

Networks of Attention in Children With the 22q11 Deletion Syndrome

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The 22q11 chromosomal deletion syndrome (22q11 DS) is associated with learning disabilities and a complex neuropsychological profile. Previous findings have suggested that executive attention deficits might underlie other neurocognitive anomalies. We administered the child Attention Network Test (ANT) to 52 children ages 5.0 to 11.5, 32 22q11 DS children (19 girls) and 20 controls (13 girls) and assessed the efficiency of segregated executive, orienting, and alerting networks. We hypothesized that 22q11 DS children have impaired executive network efficiency as compared to control siblings. The internal validity of the child ANT was confirmed for this population. Analysis of variance results showed significant main effects for flanker and cue types and no interaction effect in either 22q11 DS children or control siblings. Compared to control siblings, 22q11 DS children had significantly larger (less efficient) executive network scores, significantly increased errors on only incongruent trials, and a significant correlation between executive network scores and accuracy. The implications of these findings for future neurocognitive studies of 22q11 DS children are considered.

The 22q11 deletion syndrome (22q11 DS) results from a meiotic deletion of DNA at the q11.2 site on chromosome 22 and its estimated prevalence is 1:4,000 (du Montcel, Mendizabal, Ayme, Sevy, & Philip, 1996). In over 90% of cases the deletion is not transmitted (Morrow et al., 1995). Congenital anomalies of widely varying severity can be associated with this condition and might include heart defects, immunologic deficits, craniofacial dysmorphologies, and velopharyngeal defects such as overt or submucous cleft palate (e.g., Ryan et al., 1997). Prior to identification of a single associated deletion, different clinical labels were used to indicate a given child's congenital anomalies, including DiGeorge Syndrome (primary immunologic deficit), Velo-Cardio-Facial-Syndrome (VCFS; velopharyngeal, heart, and facial anomalies), and Conotruncal Anomaly Face Syndrome (primary heart defect with facial dysmorphologies). Whereas the physical phenotype is heterogeneous, the neurocognitive profile is far more consistent. Researchers have estimated that 90% to 100% of 22q11 DS children are learning disabled (e.g., Lipson et al., 1991; Shprintzen, Goldberg, Young, & Walford, 1981) and hypotonic, with gross and fine motor dyscoordination, associated expressive language delays, attention impairment, and behavioral anomalies (Gerdes et al., 1999). Frank mental retardation is relatively rare and may be associated with prolonged anoxia during early cardiac failure. Of urgent concern, approximately 25% of 22q11 DS children are estimated to develop early adulthood schizophrenia (Murphy & Owen, 1996; Pulver et al., 1994). In addition to clarifying remediation needs, defining the early neurocognitive profiles of 22q11 DS children may suggest precursors and mechanisms of later severe mental disease.

Initial studies of cognitive functioning in school-aged 22q11 DS children examined their IQ battery scores (e.g., Wechsler Scales) and achievement tests. Early motor delays were consistently observed in behavioral reports (e.g., Gerdes et al., 1999) although rarely if ever considered when interpreting IQ scores. Markedly higher Verbal than Performance IQ scores were noted (e.g., Moss et al., 1995; Swillen et al., 1997) and Full-Scale IQs were found to be in the low-normal to borderline range, attributable to marked subtest score scatter indicated by the Verbal and Performance IQ differences. Reading and spelling achievement scores were typically higher than arithmetic scores (e.g., Moss et al., 1999). Psychoeducational findings prompted neurocognitive investigations and lowered arithmetic ability was first explored. Citing the association between short-term visuospatial memory and arithmetic skill in normally developing and learning-impaired populations without the deletion (Buchanan, Pavlovic, & Rovet, 1998; Dickey et al., 1997; Logie, Gilhooly, & Wynn, 1994), Wang, Woodin, Kreps-Falk, and Moss (2000) assessed thirty-six 5- to 12-year-old 22q11 DS children. They found that visual Spatial Memory and not Number Recall (Kaufman-Assessment Battery for Children subtests; Kaufman & Kaufman, 1983) was specifically impaired, with the mean scaled score for spatial memory 1 *SD* below the standardization sample mean.

