.72 ± 2.30, $p = .20$; 22q11.2DS: male = 9.96 ± 2.27, female = 10.21 ± 1.72, $p = .67$).

Neuropsychological Measures

The 22q11.2DS group had lower FSIQ (W = 17.5, $p < .001$) but not CVLT scores (W = 125, $p = .38$). In both groups, there was no difference between VCI and PRI scores (TD: $t = .09$, $p = .92$; 22q11.2DS: $t = .90$, $p = .37$). There were no differences between boys and girls in either group on FSIQ ($p > .4$ in both groups), VCI ($p > .3$ in both groups), or PRI ($p > .3$ in both groups). In our sample, 16 of 36 children with 22q11.2DS (44%) were diagnosed with at least one subtype of ADHD. To examine a possible relationship between ADHD status and performance, individuals with and without ADHD were compared on accuracy, span error rate, and spatiotemporal error rate. No effect of ADHD status was observed (all $p > .6$).

Visuospatial Working Memory Task

Results from *t* tests are shown in Figure 2. The 22q11.2DS group had lower accuracy than the TD group in both the NT version ($t = -2.29$, $p = .03$) and TS version ($t = -4.23$, $p < .001$). In the TS version, the 22q11.2DS group had slower reaction times than the TD group ($t = 2.23$, $p = .03$), indicating that reduced accuracy in the 22q11.2DS group was not due to a speed-accuracy tradeoff. The mean number of trials with no responses was .36 ± 1.75 for the TD group and .69 ± 2.71 for the 22q11.2DS group. The number did differ between groups ($t = -1.35$, $p = .05$), but due to the low number of excluded trials, this difference is unlikely to substantially affect our results. Performance measures were entered into regression models to determine the roles of demographic and task predictors. The results are presented in the following sections.

Effects on Accuracy

Results are shown in Figure 3A–B. The mean accuracy was 64.77% ± 21.73% for the TD group and 44.51% ± 19.93% for the 22q11.2DS group, which differed significantly ($t = 4.81$, $p < .001$). Partial regression coefficients from the regression model are shown in Table 2. Accuracy on the NT version of the test was higher than the TS version at the lowest load for both long and short delays ($p = .002$). Accuracy decreased with increasing load for TD children on the TS version ($p < .01$) and even more on the NT version, particularly at the higher loads ($p < .001$). The 22q11.2DS group had lower accuracy than the TD children at the lowest load for both versions and both long and short delays ($p = .02$) and accuracy decreased more than in TD children at the highest loads ($p < .05$). For both groups, the decrease in accuracy with increasing load lessened with age ($p < .01$). On average, the longer delay resulted in lower accuracy for both TD children and those with 22q11.2DS ($p = .004$), but this difference lessened with increasing age ($p = .03$). Females tended to have greater decreases in accuracy at the higher loads than males ($p < .01$) for both groups. A comparison of male and female performance by group is shown in Figure 4A.

We then used the same regression model but removed Group as a factor to examine within-group effects. In both groups, accuracy decreased with increased Load and Delay ($p = .06$ for the TD group), and was lower in females and younger children. Both groups exhibited interactions of Age × Load (decrease in accuracy with increasing Load lessened with age) and Version × Load ($p = .063$

