6 Cognitive and Behavioral Characteristics of Children with Chromosome 22q11.2 Deletion Syndrome

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Enhancing Early Identification

In this initial section we will present information with the aim of increasing early identification of the chromosome 22q11.2 deletion syndrome. We will begin with a definition of the syndrome and its nomenclature and the current best estimates of its incidence. We then discuss some of the features that have the highest specificity or sensitivity for detection of the syndrome, both in terms of physical manifestations and behavioral or psychiatric disorders. We will then briefly discuss similar disorders that might be confused with or diagnosed instead of the chromosome 22q11.2 deletion syndrome. Finally, we will describe two diagnostic cases that together illustrate the range or variability of signs and symptoms that need to be considered when identifying this disorder

Definition

The chromosome 22q11.2 deletion syndrome (hereafter DS22q11.2) is considered to be the most common microdeletion syndrome known in humans (Botto et al., 2003). The syndrome was described clinically by Angelo DiGeorge during the 1960s and by Robert Shprintzen during the 1970s (Kirkpatrick & DiGeorge, 1968; Shprintzen et al., 1978). The DiGeorge syndrome was defined as being composed of immunologic deficiencies secondary to thymus hypoplasia, hypocalcemia secondary to hypoparathyroidism, and congenital cardiac anomalies (Kirkpatrick & DiGeorge, 1968). The Shprintzen syndrome, later renamed velocardiofacial syndrome (VCFS), expresses major features that are suggested by its acronym and include palate anomalies (''velo''), congenital cardiovascular defects (''cardio'') and mild facial dysmorphism (''facial''; Shprintzen et al., 1978). In the early 1990s it was discovered that both the DiGeorge syndrome and VCFS were caused by a microdeletion in the long (q) arm of chromosome 22 at band 22q11.2 (Carey et al., 1992; Driscoll, Budarf, & Emanuel, 1992; Driscoll, Spinner et al., 1992). This region is depicted in figure 6.1. Since then, the clinical diagnosis of DS22q11.2 has been verified by a cytogenetic

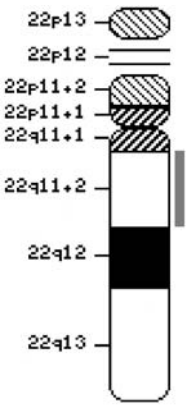

Figure 6.1
Ideogram of chromosome 22 and the deleted region of q11.22. From National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov).

test called "fluorescence in situ hybridization" (FISH; Driscoll et al., 1993). An example of the results of such a test is depicted in figure 6.2. It has also been established that, besides the above-mentioned signs and symptoms, the phenotypic spectrum of DS22q11.2 is extremely wide and includes over 180 possible congenital anomalies, learning disabilities, and psychiatric manifestations (Shprintzen, 2000). It is now widely recognized that several other previously identified syndromes also result from chromosome 22q11 deletions, including conotruncal anomaly face syndrome (Burn et al., 1993) and some cases of Cayler cardiofacial syndrome (Giannotti, Digilio, Marino, Mingarelli, & Dallapiccola, 1994) and Opitz G/BBB syndrome (McDonald-McGinn et al., 1995). This has led to some confusion about what label to use for cases in which the deletion is detected (e.g., see Wulfsberg, Leana-Cox, & Neri, 1996). Therefore, we shall adopt the most inclusive term of "chromosome 22q11.2 deletion syndrome."

Incidence

The exact incidence of DS22q11.2 is not known at this time. This is because exact incidence can be determined only if all infants born are screened for the deletion. As the FISH test is expensive, such a population-based screening would be too costly. Thus, currently there are only minimum incidence estimates based on cases referred to cardiologic clinics, genetic clinics, or registries of congenital defects. Based on studies of various ethnic backgrounds, the minimum incidence of DS22q11.2 is between 1 in 5,900 and 1 in 9,700 live births (for a review, see Botto et al., 2003). The actual incidence of DS22q11.2 is probably much higher, as the phenotypic expression of the syndrome is frequently mild and can be easily missed. In addition, cases are

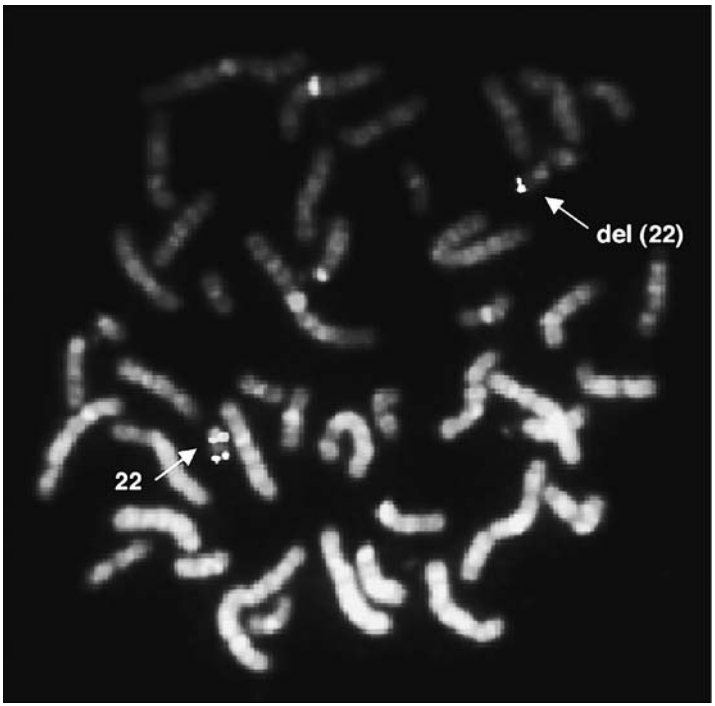

Figure 6.2
Image of fluorescence in situ hybridization test of one copy of chromosome with deleted (del) region.

missed because most clinicians are not aware of the full spectrum of the syndrome's manifestations.

In our view, a good way to efficiently increase the rate of diagnosis of DS22q11.2 is to emphasize the signs and symptoms that have high specificity and/or sensitivity for the diagnosis of the syndrome. In this light, we will now describe the physical and psychiatric manifestations of the syndrome followed by examples from two case vignettes. Then we will describe in greater detail the cognitive features of the DS22q11.2 in children and discuss some of the implications for academic achievement.

Physical Manifestations

Table 6.1 summarizes the rate of major physical diseases in the DS22q11.2 population and the rate of the chromosome 22q11.2 deletion found in all cases with the specified disease. As can be seen in table 6.1, the likelihood of the disease's being part of DS22q11.2 is dependent on its specific type. For example, the types of cardiovascular anomalies listed in table 6.1 are highly associated with DS22q11.2. Other

Table 6.1
Prevalence of characteristic physical signs and symptoms in chromosome 22q11.2 deletion syndrome (DS22q11.2) and prevalence of DS22q11.2 in these conditions

Physical Disease	% of Cases in All Individuals with DS22q11.2	% of DS22q11.2 within All Cases of Specified Disease
Cardiovascular anomalies	75	very low[a]
Tetralogy of Fallot	15–35	10–15
Ventricular septal defect with pulmonary atresia	15–30	20–50
Persistent truncus arteriosus	5–10	30–35
Interrupted aortic arch type B	5–20	60–80
Palatal anomalies	40–75	0–8
Overt cleft palate	10	
Bifid uvula	5	
Submucosal cleft palate	15	
Velopharyngeal insufficiency	30	
Facial dysmorphism	75	very low[a]
Hypocalcemia	10–30	very low[a]

[a] To the best of our knowledge was not tested.

cardiovascular anomalies, like the atrial septal defect and the transposition of great vessels are far less common in DS22q11.2 (Marino, Mileto, Digilio, Carotti, & Di Donato, 2005). The palatal anomalies are manifested in hypernasal speech. It is important to remember that in most cases the palate anomaly is not overt and can only be detected by a nasendoscopic evaluation (Shprintzen & Golding-Kushner, 1989). As mentioned previously, DS22q11.2 can affect many of the body's organs, such as the eyes, ears, limbs, and kidneys. One of the most common manifestations is the characteristic but subtle facial appearance. This can include increased vertical length of the face, even at early ages, nasal changes such as increased height and bulbous nasal tip, hooded upper eyelids, ears that are small, cupped, or overfolded, and retrusion of the lower jaw (McDonald-McGinn et al., 1999; Shprintzen, 2005). It has been reported (C. A. Morris, personal communication) that identification of the syndrome can be significantly increased when any of the above features, or abnormal movement of the palate, in combination with hypernasal speech are used to initiate testing for the deletion. Examples of the craniofacial characteristics of individuals with chromosome 22q11.2 deletions are depicted in figure 6.3. A few diseases, such as the cardiovascular anomalies listed in table 6.1, are very specific to DS22q11.2. However, in most diseases that are a possible manifestation of the syndrome, DS22q11.2 is only rarely present (see table 6.1). Therefore, referring to a FISH test based on a single symptom is probably not very cost effective (Shprintzen, 2000). We recommend testing for DS22q11.2 when two of the major physical signs listed in the table are present because a DS22q11.2 diagnosis in these cases is far more likely.