Bearden et al. (2001) administered a combined battery of tests to 29 22q11 DS children ages 5 to 16 years ($M = 10.3 \pm 2.5$) including verbal and visual memory tasks, word decoding, reading comprehension, numerical operations, and mathematical reasoning. Only the mean scaled score of visual spatial memory (Dot Location subtest, Children's Memory Scale; M. J. Cohen, 1997) was more than 1 *SD* below the standardization sample mean and differed significantly from their higher verbal memory measure (list-learning task, California Verbal Learning Test; Delis, 1988).

The neurocognitive performance of 22q11 DS children is notably complex however (Moss et al., 1999) and visuospatial memory deficits alone are unlikely to fully explain their profiles. In fact when a broader complement of abilities was examined additional areas of deficit were revealed. Fifty 22q11 DS children ages 6 to 17 ($M = 10.3 \pm 3.2$) were administered tests of memory (Verbal Learning, Story Memory, and Design Memory subtests from the Wide Range Assessment of Memory Learning; Adams & Sheslow, 1990), executive attention (Trail Making; Reitan, 1958), and a standard IQ battery (Woodin et al., 2001). Math achievement, delayed story recall, Trails B, and the Freedom from Distractibility Index of the Wechsler Intelligence Scale for Children (3rd ed.; Wechsler, 1991; a cluster measure of performance on visual attention and working memory tasks) were 1 or more *SD* below the standardization sample mean. A striking deficiency (nearly 2 *SD* below the standardization sample mean) in Trails B was noted, suggesting impaired mental flexibility and loss of visual attentional focus. Interestingly in this study, design (visual spatial) memory was within 1 *SD* from the mean. Thus lowered visual spatial memory scores were accompanied by more consistent impairment among 22q11 DS children on measures of visual attention and executive function ability.

In a recent report (Sobin et al., in press) 40 22q11 DS children ages 5 to 12 were administered the NEPSY (Korkman, Kirk, & Kemp, 1998) and the Stanford-Binet Intelligence Scale (Thorndike, Hagen, & Sattler, 1987). Five neuropsychological domains (language, visual-spatial and verbal memory, sensorimotor function, visual-spatial processing, and attention and executive function) and three cognitive domains (verbal reasoning, abstract and visual reasoning, and quantitative reasoning) were assessed. Mean scaled scores > 1 *SD* below the standardization sample means were found only on tests of visual attention, working memory, and sensorimotor function.

THE ANT AND SEGREGATED NETWORKS OF ATTENTION

Although not the only domain of interest, more closely examining visual attention in 22q11 DS children may be key in developing our understanding of their

neurocognitive development and learning difficulties. To do so, we administered the Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002) to assess the efficiency of segregated executive, orienting, and alerting networks of visual attention in 22q11.1 DS children and their control siblings. The ANT is based on a neuroanatomical model of visual attention substantiated by decades of animal and human research using single-cell activation studies of animals, brain imaging studies of neurologically impaired normal volunteers, and animal and human studies of neurotransmitter function (e.g., Mesulam, 1981, 1990; Posner & Boies, 1971; Posner, Imhoff, Friedrich, & Cohen, 1987; Posner, Petersen, Fox, & Raichle, 1988).

The *executive network* is activated when discrepant stimuli are processed, for example when a display includes incongruent components that must be visually integrated. Heightened activation in the anterior cingulate cortex occurred during the presentation of complex stimuli (Posner & Dehaene, 1994) and during tasks with conflicting cues (Stroop task; e.g., Bench et al., 1993; Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991; Pardo, Pardo, Janer, & Raichle, 1990). Neural network models linked these structures to the basal ganglia (Alexander, DeLong, & Strick, 1986) defining the brain pathways critical for executive attention. Evidence of the *orienting network* was observed when orientation to the correct location of a coming stimuli increased response time (RT; Eriksen & Hoffman, 1972; Posner et al., 1988), enhanced detection of faint stimuli (Bashinski & Bachrach, 1984; Downing, 1988), and enhanced overall brain activation (measured via scalp electrical activity; Mangoun & Hillyard, 1987). Neuroimaging studies consistently linked location orientation with activity in posterior parietal lobe (e.g., Corbetta et al., 1998; Kastner, Pinks, De Weerd, Desimone, & Ungerleider, 1999; Petersen, Robinson, & Morris, 1987), lateral pulvinar nucleus in the posterior thalamus (e.g., LeBerge & Buchsbaum, 1988; Petersen et al., 1987), and superior colliculus (e.g., Petersen et al., 1987). The locus coeruleus (LC) nuclei constitute the *alerting network* and are located in the tegmentum region of the midbrain above the pons. Neurons of the LC are responsible for regulating the sleep–wake cycle and arousal, and may also modulate the sensitivity of sensory nuclei (Waxman & DeGroot, 1995).