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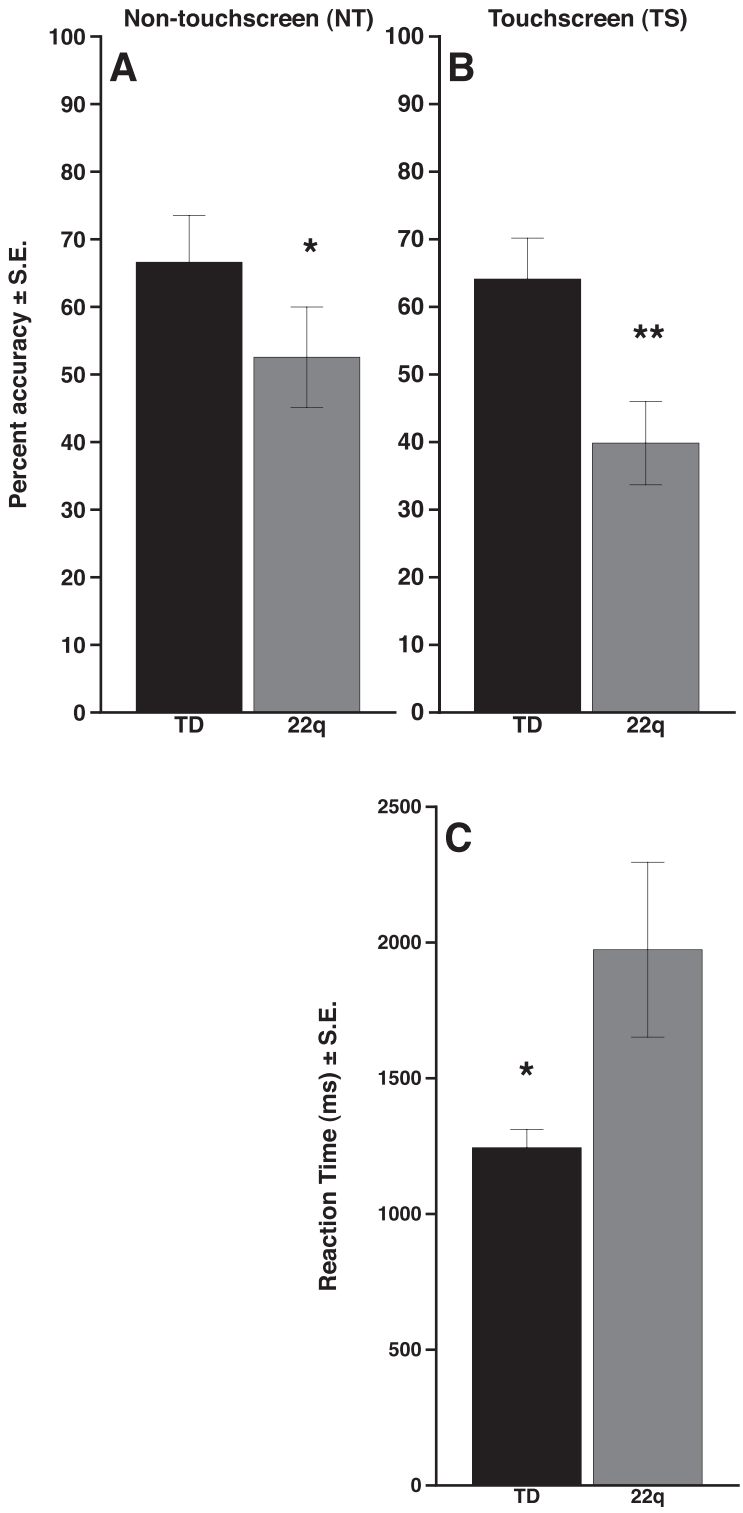

Figure 2. Behavioral results. Accuracy from TD children (black) and children with 22q11.2DS (gray) are shown from the (A) NT version and (B) TS version. (C) Reaction time from the TS version. $^{*}p < .05$. $^{**}p < .001$.