Figure 6.3
Pictures of four children (and one adult) with chromosome 22q11.2 deletion syndrome.

Psychiatric Disorders

A series of studies has shown that individuals with DS22q11.2 have very high rates of psychiatric morbidity and abnormal behaviors (Arnold, Siegel-Bartelt, Cytrynbaum, Teshima, & Schachar, 2001; Feinstein, Eliez, Blasey, & Reiss, 2002; Fine et al., 2005; Gothelf et al., 2003; Gothelf et al., 2004; Papolos et al., 1996; Prinzie et al., 2002; Shprintzen, 2000; Swillen, Devriendt, Ghesquiere, & Fryns, 2001). Starting from childhood, abnormal behaviors and increased rate of psychiatric disorders are already present in individuals with DS22q11.2. Children with DS22q11.2 tend to be shy, withdrawn, stubborn, emotionally labile, and afflicted with social and communication impairments (Swillen et al., 2001). Children and adolescents with DS22q11.2 have a high rate of nonpsychotic psychiatric disorders, including attention deficit/

hyperactivity disorder (ADHD), oppositional defiant disorder, anxiety and affective disorders, and autism spectrum disorders (Arnold et al., 2001; Feinstein et al., 2002; Fine et al., 2005; Gothelf et al., 2003; Gothelf et al., 2004; Papolos et al., 1996). It seems that most psychiatric disorders found in individuals with DS22q11.2 are also common in individuals with non-DS22q11.2 developmental disabilities. Feinstein et al. (2002) compared the rate of psychiatric disorders in children and adolescents with DS22q11.2 with that of matched IQ controls and found similar rates in both groups for all psychiatric disorders. Swillen et al. (2001) compared parents' and teachers' reports of the behavior of school-age children with DS22q11.2 with reports of matched age and IQ controls with speech and language impairments but without DS22q11.2. The results indicated that both groups exhibited similar degrees of abnormal behaviors. The only differences found were that children with DS22q11.2 were more withdrawn and controls were more aggressive. It is not surprising that children with developmental disabilities have similarly high rates of behavioral problems and psychiatric disorders because they share common risk factors for psychopathology, such as social isolation and rejection, impairments in social and daily living skills, low self-esteem, and overprotectiveness by parents. These factors could predispose them to psychiatric morbidity. Other factors include general CNS functional differences, executive function and other cognitive impairments, and we shall discuss those below.

During late adolescence and early adulthood, about 25% of individuals with DS22q11.2 develop schizophrenia-like psychotic disorders (Bassett et al., 2003; Bassett et al., 1998; Murphy, Jones, & Owen, 1999; Pulver et al., 1994). The clinical characteristics of the DS22q11.2 psychotic disorder are similar to those of non-DS22q11.2 schizophrenia patients. Higher rates of chromosome 22q11.2 deletions were found in children and adults with schizophrenia (Karayiorgou et al., 1995). This rate is especially high in schizophrenia patients with one (20%; Gothelf et al., 1997) or two (53%; Bassett et al., 1998) major physical symptoms of DS22q11.2. The strong association between DS22q11.2 and schizophrenia-like psychosis does indeed seem to be specific because the rate of schizophrenia in DS22q11.2 is about 25 times more common than in the general population and about 10 times more common than in individuals with developmental disabilities (Turner, 1989).

Infants and toddlers who suffer from severe physical diseases are usually identified by clinicians and referred for genetic testing at infancy and during the preschool years. Those children who are only mildly physically affected are easily missed, and only those that manifest marked cognitive limitations and psychiatric disorders, especially schizophrenia, are referred for genetic testing during adolescence or even adulthood.

Case 6.1—Diagnosis at preschool: Yagil Yagil was born to healthy parents after an uneventful pregnancy and labor. A few hours after the delivery, he became cyanotic and required mechanical respiration. Echocardiography demonstrated ventricular septal defect and interrupted aortic arch type B. At the age of 6 days he underwent cardiac corrective surgery. During the surgery, it was noticed that Yagil did not have any thymus tissue. After surgery, Yagil had seizures due to severe hypocalcemia. At that stage, the diagnosis of DS22q11.2 was suspected and Yagil was referred to a FISH test that confirmed the diagnosis. In addition to the aforementioned medical problems, he also suffered from recurrent ear and pulmonary infections during the first 2 years of life due to low IgG2 levels. He also had surgical repair of an inguinal hernia. On the Bayley developmental test, his development was delayed both on the mental and motor scales. He started walking at 19 months, produced his first words at 22 months, and was not yet toilet trained at the age of 4 years. His speech is hypernasal and difficult to comprehend due to occult submucous cleft palate, and his language is delayed for his age. Yagil's parents report that Yagil is stubborn and is very shy with people who are not part of his family.

Yagil is an example of a child with DS22q11.2 who is severely affected. The classical medical problems associated with the disease were manifested since infancy, including typical cardiovascular anomalies, hypocalcaemia, and recurrent infections. He also had an inguinal hernia; global developmental delays with significant speech delays; and shy, stubborn behavior, and although these findings are common in DS22q11.2, they are not specific to the syndrome.

Case 6.2—Diagnosis at adolescence: Zoe Zoe, a 17-year-old female, was hospitalized at a psychiatric inpatient unit after threatening to commit suicide and becoming physically violent toward her parents. On psychiatric evaluation, she reported delusions of reference, thinking that her classmate and even strangers in the street were saying "nasty things" about her. She also reported that figures from the TV were telling her how ugly she was. Zoe also reported that she heard voices telling her to commit suicide, and her parents noted that she was talking to herself loudly as if arguing with someone. The psychiatrist diagnosed Zoe with schizoaffective disorder, depressive type.

Zoe is otherwise a relatively physically healthy adolescent. She was born with mild ventricular septal defect (VSD) that closed spontaneously. Her attainment of developmental milestones was slightly delayed but within the normal range, and she had mild hypotonia as a young child. Her speech was mildly hypernasal. At elementary school, she had difficulties with mathematics and reading comprehension. Cognitive testing showed that Zoe's IQ score was 78. At elementary school, Zoe was also diagnosed with ADHD inattentive type and suffered from anxiety disorders. She used to cling to her parents and refused to go on a trip or to visit friends without being accompanied by her parents. At the age of 12 years, she also started having compulsions in which she repetitively touched her eye to make sure she would not develop strabismus and she compulsively hoarded paper, magazines, and advertisements and would not let anyone touch the collection. The combination of her psychiatric symptoms with a history of ventricular septal defect, hypernasal speech, and mild dysmorphic facial features raised her psychiatrist's suspicion that Zoe might have DS22q11.2. Zoe was referred for a FISH test, and the result was positive for the 22q11.2 deletion.

Zoe is an example of a physically healthy child with mild developmental delay but with severe psychiatric symptomatology. Zoe's psychiatric disorders were first noticed in elementary school and gradually escalated. Initially, ADHD developed, followed by separation anxiety disorder and obsessive–compulsive disorder (OCD), culminating at the age of 17 years with a psychotic disorder. Since Zoe's physical symptoms were very mild and included only a VSD and hypernasal speech, her diagnosis could have been easily missed. Of the myriad psychiatric symptoms that Zoe had, the schizophrenia-like symptoms were the ones that were relatively specific to DS22q11.2. Thus, it was the combination of psychotic symptoms, the few physical symptoms characteristic of the syndrome, and the borderline intelligence that raised the clinical suspicion that Zoe may be affected with DS22q11.2.

Cognitive and Academic Manifestations

In the following section we review the main findings concerning the manner in which the DS22q11.2 phenotype is expressed in terms of mental functioning. Having dealt above with psychiatric issues, we will focus here on the implications of DS22q11.2 for a child's ability to process information relating to everyday cognitive tasks and to specific academic domains like reading or arithmetic. Since the focus of this volume is on how the phenotypes of neurogenetic developmental disorders are expressed in children, we will include very little data gathered from adults with DS22q11.2. Also, given the increasing variety of research methods that are being used in the study of genotype/phenotype relationships of individuals with neurogenetic disorders, especially with respect to biobehavioral implications, we thought it valuable to initially make some distinctions between the types of data we will review, the means by which they were collected, and the interpretive strengths or weaknesses of each approach.

The majority of investigations concerning the cognitive and behavioral profiles of individuals with DS2211.2 have been carried out with two complementary sets of tools, namely, neuropsychological testing and cognitive experimentation. We will briefly review the characteristics of these two approaches and will then discuss in more detail the overall pattern of results that each has generated so far.