The ANT and similar “flanker” (referring to the stimulus display) tests of covert orienting yielded valid and reliable results in normal individuals ages 4 through adulthood (Akhtar & Enns, 1989; Enns & Cameron, 1987; Fan et al., 2002; Plude, Enns, & Brodeur, 1994; Ridderinkhof, van der Molen, Band, & Bashore, 1997). A graphic version was developed for children that replaced monochromatic arrow stimuli with colorful fish and has been shown to effectively discriminate efficiency of the executive, orienting, and alerting networks of attention in children ages 4 to 12 (Rueda et al., 2004).

ANT target screens display either a single fish, or a row of five fish that includes a central target fish and two flanker fish on each side. Flanker displays may be con-

gruent (all fish pointing in the same direction) or incongruent (central fish pointing in the opposite direction as flanker fish). Each target screen is preceded by one of four cue conditions: no cue, central cue, double cue, or correct location cue. The paradigm thus includes a total of 12 possible display screens (3 stimuli \times 4 cue conditions). The speed and angle of stimuli presentation allow only covert shifts of visual attention. The child's goal in the ANT is to indicate the direction of each central fish by pressing a right or left mouse button. RT is recorded for each trial and the means of median RTs are used for all network calculations. Executive network score is the incongruent RT – congruent RT. Orienting Network score is the center cue RT – correct spatial cue RT. Alerting network score is the no-cue RT – double cue RT.

Based on previous reports of ANT performance in other populations of school-age children (see earlier), we predicted that the ANT would discriminate executive, orienting, and alerting networks of attention in 22q11 DS children. Neurocognitive studies have suggested impairment in executive visual attention and we hypothesized that compared with control siblings 22q11 DS children would have significantly larger (less efficient) executive network scores.

METHOD

Participants

We present cross-sectional data from 52 children ages 5.0 to 11.5; 32 22q11 DS children, whose deletions were confirmed prior to study enrollment via fluorescence in situ hybridization (19 girls, M age = 7.6, SD = 1.6); and 20 control siblings (13 girls, M age = 8.3, SD = 2.0) without history of learning disability, neuropsychological impairment, neurologic disorder, or psychiatric disorder. Only one control sibling per family was included in these analyses. When these analyses were conducted, 69 children ages 5.0 to 14.9 had been administered the child ANT including 45 children with 22q11 DS and 24 control siblings. A gap in the age distribution of children with 22q11 DS occurred between ages 11.5 and 12.8. To control for developmental effects only children ages 5 through 11 were included, resulting in the exclusion of the 6 oldest children ages 12.8 to 14.9. Additionally, 7 of 45 (16%) of the 22q11 DS children, including five 5-year-olds and two 6-year-olds; and 1 of 24 (4%) of the normal control siblings (age 5) refused to complete the task. Additionally neuropsychological test results (two or more NEPSY subtests more than 1 SD below standardization sample mean) and parent corroboration of current learning difficulties for 3 of 24 (13%) control siblings resulted in their exclusion from these analyses. Sample composition issues and statistical power will be considered in the Discussion section.

