

I. The Neurocognitive Profile of Williams Syndrome: A Complex Pattern of Strengths and Weaknesses

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Abstract

■ The rare, genetically based disorder, Williams syndrome (WMS), produces a constellation of distinctive cognitive, neuroanatomical, and electrophysiological features which we explore through the series of studies reported here. In this paper, we focus primarily on the cognitive characteristics of WMS and begin to forge links among these characteristics, the brain, and the genetic basis of the disorder. The distinctive cognitive profile of individuals with WMS includes relative strengths in language and facial processing and profound impairment in spatial cognition. The cognitive profile of abilities, including what is 'typical' for individuals with WMS

is discussed, but we also highlight areas of variability across the group of individuals with WMS that we have studied. Although the overall cognitive abilities (IQs) of individuals with WMS are typically in the mild-to-moderate range of mental retardation, the peaks and valleys within different cognitive domains make this syndrome especially intriguing to study across levels. Understanding the brain basis (and ultimately the genetic basis) for higher cognitive functioning is the goal we have begun to undertake with this line of interdisciplinary research. ■

INTRODUCTION

Crystal, an ambitious 14-year-old, was overheard to say "You're looking at a professional book writer. My books will be filled with drama, action, and excitement. Everyone will want to read them. I'm going to write books, page after page, stack after stack." Crystal is quite good at creating original stories on a moment's notice, most recently spinning a tale about a chocolate princess who saves her chocolate kingdom from melting by changing the color of the sun. Remarkably, her creative talents are not limited to storytelling, but extend to music as well; she has composed the lyrics and music to a song. Considering her ease with language, her creative ideas, and her unshaking enthusiasm, her ambition to become a writer may seem plausible—however, Crystal has an IQ of 49. She fails all Piagetian seriation and conservation tasks, milestones normally attained by age 8. She has reading, writing, and math skills comparable to those of a first-grader, demonstrates visuo-spatial abilities of a 5-year-old, and cannot be left alone without a babysitter.

Crystal has Williams syndrome (WMS), a rare (1 in 25,000) genetically based neurodevelopmental disorder. Characteristics of the syndrome include specific face and physical features; a variety of cardiovascular difficulties, including supravalvular aortic stenosis (SVAS); failure to thrive in infancy; transient-neonatal hypercalcemia; delayed language and motor development; and abnormal sensitivities to certain classes of sounds (hyperacusis) (Lenhoff, Wang, Greenberg, & Bellugi, 1997; Marriage & Scientist, 1995; Bellugi & Morris, 1995). The precise genetic underpinnings of WMS are becoming clear and are currently known to involve a submicroscopic deletion of one copy of about 20 contiguous genes on chromosome 7, including the gene for elastin (Korenberg et al., this volume; Frangiskakis et al., 1996).

Work being performed in our lab and others is mapping out the cognitive profile of WMS and its distinctive identifying features (Mervis, Morris, Bertrand, & Robinson, 1999; Karmiloff-Smith, 1998; Volterra, Capirci, Pezzini, Sabbadini, & Vicari, 1996; Bellugi, Bihrlé, Neville,

Jernigan, & Doherty, 1992; Bellugi, Wang, & Jernigan, 1994; Bellugi, Hickok, Jones, & Jernigan, 1996a; Bellugi, Klima, & Wang, 1996b; Bellugi & Wang, 1998; Bellugi, Lichtenberger, Mills, Galaburda, & Karenberg, 1999a, among others). Interest in Williams syndrome arises from the uneven cognitive profile that is associated with the syndrome through these studies, including specific dissociations in cognitive functions. In this paper, we will review a series of formal and informal studies of cognitive behavior of individuals with Williams syndrome, largely from our laboratory over the past decade.

In this special issue as a whole, results are described across an array of disciplines from cognitive neuroscience to molecular genetics. This chapter and the next (Jones et al., this volume) sketch out some of the findings from studies of neurocognitive and social behavior in the same set of Williams individuals. Other chapters involve studies using brain-imaging techniques including event-related potentials (Mills et al., this volume) and magnetic-resonance imaging (Reiss et al., this volume) with the same subjects. The studies include brain cytoarchitectonics (Galaburda & Bellugi, this volume) as well as molecular genetics (Korenberg et al., this volume). The special strength of the program project is that (except for the cytoarchitectonic studies), the same subjects undergo cognitive, neurophysiological, neuromorphological, and molecular genetic probes. In this way, we can begin to link phenotype and genotype, as well as to link variability at one level with variability at other levels, in a large group of well-defined subjects. The chapters in this special issue show the linkages among cognitive, neurobiological, phenotypic, and genotypic profiles in order to create an initial picture of the functional neuroarchitecture of the syndrome. This linking occurs in several ways. By drawing on known connections between neurobiological systems and cognitive functions, we have begun to match cognitive abnormalities with their probable bases in neurobiological abnormalities. In addition, individual variation within the WMS population can be capitalized upon by predicting correlations between the strength of neurophysiological markers (in terms of event related potentials—ERPs) and performance on specific behavioral measures. Distinctive profile characteristics at the neurophysiological level (such as abnormal neurophysiological responses to face and language processing) can inform and refine our picture of aspects of the cognitive profile. Finally, we can take initial steps in the process of linking the presence or absence of copies of a small set of specific genes to the development of brain structure and function as well as to the specific cognitive profile of WMS.

Subjects

The groups of subjects with WMS who participated in the studies reported here involve a database of about

100 clinically and genetically diagnosed individuals with Williams syndrome, and are compared with Down Syndrome (DNS) individuals and normal controls, as well as with other specific disorders. Adolescent and adult individuals with WMS or DNS are part of a Program Project at The Salk Institute from the National Institute of Child Health and Human Development, “Williams Syndrome: Bridging Cognition and Gene.” Infants and young children are part of a collaborative project with the Center for Neurodevelopmental studies at the University of California—San Diego (National Institute of Neurological Diseases and Stroke; and National Institute of Deafness and Other Communication Disorders). These studies include not only children with WMS or DNS syndrome, but also other projects including children with early onset focal lesions to the right or to the left hemisphere, with language impairment or autism. Subjects from the NICHD Program Project range in age from 10 and up and those from the Center for Neurodevelopmental studies range in age from birth to 10 years. Subjects are recruited for the WMS studies through our extensive contacts with families, the Williams Syndrome Association, national and regional conferences, private physicians, geneticists, cardiologists, and others that are familiar with the research in our laboratory. All are thoroughly screened prior to induction into the study and must pass a set of clear inclusionary and exclusionary criteria. Information about each subject’s medical history is obtained from medical records, including a medical genetic evaluation confirming the diagnosis of WMS. In addition, a diagnostic interview, which tests for the common phenotypic features of the syndrome, is conducted with each subject and his/her caregiver. As part of this interview, a Diagnostic Score sheet (developed by the Medical Advisory Board of the Williams Syndrome Association) is completed (see Table 1 for a summary of some of the major diagnostic medical characteristics of WMS).

Molecular genetic testing (fluorescence *in situ* hybridization, or FISH) can now be used to confirm the deletion of one copy of the elastin gene and other surrounding genes in a small region of chromosome 7, characteristic of nearly all individuals with clinically diagnosed WMS. The studies in this paper and in subsequent papers in this volume (Jones et al., this volume; Korenberg et al., this volume; Mills et al., this volume; Reiss et al., this volume) include subjects who meet all aspects of our strict screening and diagnostic criteria for Williams or Down syndrome and, importantly, the same individuals undergo probes at these major levels.

Throughout these studies of children and adults with WMS, we report on a variety of comparison groups: Normal individuals who are variously matched with WMS individuals on chronological age, mental age, or language age, and individuals with DNS who are

Table 1. Summary of Major Williams Syndrome Medical Features

Neurological

- average IQ 55 (range 40-90)
- poor coordination
- hypersensitivity to sound
- hoarse voice

Cardiovascular

- supravalvular aortic stenosis
- peripheral pulmonary artery stenosis
- pulmonic valvular stenosis
- ventricular/atrial-septal defects

Facial Features

- full prominent lips
- stellate iris pattern
- prominent ear lobes
- wide mouth
- small, widely spaced teeth
- medial eyebrow flare
- flat nasal bridge
- short nose/anteverted nares

Other

- elastin deletion probe (FISH)
- transient infantile hypercalcemia
- developmental delay (infants height and weight < 5th percentile)

matched in age and Full Scale IQ to the WMS group. As contrasts to the WMS data, we additionally report data from infants or young children with language impairment, with early focal lesions, and individuals with autism. The majority of the initial results we report in this paper consist of data collected from WMS subjects and from those with DNS, the latter primarily as a comparison group, matched in age and IQ, as well as normal controls matched for chronological age or mental age. Williams and Down groups were chosen initially because both are genetically based disorders resulting in mental retardation, but other comparison groups are important as well.

General Cognitive Functioning

Across an array of standardized conceptual and problem-solving tasks (some verbal, some nonverbal in nature),

subjects with WMS demonstrate a consistent, serious impairment in general cognitive functioning. On general cognitive tasks such as IQ probes, most individuals with WMS rank in the 'mild-to-moderate mentally retarded' range, with global standard scores on IQ tests ranging from 40 to 90 and a mean of around 55 (Bellugi et al., 1996b). Figure 1 contrasts the distribution of Wechsler Full Scale IQ (Wechsler, 1974; Wechsler, 1981) of 82 subjects with WMS, with a typical normal distribution of Full Scale IQ scores. We can now describe what is "average" or "typical" and what is the distribution for WMS individuals on many standardized tests. As seen in the range of performance on IQ tests shown in Figure 1, there is also some variability within WMS as a group, with the WMS group mean shifted downward from the normal distribution into the mild-to-moderate range of mental retardation. Reflecting the variability in cognitive functioning, some adults with WMS live independently or semi-independently (Udwin, 1990), while others need significant help. It should be noted that arithmetic is an area of great difficulty for most individuals with WMS, but some are able to master addition and, in a small number of cases, subtraction and division as well. Reading is a challenge for some, while others have been noted to be avid readers of books, magazines, and newspapers, but often on very specific topics of interest (Howlin, Davies, & Udwin, 1998).

The typical global cognitive impairment that is seen in WMS is similar to that found in DNS in our studies.

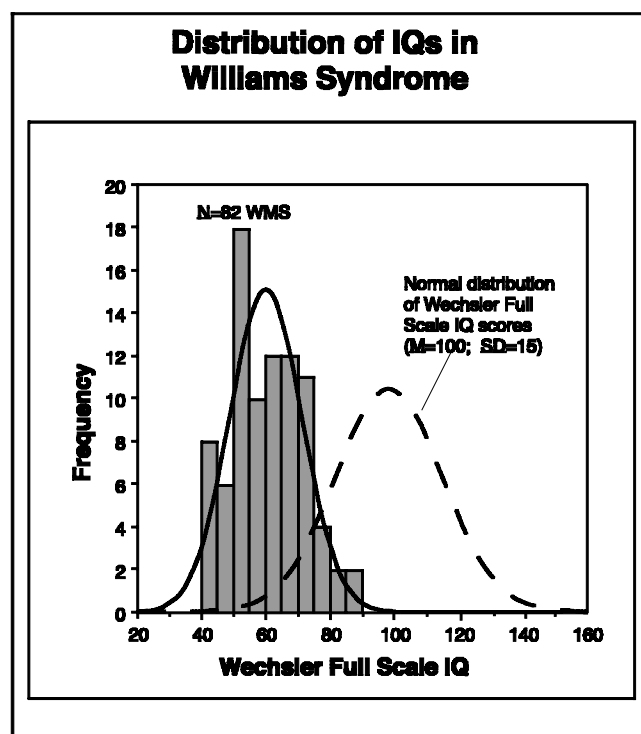


Figure 1. Wechsler Full Scale IQs in WMS range from 40 to 90, and are fairly normally distributed, with a mean IQ of approximately 55 ($SD = 11$).