The most extensive set of results so far has resulted from neuropsychological testing studies. Here, a collection, or "battery," of standardized neuropsychological tests is designed in order to generate a broad profile of the individual's abilities. Tests are usually focused on the intellectual, academic, and behavioral domains. The tests used are referred to as "standardized" because large numbers of individuals have had the tests administered to them by testers trained to present and interpret them in a reliable fashion. Standardized tests also have their scores transformed from the actual

score achieved by the individual to a score that represents that individual's competence with respect to the general population of the same chronological age. This yields a measure of "mental age" for the domain in question using "norms," which are the average scores of a large number of individuals at specific ages from a given population (usually typically developing). In this way, each individual can be scored within a percentile range so that his or her abilities on the test can be compared both *between* individuals, that is, to the normed population to determine relative advantage or disadvantage in that domain, and *within* the individual to determine domains of particular strength or weaknesses that exist.

Because of this standardization, results from neuropsychological testing studies have the advantage of being interpretable by a range of professionals, including teachers and educational psychologists, and they are often used to form the basis for an individualized educational or other remediation program for the individual concerned. They also have the advantage of being able to produce such results in a broad range of domains from a single testing session of several hours' duration. In this sense they are immensely valuable to parents, support professionals, clinicians, and researchers alike. However, one disadvantage of neuropsychological testing studies, from the perspective of researchers at least, is that they are primarily quantitative and descriptive. Despite being based on theory and evidence, these tests primarily generate what we might term "how well can you do" information. This indicates that an individual may be very good or very bad at a particular task or in a given intellectual domain but cannot directly explain why that profile is observed. By the same token, the behavior measured by such tests has, at best, a rather loose relationship to the underlying cognitive and neurobiological substrates that generate it. In other words, they reveal little about the mental representations being used, the manner in which they are processed, the brain circuits upon which those computations depend, the neurotransmitters involved, and so forth.

By contrast, there is currently only a small number of published research reports based on cognitive experimentation studies. Instead of a test battery, researchers using cognitive experimentation studies develop small sets of experiments, usually in the form of computer-based "games," carefully designed in order to test specific hypotheses about how particular cognitive functions work and the nature of the representations that they process. Results are then interpreted as a test of the hypotheses by determining whether or not the predicted performance patterns were observed. Typically, new, more detailed hypotheses emerge from such analyses, further experiments are designed, and the process progresses toward an ever more highly specified explanatory account. Informed mostly by the fields of cognitive psychology and cognitive neuroscience, many individual tests, known as "trials," are generated in order to create related sets, or "conditions," in which predictions of the speed, accuracy,

and characteristics of performance can be made based on hypotheses of how information is processed, which brain circuits are involved, and how these interact.

A simple example would be an experiment that examines the processing required to find a target object (like a letter *O*) in a set of distracting objects (usually other letters). In this "visual search" experiment, the participant is required to press a button as soon as he or she detects a single letter *O* while ignoring the distractor objects, here letter *X*s. There could be an *O* and a single *X* on one trial and an *O* and up to as many as 10 *X*s on other trials. There might be 10 such examples of each trial, whose results can be averaged together to ensure that no single unusual response is taken as the performance capabilities of the individual. These 100 trials would constitute a condition that would be called "disjunctive search." The label reflects the fact that there are no features (like shape, angle, size, or even meaning) shared by the letters *O* and *X*. It has been shown in such experiments that the targets and distractors can be detected rather independently by the visual and attention systems of the human brain. Thus, we would predict, based on existing knowledge, that detection of the *O* would be fast, that it would be accurate, and that the time taken would be little affected by the number of *X*s. The *O* almost appears to "pop out" of the field of *X*s and so requires no real search on the part of the participant's visual and attention systems. Another condition, referred to as "conjunctive search," would also have 100 trials with 10 examples each of a single *O* but now placed among 1 to 10 letter *Q*s. This condition would be called "conjunctive search" since the letters *O* and *Q* share, or contain "conjunctions" of, many features. We would predict not only that detection would be slower and less accurate but that the time taken to find the *O* would be directly related to the number of distractors (*Q*s) in the display. This is because cognitive studies have revealed the different kinds of search patterns that take place in pop-out and conjunctive search conditions. Here the participant would need to examine each letter in turn, try to decide if it is an *O* or a *Q*, and respond when the target is found. Given that a good deal is known, at least in adults at present, about which brain circuits are involved in these processes, we might also predict that individuals with known disorders to those circuits would do more poorly under certain conditions, like conjunctive search. We might also infer that should one type of performance be much worse than is usually expected, or much worse than that of a group of comparison participants in the experiment, then the circuits concerned may be expected to be dysfunctional.

Because of the knowledge required to design and interpret results from cognitive experimentation studies, they are not easily interpretable by many professionals besides the researchers themselves and so cannot immediately be used to form the basis of remedial programs in the way that neuropsychological testing results can. Furthermore, because of the complexity involved in developing and interpreting cognitive experimentation studies, they typically only produce such results in a narrow range

of domains but they do so in great detail. Their main strength, however, is that they are primarily explanatory and generate what we might term "how did you do it" information. By focusing on the mental representations being used, the manner in which they are processed, and the hypothesized brain circuits and neurotransmitters upon which those computations depend, they can generate a great deal of precise qualitative information about which mental computations were involved in producing the observed behavior. This can then be used to form the basis of detailed explanations for observed behavior and so should provide critical information for the design of specific cognitive processing interventions that potentially could change the way in the which the mind and the brain work together.

However, overly simple mappings from brain structure to cognitive function should be avoided in general—and when one is considering development, especially atypical development, they are particularly dangerous. As pointed out by Johnson et al. (Johnson, Halit, Grice, & Karmiloff-Smith, 2002), since brain development is a process of the incremental tuning and specialization of multiple areas connected as circuits, assumptions about functional impairment based on changes to single regions are likely to be inaccurate. Furthermore, due to this interactive process and the converging roles of genetics, brain activity, and environmental input, functional circuits are certain to change during development, and so any assumptions about the stability of a structure–function mapping would also be unwise when one is studying childhood. Finally, that interaction also means that brain change is being affected in a bidirectional manner, with circuitry influencing the behavioral repertoire and the behaviors influencing the changing nature of the connections.

Below we will review what has been and continues to be learned from neuropsychological testing studies of DS22q11.2 and then will review recent results emerging from cognitive experimentation studies. Then we will briefly review the current knowledge about possible relationships between those findings and changes in the brains of individuals with DS22q11.2 and also in some relevant genes. Because of the broad and descriptive capabilities neuropsychological testing studies offer, they have been able to provide a profile of both strengths and weaknesses. In contrast, the limited number of cognitive experimentation studies carried out so far has tended to focus on attempting to explain the nature of the impairments exhibited by children with DS22q11.2 in a small range of cognitive processing domains.

Overview and Typicality of Neuropsychological Profile

While the goal of this section is to focus on areas of *relative* strength and weakness, it is fairly clear that the global intellectual profile of children with DS22q11.2 is one of weakness relative to the level expected based on chronological age. On general intelligence measures, Verbal IQ (VIQ) at around 75–80, is typically higher than Performance (nonverbal) IQ, at around 70–75, and is often a little higher than Full Scale

IQ (FSIQ), although even this pattern is not universal (see Moss et al., 1999). Shprintzen (2000) suggested that overall competence appeared to drop from IQ scores in the mid 80s when preschoolers were tested to the mid 70s in the early school years. The former scores were measured using the Leiter and Stanford Binet tests while the latter came from the Wechsler tests. Shprintzen suggested that this change might be less a factor of increasing developmental delay than a factor of the differences in the tests, which focus increasingly on abstract learning for older children. Gerdes, Solot, Wang, McDonald-McGinn, and Zackai (2001) assessed 112 children under the age of 6 years using the Bayley scale (Bayley, 1969) and Wechsler Preschool and Primary Scale of Intelligence—Revised. They reported that, in this preschool group, 34% were assessed in the average range with FSIQ scores in the >85 range, 32% were in the mildly delayed range (FSIQ = 70–84), and 33% were in the significantly delayed range (FSIQ < 70). Thus, the pattern is more likely one of considerable variability, even early in life, with less complex areas of cognition showing relative strength initially. We will examine the overall pattern in more detail below.

By the early school years, most children with the deletion are experiencing fewer problems in domains related to language than in nonverbal domains. In one example of many similar reports, Moss and colleagues (1999) found that, in a group of 33 individuals with DS22q11.2, FSIQ was 71.2 ± 12.8 (mean $\pm$ standard deviation), VIQ was 77.5 ± 14.9, and Performance IQ (PIQ) was 69.1 ± 12.0. While it has been pointed out several times (e.g., Campbell & Swillen, 2005; Wang, Woodin, Kreps-Falk, & Moss, 2000) that not every individual with the deletion exhibits exactly the same Verbal IQ higher than PIQ profile, general intellectual performance tends to be around 10–25 points below the "normal" or average value of 100. At least two published reports of case studies, however, have pointed to some alternate patterns of manifestation. One extreme case, reported by Kozma (1998), describes a 22-year-old female with a confirmed chromosome 22q11.2 deletion who had an FSIQ of 13 and language skills of between 1 and 8 months' developmental age. She had also been given a diagnosis of autism at 3 years of age. Whether or not this unusual pattern was due to injury or insult secondary to the chromosome 22q11.2 deletion is unclear. A more extensive report of a 7-year-old boy (Stiers et al., 2005) describes a profile where the FSIQ of 73 revealed no significant differences between verbal and nonverbal subtest performance, an overall lack of visuospatial processing impairments, and some relative strengths in the area of attention and memory span. This pattern appears to be consistent with a minority of the children reported by Wang et al. (see figure 1 in Wang et al., 2000) and suggests that the profile of significantly stronger verbal than nonverbal skills is not specific to or highly diagnostic of DS22q11.2 and that more detailed examination of the cognitive profile, as discussed below, is necessary.