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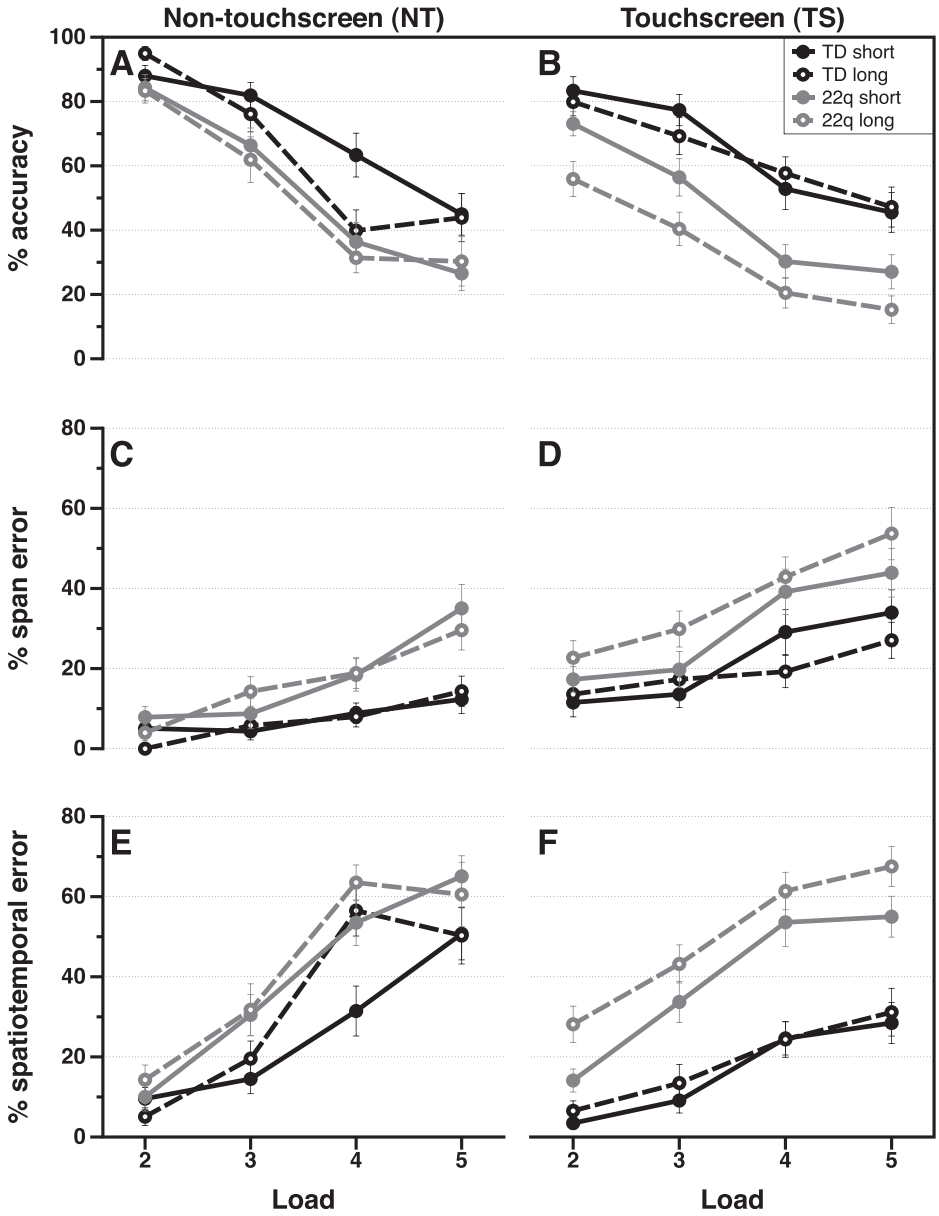

Figure 3. Task performance by Version, Load, and Delay. Dependent measures from the NT version (A, C, E) and TS version (B, D, F) are shown. TD children (black circles) and children with 22q11.2DS (gray squares) each completed either the TS or NT version. The effect of short delay (solid line, closed marker) and long delay (dashed line, open marker) are shown on percentage of trials that (A–B) were correct, (C–D) had a span error, and (E–F) had a spatial and/or temporal error. Error bars represent standard error.

for the 22q11.2DS group; accuracy in NT was higher than in TS at the lowest Load). However, only the 22q11.2DS group exhibited a main effect of Version (decreased accuracy in NT relative to TS), and Gender × Load interaction (larger decreases in accuracy at the higher Load in females than males).

Effects on Span Error Rate

Results are shown in Figure 3C–D. The mean number of trials with span errors was 6.86 ± 6.79 for the TD group and 12.49 ± 7.93 for the 22q11.2DS group, which differed significantly ($t = -3.75$, $p < .001$). Partial regression coefficients from the regression model are shown in Table 3.

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Table 2
Regression Model for Accuracy

Predictor		Coefficient	*SE*	*p* value
(Intercept)		0.770	0.053	< .001
Group	22q	−0.103	0.044	.02
Gender	Female	−0.015	0.042	.72
Age	Age	0.001	0.001	.12
Version	NT	0.136	0.042	.002
Load	Load3	−0.115	0.044	.01
	Load4	−0.351	0.044	< .001
	Load5	−0.423	0.044	< .001
Delay	DelayLong	−0.077	0.026	.004
*Group * Load*	22q * Load3	−0.067	0.036	.07
	22q * Load4	−0.111	0.036	.003
	22q * Load5	−0.073	0.036	.05
*Group * Delay*	22q * DelayLong	−0.050	0.026	.05
*Gender * Load*	Female * Load3	−0.095	0.037	.01
	Female * Load4	−0.067	0.037	.07
	Female * Load5	−0.111	0.037	.003
*Age * Load*	Age * Load3	0.002	0.001	.004
	Age * Load4	0.003	0.001	< .001
	Age * Load5	0.003	0.001	< .001
*Age * Delay*	Age * DelayLong	0.001	0.001	.03
*Version * Load*	NT * Load3	−0.052	0.037	.16
	NT * Load4	−0.138	0.037	< .001
	NT * Load5	−0.139	0.037	< .001

On average, there were more span errors made on the TS version than the NT version ($p < .001$). Errors increased at the higher loads relative to the lower loads for both versions ($p < .001$) in the TD children and increased even more in the children with 22q11.2DS ($p = .02$). This increase lessened with age for both groups ($p < .02$). Females made a greater number of errors on long delays than short delays compared to males ($p = .03$). A comparison of male and female performance by group is shown in Figure 4B.