Equal Cognitive Impairment in Williams and Down Syndrome Adolescents

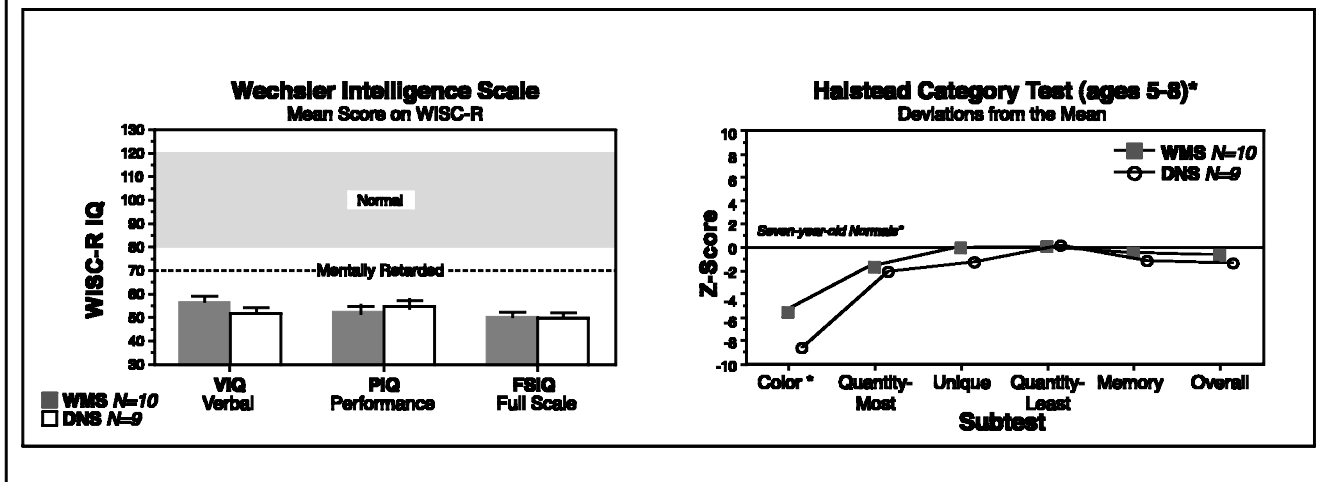


Figure 2. Subjects with WMS and DNS consistently score below 'normal' on tests of general cognitive ability, such as the WISC-R (Wechsler Intelligence Test for Children—Revised) (left) and the Halstead Category Test (right).

As shown in Figure 2, adolescents with WMS and those with DNS in our studies score equally poorly across the board on IQ tests such as the Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1974) or Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1981). In each of these subject groups, there was no clinically significant difference between Verbal and Performance IQ scores on the Wechsler scales. In addition, both groups showed equal degrees of impairment on cognitive probes such as the Halstead Reitan Neuropsychological Battery (Reitan & Wolfson, 1985), and general tests of conceptual knowledge, information, or math achievement, and Piagetian tests of conservation, including conservation of number, weight, and substance (Bellugi et al., 1992; Bellugi et al., 1994; Bellugi et al., 1996b).

Adolescents and adults with WMS have been found to have a conceptual understanding of basic biological categories of living things such as people, animals, and plants, that is only equivalent to that of normal 6-year-olds (Carey, 1985). The limited biological knowledge and understanding of subjects with WMS is also evident in their failure to attain the level of conceptual restructuring that most normal children achieve by age 10 or 11 (Johnson & Carey, 1998; Rossen, Klima, Bellugi, Bihle, & Jones, 1996). For example, adolescents and adults with WMS have difficulty differentiating *not alive* into the conceptual categories of *dead*, *inanimate*, *unreal*, or *nonexistent*. A specific example of the limits of conceptual knowledge in WMS is from a reported instance of a 21-year-old woman with WMS (Verbal IQ of 69) who was literate and read several books on her favorite topic: Vampires. When this subject was asked what a vampire is, she responded reasonably and clearly that a vampire is "a man who climbs into ladies' bedrooms at night and sinks his teeth into their necks."

When asked why vampires do that, she thought for a bit, and then said, "Vampires must have an inordinate fondness for necks" (Johnson & Carey, 1998).

Along with their general cognitive deficits, individuals with WMS typically have difficulty in mathematics and its application to everyday life, such as making change, balancing a checkbook, and cooking from recipes. In our studies, many individuals with WMS would rather receive 50 pennies than five dollars as a reward. These difficulties are in keeping with their difficulties in mastering Piagetian conservation. Another probe, the Cognitive Estimation Test, assessed WMS subjects' abilities to estimate length, weight, and similar concepts (Dehaene, 1997). The test was administered to 10 adolescents and adults with WMS. Many responses to the questions asked in this task were very far off the mark. For example, when asked, "What is the length of a dollar bill?" a 15-year-old subject with WMS responded, "five feet"; an 18-year-old subject with WMS responded, "four feet"; and a 20-year-old subject with WMS responded, "one inch." On another question, "What is the normal length of a bus?" individuals with WMS responded: "30 inches" (a 12-year-old); "3 inches or 100 inches maybe" (a 15-year-old); "2 inches, 10 feet" (a 24-year-old). Each of these examples shows the great difficulty that adolescents and even adults with WMS have in estimating values that are easily estimated by many younger, normally developing children (Kopera-Frye, Dehaene, & Streissguth, 1996).

Relatively Spared Expressive Language in Williams Syndrome

Considering the general cognitive impairment exhibited in WMS, their noticeable facility with complex language

(albeit not always used correctly) often comes as a surprise to people who encounter individuals with this syndrome. Adolescents and adults with WMS tend to be articulate, and are talkative to the point of being loquacious. This relative strength is in contrast to the considerable linguistic deficits in individuals with DNS, who typically present with major deficits in syntax. We have investigated many facets of language processing in WMS. We briefly describe the development of language in the WMS population and then provide a brief overview of aspects of language: Grammar, lexical semantics, and narrative production.

Stages of Language Development

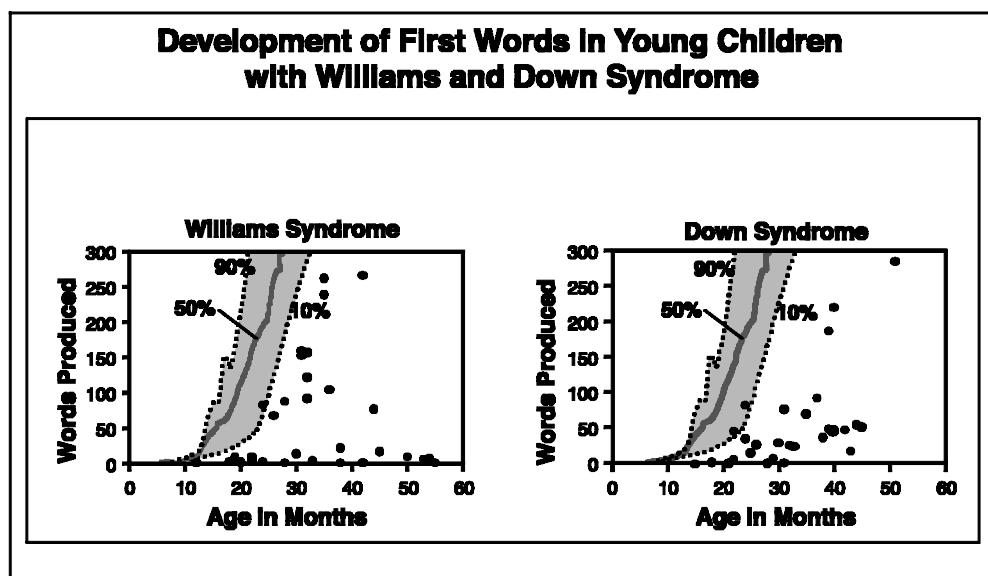
Although mature WMS linguistic performance shows that language is a major strength in the WMS cognitive profile and radically different from typical DNS, the initial stages of development do not clearly predict this. In older children and adolescents with WMS, linguistic abilities seem relatively preserved, whereas in older DNS individuals, linguistic abilities are far below those of WMS. Hence, in their mature state, the behavioral phenotypes of WMS and DNS test the outer limits of the dissociations that can occur between language and cognition.

How do these contrasting profiles come about? In our studies of younger children with WMS and DNS, we are pushing these two profiles back to their origins, seeking the point at which language and other aspects of cognition diverge over time. The behavioral phenotype of WMS undergoes dramatic change across the first years of life, starting out with extreme delay at all developmental milestones, including language, but with islands of sparing in the perception of sounds and faces. By uncovering differences between WMS and DNS syndrome children

in the first stages of prespeech and language development, and comparing them with other populations, we can obtain insights into the factors responsible for the contrasting profiles of language and cognition displayed later in development.

Onset of Words. The onset of first words was studied using a parental report of language acquisition, the MacArthur Communicative Development Inventory (CDI; Fenson et al., 1993), in a sample of 54 children with WMS and 39 children with DNS (ranging in age from 12 to 60 months). Surprisingly, there were no significant differences reported in the onset of first words between children with WMS and DNS (Singer-Harris, Bellugi, Bates, Jones, & Rossen, 1997). Although both groups were found to be equally and massively delayed as compared to normally developing children at the initial stages (see Figure 3), differential patterns of language acquisition emerged. Relative to one another, children with DNS exhibited an early advantage for communicative gestures, while children with WMS displayed a strong advantage for grammar later in development. Moreover, there was a tendency for comprehension levels to be high relative to production in DNS and an opposite tendency in WMS infants and toddlers. Parents of DNS children reported that their children could understand many words but not produce them; parents of WMS children often reported the opposite: That their young WMS children could say many words they did not understand. A 4-year-old WMS child brought to the lab for testing could accurately repeat words such as 'encyclopedia' or 'Britannica' with clarity and precision, although investigation showed that she could not describe or even provide hints that she understood any aspect of the meaning of the words.

Figure 3. The total number of words produced by young children (infants and toddlers) on the MacArthur Communicative Development Inventory (CDI) for children with WMS (left) and DNS (right) shows considerable variability and equally delayed onset of words in both groups. Shaded area represents trajectories of normal children in a large study using the CDI.



From First Words to Grammar. The next phase of development is characterized by dramatic changes in language in normal children and in WMS, including the rapid acquisition of basic morphosyntactic structures. In normal children, these events take place between 16 and 30 months of age. As grammar emerges, children with WMS in general improve dramatically, whereas children with DNS tend to plateau rather early in development, falling further and further behind. WMS young children then move ahead in grammar acquisition compared to DNS and, in fact, the linguistic phenotypes of the two groups diverge at the point where grammar is acquired and beyond, a provocative finding in view of the contrasting profiles that observed later in life. In some ways, results suggest that DNS language comprehension has a delayed but relatively normal developmental pathway in infancy, whereas WMS language development may be more deviant from the outset (Karmiloff-Smith et al., 1997; Singer-Harris et al., 1997; Rossen et al., 1996).

Grammar

The general cognitive impairment seen in adolescents and adults with WMS stands in stark contrast to their relative strength in language, their facility and ease in using sentences with complex syntax, not generally characteristic of other mentally retarded groups (Rossen et al., 1996). To assess their comprehension and use of complex syntax, several studies were conducted.

On tasks that measure grammatical abilities, adolescents and adults with WMS showed relatively strong abilities compared with DNS. For example, on a task of comprehension of passive sentences, subjects had to choose which of four pictures best fit the meaning of the sentence, such as “the horse is chased by the man.” The sentences in the study were semantically reversible passives, such that “the man is chased by the horse” is also a well-formed grammatical sentence. Therefore, since either the horse or the man can do the chasing, to correctly perform the task, the subject must have an understanding of the underlying syntax of the sentence. Adolescents with WMS showed relatively strong performance compared to DNS who performed close to chance (Bellugi, Bihrlé, Jernigan, Trauner, & Doherty, 1990; Bellugi et al., 1996b).

On several other syntax tests, subjects with WMS scored significantly higher than subjects with DNS: (a) the Test for Reception of Grammar (TROG; Bishop, 1982), (b) the Kempler Test of Syntax (Kempler & VanLanker, 1993), (c) the Curtiss–Yamada Comprehensive Language Evaluation (CYCLE; Curtiss & Yamada, 1988), and (d) the Clinical Evaluation of Language Fundamentals (CELF; Semel, Wiig, & Secord, 1987). On a probe of detection of syntactic and semantic anomalies (Dennis & Whitaker, 1976), again the WMS group scored significantly higher than the DNS group.