Areas of Relative Strength from Neuropsychological Testing Studies

The cognitive profile of DS22q11.2 has often been described as fitting the profile of a "nonverbal learning disorder" (e.g., Swillen et al., 1999), which suggests that verbal abilities are greater than nonverbal ones. As stated above, in the most general sense this is true of the majority of the population of children with DS22q11.2. However, the story concerning language and communication is a somewhat complex one of both strengths and weaknesses.

Language As stated above, abilities in the verbal domain are typically, but not always, superior to those in the nonverbal domain. Within the verbal domain, receptive language is generally the strongest component (e.g., Moss et al., 1999). However, this pattern is generally true of language learning in general and so may be less an indication of a significant dysfunction in neurocognitive basis of language expression than the manifestation of a typically functioning system that is slow in maturing due to a more global developmental delay. Either or both of these conditions might be true depending on the child in question, and so, clearly, further research is needed in order to examine this question. In one counterexample to the typical pattern (Glaser et al., 2002), stronger expressive than receptive language was found in a group of 27 children and adolescents with DS22q11.2. The authors suggest that the profile was due either to the therapeutic effects of speech therapy on expressive abilities or the progressively handicapping effects of abstract thinking impairments on expressive language abilities that require more abstraction and complexity. However, the age range in their sample was very large and included individuals from as young as 6 to as old as 19 years. There is, of course, considerable change in language abilities during that developmental window. Thus, it is unclear whether the profile would have been the same had they analyzed the youngest and oldest participants separately. Indeed, it might have been the inclusion of the older individuals that produced their reversed pattern, since that is the major difference from the other studies that have reported the more typical pattern of language development. Those studies instead focused on younger children in a smaller age range. Evidence for this interpretation comes from a larger study carried out by Solot et al. (2001) of 79 children with DS22q11.2 in two age ranges: 7 to 66 months and 5.9 to 16.7 years of age. In this study, the preschool children (7–66 months) were analyzed separately from the school-age ones (5–16 years). Solot et al. reported that receptive language scores were significantly higher than expressive scores for the younger children but that the pattern was reversed for the older ones. Some aspects of language and communication, however, are seriously impaired or delayed, and we will examine those below.

Reading and Spelling In a large study (Woodin et al., 2001) of 81 children with DS22q11.2, 50 of whom were school-age (6–17 years), it was reported that broad

reading and spelling abilities were relative strengths at a similar level, both in the low-average range. The findings were slightly different from those in an earlier study (Moss et al., 1999) that included some of the same individuals. In the earlier study, scores for reading comprehension and single-word reading were similar; however, Woodin et al. found that word reading was better developed than was comprehension.

Memory Rote verbal memory, which is the ability to repeat back after a delay a list of verbally presented items, was found to be at the level expected for chronological age, and thus not impaired, in a small study of school-age children (Swillen et al., 1999). In a larger study (Woodin et al., 2001), 50 children with DS2q11.2 ages 6–17 years of age were assessed with a variety of standardized tests of memory. The authors report a remarkable area of strength on tests of memory that required reproduction of lists of unrelated words and of categorically related words (such as those found in a shopping list). In fact 72% of the group scored in the low-average to very superior range despite 62% of the group having scored in the borderline to moderately deficient range on overall IQ scores! As part of a broader study, Wang and colleagues (2000) found that two thirds of a group of 36 children with DS22q11.2 ages 5 to 12 years scored within normal limits on a memory test requiring them to recall lists of numbers. Furthermore, a related study (Bearden et al., 2001) reported similar results for memory of objects made up from everyday shapes. In a small study of 9 children with DS22q11.2, Lajiness-O'Neill et al. (2005) found that, on the standardized Test of Memory and Learning (Reynolds & Kamphaus, 1992), performance on verbal memory tasks was in the low-average range. Unexpectedly, and inconsistently with other studies (e.g., Woodin et al., 2001), they found that performance on memory for stories was the same as that of controls. Also, their delayed recall abilities (which included verbal and nonverbal material) were at the high end of the low-average range, presumably due to the relative strength in verbal memory.

Areas of Relative Weakness from Neuropsychological Testing Studies

Language While some aspects of language do represent an area of relative strength, as described above, there are also aspects of language that are far weaker. Specifically, the relative strength of receptive language reflects a relative weakness in expressive language. In a short-term longitudinal study of four children with DS22q11.2 ages 6 to 30 months, both aspects were found to be impaired by the age of 12 months. The authors concluded that the developmental delay in expressive language was greater than what would be predicted by the overall delays experienced by the children in the study (Scherer, D'Antonio, & Kalbfleisch, 1999). However, the almost total lack of a vocabulary and several restrictions in speech sounds led the authors to conclude that the children with DS22q11.2 "were essentially non-oral through 30

months of age'' (p. 721). Evidence that the receptive/expressive imbalance appears to persist (Gerdes et al., 1999; Moss et al., 1999; Solot et al., 2000) suggests that a specific language problem exists rather than the pattern being due to a simple slowing of typical development where expressive language gradually catches up with receptive abilities. Shprintzen (2000) suggested that the receptive/expressive difference

> demonstrates that speech intelligibility is likely to be at the root of the problem. Expressive language output tends to dramatically increase after four years of age when both speech therapy and surgery have often been applied to resolve the speech disorder. (p. 144)

While there is clear merit to this view, it does not rule out a more ''central'' delay in neurocognitive development related to expressive language, which includes the development of circuits linking the slowly developing frontal lobes and neocerebellum (Diamond, 2000). In fact, Solot et al.'s larger study (Solot et al., 2000) of 53 children with DS22q11.2 ages 7–66 months found a persisting and significant expressive language deficit, and language scores tended to follow the pattern of overall intelligence scores. By 4 years of age, 30% of the sample was still nonverbal or not speaking in sentences.

Reading and Spelling As mentioned above, while spelling and early reading are relative strengths, reading comprehension is considerably impaired in children with DS22q11.2. Woodin et al. (2001) reported that, although broad reading scores were in the low-average range, there was a significant difference between the much better developed word reading skills of children with DS22q11.2 and their much poorer reading comprehension abilities.

Memory In contrast to the surprising strength on rote verbal memory reported by Woodin et al. (2001), their participants with DS22q11.2 showed a significant impairment on a more complex memory task, which involved the delayed recall of story details. Here, performance was in the borderline range (between average and mild ''mental retardation''). The same children also showed considerable weakness on a visual–spatial design memory test that is quite characteristic of their overall visuospatial difficulties. This study involved a larger sample than the one reported on by Wang et al. (2000), where a different test of spatial memory produced below average performance. Another subsample was also evaluated on several other tests, and Bearden et al. (2001) reported a significant discrepancy between the near average scores found on verbal memory tests and significantly lower scores on tests of memory for locations of dots on a grid, a measure of visuospatial memory. Furthermore, the results showed that the difference was due to the nature of the to-be-remembered information, since scores on memory for the shape of objects were similar to those for verbal memory and significantly higher than for those involving the locations of dots. Similar patterns of results where verbal memory was better than visual–spatial

memory using different tests have been reported by other recent studies (Lajiness-O'Neill et al., 2005; Sobin, Kiley-Brabeck, Daniels et al., 2005).

Executive Function and Working Memory Few neuropsychological testing based studies have focused explicitly on executive function. However, Woodin et al. (2001) reported a significant impairment on the B subtest of the Trail Making test on the Wechsler Intelligence Scale for Children (3rd ed; WISC–III) when compared to the A subtest. This task requires the child to find and connect with a pencil line a series of sequentially labeled locations (e.g., A, B, C or 1, 2, 3) that are spatially distributed on the page. The difference between the A and B versions is that the latter adds inhibitory and working memory loads, since children have to not just connect up locations denoted by letters in sequence (e.g., A then B then C) but have to switch between letters and numbers (e.g., A then 1 then B then 2 ...). Working memory, which requires not just storage but also computation of intermediate results or application of rules, was also found by Sobin, Kiley-Brabeck, Daniels et al. (2004, 2005) to be an area of specific impairment.