We then used the same regression model but removed Group as a factor to examine within-group effects. In both groups, span errors increased with Load, decreased with Age, and were more frequent in the TS than NT version. Only the TD group exhibited an interaction of Gender × Delay (larger increase in errors with longer Delay in females than males), and only the 22q11.2DS group exhibited increased errors with longer Delay ($p = .058$) and interaction of Gender × Load (increased errors at the highest Load in females but not males).

Effects on Spatiotemporal Error Rate

Results are shown in Figure 3E–F. The 22q11.2DS group committed more spatial-only ($t = -4.63$, $p < .001$) and temporal-only ($t = -3.89$, $p < .001$) errors than the TD group. The mean number of trials with spatiotemporal errors was 11.29 ± 8.76 for the TD group and 20.73 ± 7.85 for the 22q11.2DS group, which differed significantly ($t = -5.65$, $p < .001$). Partial regression coefficients from the regression model are shown in Table 4. On average, there were more spatiotemporal errors for both groups when there was a long delay compared to a short delay ($p < .001$). Errors increased with increasing load on the task for TD children on the TS version ($p < .02$) with an even greater increase in the children with 22q11.2DS ($p < .01$). On average, there were more errors on the NT version relative to the TS version of the task with increasing load, particularly at the highest loads ($p < .001$). The increase in errors with increasing load lessened with age ($p < .01$). Females in both groups experienced more errors

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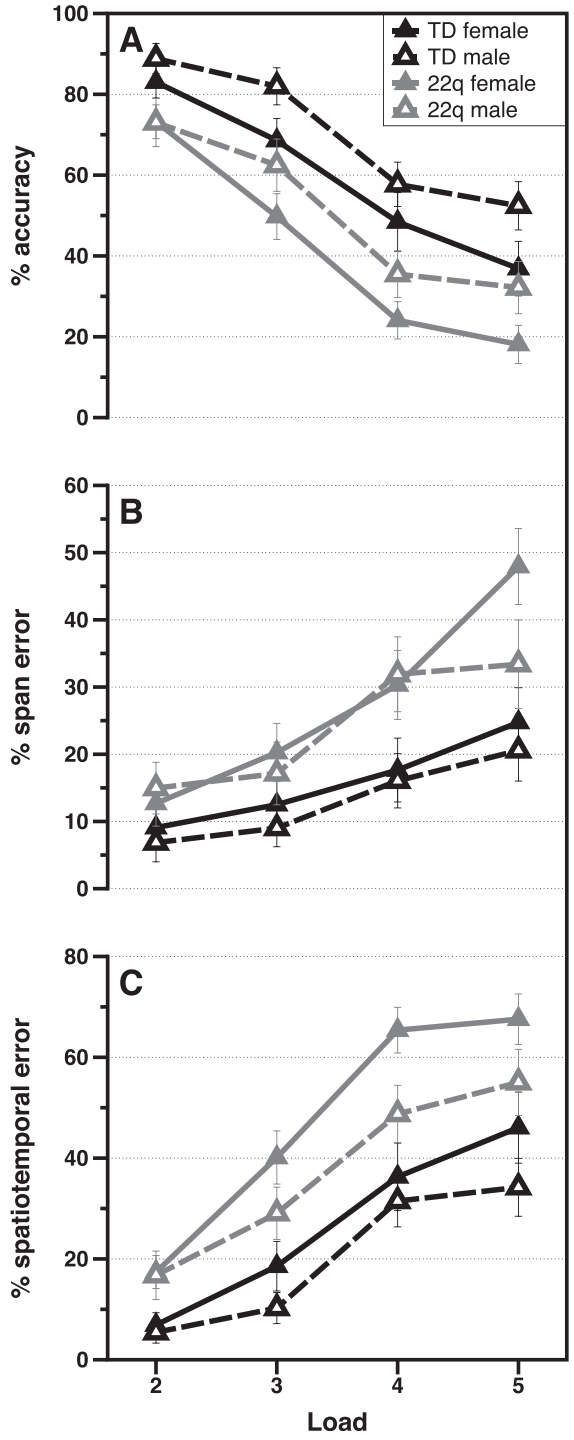

Figure 4. Task performance by Gender and Load. Dependent measures from TD children (black circles) and children with 22q11.2DS (gray squares) collapsed across task version are shown. Female (solid line, closed marker) and male (dashed line, open marker) performance are shown as percentage of trials that (A) were correct, (B) had a span error, and (C) had a spatial and/or temporal error. Error bars represent standard error.

with increasing load than males ($p < .05$). A comparison of male and female performance by group is shown in Figure 4C.