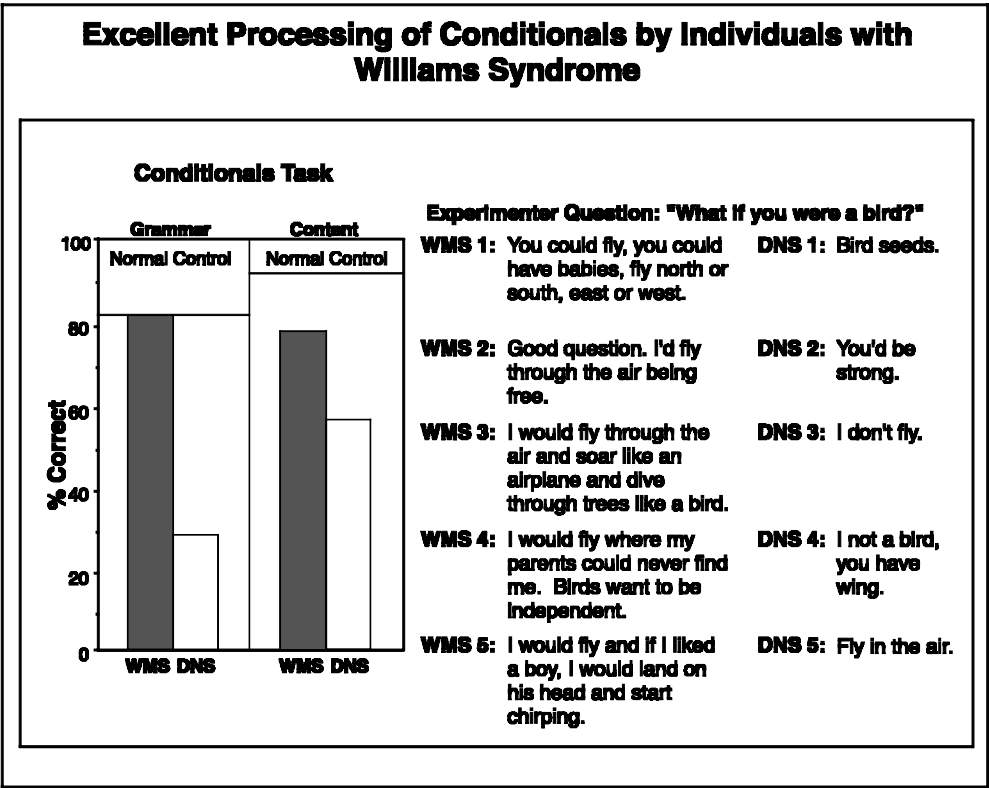
The ability to detect and correct anomalies in the syntax of a sentence may depend on the knowledge of syntactic constraints and the ability to reflect upon grammatical form. Some of these are metalinguistic abilities that, in normal children, are mastered considerably after the acquisition of grammar. These skills are more fully developed in WMS than in DNS. In addition, the spontaneous language production of adolescents and adults with WMS shows that they typically produce a variety of grammatically complex forms, including passive sentences, conditional clauses, and embedded relative clauses, although there are occasional morphosyntactic errors, and even some systematic ones, e.g., in language about spatial relations (Karmiloff-Smith, 1998; Lichtenberger & Bellugi, 1998; Rubba & Klima, 1991).

Individuals with WMS display a stronger ability to process conditional questions (“What would you do if ...”) than individuals with DNS (Figure 4). In a sample of 14 subjects, half with WMS and half with DNS, the individuals with WMS responded correctly to the conditional questions 83% of the time, while the individuals with DNS responded correctly only 29% of the time ($t = 4.03$; $p < .01$). Teens and adults with WMS tended to respond in complete sentences whose content indicated they understood the question and, importantly, tended to respond with the appropriate grammatical marking. For example, when subjects were asked questions such as “What if you were a bird?,” responses included: “I would fly through the air and soar like an airplane and dive through trees like a bird and land like a bird,” “I would fly where my parents could never find me. Birds want to be independent,” and “I would fly and if I liked a boy, I would land on his head and start chirping.” These types of responses were in contrast to those of the subjects with DNS which included sentence fragments, such as “fly in the air,” and included content sometimes indicating that the question might have been misunderstood, such as, “bird seeds.”

Lexical Semantics

Although individuals with WMS demonstrate considerable linguistic abilities given their level of other cognitive abilities, even to the naive ear, aspects of their language—particularly their vocabulary—sometimes strike people as unusual. One of the first groups of WMS we studied was referred by a cardiologist who asked if there was interest in studying a group of individuals with a heart defect who “talked funny.” In casual conversation with WMS individuals, one may notice that they sometimes use unusual, rather sophisticated words—unexpected, considering their overall level of cognitive functioning (e.g., “commentator,” “sauté,” “mince,” and “alleviate”). Sometimes, these words are used correctly, but other times they are partially, but not completely, appropriate in the accompanying context.

Figure 4. Individuals with WMS (12 years and older) perform significantly better than those with DNS (age- and Full Scale IQ-matched to WMS subjects) on syntactic processing tasks (e.g., conditional sentences) on both grammar and content. Examples of responses by subjects with WMS and DNS are shown. Normal control levels are shown by a line.



For example, one subject stated “I have to evacuate the glass” as she emptied a glass of water. The transitive verb ‘evacuate’ conveys emptying something, but most often this refers to removing people from something that is containing them, as in ‘evacuate the city’. The

erroneous word choices are often in the right semantic field, but they sometimes fail to convey semantic nuances appropriate for the context.

Across a realm of studies, WMS individuals appear to show a *proclivity* for unusual words, not typical of

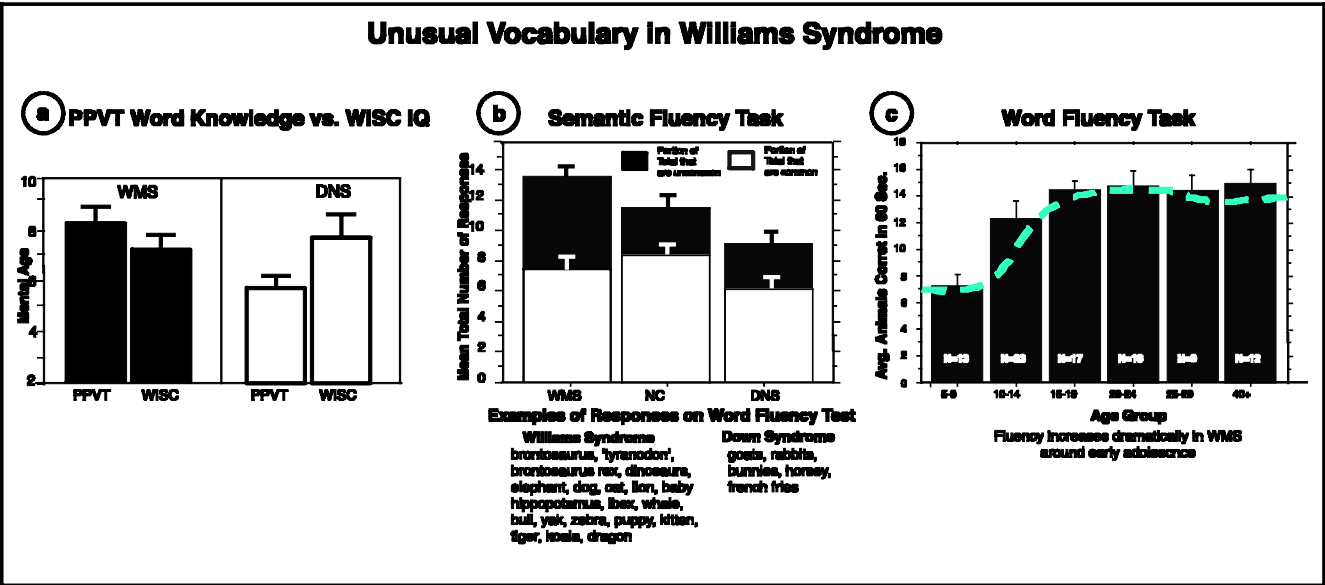


Figure 5. (a) Although the WMS and DNS subjects had comparably low IQ scores, WMS subjects scored significantly higher than their mental age on a probe that taps lexical knowledge, whereas DNS scores significantly lower than their mental age. (b) On a semantic-fluency task requiring subjects to produce as many names as possible in 60 sec, WMS adolescents produce far more responses than the DNS group; in fact, as many as mental age matched normal controls. WMS also produced significantly more uncommon words than their DNS counterparts or than the matched controls. (c) On the semantic-fluency test, there is a steady rise in the numbers of examples from WMS across the age span from 5 to 40 years; in particular, there is a sharp increase in fluency around the age of 11.

normal or DNS subjects. Despite their low IQ scores, adolescents with WMS were typically correct in matching such words as ‘canine,’ ‘abrasive,’ and ‘solemn’ with a picture on the Peabody Vocabulary test; note that WMS score higher than their mental age on that test, whereas DNS score lower than their mental age (Figure 5a). In a task of semantic organization, subjects were asked to name all the animals they could think of in a minute. WMS subjects not only gave significantly more responses than mental-age matched normal controls, some also produced more uncommon animal names than DNS subjects or control subjects (Rossen et al., 1996; Wang & Bellugi, 1993). For example, one WMS subject said in sequence, “tiger, owl, sea lion, zebra, hippopotamus, turtle, lizard, reptile, frog, beaver, giraffe, chihuahua,” and another said, “... ibex, whale, bull, yak, zebra, puppy, kitten, tiger, koala, dragon.” Many of the DNS subjects, in contrast, repeated animals or included non-animals in their responses; for example, one DNS individual said, “goats, rabbits, bunnies, horsey, french fries ...” (see Figure 5b). Some important developmental trends have been noted in the within-category naming abilities of individuals with WMS (Rossen et al., 1996). For example, in a sample of 84 individuals with WMS from 5 to 40 years who were administered the semantic-fluency task, age-related increases were noted in performance; there was a significant positive correlation between production of words and age ($r = .34$, $p < .001$) with a steep rise around the age of 11 (Figure 5c).

To gain insight into the nature of semantic organization, individuals with WMS, DNS, and fourth-grade normal controls were given a series of experimental

probes to investigate their processing of homonyms, words with more than one meaning. These tasks examine the relative salience of primary (higher frequency) and secondary (lower frequency) meanings of homonyms, such as SWALLOW (gulp, bird); WATCH (to look, time); FEET (toes, measure). We constructed the list of homonyms chosen so that one meaning (the primary meaning) was more common than the other meaning (the secondary meaning), according to comprehensive norms (Rossen et al., 1996). Three tasks were performed using the homonyms: Free association, similarity judgment, and definitions. The free-association task required the participants to say the first word that came to mind after hearing a homonym. In this task, all three groups responded similarly, offering associates related to the primary meaning of the homonym.

In the similarity-judgment task, subjects were presented with word triads composed of the homonym, and words related to the primary and secondary meanings (Rossen et al., 1996; example shown in Figure 6a). Subjects were asked to repeat the word triad after the experimenter and then pick which two words “go together best.” Normal controls tended to choose the primary meanings more frequently than secondary meanings as did the subjects with DNS. Subjects with WMS, in contrast, provided an equal number of primary and secondary meanings, suggesting anomalous semantic organization (see Figure 6b).

For the definitions task, subjects were asked to “tell me everything you know about what (the homonym) means.” If the subject did not provide both meanings spontaneously, the experimenter probed for another

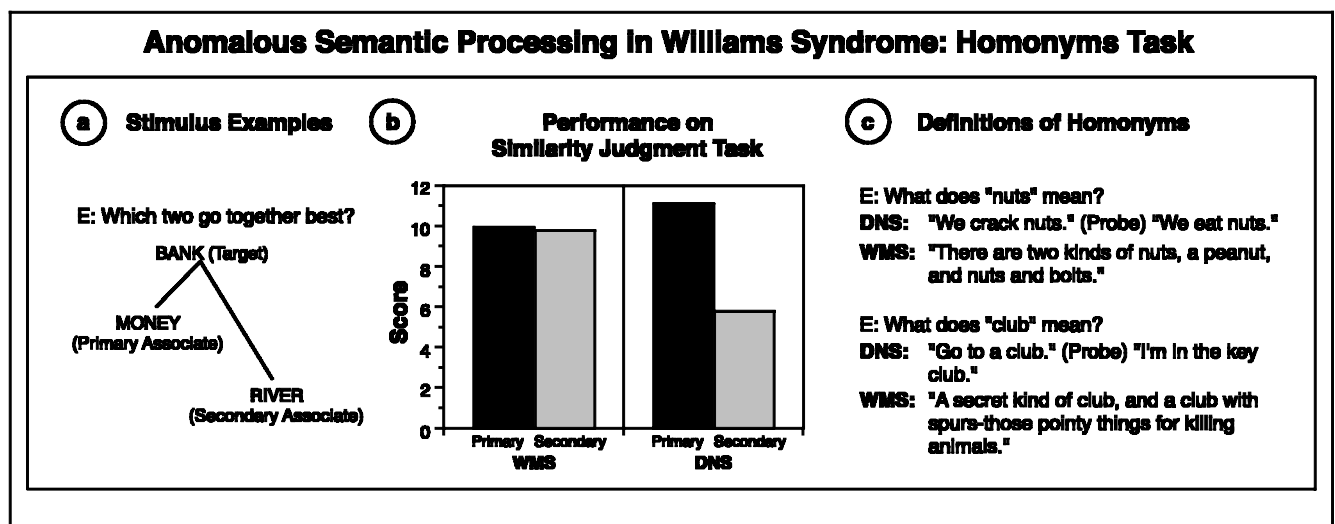


Figure 6. (a) The figure shows stimulus examples of homonyms task with primary and secondary meanings (e.g., ‘bank’). (b) Subjects with DNS and normal mental age controls provide more primary meanings than secondary meanings of the homonyms, as would be expected. Subjects with WMS, in contrast, provide an equal number of primary and secondary meanings, suggesting anomalous semantic organization. (c) Sample responses show that WMS subjects are able to access both the primary and secondary meanings of homonyms while DNS subjects access only one meaning, sometimes with two responses. For the meaning of ‘club,’ a DNS individual said “Go to a club” and then “I’m in the key club” whereas a WMS individual said: “A secret kind of club, and a club with spurs ...”

meaning: “Can you tell me anything else that (the homonym) means?” WMS were just as likely as controls to provide definitions compatible with the primary meaning of the homonyms. However, just as in the similarity-judgment task, they were also significantly more likely than controls or DNS to provide, in addition, definitions compatible with the secondary meaning of the homonym (see Figure 6c). Taken together, the data from the similarity-judgment task and the definitions task suggest that there may be some unusual aspects to semantic processing in WMS involving, perhaps, attenuation of the usual effect of frequency or familiarity.