Attention As measured by neuropsychological testing based studies, attention is a rather broadly defined domain of functioning. As we shall see below in our presentation of results from the Attentional Networks Test (ANT), attention can be decomposed into rather specific types of functions that are deployed in the service of very different goals and that are known, in adults at least, to depend on very different neural circuits. However, neuropsychological testing studies tend to give a rather more general view of attentional function. As discussed elsewhere in this chapter, there is an elevated rate of attention deficit disorders, mainly ADHD, in children with DS22q11.2, but this is a clinical diagnosis and not a specification of which attentional functions are impaired. ADHD diagnoses focus on three domains of symptoms—inattention, motor hyperactivity, and behavioral impulsivity—and so do suggest that certain measurable functions are likely to be worse in affected children than in controls. Consistent with this, Woodin et al. (2001) reported that scores on the Freedom from Distractibility index from the WISC–III test were significantly lower than those on the Verbal Comprehension index in their sample of 50 school-age children with DS22q11.2. Similarly, Sobin, Kiley-Brabeck, Daniels et al. (2005) found that, on the NEPSY (Korkman, Kirk, & Kemp, 1998) Visual Attention subtest, scores for omissions (indicating visual inattention) indicated an area of relative weakness for children with DS2211.2.

Motor Abilities A very common feature of children with DS22q11.2 is low muscle tone, and this can certainly negatively affect gross motor skills. However, some motor skills are better indicators of functioning levels in the neural system than the musculoskeletal system, and those tend to be the ones measured by neuropsychological

testing studies. Tasks that require fine motor manipulation, sequenced actions, reaching for specific targets, and timed actions are particularly good examples. In Sobin, Kiley-Brabeck, Daniels et al.'s (2005) study, several such tests were included. Scores on tests of motor dexterity (Finger Tapping), kinesthetic/tactile awareness (Imitating Hand Positions) and graphomotor control (Visuomotor Precision) from the NEPSY battery were all at least 1 *SD* below average, the criterion used for an area of relative weakness. It is likely that one component of the weak performance on some of these tasks is the particular weakness in visual–spatial tasks that children with DS22q11.2 have.

Summary of Strengths and Weaknesses from Neuropsychological Testing Studies

The pattern revealed by the studies just reviewed is quite consistent, though not to the extent that those with slightly different profiles should not be considered to have DS22q11.2. Verbal abilities are usually stronger than nonverbal, but this is not always the case. Language abilities are strongest in the receptive mode, and the expression of early, concrete concepts and early word reading and spelling are also strong. They are weak in the expressive mode, with many children being essentially nonoral in the early speech years, though expression does improve in later childhood. In contrast to the effective decoding and understanding of individual words in early reading, most children with DS22q11.2 show marked impairments in the integration of patterns and relationships of meanings between words as is necessary in reading comprehension, and this negatively impacts a wide range of academic activities. Children with DS22q11.2 show remarkable strengths in simple verbal memory tasks like storing and retrieving strings of related or unrelated items or even objects. They have significant problems again when the spatial relationships between items have to be remembered and, just as with reading comprehension, when complex semantic sequences or relationships must be remembered in story memory tasks. Executive Function and Attention tests show impairments of several types. One example is for concurrent storage and manipulation of memory items, which is necessary for most working memory tasks and for "applied" tasks like arithmetic or reading comprehension. Another is when rules must be held and used to alter behavior (as in the Trails B task), and another is when suppression or inhibition of irrelevant or distracting information is required. Weaknesses are also found in finely tuned or timed visually guided motor tasks, which is consistent with a general weakness in the visual–spatial domain.

Areas of Relative Weakness from Cognitive Experimentation Studies

As stated earlier, and demonstrated above, neuropsychological testing studies provide us with a broad descriptive profile of both strengths and weaknesses in the

cognitive phenotype of DS22q11.2. They also provide some clue as to the neurocognitive basis of that profile, although they are not able to generate explanations for the level of performance observed. We will turn now to the smaller number of cognitive experimentation studies that have been designed in order to try to explain some of the impairments just described. Necessarily, this complementary approach is much narrower in focus because groups rather than individuals have to be tested. This is because the measures these tests generate are not normed or standardized. Instead, performance measures from groups of individuals are analyzed for patterns of average performance and variability. Well-designed studies, however, reveal the "how it works" information underlying the impairments observed and can be used to generate hypotheses about the neural substrate that might be involved. So far, the focus of these studies has only been on areas of weakness for individuals with DS22q11.2 because the goal has largely been to explain the impairment in the interest of eventually developing remedial interventions. Perhaps the most comprehensive such program of experimental work with the DS22q11.2 population so far has come from studies directed by one of us (Tony J. Simon). The details of many of the studies are described elsewhere (Bish, Ferrante, McDonald-McGinn, Zackai, & Simon, 2005; Simon, Bearden, McDonald-McGinn, & Zackai, 2005; Simon, Bish et al., 2005), and so we will review just the main points here.

The cognitive experimental work in those studies is strongly motivated by a theoretical hypothesis influenced by a great deal of work in cognitive psychology, cognitive neuroscience, and clinical neuropsychology. Most of the preceding results were generated from studies of adults, and so, bearing in mind the caveats about atypical neurocognitive development discussed earlier, we had to be aware that predictions based on our hypothesis would not be likely to exactly match the adult patterns. The organizing principle behind the hypotheses is that relatively complex and varied cognitive abilities or impairments might be explained in terms of the function of a small set of "lower level" broadly applicable functions. These are then "co-opted" by new tasks or problems that are presented during development. In this way, they act as the building blocks for the construction of these higher level processes and abilities. A good example is how basic abilities for the representation of objects can form the foundation for simple numerical abilities (e.g., Simon, 1997). This is because simple comparison, estimation, and counting are, at root, tasks requiring the determination of how many objects exist in a set or in each of several sets. These necessarily involve processes related to the representation of objects and searching among sets of objects or locations, among others. The main hypothesis that emerged from our analyses was that many of the key cognitive nonverbal impairments (and to some extent the behavioral and psychiatric ones also) seen in children with DS22q11.2 are, at their most basic level, due to dysfunctions in various aspects of

the visual attention system. That is because visual attention is involved in searching for and selecting objects and locations (for a more detailed discussion of this, see Simon, Bish et al., 2005). There is now much evidence (e.g., Corbetta, 1998; Posner & Petersen, 1990) from studies with adults that this system seems to depend primarily on neural circuits in the parietal and frontal lobes of the brain (and somewhat on the cerebellum also) that are referred to as the "frontoparietal network." A small amount of much more recent evidence from studies with children (e.g., Bunge, Dudukovic et al., 2002; Rueda, Posner et al., 2004) suggests that this network also supports the same functions in children, though likely not in exactly the same way, to the same extent, or with the same degree of exclusivity as it does in adults. Therefore, we designed experiments to test the ability of 7- to 14-year-old children with DS22q11.2 and typically developing controls to carry out several tasks that we thought should tap into different functions of this network to a greater or lesser degree. We will discuss each of the domains of processing below.

Visual–Spatial Attention Our most basic task was one specifically designed to assess a key function of the attention system, namely, the ability to detect objects in the visual environment in the presence of helpful or confusing cues about their location. This is considered the lowest level task in our set of experiments because it requires little or no conceptual information and most directly taps into the workings of the spatial attention system. In the "Cueing" task children saw a central stimulus (a solid black diamond) on either side of which was a square box. Targets were black-and-white diamond checkerboards appearing inside the boxes, and their appearance was cued by a white triangle appearing within the black diamond, pointing either left or right. A valid cue pointed in the same direction as the subsequent appearance of the target, while an invalid cue pointed in the opposite direction (see figure 6.4 for an example). Neutral cues were white diamonds that almost filled the whole black diamond, thus pointing both ways and providing no location information about the upcoming target. The child's task was to press the left button on a button box when a target was detected on the left and the right button for a target on the right (for full task details see Simon, Bearden et al., 2005). Most of the cues correctly predicted the

Figure 6.4
Example of stimuli from Cueing task showing valid cue (left-pointing white triangle in center diamond) and checkerboard target on left.

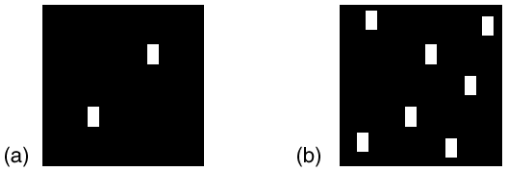

Figure 6.5
Example stimuli from enumeration task for (a) small (subitizing range) and (b) large (counting range) set sizes. (Actual stimuli were green squares on red background.)

target's location, but a small percentage were invalid and required disengagement from the (incorrectly) cued location and reorienting to the correct location of the target. Adults with damage to the posterior parietal lobes (PPLs) have particular difficulty when this disengage function is required. Thus, we predicted that, since that function depends on PPL in adults, it would be likely to produce poorer performance in children with DS22q11.2 on the invalid trials if our frontoparietal network hypothesis was correct. That pattern was exactly what we found and led us to conclude that the "results suggest that children with DS22q11.2. are significantly impaired at navigating the visuospatial environment in the absence of specific indications of where to direct their attention. They are particularly handicapped under conditions where previously allocated attentional resources need to be disengaged and reallocated to other locations in a self-directed fashion" (Simon, Bish et al., 2005).