Apparatus and Stimuli

The ANT was created with the E-Prime commercial application program and was loaded onto an IBM-compatible laptop computer running Microsoft Windows 95. The task was presented on a Vivitron 14" SVGA monitor. Responses were made on a symmetrical 5V 20mA – 2¼" Microsoft Basic Mouse 3.0 PS/2. The stimuli were bright yellow fish with black arrow-like gills pointing in the direction that the fish was facing and shown against a blue background. Single fish were placed at a .55° of visual angle and the contours of adjacent fish were separated by .06° of visual angle. Central fish plus four flanker fish consisted of a total 3.08° visual angle. The stimuli were presented either 1.06° above, 1.06° below, or at the point of central fixation. One session of the ANT consisted of 24 practice trials and 144 test trials and required approximately 20 min to complete. Test trials were divided into three blocks, each consisting of 48 randomly distributed trials, 4 each of 12 possible conditions (3 cue conditions × 4 flanker conditions). One trial of the ANT consisted of the presentation of five consecutive screens within approximately 4 sec: Screen 1, central cross (400 msec); Screen 2, cue or no cue condition (100 msec); Screen 3, central fixation cross (400 msec); Screen 4, target (required RT < 1700 msec); Screen 5, central fixation cross (3500 msec – RT of Screen 4). Children were allowed 1.7 sec to respond after which the nonresponse was recorded as a missing trial. A correct response resulted in auditory ("Woohoo!") and visual (bubbles coming from fish's mouth) feedback lasting approximately 3 sec.

Procedure

Participants were seated approximately 60 cm from the display screen and were instructed to indicate the direction of the central fish by pressing either the left or the right mouse button. The experimenter demonstrated how to hold the mouse and children were instructed to leave their hands in the same position for the duration of each block. The experimenter sat with each child through the practice trials to ensure that the child understood the instructions. After the practice trials, the experimenter sat out of the child's peripheral vision. Deviations in hand position were corrected as needed during the test sessions. If the child became distracted the experimenter would redirect the child's attention by repeating the basic task instruction. All sessions were completed before 1 p.m. to control for circadian effects.

RESULTS

Data were entered into a Statview database and analyzed using Statview/PC and SAS/PC Version 6.0. The means of median RTs for left- (783.91, *SE* = 38.71) and right-facing (772.24, *SE* = 31.39) stimuli and for upper (793.12, *SE* = 32.21) and

lower (781.38, *SE* = 30.20) positioned stimuli were compared and did not differ. In all subsequent analyses the median RTs from these trial types were combined. Table 1 gives the median RT, accuracy, and missed trial means for group by condition.

Flanker and Cue Effects

Analyses of variance (ANOVAs) were used to examine the internal validity of the child ANT for this population by determining whether flanker type and cue condition independently influenced RTs for 22q11 DS children and their control siblings (Table 2). ANOVAs were calculated for each group separately for comparison to previous reports. Only main effects were significant for both groups of children. For both groups Fisher’s Post Hoc Least Squares Difference (PLSD) indicated that the flanker effect was attributable to RT differences in neutral versus incongruent, and congruent versus incongruent conditions (*p* < .01 for both differences). The cue effect was attributable to RT differences in the no cue versus double cue, and no cue versus spatial cue conditions (*p* < .01 for both differences).

An ANOVA was also used to examine the influence of flanker and cue types on response accuracy (Table 3) and on number of missed trials (Table 4). Response accuracy was the percentage of trials for which the correct button was pressed. Flanker type was associated with lowered accuracy only among 22q11 DS chil-

TABLE 1
Median Response Time, Accuracy, and Missing Rate Means for 22q11 DS Children and Control Siblings

<i>Cue Condition</i>	<i>Flanker Type</i>					
	<i>22q11 DS</i>			<i>Control Siblings</i>		
	<i>None</i>	<i>Congruent</i>	<i>Incongruent</i>	<i>None</i>	<i>Congruent</i>	<i>Incongruent</i>
Median response times						
No cue	873.0	820.2	950.9	776.9	798.7	899.6
Center cue	798.1	799.8	923.0	731.4	724.3	844.3
Double cue	733.8	790.8	891.2	697.5	726.8	813.4
Spatial cue	740.9	760.7	901.0	671.3	712.3	759.7
Accuracy						
No cue	(.88)	(.86)	(.71)	(.95)	(.92)	(.90)
Center cue	(.88)	(.90)	(.78)	(.95)	(.97)	(.93)
Double cue	(.89)	(.86)	(.75)	(.94)	(.95)	(.93)
Spatial cue	(.91)	(.89)	(.78)	(.95)	(.96)	(.93)
Missed trials						
No cue	(.07)	(.07)	(.12)	(.03)	(.05)	(.03)
Center cue	(.06)	(.05)	(.08)	(.02)	(.03)	(.03)
Double cue	(.04)	(.07)	(.07)	(.02)	(.03)	(.03)
Spatial cue	(.04)	(.07)	(.09)	(.02)	(.01)	(.03)