There is other related evidence to suggest unusual semantic processing in individuals with WMS. Event-related brain potentials (ERPs) were recorded during auditory sentence comprehension (Mills, Neville, Appelbaum, Prat, & Bellugi, 1997). Subjects heard sentences that included a semantic anomaly, such as “I have five fingers on my moon.” The semantic anomaly “moon” instead of the expected word “hand” evoked the N400 component of the waveform. Analysis of the N400 showed that the WMS subjects did not produce the typical scalp distribution found in normal subjects, but rather, showed a more distributed N400 response, not the right-greater-than-left asymmetry typical of normal subjects. This finding may be related to the unusual semantic proclivities shown by WMS in the tasks described above. Furthermore, the neural systems underlying syntactic processing may also turn out to be different from normal, despite the relative

sparing of language abilities in WMS subjects compared to DNS (Mills, 1998; see also Mills et al., this volume).

Comparison of Language in WMS with Other Contrast Groups

In our studies, we have had the opportunity to contrast aspects of language development across diverse groups of subjects, ages 4–12, as part of a project with the Center for Neurodevelopmental Studies, to gain a fuller understanding of language abilities in children with WMS. On a sentence-repetition task, the Carrow Elicited Language Inventory (CELI; Carrow, 1974), we compared children with WMS ($N = 29$) to children who were classified as language impaired ($N = 24$) and to children with early focal brain lesions ($N = 14$), as well as to 86 normal control children. The language impaired children were defined as those with Wechsler Performance IQs of 80 or better, but whose scores were at least 1.5 standard deviations below the mean on a standardized test of language production. All four groups showed clear progress in language development across the age range (including the children with WMS who, in contrast, show no development on cognitive tests such as Piagetian tests of conservation). The WMS group repeated significantly fewer sentences correctly (59.6%) than did the normal group (84.8%) ($F(1,113) = 28.73$, $p < .0001$). However, the performance of individuals with WMS was *not* significantly different from that of children who were language impaired or

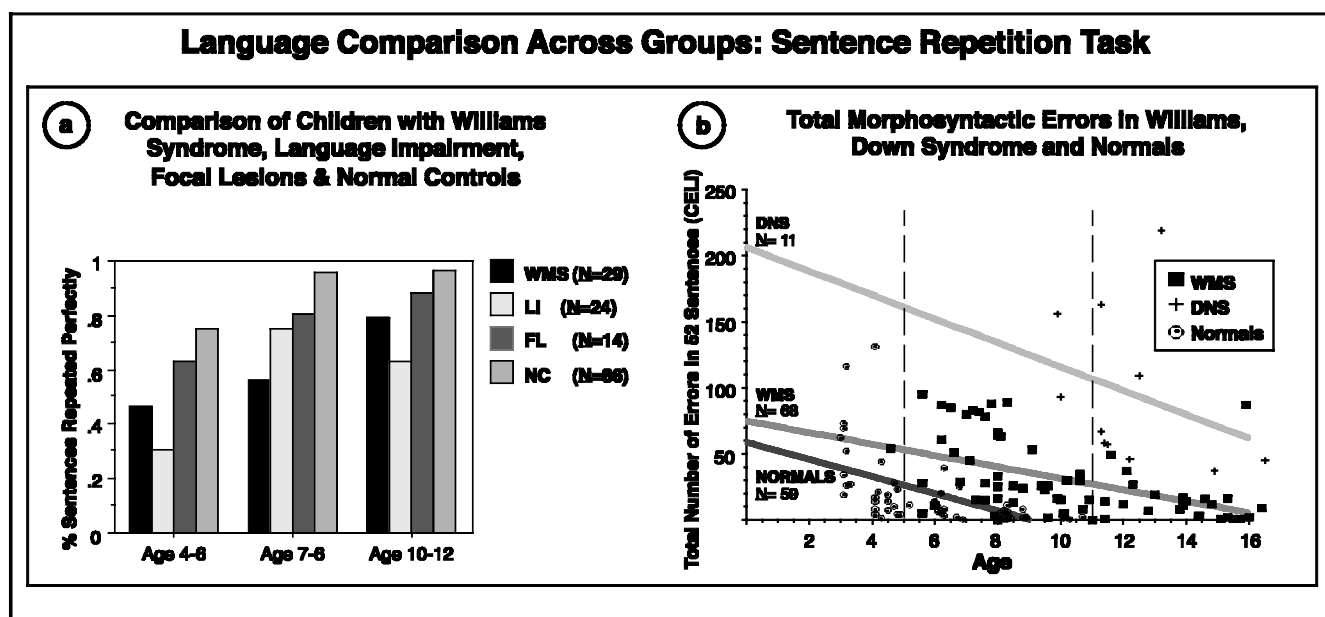


Figure 7. (a) On a task of sentence repetition, children with WMS, children with early focal lesions, and children with language impairment are not significantly different from one another in their ability to correctly repeat sentences at all ages. (b) The number of morphological errors made during the sentence-repetition task in a group of children with WMS, with DNS, and a group of normally developing children. The number of errors decreases consistently from ages 5 to 16 in children with WMS, which is similar to a developmental trend seen in normals at a younger age.

who had focal brain lesions (see Figure 7a). This is of interest because there was no global cognitive impairment in the language impaired or focal lesion groups, yet subjects with WMS, this genetically based group of mentally retarded individuals, performed at a level on this language task that was comparable to that of these contrast groups.

In another comparison using a sentence-repetition task, groups of children with WMS ($N = 68$) and a small number of children with DNS ($N = 11$), who were functioning at about the same level of general cognitive ability, were contrasted with normal controls ($N = 59$). The number of morphosyntactic errors in the sentences across the age span was examined for each group (Figure 7b). Normally developing subjects showed a decreasing number of errors from ages 2 to 8 years and obtained a nearly perfect score between ages 8 and 9, on average. Similar to the developmental trends mentioned earlier, subjects with WMS also showed clear developmental progress on this task, although slower than normal, with a decreasing number of morphosyntactic errors from ages 4 to 14 and, on average, were making few errors by ages 14–16 years. In contrast, the subjects with DNS showed a significant amount of variability in their performance with a decreasing number of morphosyntactic errors as they progressed through early childhood into adolescence, but they continued to exhibit errors in performance at age 16.

In summary, across a variety of language tasks, the subjects with WMS perform far better than age- and IQ-matched individuals with DNS and, in a direct language comparison, perform similarly to subjects with language impairment without mental retardation or subjects who have had early focal lesions (Bellugi, Losh, Reilly, & Anderson, 1998). Although subjects with WMS typically start with a delay in the production of first words that is equal to that of subjects with DNS, by adolescence and adulthood, language is clearly a relative strength of WMS; thus, the early stages of language do not predict the later ones. The distribution of abilities across the major domains consisting of language and visuo-spatial abilities in WMS can be seen in Figure 8, which shows scores across 120 individuals with WMS for a standardized vocabulary test, the Peabody Picture Vocabulary Test—Revised (PPVT-R; Dunn & Dunn, 1981) and a standardized task that requires copying geometric shapes, the Developmental Test of Visual-Motor Integration (VMI; Beery, 1997). The contrast between performance in the two domains, language and spatial abilities, is striking. Whereas lexical abilities in WMS individuals on the PPVT-R are higher than their mental age (with a few individuals even within the normal range, see also Figure 5a), visuo-spatial abilities are markedly low across individuals with WMS of all ages. As we discuss next, this pattern of performance in WMS is opposite that of individuals with DNS.

Distribution of Language and Spatial Measures in Williams Syndrome

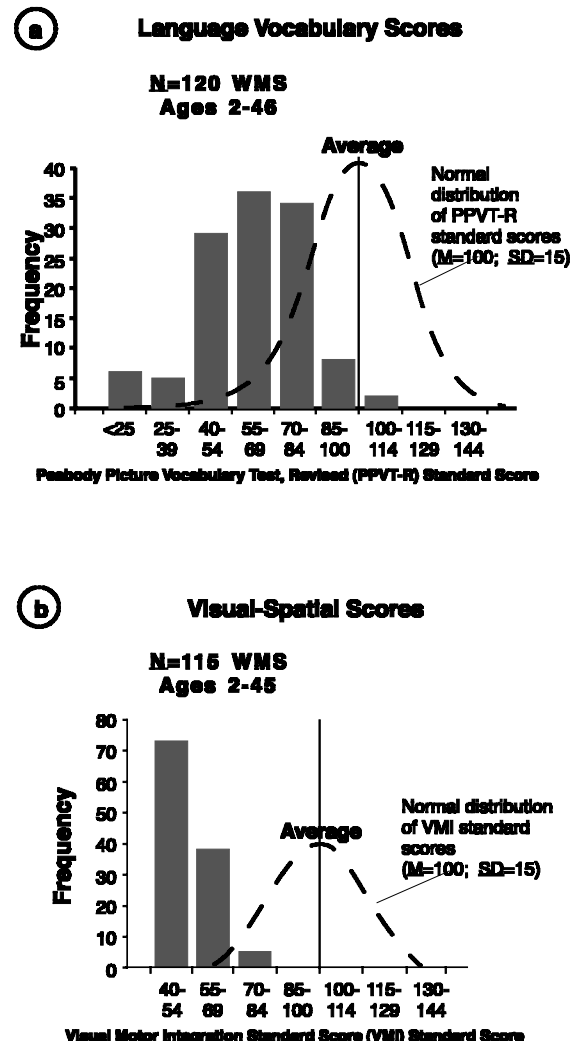


Figure 8. (a) On the Peabody Picture Vocabulary Test—Revised (PPVT-R), the WMS group shows a distribution in performance with some subjects performing in the normal range. (b) On the Developmental Test of Visual–Motor Integration (VMI), the WMS group shows significantly worse performance in their visual-motor skills in contrast to their lexical knowledge. Most subjects, regardless of age, score on the floor of the spatial task.

Controversial Issues in Language and Cognition

As interest in WMS has grown, the number of studies has rapidly increased. Controversial issues have been raised by the research on WMS, some having to do with the relation between language and other aspects of cognition, which continue to be a matter of debate (Clahsen & Almazan, 1998; Bates, 1997; Karmiloff-

Smith et al., 1997; Stevens & Karmiloff-Smith, 1997; Levy, 1996; Pinker, 1994; Pinker, 1997). Some consider the syndrome as a good example of the modularity of language as a system separate in significant respects from other general cognitive abilities. Others argue that since adults with WMS have been found to function in relevant ways at the level of 5- to 7-year-olds, that level would provide a sufficient substrate of cognitive abilities for the development of complex syntax and, accordingly, WMS does not represent a dissociation between language and general cognitive functions. Levy (1996) argues that there may be “uniquely preserved accessing privileges for language which may enable individuals with WMS to reach levels of performance that they cannot reach through other modalities.” There are unresolved questions about the relationship between syntax and semantics, about the intactness of levels of language in WMS. Yet, most researchers generally agree that the structural aspects of language (e.g., morphology and syntax) are a relative strength in WMS, perhaps different from other syndromes that involve mental retardation (Bellugi & Wang, 1998; Karmiloff-Smith, 1998; Volterra et al., 1996).

The Intersection of Language and Affect

A distinctive facet of the language abilities of individuals with WMS is their ability to use their considerable linguistic skills to engage others socially (Bellugi et al., 1996b). Many individuals with WMS display a strong impulse toward interpersonal contact and a proclivity for affective expression, although their social behavior is not always appropriate (Einfeld, Tonge, & Florio, 1997). The intersection of language and social behavior in individuals with WMS has been investigated through a series of narrative tasks in which subjects are asked to ‘tell’ a story from a series of static images in a wordless picture book (Bellugi & Wang, 1998; Bellugi et al., 1998; Bellugi, Mills, Jernigan, Hickok, & Galaburda, 1999b). The following paper (Jones et al., this volume) provides examples of the affectively expressive language used by subjects with WMS compared to subjects with DNS. The most obvious characteristic differentiating subjects with WMS from those with DNS and age-matched normal controls is in their use of narrative enrichment devices during this story-telling task. The information conveyed by the enrichment devices goes beyond what is explicitly presented in the static pictures themselves. By linguistic means (through choice of words and use of prosody), the emotions and thoughts of the characters pictured are expressed, and also the emotions and evaluations of the ‘narrator’—in this case, the particular WMS individual.