Enumeration Our "Enumeration" task (see figure 6.5) related Cueing to numerically related cognition because evidence from adults shows some cognitive processes are common to both tasks. This task is considered higher level than the Cueing task because it requires some conceptual (the number list) and procedural (how to count) knowledge. Regardless of the number of target items presented for enumeration, each must be detected and represented uniquely, designated as a target for enumeration, and subjected to further processing. When the number of items is very small (e.g., fewer than four), children and adults appear to be able to carry out the individuation process rather effortlessly (e.g., Chi & Klahr, 1975; Trick & Pylyshyn, 1993, 1994), just like in our earlier *O* and *X*s example. However, for larger sets it appears that most, if not all, of the targets are processed one at a time or in a series of small groups, just as in our earlier *O* and *Q*s example. Each item is chosen as the current target, attention is directed to it, a record is made of having processed it, the next counting word is retrieved, and the total of items processed so far is incremented. The process is repeated until the child decides that all of the items have been dealt with. Counting has been shown, again primarily in adults, to depend on the frontoparietal network, while subitizing, or enumeration of very small sets of items, does not (Piazza, Giacomini, Le Bihan, & Dehaene, 2003; Sathian et al., 1999).

In the task, children were required to respond by speaking into a microphone, as quickly as possible, the number of objects (1–8) that were presented on a computer display. Targets were small bright green squares presented on a red background square (Simon, Bearden et al., 2005). We predicted that subitizing performance would not differ between the groups because we would not expect it to depend on frontoparietal function, while counting, which we hypothesized would depend on the frontoparietal network, would be expected to produce poorer performance in children with DS22q11.2 than in controls. That is precisely the pattern that we found, leading us to conclude that the ''results again illustrate that self-directed navigation of the visuospatial environment, this time in the service of obtaining a count of the number of items presented, is a particularly difficult and error prone task for children with DS22q11.2'' (Simon, Bish et al., 2005).

Magnitude Estimation and Mathematical Reasoning To further probe the hypothesis that the relationship between space and quantity would be disturbed in children with DS22q11.2 and that this would impair numerical reasoning, we added a magnitude comparison task. This is the highest level in our set of experiments because of the knowledge of quantities and their relationships to one another, as well as some basic reasoning capabilities that are required. We used a numerical ''distance effect'' task in which children were required to judge whether a set of dots or an Arabic numerical had a value ''greater than'' or ''less than'' five. The stimuli consisted of the values ''one,'' ''four,'' ''six,'' and ''nine'' (for more details, see Simon, Bearden et al., 2005). To respond in the distance effect task, one must first determine the value associated with the stimulus and then retrieve the value of the comparison. Both values are then typically represented as if on a mental ''number line'' for comparison with the numerical ''distance'' between the two values on the scale determining the difficulty of the comparison. In adults, such tasks appear to be primarily dependent on posterior parietal regions (e.g., Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999; Göbel, Walsh, & Rushworth, 2001; Pinel et al., 1999). Therefore, we predicted that children with DS22q11.2 should perform less well than control children if our hypothesis about frontoparietal dysfunction was correct. Our results indicated that children with DS22q11.2 could not perform as well or accurately as control children when making relative magnitude judgments. We concluded that

> this may be due to difficulty in navigating the visuospatial environment (as reported for the cueing task), and in using visuospatial searches to determine numerical quantities (as reported for the enumeration task), which may indicate an anomalous mapping of quantity and space. Those impairments could conceivably create atypical spatial representations of relative magnitude or ''symbolic distance.'' (Simon, Bish et al., 2005)

In a newer version of this task, we asked children to simply choose the larger of a pair of objects, either bars varying in length differences of 1 to 7 cm or Arabic

numbers varying in numerical differences of 1 to 7. Our results, as yet unpublished, show that children with DS22q11.2 require differences between the two values to be much greater than do control children before they find them easy to distinguish from one another. Given that both versions of the task had the same effect, we can conclude the impairment is not one of visual discrimination but one more dependent on the conceptual representation and comparison of quantity. It is as if the visuospatial impairments described above produce a representation system for magnitude that has poorer resolution, that is, with less detail represented, than that of unaffected children, so that subtle distinctions are harder to make. Therefore, much greater differences are required before children with DS22q11.2 can tell two values apart. This, of course, can handicap many aspects of numerical development. Further evidence for this comes from a recently published paper on the perception of time durations in individuals with DS22q11.2 (Debbane, Glaser, Gex-Fabry, & Eliez, 2005). Forty-two affected individuals ages 6–32 years were compared to 35 controls on two tasks. In one, each participant was asked to tap first one and then both index fingers in time with a string of tones. When the tones were stopped, the participants' task was to continue tapping at the same rate. Spacing between tones was varied on different trials. The results showed that individuals with DS22q11.2 consistently tapped more quickly, that is, they estimated the durations between tones to be much shorter than they really were. This was not done by the controls. In the second task, two sounds were presented consecutively and the task was to determine which was longer. Here, just as in our two-option numerical magnitude comparison task, individuals with DS22q11.2 required a much greater difference between the two tones than did controls in order to tell them apart. The fact that Debanné et al. found significant correlations between performance on both of the tasks led them to conclude that "an underlying temporal perception mechanism [was] common to both tasks" (p. 1758).

Our interpretation goes further to concur with an emerging view (e.g., Walsh, 2003) that a common representational and processing system is likely to underlie a large range of magnitude-related tasks (concerning time, space, quantity, intensity, etc). Indeed, there is now a growing body of neuroimaging data from adults that supports this view and that points to the posterior parietal cortex as a critical brain region (e.g., Cohen Kadosh et al., 2005). Further evidence comes from a study of mathematical reasoning carried out using functional magnetic resonance imaging (fMRI) with children who have DS22q11.2 (Eliez, Blasey, Menon et al., 2001). They performed more poorly on simple math problems than those without the deletion and showed less activation than did controls in a posterior parietal brain region, the angular gyrus, that is typically activated by adults during such tasks. They also showed an unusual brain response by showing more activation than controls of the supramarginal gyrus, which is a much less typically activated parietal region when

adults carry out such tasks. This suggests that individuals with the deletion may develop an atypical and less effective neural circuit to support mathematical reasoning than do unaffected children and that this may partly explain their struggles in that academic domain. Thus, the data we have reviewed here lead us to conclude that there is considerable evidence in support of our frontoparietal impairment hypothesis and that general magnitude processing, which appears in adults to depend heavily on PPL processing, is an area of particular difficulty for children, and indeed adults too, with DS22q11.2.

Executive Function and Inhibition We turn now to experimental analysis of executive function, which also plays an important role in the processing required by the spatial and numerical tasks described above. We described earlier how neuropsychological testing studies had showed weaknesses in tests of so-called executive function such as the Trails B. The focus in our experiments was on one aspect of executive function, specifically, children's responses to conflicting information in terms of inhibitory function. In order to test this, we used an adaptation of the ANT previously altered for use with children (Rueda, Fan et al., 2004). It is a single task that tests three related attentional functions: alerting, spatial cueing, and executive control. The ANT requires participants to identify the orientation (left or right) of a specific target, here a friendly green alien in an arrow-shaped spacecraft, either alone (the single condition) or in the presence of two identical characters (referred to as "flankers") on each side that face in the same direction (the congruent condition) or in the opposite direction (the incongruent condition) as the target. (See figure 6.6 for example stimuli). The predicted executive control problems in children with DS22q11.2 were evaluated in two ways using the ANT. First, we investigated whether children with DS22q11.2 demonstrated difficulty with trials containing increasing amounts of conflicting information, that is, a comparison of trials with no flankers, congruent flankers, or incongruent flankers. Slowed response time (RT)

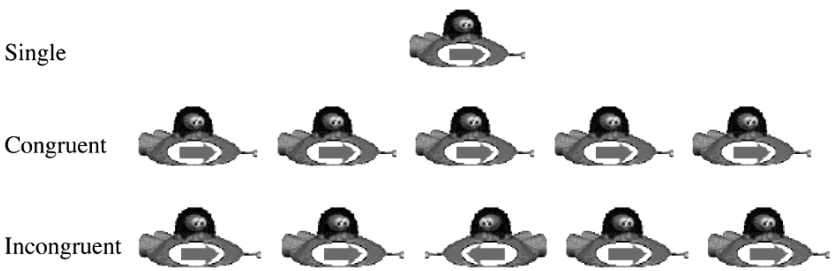

Figure 6.6
Example stimuli from Attentional Networks Test showing single target (top), central target with congruent flankers (center), and central target with incongruent flankers (bottom).

and/or errors on incongruent trials indicate problems with focusing on and processing only task-relevant information and "filtering out" irrelevant information. Second, we investigated dynamic adaptation to conflicting information by examining the Gratton effect (Gratton, Coles, & Donchin, 1992). The Gratton effect is a pattern of more efficient performance (i.e., RT is reduced and accuracy is high) on consecutive identical trials (e.g., two congruent flanker trials in a row) than when the amount of conflicting information changes from trial to trial (e.g., a congruent flanker trial followed by an incongruent flanker trial). Essentially, the Gratton effect measures the ability of the child to benefit from the already established allocation of attentional resources. Processing for tasks like the executive function component of the ANT appears to depend mainly on the anterior portions of the frontoparietal network, particularly the dorsolateral prefrontal cortex as well as the anterior cingulate, though posterior parietal cortex can be involved also (Bish et al., 2005; Bunge et al., 2002). For the flanker trials, we found that both children with DS22q11.2 and controls had significantly more difficulty with incongruent than congruent flankers but that children with DS22q11.2 showed a significantly greater impairment than did controls. This result was essentially a replication of one published using a different variant of the same task (Sobin et al., 2004). Our interpretation was that this indicated "dysfunction of the executive control network, in that children with DS22q11.2 were less able to inhibit the processing of irrelevant information such that it negatively affected their performance" (Simon, Bish et al., 2005). Our further, unexpected, finding that children with DS22q11.2 showed a benefit in performance rather than a cost from the presence of the congruent flankers suggested that they may be unable to narrow the focus of attention to the target item and so processed all the stimuli to the same degree (Bish et al., 2005).