We then used the same regression model but removed Group as a factor to examine within-group effects. In both groups, spatiotemporal errors increased with Load and Delay, and decreased with Age. Both groups exhibited an interaction of Age × Load (increase in errors with increasing Load lessened with Age). Only the TD group exhibited more frequent errors in the NT than TS version and an interaction of Version × Load (greater increase in errors with increasing Load in NT than TS). Only the 22q11.2DS group exhibited more errors in females and an interaction of Gender X Load (greater increase in errors with increasing Load in females than males).

Effect of Previous Load on Overestimation Rate

Results are shown in Figure 5A. The mean number of trials with overestimation errors was .96 ± 1.34 for the TD group and 3.92 ± 3.59 for the 22q11.2DS group, which differed significantly ($t = -5.45$, $p < .001$). Due to a relatively low number of overestimation errors, and to conserve statistical power, we considered the load of the previous trial to be either Low (2–3 items) or High (4–5 items). To more closely represent the binarized overestimation rate used in the regression analysis, the figure displays the number of participants who overestimated at least once following Low or High load trials. Chi-squared and McNemar's chi-squared tests were used to assess significance. A similar pattern was produced when displaying the percentage of trials with overestimation errors following Low load or High load trials (results not shown).

Partial regression coefficients from the regression model are shown in Table 5. On average, the children with 22q11.2DS were much more likely to commit an overestimation error than TD children ($p < .001$). A long delay was also associated with an increased likelihood of committing an overestimation error ($p < .03$). On average, if the previous load was High, there was an increased likelihood of an overestimation error ($p = .002$) compared to if the previous load was Low. There was no difference by Age ($p = .11$), Gender ($p = .48$), or Version ($p = .36$).

We then used the same regression model but removed Group as a factor to examine within-

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Table 3
Regression Model for Span Error Rate

Predictor		Coefficient	*SE*	*p* value
(Intercept)		−1.347	0.115	< .001
Group	22q	0.215	0.092	.02
Gender	Female	−0.084	0.098	.39
Age	Age	−0.003	0.002	.13
Version	NT	−0.413	0.093	< .001
Load	Load3	0.046	0.109	.67
	Load4	0.486	0.109	< .001
	Load5	0.506	0.109	< .001
Delay	DelayLong	−0.037	0.044	.41
*Group * Load*	22q * Load3	0.019	0.089	.83
	22q * Load4	0.206	0.089	.02
	22q * Load5	0.206	0.089	.02
*Gender * Load*	Female * Load3	0.108	0.089	.23
	Female * Load4	−0.035	0.089	.70
	Female * Load5	0.225	0.089	.01
*Gender * Delay*	Female * DelayLong	0.137	0.063	.03
*Age * Load*	Age * Load3	0.000	0.002	.94
	Age * Load4	−0.004	0.002	.02
	Age * Load5	−0.005	0.002	.01
*Version * Load*	NT * Load3	0.043	0.089	.63
	NT * Load4	−0.043	0.089	.63
	NT * Load5	0.067	0.089	.46

group effects. In the 22q11.2DS group only, increased likelihood of overestimation was associated with higher Load in the previous trial. There was a trend toward decreased overestimation with increasing Age in the TD group (p = .066) and increased overestimation with longer Delay in the 22q11.2DS group (p = .070).

The interference effect was calculated as percentage of trials with overestimation errors following High load trials minus percentage of trials with overestimation errors following Low load trials. As seen in Figure 5B, the 22q11.2DS group had a significantly larger interference effect relative to the TD group (t = 1.98, p = .05), indicating they were more likely than the TD children to overestimate more frequently with an increasing number of items in the previous trial.

Discussion

In the present study, we sought to accomplish four goals. First, we replicated the finding of a relative strength in verbal working memory and relative weakness in visuospatial working memory in children with 22q11.2DS relative to TD controls. We observed this as reduced accuracy in a visuospatial WM task in children with 22q11.2DS relative to TD children, but no differences in CVLT scores.