As will be shown in the next paper, individuals with WMS show an abundance of affectivity in both prosody and lexical devices and appear to be able to manipulate

affective linguistic devices for the purposes of story-telling. (Affective prosody was measured by noting how frequently paralinguistic affective expression was used, including pitch change, vocalic lengthening and modifications in volume.) Affectivity in lexical devices was measured in the frequency of exclamatory phrases and other devices to engage the audience (e.g., ‘*Suddenly splash!* The water came up’; ‘*Lo and behold!*’). This pattern of increased linguistic affectivity was found to be strikingly different from what was found in subjects with DNS, as well as in normal individuals at any age or in the other contrast groups studied (e.g., individuals with early focal brain lesions and Language-Impaired children).

In sum, in adolescents and adults with WMS, language is typically used effectively (and sometimes effusively) in social situations. Perhaps, a prime characteristic of individuals with WMS is a strong impulse toward social contact and affective expression. Thus, the social and language profiles of individuals with WMS are also in striking contrast to individuals with other disorders such as autism.

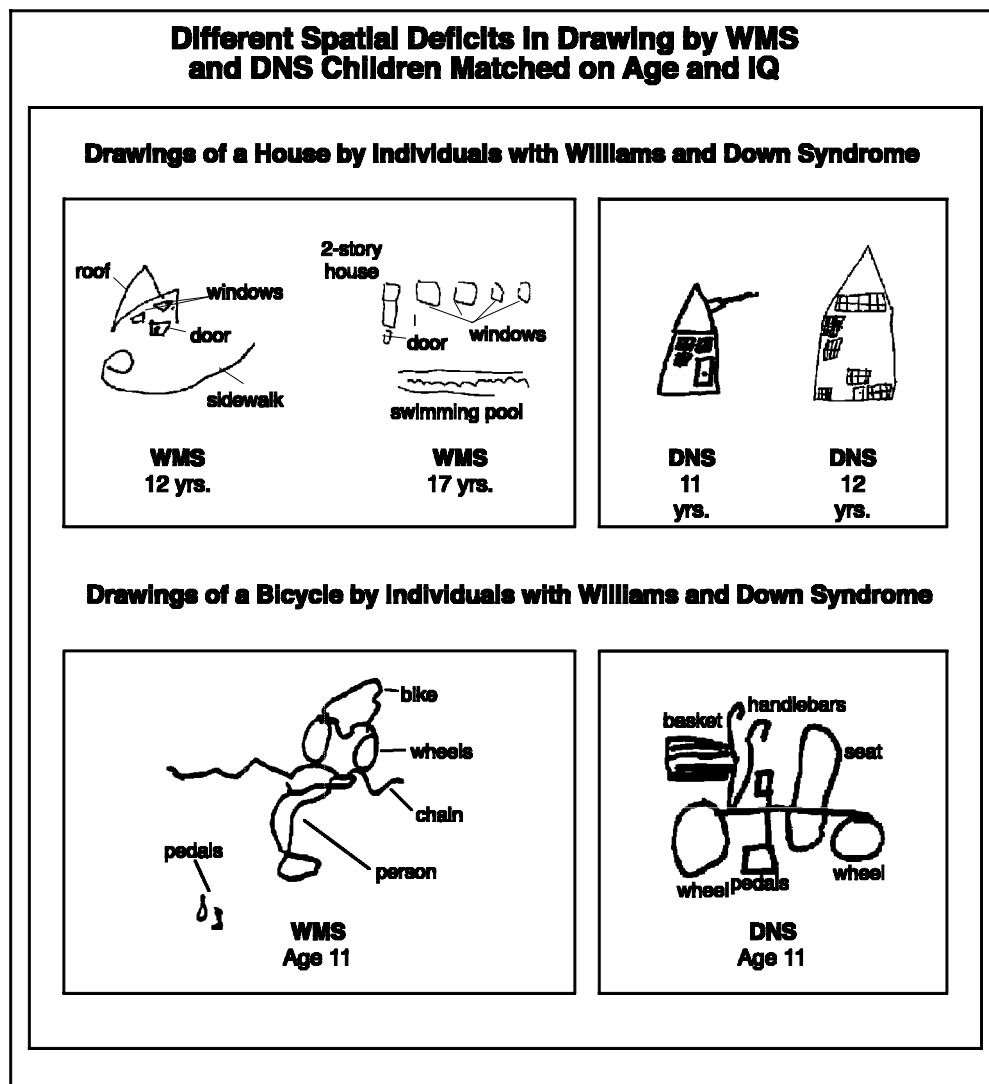
The Domain of Spatial Cognition: Peaks and Valleys of Abilities

Unlike language, with its well-defined levels of phonology, morphology, syntax, and discourse, the domain of spatial cognition has largely resisted fractionation into components (c.f., Stiles-Davis, Kritchevsky, & Bellugi, 1988). By comparing the spatial cognitive deficits in WMS and DNS, we can examine different patterns that might emerge as a result of different genetic anomalies (Bellugi et al., 1990; Bellugi et al., 1992; Bellugi et al., 1999a; Bihrlé, Bellugi, Delis, & Marks, 1989; Bihrlé, 1990). A discussion of some of our specific findings follows.

Differing Patterns of Spatial Deficits in WMS vs. DNS

In order to explore spatial cognition, a battery of standardized tasks was administered to subjects with WMS and DNS. WMS subjects were found to be severely impaired on the Block Design subtest of the WISC-R (Wechsler, 1974), and on the VMI (Visuo-motor Integration, Beery, 1997). The Block Design task requires the subject to arrange a set of blocks (with sides colored red, white, and half-and-half) so they replicate increasingly complex stimulus patterns. The VMI task requires the individual to copy geometric shapes ranging from straight lines and triangles to more complex interpolated three-dimensional shapes. When subjects with WMS are asked to draw, whether copying an illustration or doing free drawing, the product typically has poor cohesion and lacks overall organization within the images. In other populations, important developmental trends have been noted on the VMI; individuals with

Figure 9. Free drawings of houses by age- and IQ-matched adolescents with WMS and DNS show different spatial deficits. The drawings by subjects with WMS contain many parts of houses but the parts are not organized coherently. In contrast, the DNS subjects' drawings are simplified but have the correct overall configuration of houses. Similarly, drawings of a bicycle by a subject with WMS shows the 'person' upside down, the pedals off to the side, and the chain floating in the air, all in a disorganized fashion (verbal labels were added by the subject as he drew). In contrast, the matched subject with DNS produces a simplified but recognizable drawing with the correct overall configuration of a bicycle.

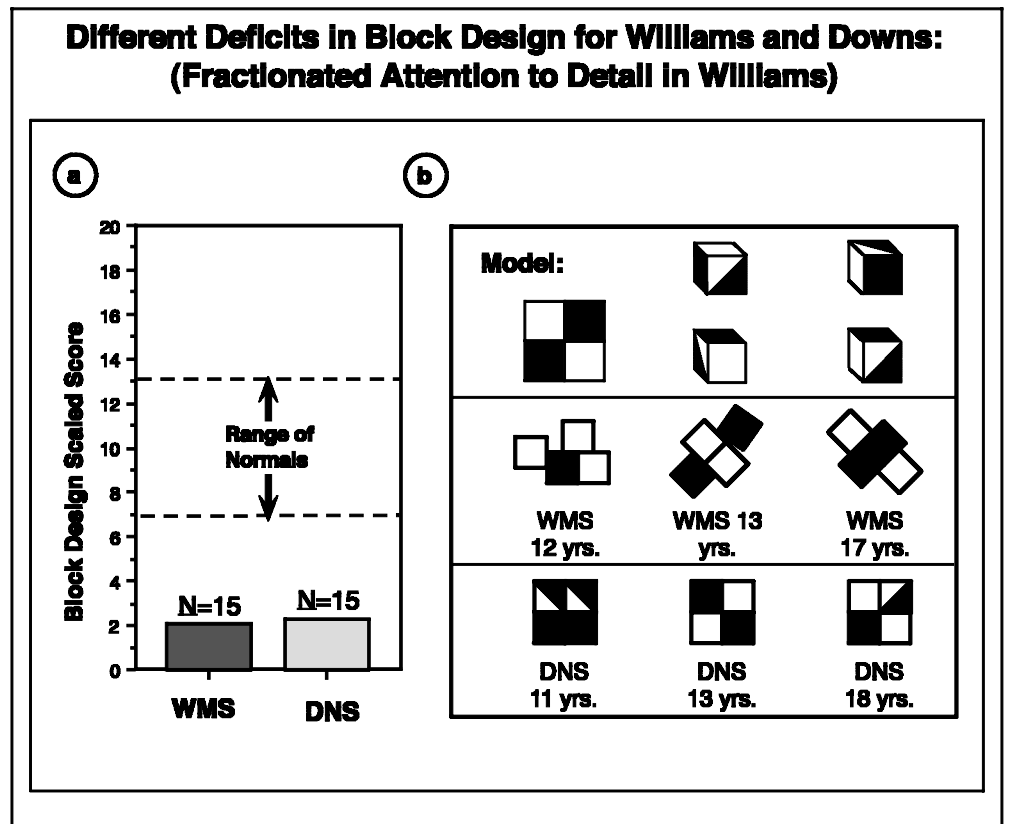


prenatal focal lesions to the right hemisphere exhibit good recovery over time and improved performance on this task by age 8 years. In contrast, even into adulthood, individuals with WMS tend to plateau and remain basically at the level of normally developing 5-year-olds (Beret, Bellugi, Hickok, & Stiles, 1996). Frequently, we have noted WMS individuals verbally mediating their way through drawings, thus enabling us to add the individual's own verbal labels to interpret the components of the drawing (Figure 9). For example, drawings of houses by WMS individuals may show a door, a roof and windows, but the parts might be depicted in an unrecognizable relationship to each other (e.g., windows stretched out across the page outside of the boundaries of the house). In contrast, comparable subjects with DNS might produce drawings with little detail, but showing good closure and form, with appropriate relationships among the elements (see Figure 9, top). The illustration also shows drawings of a bicycle by individuals with WMS and with DNS both age 11, and both with IQs in the 50s (Bellugi, 1998). Note that the

drawing of a bicycle by the individual with DNS is simple and lacks extensive detail, yet it is recognizable and has good closure and integrated form to the parts. In contrast, the drawing of a bicycle by the individual with WMS is highly fragmented; the pedals are off to one side, the person is upside down, and the chain is floating in the air (see Figure 9, bottom).

In a study using the Block Design subtest of the WISC-R (Wechsler, 1974), spatial-cognitive deficits were found in subjects with both WMS and DNS, with equally poor levels of performance (WMS $N = 15$; DNS $N = 15$). However, examination of the *process* by which they arrived at their scores reveals striking differences between the two syndromes (Bellugi et al., 1996b; Bellugi et al., 1999b; Wang, Doherty, Rourke, & Bellugi, 1995). Although they failed to provide correct designs, the subjects with DNS generally kept the global configuration of the block arrangements, with details of the internal configurations of the designs incorrect. Subjects with WMS, by contrast, failed to keep the global configuration of the designs, appearing biased toward the

Figure 10. (a) On average, adolescents with WMS and DNS were similarly impaired on the WISC-R Block Design subtest. (b) Although the end score is equally poor for WMS and DNS (scaled scores more than 2 SD below normal), they fail in very different ways. Subjects with WMS typically show disjointed and fragmented designs, while age- and IQ-matched DNS subjects tend to make errors in internal details while maintaining the overall configuration.



details of the designs (see Figure 10). They frequently placed the blocks in apparently haphazard, noncontiguous arrangements. In a process analysis comparing adolescents with WMS and DNS, those with WMS were found to make far more moves, and very frequently made these moves in continuously fragmented patterns. Thus, across several spatial-cognitive tasks (copying drawings, free drawings, block design), there are marked and specific spatial deficits that have been found in WMS (Bellugi, 1998).

Seeing the Forest or the Trees

To investigate and characterize these various visual-cognitive impairments, an experimental task that distinguishes two levels of structure, involving both local and global features in a balanced array was used. Items were composed of local components that together constituted a global form (i.e., a big 'D' made up of little 'Y's). On these tasks, characteristic deficits that separated the subjects with WMS from those with DNS were found (Bihle et al., 1989). When asked to draw the designs made of two levels of hierarchical structure, both groups failed, but in distinctively different ways. In these paradigms, subjects with WMS typically produced primarily the local forms sprinkled across the page, and were impaired at producing the global forms. Subjects with DNS showed the opposite pattern; they tended to produce the global forms without including

the local forms (see Figure 11). This was true whether subjects had to reproduce forms from memory (after a 5-sec delay) or whether they were asked to copy the forms that lay in front of them. In a follow-up study using a larger number of subjects with WMS ($N = 35$), WMS subjects were again found to show more of a bias toward the local level of the stimuli than to the global level ($p < .01$). In perceptual-matching tasks as well, using hierarchical figures, subjects with WMS showed a distinct local bias. These results suggest differential processing patterns in WMS and DNS, and highlight what may be a bias toward fractionation of the gestalt and over attention to detail, at the expense of the whole (Atkinson, King, Braddick, & Nokes, 1997; Wang et al., 1995; Bihle et al., 1989; Bellugi et al., 1999a).