We also found an atypical pattern of conflict monitoring in children with DS22q11.2 on the Gratton effect. Instead of benefiting from inhibition generated in response to incongruent flankers when an identical trial followed and thus performing more efficiently on the following trial, children with DS22q11.2 failed to benefit and their performance was even more negatively affected by the second trial's conflicting information. This led to poorer performance, unlike the controls, who showed the opposite and more typical pattern. We concluded that the results indicate "an inability on the part of children with DS22q11.2 to dynamically respond to a flow of facilitatory or conflicting information and to adjust their attentional resources accordingly, particularly when presented with incongruent distracting stimuli" (Simon, Bish et al., 2005). Patterns similar to this have been observed in individuals with schizophrenia (e.g., van Veen & Carter, 2002), and so it may be the case that individuals with the poorest performance on such tasks could be identified, along with a great deal of related data, as being those with increased risk for psychiatric disorders later in life.

Another similar cognitive measure of this sort tests a behavior known as prepulse inhibition (PPI). This is a psychophysiological measure of what is referred to as ''sensorimotor gating''. It is so labeled because, when a startle-eliciting stimulus like a loud noise is preceded by a warning signal, frontal brain circuits act to inhibit the startle circuit's response to the noise, probably serving a protective function by suppressing extreme neural signals. As such, it is a good measure of inhibitory function, and studies have shown that it is reduced in children with disorders like Tourette's and fragile X syndromes that are associated with inhibitory impairments. Sobin, Kiley-Brabeck, and Karayiorgou (2005) found that children with DS22q11.2, especially boys, produced a significantly reduced PPI compared with the sibling comparison group, and they interpreted this as indicating impairments in inhibitory function. In some exploratory analyses, they also found that, for children with DS22q11.2, those who had early indicator symptoms associated with schizophrenia had a significantly reduced PPI compared to others without such symptoms.

Another psychophysiologic measure that is also markedly altered in individuals with impairments to executive function or who have schizophrenia is the mismatch negativity (MMN) signal. This is a clear and consistent electrophysiological signal elicited by a discriminable change within a repetitive sequence of auditory stimuli. Possibly the first functional imaging study ever carried out with children who would now be diagnosed with DS22q11.2 (Cheour et al., 1997) showed this signal to be much reduced in 11 affected children ages 6 to 10 years. More recently, a larger study of older children and young adults with DS22q11.2 (Baker, Baldeweg, Sivagnanasundaram, Scambler, & Skuse, 2005) showed a significantly reduced MMN signal in the frontal lobes in those with DS22q11.2 when the dimension of change in the stimuli was its duration but not pitch or a combination of the two. This result not only provides further evidence for executive function impairment but, because the only significant dimension of impaired response was duration, it also links back to problems in DS22q11.2 with the magnitude judgment system. The authors, who were interested in MMN as a signal for schizophrenia risk, also showed a relationship between a reduced MMN signal and the methionine (Met) variant of the COMT gene in their participants with DS22q11.2. However, it should be noted that Met is not the variant that is usually thought to contribute to increased risk for schizophrenia.

Thus, several cognitive experimentation studies of individuals with DS22q11.2 have found different and related impairments in executive function that are also seen in individuals with schizophrenia and so raise the possibility that this kind of measurable cognitive dysfunction could conceivably be a contributing factor to the emergence of schizophrenia later in life. Clearly, impairment on such a task should *not* be taken as any kind of indication that schizophrenia will necessarily follow, but measures such as these, along with a range of other behavioral, biological, and

psychophysical observations, might be valuable as a means of assessing very early risk for such psychiatric problems later in life. This might then enable early treatment and follow-up strategies to be developed and evaluated with respect to their effectiveness in suppressing the debilitating symptoms of such disorders.

Summary of Strengths and Weaknesses from Cognitive Experimentation Studies

An increasing number of experimental studies have shown impairments in children with DS22q11.2 that appear to be consistent with the hypothesis of dysfunction in the frontoparietal neural network. Tasks at different levels of complexity that are thought to depend more on the posterior parietal regions, such as visual-attentional orienting or search for objects or locations, simple enumeration, and simple magnitude judgment, all showed characteristic impairments in children with DS22q11.2. Although not every child's performance is identical, difficulties on tasks such as these appear to be particularly consistent in children with the deletion. However, the fact that they are also common in many other populations with so-called "nonverbal learning disorders" means that they are not specific to or diagnostic of the deletion. Tasks that are thought to be more dependent on frontal aspects of the network, such as cognitive control, inhibition of irrelevant information of inappropriate responses, or sensorimotor gating, all showed impairments too. Since there are fewer studies of this sort, the early indications of slightly greater variability in these tasks than those thought to be more dependent on posterior circuits may not be warranted in the long term. However, since many impairments of these so called "frontal" tasks share some characteristics found in populations of people with psychiatric disorders that are more common in the DS22q11.2 population, performance on these tasks and analysis of that variability may serve as an important component of the important task of trying to assess early risk for those disorders.

Neural and Genetic Correlates

Several brain development anomalies characteristic of DS22q11.2 have been noted in recent years due to the increasing availability of magnetic resonance imaging (MRI) scanners for research studies. Developing a clearer picture of what these are might enable researchers to use other data to develop explanatory accounts of anomalous neurocognitive development in DS22q11.2. Some features are easily seen from a clinical scan, while others have been described only as the result of detailed analytical research methods. Examples of the former include enlargements in the sylvian fissure and ventricular spaces (particularly the lateral ventricles) and reductions in the cerebellar vermis. Examples of the latter include reductions in posterior gray and white matter and changes to corpus callosum or other neural connectivity as measured in

Table 6.2
Major brain differences reported in children with chromosome 22q11.2 deletion syndrome

Brain Region	Major Findings	Reference
Sylvian fissure	Increased anterior interopercular distance (left)	(Bingham et al., 1997)
	Reduced gray matter, increased CSF (right)	(Simon, Ding et al., 2005)
Posterior fossa	Reduced fossa and cerebellar vermis	(Mitnick et al., 1994)
	Reduced cerebellar vermis, midbrain, and pons	(Eliez, Schmitt et al., 2001)
	Reduced cerebellar vermis, midbrain, and pons	(Simon, Ding et al., 2005)
Ventricles	Enlarged ventricular spaces (especially lateral ventricles)	(Simon, Ding et al., 2005)
Temporal lobes	Reduced superior temporal gray matter (left)	(Eliez, Blasey et al., 2001)
	Reduced temporal gray matter (right)	(Simon, Ding et al., 2005)
Basal ganglia	Enlarged caudate head (left > right)	(Eliez et al., 2002)
Corpus callosum	Increased fractional anisotropy in posterior corpus callosum to occipital lobes.	(Barnea-Goraly et al., 2003)
	Increased fractional anisotropy in posterior corpus callosum, parietal, and occipital lobes.	(Simon, Ding et al., 2005) (Shashi et al., 2004)
	Enlarged isthmus	(Antshel et al., 2005)
	Enlarged callosum and all regions but genu	

terms of fractional anisotropy, an indirect measure of fiber tract orientation measured with the use of diffusion tensor MRI. Table 6.2 presents the most reliably reported findings in both categories along with representative publications.

We should stress that, at this time, the significance of these neurodevelopmental anomalies remains unclear, especially with respect to their effect on cognition and behavior. However, careful interpretation and use of data from cognitive neuroscience studies, as is done in the cognitive experimentation method, can be a very powerful means of generating hypotheses about the neural substrate of the observed cognitive impairments, so long as the caveats discussed earlier are borne in mind. Thus, while it is important to build up an increasingly sophisticated picture of brain development in children with DS22q11.2, at present the diagnostic implications of that pattern can, at best, only be a contributing factor to explaining the DS22q11.2 phenotype, and it is unlikely that any one feature or pattern of features will be specific enough to be used diagnostically.