TABLE 2
Analysis of Variance for Means of Median Response Time

Source	df	F	h	p
22q11 DS children				
Flanker type	2	17.59**	.29	< .000
Cue type	3	3.43*	.16	.017
Flanker × Cue	6	.52	.09	.790
S within-group error	372	(39127.7)		
Control siblings				
Flanker type	2	9.07**	.26	.000
Cue type	3	4.34**	.22	.005
Flanker × Cue	6	.18	.06	.983
S within-group error	228	(30021.4)		

Note. Values in parentheses represent mean square errors. S = subjects.

* $p < .05$. ** $p \leq .01$.

TABLE 3
Analysis of Variance for Mean Accuracy

Source	df	F	h	p
22q11 DS children				
Flanker type	2	19.04*	.30	< .000
Cue type	3	.89	.08	.444
Flanker × Cue	6	.23	.06	.968
S within-group error	372	(.038)		
Control siblings				
Flanker type	2	1.65	.12	.195
Cue type	3	.87	.10	.457
Flanker × Cue	6	.44	.10	.855
S within-group error	228	(.009)		

Note. Values in parentheses represent mean square errors. S = subjects.

* $p \leq .01$.

dren and Fisher's PLSD indicated that lower accuracy on incongruent trials accounted for this result with significant differences between neutral and incongruent, and between congruent and incongruent flanker conditions ($p < .01$ for both differences). Missing trials represented the number of trials for which no response was made within 1.7 sec of the stimuli screen (in which case the screen returned to the central cross and a new trial was begun). Flanker type was associated with an increased number of missing trials only among 22q11 DS children, with significant differences accounted for by more missed trials in the incongruent flanker condition. Fisher's PLSD showed significant differences in missed trials between neutral and incongruent flanker conditions ($p < .01$).

TABLE 4
Analysis of Variance for Mean Missed Trials

Source	df	F	h	p
22q11 DS children				
Flanker type	2	3.22*	.12	.041
Cue type	3	.90	.08	.442
Flanker × Cue	6	.38	.08	.894
S within-group error	372	(.015)		
Control siblings				
Flanker type	2	.54	.07	.585
Cue type	3	1.52	.14	.210
Flanker × Cue	6	.33	.10	.919
S within-group error	228	(.003)		

Note. Values in parentheses represent mean square errors. S = subjects.

* $p < .05$.

Comparison of Network Efficiency

A two-tailed unpaired *t* test was used to test whether median executive network scores of 22q11 DS children were larger (less efficient) than those of control siblings. Executive network scores of 22q11 DS children were significantly larger than those of control siblings: *M* difference = 35.0, $t(50) = 2.03$, $p = .041$; sibling *M* = 88.73, *SD* = 47.72; 22q11 *M* = 123.70, *SD* = 67.10. The standard deviation differences between the samples were noted, however an *F* test of the variance ratio, although large, was not significant (var ratio $f = .506$, num/den $df = 19/31$, $p = .11$). Secondary analyses were used to examine possible differences in orienting and alerting network scores and in accuracy and number of missed trials. Orienting, alerting, and overall RT median means did not differ (orienting *M* difference = 12.79, $t = .72$; sibling *M* = 52.25, *SD* = 54.24; 22q11 *M* = 39.46, *SD* = 67.22; alerting *M* difference = 3.02, $t = .15$; sibling *M* = 79.14, *SD* = 52.01; 22q11 *M* = 76.13, *SD* = 78.74). However children with 22q11 DS were significantly less accurate than control siblings: *M* difference = .10, $t(50) = 2.55$, $p = .014$; sibling *M* = .94, *SD* = .07; 22q11 *M* = .84, *SD* = .17. Results from the preliminary ANOVAs indicated that incongruent (executive) trials accounted for lapses in accuracy as well as number of missed trials among only the children with 22q11 DS. Together these findings may reflect greater difficulty experienced by 22q11 children on incongruent trial conditions.