Face Processing: An Island of Sparing in WMS

Despite their severe spatial-cognitive dysfunctions, there are domains in which subjects with WMS display selective sparing of abilities. Subjects with WMS demonstrate a remarkable ability to recognize, discriminate, and remember unfamiliar and familiar faces (Rossen, Jones, Wang, & Klima, 1995a). However, this ability was not noted in individuals with DNS. In fact, the performance of the WMS group is at a near-normal level (Jones, Hickok, & Lai, 1998a; Rossen, Smith, Jones, Bellugi, & Korenberg, 1995b). These strengths include abilities related to the perception of faces,

Differential Impairment on a Local/Global Processing Task in Williams and Down Syndrome

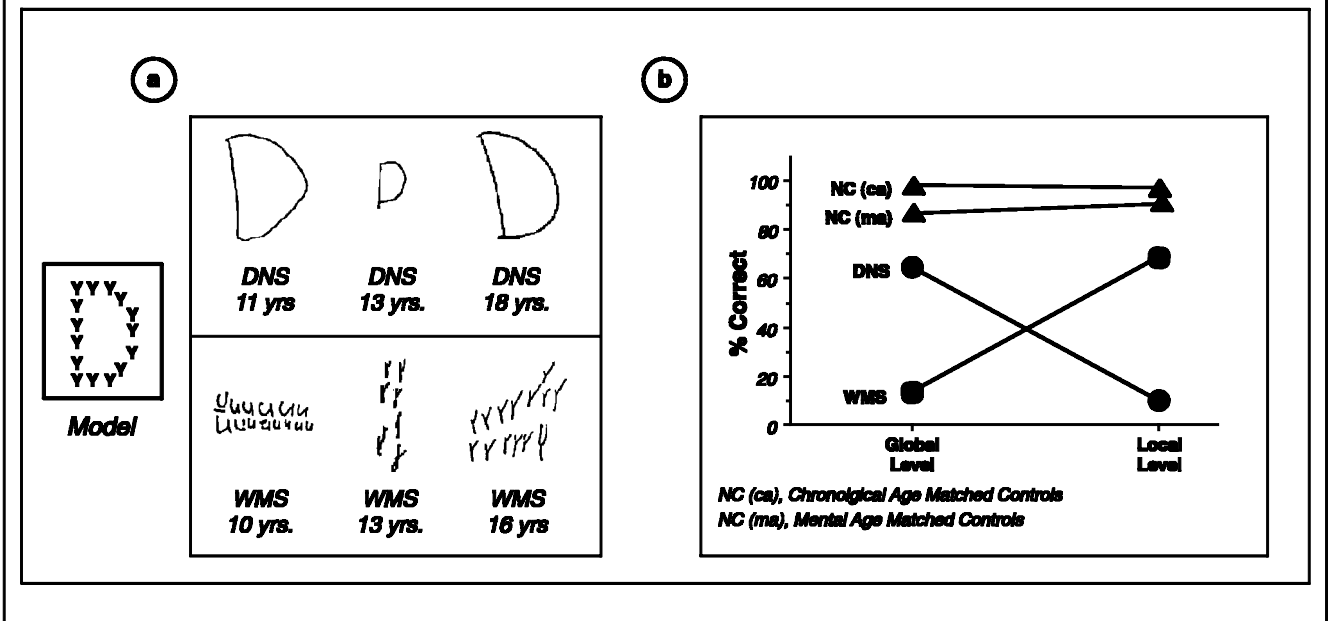


Figure 11. (a) On the Delis Hierarchical Processing task, subjects are asked to copy a large global figure made of smaller local forms (e.g., a ‘D’ made out of ‘Y’s). Both groups fail but in significantly different ways: Subjects with WMS tend to produce the local elements sprinkled across the page, whereas age- and IQ-matched DNS subjects tend to produce only the global forms. (b) When drawing these designs from memory or from copy, subjects with WMS tend to reproduce the local level of the stimuli with more accuracy, subjects with DNS tend to reproduce the global level of the stimuli with more accuracy. Normal chronological age-matched subjects reproduce both levels of the figure with approximately equal accuracy.

such as the ability to recognize faces when seen in various lighting conditions and orientations. Across an array of tasks involving faces, individuals with WMS outperform those with DNS (Jones et al., 1998a; see Figure 12). The Benton Test of Facial Recognition (Benton, Hamsher, Varney, & Spreen, 1983b) is a face-discrimination task in which subjects are asked to identify which ones of six faces match the target individual. The faces involve the same individual under different conditions of lighting, shadow, and orientation. The Warrington Recognition Memory Test (Warrington, 1984) is a recognition-memory task that presents the subject with unfamiliar faces. The Mooney Closure Task (Mooney, 1957) is considered a closure task in which black and white photographs of faces are shown with many background and facial details ablated by shading. Subjects are required to decide whether the face is a male or female or whether it is someone young or old. In separate studies using the Benton Test of Facial Recognition (WMS, $N = 71$; DNS, $N = 16$), the Warrington Recognition Memory Test (WMS, $N = 17$; DNS, $N = 10$), and the Mooney Closure Task (WMS, $N = 33$; DNS, $N = 10$), subjects with WMS, despite their marked visuo-spatial deficits, performed remarkably well; their performance was significantly better than that of subjects with DNS and as proficient as normal age-matched controls (Jones, Rossen, Hickok, Jernigan, &

Bellugi, 1995b). Thus, while there are gross deficits in general cognitive abilities, subjects with WMS typically exhibit a distinctive pattern of peaks and valleys in visuo-spatial cognition: An emphasis on local over global processing and extreme fractionation in drawing; yet an island of sparing for processing, recognizing, and remembering faces (Rossen et al., 1995b; Bellugi et al., 1994; Bellugi et al., 1999b).

Dissociation between Spatial Cognition (Impaired) and Face Processing (Spared)

The performance of individuals with WMS on face-processing tasks stands in contrast to their profound impairment on the other visually based cognitive tasks we have described above (drawing, constructing designs of blocks, reproducing hierarchically organized figures). We wondered whether the deficit in WMS might be primarily with tasks that involve spatial construction, or whether the spatial deficit extends to spatial *perception* as well. Two tasks that are nonlinguistic and depend on visual perception only were used to address this question. Both tasks involve processing pictures, and require pointing to the correct answer, but do not involve visuo-constructive abilities. Both tasks were developed by Arthur Benton of the University of Iowa as perceptual tasks that may be especially sensitive to right-hemi-

Superior Face Processing in Williams Syndrome

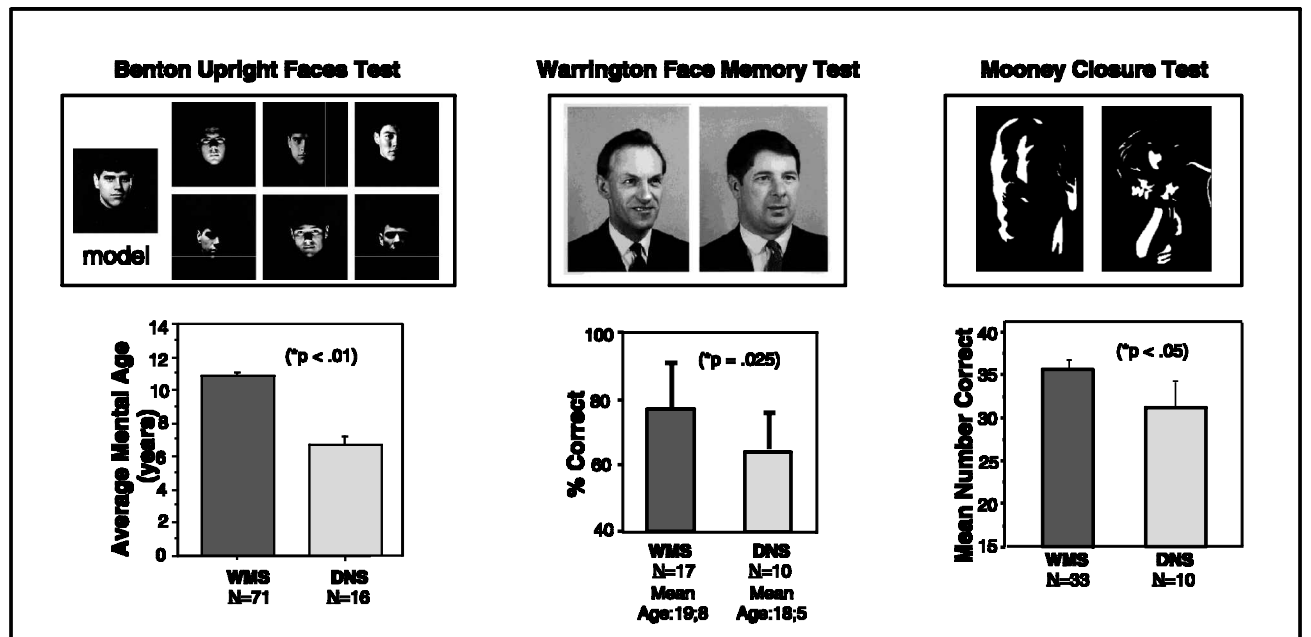


Figure 12. Across three tasks involving face processing (Benton Face-Recognition Task, Warrington Face-Memory Task, and Mooney Closure Task), subjects with WMS perform significantly better than their age- and IQ-matched DNS counterparts, indicating that face processing is indeed an area of remarkable sparing in WMS.

sphere damage in adults. One is the Judgement of Line Orientation (Benton, Hamsher, Varney, & Spreen, 1983a), a task of spatial cognition that requires a subject to look at a target pair of lines and then point the lines in an array that matches the target pair of lines. The other is the Benton Test of Facial Recognition (Benton et al., 1983b). On the line-orientation task, a sample of 16 subjects with WMS performed in the range considered “severely deficient” for adults; most of those with WMS could not even pass the pretest. In contrast, the group of individuals with WMS who failed the line-orientation task, performed very well, indeed, almost at the normal level for adults, on the face-recognition task (Figure 13). In a larger sample of WMS, the same dissociation in visuo-spatial abilities was found: Specifically, subjects with WMS ($N = 23$) performed significantly better on the face-recognition task (mean percent correct = 82.8) than on the task involving line-orientation judgment (mean percent correct = 31.0) ($t = -12.92$; $p < .0001$).

The Intersection of Space Representation and Language Representation in WMS

As has been discussed thus far, the dissociation between linguistic abilities (disproportionately spared) and visuo-spatial cognitive abilities (disproportionately impaired, except for certain aspects of face processing) is one of the hallmarks of the cognitive profile of WMS. There is a clear spatial-cognitive deficit in nearly all individuals with

WMS across both constructive and perceptual realms (observed on tasks that involve copying block designs, drawings, and hierarchical figures, as well as line-orientation judgment) (Bellugi, Lai, & Wang, 1997; Beret, Lai, Hickok, Stiles, & Klima, 1997). In language studies with individuals with WMS, we observe that even adults tend to occasionally misuse spatial prepositions in narratives (Rubba & Klima, 1991). For example, in a story-telling task from a wordless picture book about a boy and his dog and their search for a missing frog, statements are noted such as: “The boy was so sad, his tears were falling off from his eyes”; “The dog has the jar in his face” (the picture shows the dog with his head in a jar). Such errors made by subjects with WMS on this story-telling task suggested that the use of language to describe spatial relations was potentially problematic and warranted further study.