Unlike the samples reported previously (Jacobson et al., 2010; Moss et al., 1999; Oskarsdóttir et al., 2005; Swillen et al., 1997; Swillen et al., 1999), the group of children with 22q11.2DS recruited into our study did not exhibit significantly higher verbal than nonverbal domain IQ scores. In our sample, VCI score was greater than PRI score, but not significantly so. These conflicting findings may be partly attributable to the use of particular intelligence measures (e.g., we used VCI and PRI from the WISC-IV instead of VIQ and PIQ from the WISC-III or other test, respectively), and different age ranges, thus requiring the use of distinct age-appropriate tests. We found that in both groups, there were no gender differences in FSIQ, VCI, or PRI scores. This replicates a reported lack of a gender difference (Woodin

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Table 4
Regression Model for Spatiotemporal Error Rate

Predictor		Coefficient	*SE*	*p* value
(Intercept)		0.059	0.049	.23
Group	22q	0.164	0.046	.001
Gender	Female	0.009	0.037	.81
Age	Age	−0.001	0.001	.11
Version	NT	0.031	0.047	.51
Load	Load3	0.106	0.045	.02
	Load4	0.268	0.045	< .001
	Load5	0.329	0.045	< .001
Delay	DelayLong	0.058	0.013	< .001
*Group * Version*	22q * NT	−0.119	0.06	.05
*Group * Load*	22q * Load3	0.096	0.037	.01
	22q * Load4	0.129	0.037	.001
	22q * Load5	0.109	0.037	.003
*Gender * Load*	Female * Load3	0.079	0.037	.03
	Female * Load4	0.09	0.037	.01
	Female * Load5	0.105	0.037	.004
*Age * Load*	Age * Load3	−0.002	0.001	.004
	Age * Load4	−0.003	0.001	< .001
	Age * Load5	−0.003	0.001	< .001
*Version * Load*	NT * Load3	0.038	0.037	0.3
	NT * Load4	0.152	0.037	< .001
	NT * Load5	0.163	0.037	< .001

et al., 2001), yet contrasts with previous findings in which boys had higher FSIQ and PIQ scores than girls (Antshel et al., 2005). Thus, the effect of gender on intellectual functioning in 22q11.2DS remains inconclusive.

Second, we examined the effect of gender and age on visuospatial WM performance. We found that in both groups, girls tended to make more errors than boys. This replicates previous findings of a male advantage on visuospatial tasks (Johnson & Bouchard, 2007). These results remain when including neuropsychological scores in the models (results not shown), indicating that our findings are not due to gender differences in intelligence scores. Additionally, both TD children and children with 22q11.2DS exhibited improved accuracy with age.

Third, we extended the finding of visuospatial WM impairment by varying task demand, delay, and memory load. We found that children with 22q11.2DS were more sensitive to task demand than TD children, and made more of each type of error (span and spatiotemporal) than TD children with increasing load, indicating that spatial and/or temporal processing impairments may underlie the performance impairments. Because children with 22q11.2DS committed more spatial-only and temporal-only errors than TD children, we conclude that both spatial and temporal processing is impaired. Children with 22q11.2DS produced more span and spatiotemporal errors with longer delays than TD children, which could be due to increased susceptibility to memory degradation, or inefficiency of memory retrieval, as opposed to encoding. Increased errors were driven more by increased spatiotemporal errors than span errors, since the effect of delay was significant in one model but not the other (Tables 3–4). Similarly, the effect of increased load was significant for all loads in the spatiotemporal error model, but only for higher loads in the span error model. Because span errors are purely temporal in nature, these patterns suggest that spatial information may be lost sooner than temporal information in children with 22q11.2DS. Because performance did not differ between indi-

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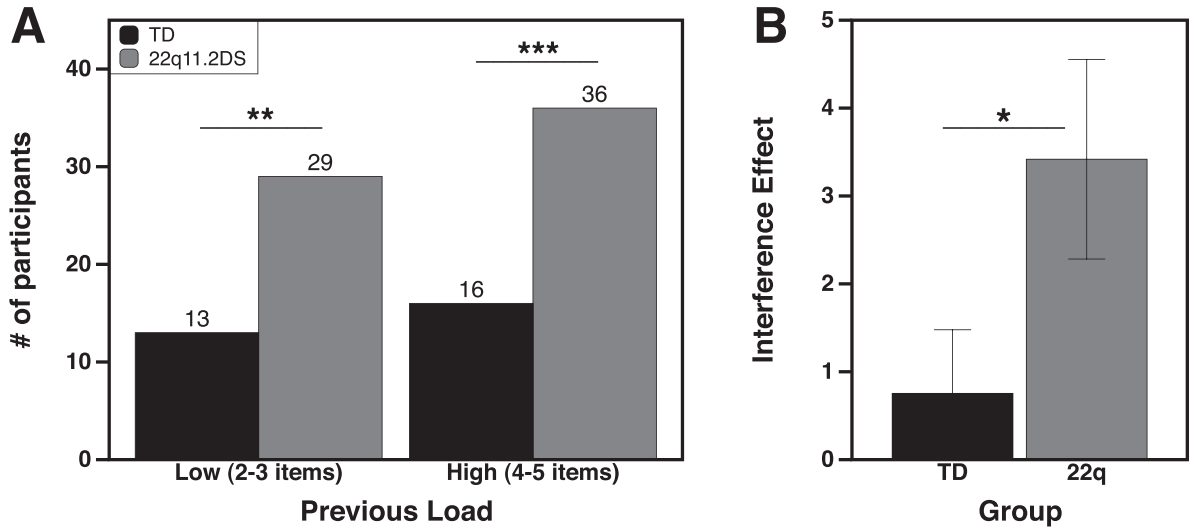