Associations Among Networks and With RT, Accuracy, and Missing Trials

Correlations among networks would suggest a lack of functional segregation among them. To examine the possible interdependence of networks as measured

by the ANT, executive, orienting, and alerting network scores were correlated. Network score associations with RT, accuracy, and missed trials were also examined (Table 5). Network scores were not correlated in either group of children. In only the 22q11 children the larger (less efficient) the executive network score the slower the RT and the lower the accuracy. In both groups of children slower RT was associated with less accuracy and with more missed trials. Thus longer RT did not enhance the accuracy of the slower responders. Lower accuracy was also associated with a greater number of missed trials in both groups of children although overall, control siblings missed an average of 3% of trials as compared to 7% missed by 22q11 DS children.

DISCUSSION

A total of 52 children between the ages of 5.0 and 11.5 completed the child ANT including 32 with 22q11 DS and 20 control siblings without a history of learning disabilities, neuropsychological impairment, neurologic illness, or psychiatric illness. Based on past findings of impaired visual executive attention on neuropsychological and neurocognitive tests we predicted that executive network scores would be less efficient (larger) among children with 22q11 DS as compared to sibling controls.

Flanker tests of covert orienting are well-known in the infant (e.g., Clohessy et al., 2001), child (e.g., Wainwright & Bryson, 2002), and adult literature (e.g.,

TABLE 5
Intercorrelations Between Attention Network Scores, Reponse Time,
Accuracy, and Missing Trials

<i>Index</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>
22q11 DS						
1. Executive	—	.011	-.052	.440*	-.452*	.367
2. Orienting		—	-.132	.202	-.091	.358
3. Alerting			—	-.019	.026	-.102
4. Median response time				—	-.478*	.680*
5. Mean accuracy					—	-.739*
6. Mean missed						—
Control siblings						
1. Executive	—	-.019	.020	.259	-.245	.181
2. Orienting		—	.086	-.234	-.075	.090
3. Alerting			—	.254	-.286	.244
4. Median response time				—	-.655*	.676*
5. Mean accuracy					—	-.953*
6. Mean missed						—

* $p \leq .01$.

Berlucchi, Chelazzi, & Tassinari, 2000), but fewer studies have been published to date reporting on the child ANT (Fan et al., 2002). In our affected (22q11) and unaffected (sibling) groups we found significant and independent effects of both flanker type and cue type, suggesting that the child ANT is an internally valid measure of covert orienting in both populations.

Based on past neurocognitive and neuropsychological studies we predicted that 22q11 children would have larger (less efficient) executive network scores as compared with sibling controls. This hypothesis was supported. Further, significantly increased error and missing rates on only incongruent trials among only 22q11 DS children, and the large correlation found between executive network score and accuracy appeared to substantiate that 22q11 DS children had greater difficulty with incongruent trials as compared to sibling controls. At the same time, the standard deviation for executive network scores of only 22q11 DS children was large, weakening the result, but perhaps also indicating a meaningful aspect of their performance, requiring examination in future studies. For example, devising a statistical strategy for characterizing types of RT variability may be an important addition to ANT analyses in attention-impaired populations. Methodologically, the child ANT imposes an RT limit. For this and other attention-impaired populations, using a version of the ANT with no time limit might decrease the number of missing and inaccurate (incongruent) trials, increase the total number of trials included and, perhaps, reduce sample error.

Prior to the suggestion of visual executive attention impairment in 22q11 DS children, specific deficits in visual spatial memory (dot location) were reported and were the basis for suggesting that the cognitive deficits of 22q11 DS children might be attributable to right temporal-parietal hemispheric abnormalities, perhaps the result of anomalous neural crest migration (Bearden et al., 2001). Parietal lobe function has been associated with orienting network efficiency. If parietal abnormalities were typical of 22q11 DS children, deficits in orienting might have been expected, but this was not the case. A separate study is needed to directly examine orienting network efficiency and visual spatial memory in 22q11 DS children.