Testing individuals with WMS on tasks that involve the use of both linguistic and spatial abilities may result in one of two possible outcomes. Their strong language skills may mask their poor spatial abilities, or their poor spatial skills may interfere with their strong language abilities. An investigation of how subjects with WMS use prepositions to describe spatial relations was conducted in order to understand the intersection between their spared language and impaired spatial cognition. Two tasks were developed that measured an individual’s ability to comprehend and produce specific spatial prepositions. Data were collected from 28 WMS subjects

Peaks and Valleys of Ability in Visual Processing in Williams Syndrome: Lines vs. Faces

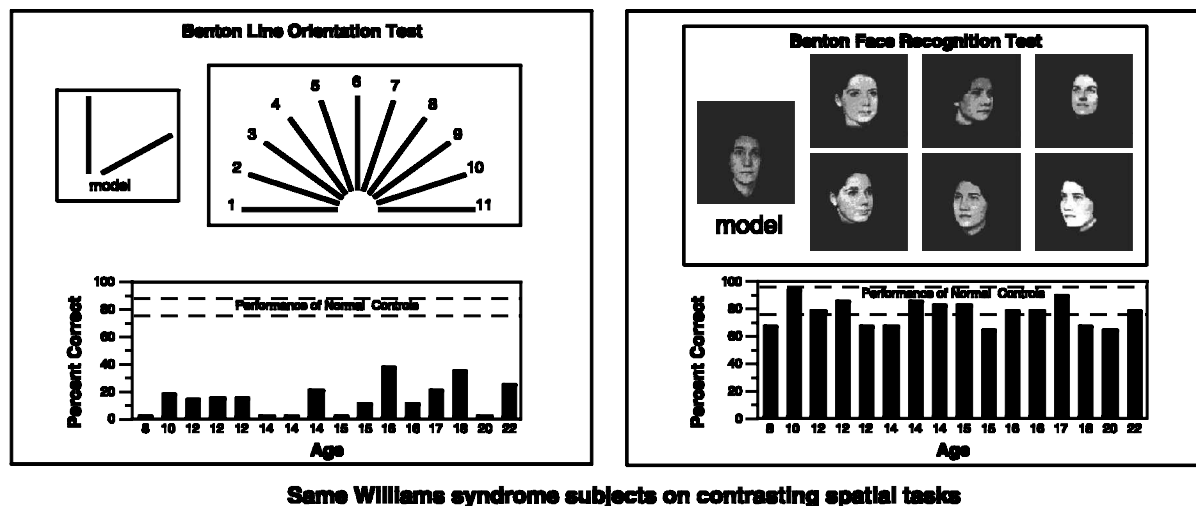


Figure 13. The strengths and weaknesses in visuo-spatial processing in WMS show an unusual profile. The results are shown from two tasks that are both visuo-perceptual tasks, sensitive to right-hemisphere damage, where the correct answer requires only pointing to a picture without any constructional component. Note that the same subjects with WMS perform very differently on the two tasks. The contrast in performance on line orientation (Benton Judgement of Line Orientation, mean percent correct = 36.67) and face discrimination (Benton Face Recognition, mean percent correct = 92.59) is shown for 16 subjects with WMS ($t = 18.69$; $p < .0001$). On the Line-Orientation task, several individuals with WMS could not even pass the warm up items. In great contrast, exactly the same subjects with WMS perform remarkably well on a very difficult face discrimination task that involves recognizing the same individual under different conditions of lighting, shadow, and orientation. In both tasks, performance of normal individuals is indicated by the broken lines.

(mean age: 19; range: 10 to 41 years) and 27 normal controls in the fifth and sixth grade (mean age: 11.25; range: 9.99 to 12.30 years), who were significantly younger than the experimental group (Lichtenberger & Bellugi, 1998).

In a test of comprehension of spatial prepositions, subjects were required to listen to auditorily presented spatial prepositions and choose one of four pictures that best represented the preposition or spatial phrase (e.g., through, between, above, in front of). Despite the age difference between normal control and WMS subjects, normal controls performed significantly better on the spatial preposition comprehension test ($p < .05$). In fact, the normal controls performed at ceiling, making only .2% errors on average. In contrast, the WMS subjects made an average of 11.5% errors.

The second task assessed expressive abilities with spatial language, as tapped by the production of spatial prepositions. In this task, subjects were asked to look at pictures in which a colored item was placed in relation to another item not colored, a task modeled after Bowerman (Bowerman, 1996). For example, a drawing of a boy (colored yellow) was depicted in front of a drawing of a chair, a drawing of an apple (colored yellow) was depicted inside of a transparent bowl. The subject's task was to tell where the shaded item was in relation to the other item. Subjects with WMS again

made significantly more errors when compared to the group of younger normally developing subjects ($p < .001$). On average, the WMS group produced errors in 30.2% of their verbal responses, but the group of normally developing children had a significantly smaller rate of errors. Examples of the kinds of errors made by the WMS group on the spatial preposition production task are shown in Figure 14.

As shown in Figure 14, individuals with WMS were noted to make errors in describing the spatial relationships that included *reversing* the subject and object of the sentence and those that were semantically inappropriate in other ways. For the item showing a *tree (colored) in front of (or beside) a church*, none of the normally developing younger children made responses that were irregular other than being atypically general in their descriptions. For example, some of the normally developing subjects responded, "the tree is by the church." However, some of the individuals with WMS made errors such as using a preposition that denotes a spatial relationship opposite from what was pictured, e.g., "tree behind a house," or produced responses that were inappropriate given the target picture, e.g., "the tree is growing on top of a castle." These types of language errors about spatial relationships made by some individuals with WMS in the spatial language production task were never observed even in the young-

The Dissociation between Language and Spatial Representation in Williams Syndrome

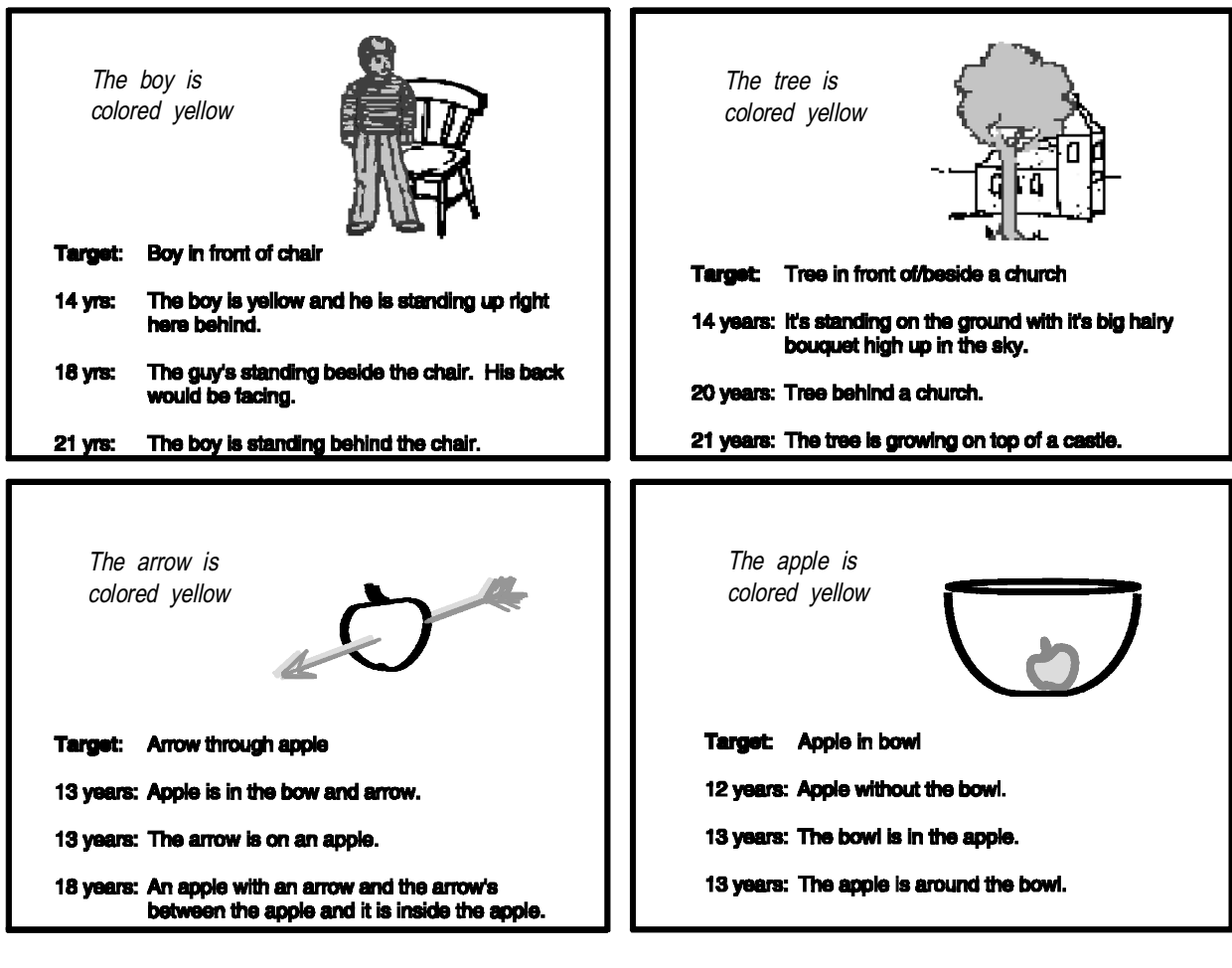


Figure 14. Experimental tasks were developed to investigate the intersection of language and spatial representation in WMS, including production and comprehension tasks (modeled after Bowerman, 1996). Shown here are sample errors made by WMS individuals aged 12 and older on a task involving the production of spatial prepositions and language about space. Note that on the actual stimuli pictures, one of the objects in the picture is colored yellow (but here is shaded) to represent the target item, as in the picture of an arrow passing *through* an apple. Individuals with WMS exhibit difficulty in the mapping between language and spatial representation, e.g., 'The arrow is on the apple,' or 'An apple with an arrow and the arrow's between the apple and it is inside the apple.' (Lichtenberger & Bellugi, 1998).

er normally developing group (Lichtenberger & Bellugi, 1998). Thus, from this initial task, it appears that the WMS individuals in particular may be having difficulty in the mapping between spatial representation and language representation. This area of investigation, involving a dissociation between language and spatial representations in WMS, should provide new understanding of the mapping between these domains.

Distinct Developmental Trajectories Across Cognitive Domains

Previous studies have shown that WMS results in a highly uneven profile of specific deficits, preservations, and anomalies both within and across cognitive domains. However, there has been little information available regarding the developmental profile in this rare disorder.

A study by Jones, Hickok, Rossen and Bellugi (1998b) (see also, Jones, Rossen, & Bellugi, 1995a) examined questions of development of specific cognitive domains in a cross-sectional study of 71 individuals with WMS (ages: 5 to 29 years; mean age: 14.9 years). Using standardized measures of receptive vocabulary, copying drawings, and face recognition, the study examined the patterns of age-related changes in WMS, using individuals with DNS as a basis for comparison.

The results indicate that subjects with WMS perform very differently on the three types of tasks during school-age, adolescence, and adulthood and also show distinct changes across the age range (see Figure 15a). In the WMS cohort, a specific development trajectory was found for each cognitive domain measured in contrast to the DNS cohort (Figure 15b). For instance, in the area of receptive vocabulary, children with WMS

Distinct Trajectories in Cognitive Domains in Williams Syndrome but not In Down Syndrome

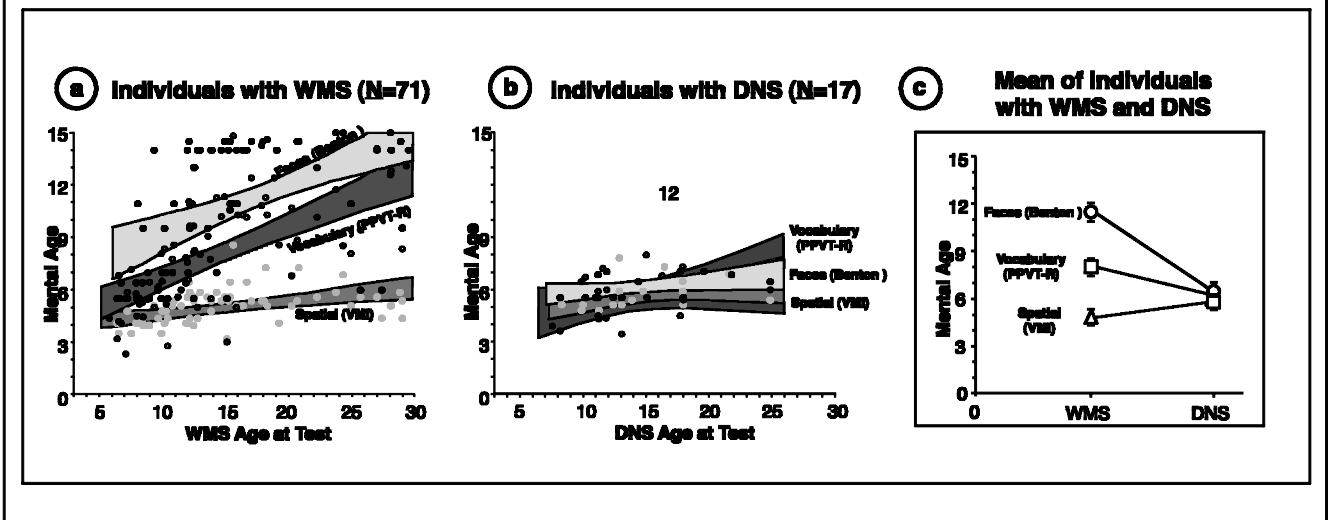


Figure 15. Developmental trajectories of contrasts between language, face and space processing in WMS are shown. (a) Subjects of all ages with WMS show distinctly different trajectories in three domains: Lexical knowledge, spatial cognition, and face processing. On a standardized test of vocabulary, subjects with WMS start with low scores and then show a sharp increase with age. On a spatial task that involves copying geometric shapes, the performances of subjects with WMS are consistently below those of subjects with DNS, and plateau at an early age. On a task of face processing, subjects with WMS perform extremely well even at very young ages. (b) Subjects with DNS showed essentially the same developmental trajectory across the three domains. In contrast, subjects with WMS show three distinctly different trajectories. (c) Planned contrasts show that performance on the three tests differs significantly within the WMS group, even when controlled for age. No between-test differences are found in the DNS group (reproduced from Jones et al., 1998a; Jones et al., 1998b).

were found to be significantly delayed early on, but then improved with increasing age. Once past this initial delay in language, subjects with WMS showed an increase in abilities throughout childhood, adolescence, and into adulthood. In contrast, in the visuospatial domain, subjects with WMS showed pronounced impairment and limited change in ability across the age-range studied. Development of face-recognition abilities in WMS was distinct from development in the visuospatial and receptive vocabulary abilities in the study. With face recognition, young children with WMS performed at a higher level, on average, than would be expected for their age, and performed well throughout development. In contrast to the other areas sampled, the face recognition can be characterized as a relative strength for WMS across the age span.