Although the precise genetic basis of DS22q11.2 has been described in terms of the size and location of the deletion, there is currently little knowledge about the role of specific genes in the physical or behavioral manifestations of the disorder. However, specific gene variants, both within and outside the chromosome 22q11 region, have also been related to elevated risk of disorders such ADHD, schizophrenia, OCD, and bipolar disorder in the general population, as well as specifically in those with DS22q11.2 (e.g., Karayiorgou et al., 1995; Lachman et al., 1997; Liu et al., 2002; Papolos et al., 1996; Swanson et al., 2001). As discussed above, a good deal of

attention has been paid to the role of one gene in particular in the cognitive and behavioral profile of DS22q11.2. The gene coding for the enzyme catechol-O-methyltransferase (COMT) is of particular interest with respect to cognition and behavior to DS22q11.2, given its location in the deleted region of the chromosome in patients with the disorder (Grossman, Emanuel, & Budarf, 1992), and its known role in metabolic degradation of synaptic dopamine and norepinephrine (Lachman et al., 1996), which are critical neurotransmitters in terms of their relation to executive function and disorders related to inhibitory behavior (e.g., Egan et al., 2001). The COMT gene contains a functional polymorphism ($Val^{158}Met$) that determines high and low activity, respectively, of this enzyme (Lachman et al., 1996). Homozygosity for (i.e., carrying only) the low-activity methionine (Met) allele is associated with a three- to fourfold reduction of COMT enzyme activity compared with those carrying only the high-activity valine (Val) variant, resulting in reduced degradation of synaptic catecholamines in individuals with the Met allele. Although results are somewhat inconsistent, probably due to the ethnicity, ages, and IQ levels of the participants tested, there is evidence to suggest that the Val variant of COMT may be associated in adults with both a slightly increased risk for schizophrenia (Glatt, Faraone, & Tsuang, 2003) and poorer performance on cognitive tasks known to depend on the prefrontal cortex, such as attention, working memory, and executive functions (Bilder et al., 2002; Egan et al., 2001; Malhotra et al., 2002).

Because of this, and of COMT haploinsufficiency (i.e., the absence of one copy of the COMT gene) due to the chromosome 22q11.2 deletion, several authors have linked COMT to some of the behavioral impairments and the elevated incidence of psychosis in DS22q11.2 (Graf et al., 2001; Henry et al., 2002). In the first prospective longitudinal study of this suspected link, Gothelf et al. (2005) demonstrate a clear relationship between the Met allele and increased incidence of psychotic symptoms and more severe decline in VIQ and language abilities and gray matter prefrontal volumes during adolescence. Our own studies (Bearden et al., 2005; Bearden et al., 2004) have shown a link between COMT, executive function, and behavioral symptomatology. The Val allele was associated with poorer performance on a composite executive function measure and with increased scores for behavior problems, especially internalizing and externalizing, on the Child Behavior Checklist (CBCL; Achenbach, 1984). However, the MMN study by Baker et al. (2005), described earlier, showed that their 8 participants with DS22q11.2 who had the Met allele had poorer working memory and expressive language abilities as well as a reduced MMN signal.

A similar, though less fully investigated, relationship to schizophrenia and sensorimotor gating has been proposed for the proline dehydrogenase gene (see Stevens & Murphy, 2005), though Gothelf and colleagues (2005) did not find a similar relationship to the one they reported for COMT. At this point, however, little is really known about the roles of other genes from the chromosome 22q11.2 region in the

DS22q11.2 neurocognitive phenotype. Some further aspects of this relationship are, however, beginning to be discussed (for one example, see Simon, Bish et al., 2005). As is the case with brain structure and function, no single gene or pattern of gene expression differences is currently known to be diagnostic of the DS22q11.2 phenotype, though it is certainly possible that in the near future, a genetic basis for some of the typical and specific features may be found.

Summary

DS22q11.2 is the most commonly occurring microdeletion syndrome known in humans and is one of the most common genetic causes of developmental disability. However, because of (a) the relatively recent characterization of the precise genetic basis of the syndrome and (b) the fact that a large proportion of children with the deletion are only mildly physically affected, the syndrome has a low rate of identification in the general medical community. Furthermore, the cognitive and behavioral implications are still poorly understood. Identification is further complicated by the fact that over 180 physical and behavioral anomalies have been associated with the disorder, and the precise presentation of each individual is a variable combination of those. The lack of a single diagnostic label for individuals with the deletion has only added to the confusion. Of the many signs and symptoms associated with the syndrome, only relatively few are specific to it. Because of this, we have tried in this chapter to identify those and to distinguish them from the nondiagnostic ones. We have also attempted to present typical patterns of the many nonspecific characteristics that may be used to increase the chances of identifying the syndrome, and we have alerted the reader to the variations in those patterns. The first section of the chapter presented the physical diseases that are most diagnostic and then discussed the issue of psychiatric disorders. The two diagnostic case studies described how differently the syndrome can present. Some children can be severely affected with physical disorders and have mild behavioral problems that are common to a range of childhood disorders. Other children can appear quite healthy and even well-adjusted but manifest serious psychiatric disorders, especially as they approach late childhood and early adulthood.

In almost every case of a child with the syndrome there is likely to be some degree of developmental delay, but the pattern is not uniform nor is it specific to DS22q11.2. In fact, children with the deletion are frequently described as having a "nonverbal learning disorder," and this profile is characteristic of children with other neurogenetic disorders with differing behavioral profiles and varying levels of overall intellectual ability (such as Turner, fragile X, and Williams Beuren syndromes) as well as many children with no known disease. Rather, too much attention has been paid to the advantage of verbal over nonverbal abilities that is characteristic of nonverbal

learning disorder and typically used to describe most children with DS22q11.2. As shown by several studies described above, this pattern is not manifested by every child with the deletion and is even reversed in a minority of cases, such as the one reported by Stiers et al. (2005). There are also cases of individuals who have the deletion and who present with a radically different behavioral profile, such as the profoundly handicapped female described by Kozma (1998). However, it is likely that in most cases such presentations are due to some insult or injury that is independent of DS22q11.2.

While no behavioral and cognitive profile specifically diagnostic of children with DS22q11.2 exists, neuropsychological testing and cognitive experimentation studies have generated competence patterns that can be used to increase the likelihood of detecting the deletion when considered in conjunction with other features in the physical presentation. One of the most typical patterns is as follows. A marked delay in initial word use is apparent with the child being essentially nonverbal late into his or her second year. The problem often persists in the form of very limited expressive language abilities until at least age 4. Simple rote memory and word reading are in the average range in the early school years, but complex memory (e.g., for stories) and reading comprehension are impaired. These weaknesses are also somewhat persistent beyond that age. In general, a child with the deletion shows significant impairments in all tasks with a spatial component. These include memory for spatial locations (as opposed to details of objects) and tasks involving spatial reasoning (such as the relative locations of objects), visuomotor construction (such as the WISC Block Design task), or any task that requires representing and mentally manipulating the spatial relationships between the parts of an object or between the locations of multiple objects in relation to other objects, or to the child himself or herself. Most aspects of attention will also be impaired, especially the spatial component of attention where the visual field must be scanned or navigated in order to select specific items. Complementary aspects of attention, particularly the "executive" component that helps to control such searches and that is involved in the inhibition or ignoring of irrelevant information, will also show impairments. In the behavioral domain, the child may well show some combination of the inattentive or combined (as opposed to the hyperactive) type of ADHD and shy, stubborn behavior. Such a profile, along with some of the specific and characteristic physical manifestations, will be a strong indication of the presence of the deletion.

Of course, there are many children in whom not all of these difficulties are equally expressed and a minority who even show relative strengths in domains where the majority show weaknesses. This makes the task of identifying the syndrome more complex. In the behavioral domain, less common clues, though ones that occur at a much higher rate than in the general population, include symptoms associated with schizophrenia. However, these are rarely observed before late adolescence. In short,

DS22q11.2 is a complex disorder with considerable variability and changes during development. There are few medical or behavioral symptoms that are specific to the disorder, and so identification is complex. We have attempted in this chapter to broadly describe the most characteristic presentations and to illustrate some of the variations also. If used together, these should help clinicians and other professionals to more easily determine whether a given child is a candidate for the FISH test, which can definitively determine whether or not a diagnosis of DS22q11.2 should be made. A positive result can often be a relief to parents in search of an explanation for their child's constellation of problems and should be used to ensure that the child receives all the medical, behavioral, and cognitive/academic interventions and services to enable the fulfillment of his or her individual potential.

Acknowledgments

First and foremost, we would like to thank the families that have participated in our research programs and those of others whose work we have referenced. Tony J. Simon would also like to thank the team at the 22q and You Center at Children's Hospital of Philadelphia for their support and recruitment of study participants. This work was funded by National Institutes of Health Grant R01HD42974 (Tony J. Simon), an Israel President Ph.D. Stipend (Merav Burg-Malki), and the Keren Shalem Fund for the Development of Services for the Retarded in the Local Councils and Reut Foundation (Doron Gothelf).

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