Figure 5. Proactive interference effect. (A) Number of participants who overestimated at least once following Low load (2–3 items) or High load (4–5 items) trials for TD children (black) and children with 22q11.2DS (gray). (B) Interference effect, calculated as percentage of trials with overestimation errors following High load trials minus percentage of trials with overestimation errors following Low load trials, is shown for both groups. Error bars represent *SE*. $^{*}p < .05$. $^{**}p = .001$. $^{***}p < .001$.

viduals with and without ADHD, we concluded that preexisting general impairments in attention did not account for our results.

Manipulating task version across participants suggests that a purely computer-based task lacking experimenter intervention is generally more sensitive to group differences. This may be due to a lack of unintended performance cues (e.g., indication of when the correct number of responses have been made, thus precluding additional responses), positive feedback, or distraction during the delay period. It is possible that the NT version of the task was more difficult because participants must divide their attentional resources between the computer and the experimenter. However, we believe this is unlikely to be a predominant factor, because the experimenters noted that participants predominantly fixated on the screen during the encoding and maintenance periods, and on the paper during the response period (i.e., not fixated on the experimenter).

We also observed that both groups exhibited more span errors in the TS than NT version, and the TD group exhibited more spatiotemporal errors in the NT than TS version, while the 22q11.2DS group had a high rate of spatiotemporal errors for both versions. This divergent pattern of results was unexpected, and indicates that distinct task versions can produce a differential pattern of results. We speculate that the TD children were more motivated to perform well when less supervised (TS vs. NT) and therefore committed

Table 5
Regression Model for Overestimation Rate

Predictor		Coefficient	*SE*	*p* value
(Intercept)		−2.314	0.301	< .001
Group	22q	1.42	0.247	< .001
Gender	Female	−0.173	0.243	.48
Age	Age	−0.008	0.005	.11
Version	NT	−0.326	0.253	.20
Delay	DelayLong	0.374	0.152	.01
Previous Load	PrevLoad Low	−0.452	0.149	.002

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fewer spatiotemporal errors, but parsing temporal context (one trial from the next) was more difficult in the TS than NT version, and therefore resulted in increased span errors.

Fourth, we examined whether temporal context (proactive interference) affects visuospatial WM performance. We found that children with 22q11.2DS were more likely than TD children to attribute more items to the current trial when the previous trial had more items than when the previous trial had fewer items. This suggests that children with 22q11.2DS had more difficulty distinguishing temporal context, a prerequisite to correctly attribute memory representations to one trial or the next. This could be due to decreased resolution of the mental representation of temporal context, such that a blurry representation of how long ago the trial started allows item representations from the previous trial to be erroneously categorized as item representations from the current trial.

Similarly, spatiotemporal errors might be caused by decreased resolution of the mental representations of spatial or temporal context, such that an item appearing in one location is thought to have appeared in a neighboring location, or two items appearing in sequence are thought to have appeared in the reverse sequence. Collectively, these findings of increased span error, spatiotemporal error, and proactive interference support the "spatiotemporal hypergranularity" hypothesis, that the spatial and temporal resolution of attention is reduced in individuals with 22q11.2DS (Simon, 2008).

Relation to Cognitive Models of WM

According to the Baddeley and Hitch (1974) model, working memory includes the phonological loop, visuospatial sketchpad, and central executive. Verbal information is processed and stored in the phonological loop, spatial and object information is processed and stored in the visuospatial sketchpad, and the central executive coordinates the two systems. Baddeley (2000) later added the episodic buffer into the model, a storage system which links information between the phonological loop and visuospatial sketchpad. While it is possible that participants mentally verbalized the item sequence (e.g., "frog starts in upper-left corner, jumps two to the right and one down"), and may have used the episodic buffer to translate this verbal information into spatial movements, we suggest that this task predominantly taxes the visuospatial sketchpad, because the task required memory for spatial locations.