The WMS findings are even more impressive when they are compared to an age-matched sample of individuals with DNS (ages: 7 to 28 years; mean age: 14.5 years). The DNS group performed similarly on all three standardized tasks of receptive vocabulary, spatial ability and face processing (see Figure 15c). Thus, there was no evidence of age-related changes in DNS in the separate cognitive domains involved. In contrast, three distinctly different trajectories of development across age were found in WMS, yielding evidence for the separability of language, spatial abilities, and face processing in human behavior. Subjects with WMS present a rare opportunity

to study the separability of cognitive domains that normally develop together, and to characterize the trajectories of their development across the age span (Bellugi et al., 1999b).

Consistency (and Variability) in the Williams Cognitive Phenotype

The studies discussed in this paper, as well as in the other papers that follow in this volume, provide the opportunity to link variability in the phenotypic expression of the cognitive profile to variability in the expression of markers of brain structure, brain function and, ultimately, the gene. We have focused on the prototypical cognitive profile of WMS, which appears to distinguish this syndrome from DNS and, perhaps, other syndromes as well (see also Mervis et al., 1999). At the same time, we can address the extent to which there is some variability within the consistent profile of dissociations in higher cognitive function in WMS. Figure 16 shows aspects of the prototypical profile of WMS showing peaks and valleys of abilities within cognitive functions which we have so far elucidated—impairment in general cognition as measured by IQ tests, disproportionate strength in aspects of language, co-occurring with marked spatial cognitive deficits but excellent face processing. In addition to scores from such general cognition batteries as the

Cognitive Domains In Williams Syndrome Subjects

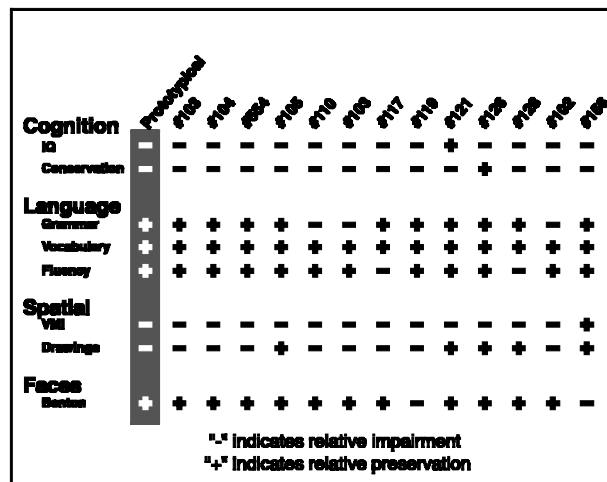


Figure 16. The prototypical cognitive phenotype for individuals with WMS is shown for the domains of cognition, language, spatial ability, and face processing ability. Most of the individuals in this WMS sample have cognitive profiles that show similar areas of relative impairment and relative strength.

WISC-R and WAIS-R, we now have a large database of results from general cognitive, language, and visuo-

spatial tasks on a significant number of individuals with WMS. We are quantifying what is typical, or the "normal-range" of functioning, for WMS on each of the standardized tests in our database. Thus, we can examine the extent to which each individual diagnosed with WMS falls within or outside the range of what is typical (or "normal" for WMS) as a group. Studies of the variability in neuro-behavioral profile within WMS are proving critical for exposing the relationships between cognitive and neural phenotypes and, ultimately, the genotype.

Social, Neural, and Genetic Markers: Elucidating the Phenotype

In this broad program studying the phenotype of WMS, we have described the cognitive profile and are now in a position to expand the phenotypic description to include social, neural, and genetic aspects of WMS. Studies of WMS social behavior described in the next chapter show that the behavioral phenotype also typically includes a type of "hyper-sociality." WMS individuals tend to be overly friendly with strangers, and even as infants show more positive and less negative behavior than normals in social situations, and are dramatic story tellers (Jones et al., this volume; Bellugi et al., 1998). This highly social interpersonal style noted in formal testing as well as in

Distinctive Brain Morphology In Williams and Down Syndrome

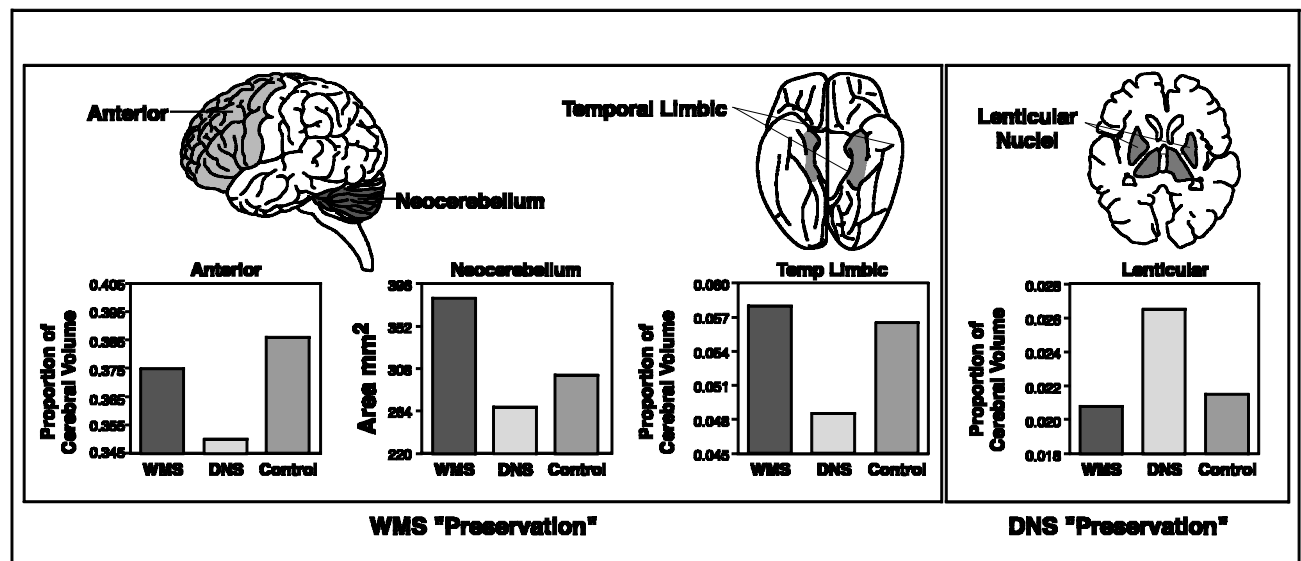


Figure 17. In vivo MRI studies involving computer-graphic analysis of brains of individuals with WMS suggest an anomalous morphological profile that consists of a distinct regional pattern of proportional brain volume deficits and preservations. (a) There is relative preservation of anterior-cortical areas and enlargement of neo-cerebellar areas in WMS subjects. These are two areas that have undergone the most prominent enlargement in the human brain relative to lower primates. (b) There is relative preservation of mesial-temporal lobe in WMS subjects. In conjunction with certain areas of frontal cortex, this area is thought to mediate certain aspects of affective functioning. (c) In DNS individuals, there is relative preservation of subcortical areas (lenticular nuclei) that is not seen in WMS, perhaps relevant to the significantly better motor skills in DNS subjects (adapted from Bellugi et al., 1996b).

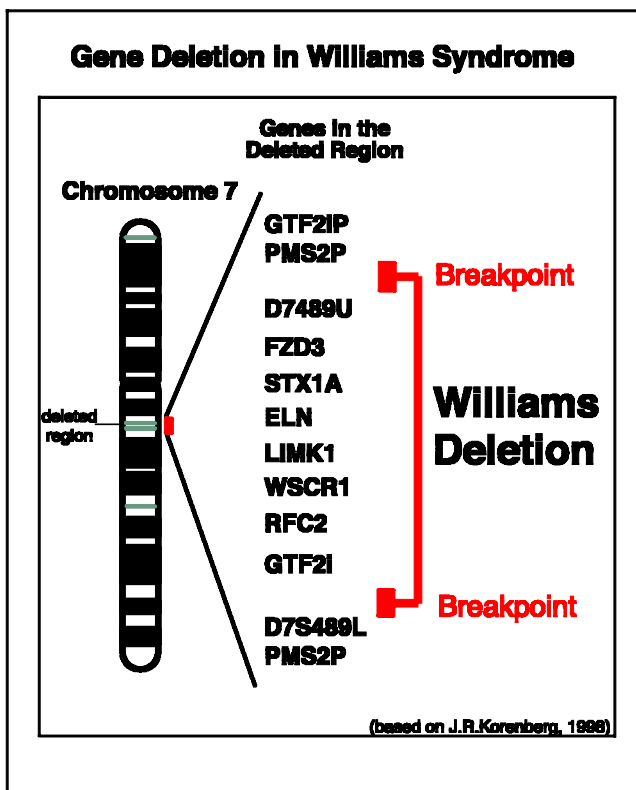


Figure 18. A genetic marker for WMS is the deletion of one copy of a small set of genes on chromosome 7, band 7q11.23, shown in the ideogram. This region is expanded to the right to illustrate genes that are missing one copy in WMS, including the gene for elastin. The regions involving the common breakpoints in WMS are also illustrated (see Korenberg et al., this volume). Thus, WMS is characterized genetically by deletion of one copy of a small set of genes on chromosome 7, including the gene for elastin (illustration based on Korenberg et al., 1998).

experimental paradigms provides another critical (and quantifiable) aspect of the WMS phenotype, marking it as different from normal and directly opposite from autism.

Our studies of brain function and brain morphology suggest that there are neural abnormalities that also serve as markers for WMS, distinguishing aspects of the neurobiological phenotype (Bellugi et al., 1999a). There are unique electrophysiological patterns present during paradigms of language processing and face processing (Mills et al., 1997; Mills, 1998; Mills et al., this volume). These distinctive electrophysiological patterns which are characteristic of WMS are different from those found with normal controls at any age or from other groups. Additional neural characteristics providing possible markers of WMS include enlargement of the neocerebellar vermis in the context of an overall smaller brain size (see Figure 17), and differential development of the paleocerebellum (small) and the neocerebellum (enlarged) in WMS (Jernigan & Bellugi, 1994; Bellugi et al., 1994; Bellugi & Wang, 1998) as well as disordered neurons on histology (Galaburda, Wang, Bellugi, &

Rossen, 1994; Galaburda, 1998; Galaburda & Bellugi, this volume).

Beyond these neural characteristics, the deletion of one copy of a small set of genes in a distinct region on chromosome 7 (band 7q11.23) characterizes nearly all clinically identified WMS and provides a genetic marker for WMS (Bellugi et al., 1999b; Korenberg et al., 1996, Korenberg et al., 1997, Korenberg et al., 1998; Korenberg et al., this volume). Figure 18 shows a simplified diagram of the hemizygous deletion in a small region on chromosome 7, and some of the genes in that region that are currently being identified (see Korenberg et al., this volume).

The cognitive profile of Williams syndrome represents an unusual pattern of strengths and weaknesses, indeed, dissociations within and across cognitive domains, as we have shown in this chapter. Phenotypic characteristics of WMS at the social, neural, and genetic levels, provide an additional opportunity to forge links from cognition to underlying neural substrates and to the genetic basis of the syndrome.

CONCLUSION

The results of these studies should provide clues to long-standing theoretical issues in language and brain organization and, in addition, have the potential for connecting the cognitive and social profile of a specific genetically based disorder, with its brain bases, and with its genetic underpinnings. We are investigating major dissociations among and within diverse cognitive functions: Selectively spared grammatical capacity in the face of marked cognitive deficits. Dissociations within language (grammar, semantics) as well as within other domains of cognition (impaired spatial cognition, remarkably spared face processing) are also present. In subsequent papers, we explore these dissociations in terms of their implications for the neural systems underlying cognitive domains and their implications for neuronal plasticity. One of the greatest challenges in understanding the brain basis of higher cortical functions lies in being able to link investigations across disciplines within the neurosciences.

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