Why 22q11 DS children should be deficient in executive network efficiency might be explained by considering the specific genes that are deleted in this syndrome. Executive network efficiency is associated with activation in the anterior cingulate, a region linked to basal ganglia structures via a well-defined striato-cortical circuit loop—one of four connecting basal ganglia structures to segregated cortical regions (Alexander et al., 1986). The mesolimbic dopamine cell group originating in the ventral tegmentum innervates the anterior cingulate. Direct innervation of and limbic-loop feedback to the anterior cingulate cortex depends primarily on dopamine, glutamate, and GABA pathways (Martin, 1989). Two deleted genes in particular, catechol-O-methyltransferase (COMT) and proline dehydrogenase (PRODH) might be expected to markedly impact these pathways. Nu-

merous studies have demonstrated that COMT is a key modulator of dopaminergic transmission (e.g., Gogos et al., 1998; Napolitano, Cesura, & Da Prada, 1995); PRODH metabolizes proline, and also initiates the conversion of proline to glutamate (S. M. Cohen & Nadler, 1997; Johnson & Roberts, 1984); glutamate is the precursor of GABA; thus lowered proline dehydrogenase may produce downstream reduction of GABA levels as well. A mouse model of PRODH deficient mice has indicated behavioral effects of PRODH imbalance (Gogos et al., 1999). The absence of COMT and PRODH genes in 22q11 DS children may result in dopaminergic, glutamatergic, and GABAergic dysregulation and disruption of the development and regulation of neural pathways so heavily dependent on these neurotransmitters. Executive network inefficiency is only one clue to the many possible neurocognitive effects of these missing genes. Longitudinal developmental studies are necessary to understand the complex neurocognitive profile observed in 22q11 DS children.

Limitations

The extent to which these results are representative should be considered. Fourteen percent (7/49) of the 22q11 children who attempted the ANT did not complete the protocol. All of them became restless within the first block of trials and lacked the motivation to maintain responding to the repetitive stimuli. All of the non-completers were age 6 or below. They were observed to be developmentally immature throughout testing, with poor frustration tolerance, impulsivity, and an unwillingness to tolerate repetition. How they would have scored had they been able to complete the ANT cannot be surmised. For now, these results are likely to be representative of at least 85% of 22q11 DS children.

Of 24 normal control siblings tested, 3 were found to score 1 or more *SD* below the mean on at least two neuropsychological (NEPSY) subtests. When parents were queried, they confirmed learning difficulties in the classroom and teacher concerns, although a learning disability had not been formally diagnosed. This represents 13% of our current sibling control population, approximately two times greater than that estimated in the general population (Centers for Disease Control, 1997-1998). The 22q11 DS was genetically transmitted in only one of our current families (and in an estimated 8% of families in the general population; Morrow et al., 1995), providing no obvious explanation why siblings of 22q11 DS children would be at any greater risk for learning disability than children in the general population. The cognitive status of siblings of 22q11 DS children has not been reported in the literature to date, but sibling studies in other chronically ill populations suggest that learning problems can be secondary to adjustment issues. Although a majority are not at higher risk (Gallo, Breitmayer, Knafl, & Zoeller, 1992), a minority of siblings can develop problems with mood, underachievement, or self-esteem (Faux, 1992; Gallo, Breitmayer, Knafl, & Zoeller, 1991; Thibodeau,

1988). Implicit compensatory demands for excellence from unaffected siblings of average ability can also create debilitating pressure. These are all possibilities that require further exploration in the siblings of 22q11 DS children. Because we are attempting to define the learning disability and neurocognitive profile of 22q11 DS children, we have chosen to screen from our analyses controls with neuropsychological test scores in the impaired range, but we maintain their data for future analyses and consideration. The analyses presented here include controls with no suspected neurocognitive deficits at the time of their testing.

We included in these analyses the maximum number of children available. A post hoc power analysis was conducted using the means, standard deviations, and cell sizes from our primary analysis comparing executive network scores of 22q11 DS children and control siblings. Power was found to be .70, which is acceptable but not optimal. Whether the results will be maintained in a larger sample remains to be seen.

This population currently includes only White children and the applicability of our findings to children of other racial backgrounds may be limited.

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