The embedded-process model of working memory emphasizes links between memory and attention (Cowan, 1999). According to this model, activated memory can be within the focus of awareness and attention, or not. Thus, this model provides a theoretical link between attention orienting impairments in children with 22q11.2DS and the working memory impairments observed in this study. Specifically, individuals with atypical orienting abilities may take longer to shift attention from the location of the previous item to the location of the current item, thus resulting in decreased available time to encode the new location. The model also suggests that decreased working memory capacity may be due to limitations of attention (e.g., selection bottlenecks).

Limited attention capacity has been reported across a variety of paradigms in individuals with 22q11.2DS (Bish, Ferrante, McDonald-McGinn, Zackai, & Simon, 2005; Cabaral et al., 2012; Simon et al., 2005), Future studies collecting eye position data are needed to test how this model can enhance our understanding of individuals with 22q11.2DS.

Finally, working memory capacity limitations may be due to time limitations (McAfoose & Baune, 2009). For example, individuals with reduced capacity may maintain items in active memory for shorter durations than individuals with larger capacity. This possibility is supported by evidence that children with 22q11.2DS exhibit impaired judgment of temporal duration (Debbané et al., 2005; Gabriel Mounir et al., 2011) and frontal hypoactivation during an N-back WM task, which requires maintenance of temporal order of items (Kates et al., 2007). Increased span errors in the 22q11.2DS group could be due to decreased capacity due to time limitations, or to difficulty parsing temporal context. Alternative task designs are needed to dissociate spatial and temporal memory.

Implications

The results of this study could be used to develop adaptive strategies when teaching children with 22q11.2DS. If spatial and temporal processing are impaired, information may be best presented: (a) with fewer targets at a time, (b) with fewer distractors at a time, (c) with increased distinc-

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tiveness of targets to avoid confusion or crowding, and (d) slowly. Limited working memory capacity can be addressed by presenting smaller chunks of information at a time, and encouraging verbalization of information to decrease reliance on the visuospatial sketchpad. The effects of task version we observed suggest that children with 22q11.2DS would learn better from computer training if adult supervision were involved. Finally, proactive interference effects suggest that clearly emphasizing a switch to a new task may translate to facilitation of goal updating in children with 22q11.2DS.

Limitations

Our interpretations are limited because we are not yet able to specify a definitive mechanism underlying performance impairments. Although our findings suggest maintenance or retrieval mechanisms may be at the source of the impairment, it is possible that participants did not have enough time to encode the items. However, this is unlikely to be the case, because there was no group difference in performance in trials with a short delay and the lowest load (results not shown). This indicates that the presentation rate was sufficiently slow for successful encoding. An alternate task design including manipulation of distraction level during the delay phase would allow us to determine whether maintenance or retrieval processes are most affected.

Another limitation of this task is that it does not cleanly delineate between spatial and temporal working memory, because each trial required memory for the temporal order of spatial locations of items. Therefore, the analyses here considered spatial-only, temporal-only, and spatial-and-temporal errors all as one type. An alternate task design with spatial-only memory trials and temporal-only memory trials would allow us to better specify whether children with 22q11.2DS have spatial, temporal, or spatial *and* temporal impairments. The proactive interference analysis should ideally examine the parametric effect of previous load on overestimation rate. However, due to a relatively low number of overestimation errors, we combined previous load conditions to conserve statistical power. Finally, our cross-sectional design with age as a regressor may not precisely capture the development of visuospatial WM abilities in children, since children with 22q11.2DS may exhibit a typical pattern of development, but simply with an age delay. A longitudinal design would be more appropriate to examine the development of these abilities.

Conclusion

In this study, we presented, for the first time, a detailed description of the factors influencing visuospatial working memory performance in children with 22q11.2DS and typically developing children. Manipulation of memory load and delay indicates that children with 22q11.2DS may exhibit impaired memory performance due to reduced maintenance and/or retrieval ability, and manipulation of task version indicates that tasks that do not involve experimenter intervention may be more sensitive to group differences. Examination of error types indicates that both spatial and temporal errors are increased in 22q11.2DS. In addition, children with 22q11.2DS were more susceptible to proactive interference effects, suggesting poorer resolution of temporal attention. These findings indicate that spatial and temporal attention is impaired in 22q11.2DS, which negatively impacts visuospatial working memory performance.

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