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Williams syndrome: an exploration of neurocognitive and genetic features

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Abstract

We report here on significant attempts to forge links between neurodevelopmental disorders, development of specific neuropsychological abilities, and the functional establishment of patterns of brain organization. Such research programs are providing converging evidence for the coherence or dissociability of components of cognition (e.g. language, spatial cognition) and will allow development of theoretical explanations for the underlying architecture of human cognition. Williams syndrome involves focal rather than generalized cognitive deficits, and offers an important opportunity for linking brain findings to specific atypical cognitive profiles. The unusual neurocognitive profile of Williams syndrome makes it a compelling model of the pathways between genes and human cognition. It is becoming clear that the syndrome's unique genomic organization may also make it an important model of human chromosomal evolution and disease. These studies with a specific neurodevelopmental disorder that presents a rare dissociation of higher cortical functioning may provide opportunities to explore some of the central issues of cognitive neuroscience that tie cognitive functions to brain organization and ultimately to the human genome.

Keywords: Language; Spatial cognition; Molecular genetics; Williams syndrome; Dissociations in cognitive functions; Neural systems

1. Introduction: Williams syndrome as a model for linking gene, brain and cognition

This paper is about a particular syndrome, Williams syndrome, which typically involves mental retardation, a specific heart defect and a constellation of other medical features. It is also about the ways we think a broad biological perspective on conditions such as Williams could inform the field of cognitive neuroscience, a perspective accommodating findings from behavior, brain physiology, brain structure and brain cytoarchitectonics. We provide a behavioral and neurological profile of a relatively large group of individuals, comparing Williams syndrome (WMS) with another form of mental retardation, Down syndrome (DNS). We found striking contrasts in the behavioral profiles of the two syndromes. In Williams syndrome, language abilities tended to be a relative strength, compared to age- and IQ-matched Down syndrome subjects, where language abilities represented a definite weakness. We also have uncovered apparent dissociations in Williams syndrome subjects between aspects of visual-based cognition. Performance on face processing tasks appeared remarkably 'spared' but other aspects of visual based cognition showed signs of marked impairment in Williams syndrome subjects, below the level of the Down syndrome subjects. What has emerged is an unusual profile of cognitive dissociations in two different genetically based syndromes. We explore these contrasting behavioral profiles and complement them by studies of neuroanatomy and neurophysiology, suggesting specific abnormalities in brain structure and function. We also probe the molecular genetic basis of Williams syndrome. In these studies, we apply the same probes across all levels from cognition to brain to gene in a large group of subjects [1–4].

Cognitive neuroscience is inherently multidisciplinary, examining processes of development from diverse perspectives, all of which converge on the central issue of the development of higher cognitive functions in man. In our studies, we examine the cascade of events from the cognitive to the neurobiological level, using different modes of brain imaging that would not have been possible a decade ago. We also take advantage of exciting advances in molecular genetics. This permits coordinated studies of the links among higher cognitive functions, brain structure, brain function and brain cytoarchitectonics. We feel that some of the central issues of cognitive neuroscience may be further illuminated by extending such inquiries to the level of molecular genetics. In this paper we contrast children with different genetically-based disorders such as

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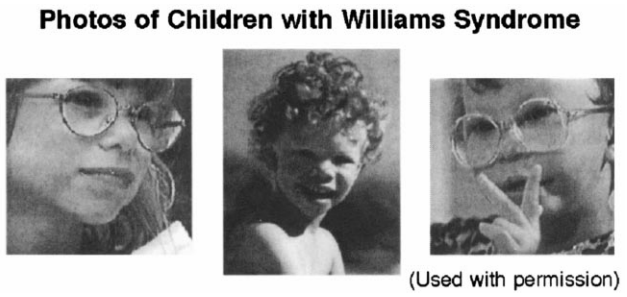

Fig. 1. Photos of individuals with Williams syndrome. Note the similarity in facial features.

Williams syndrome and Down syndrome at these multiple levels.

1.1. Comparison of different genetically based disorders

1.1.1. Why Williams syndrome?

Williams syndrome is a rare genetic disorder of previously unknown etiology that typically results in a characteristic heart defect (supravalvular aortic stenosis) and other medical characteristics. It is associated with mental retardation and a specific facial appearance (see Fig. 1) and affects behavior in highly specific ways. The British cardiologist J.C.P. Williams and his colleagues [5] labeled the syndrome following a clinical study of four patients with supravalvular aortic stenosis associated with mental retardation and a peculiar facial appearance. Our studies are also finding a characteristic cognitive and neuroanatomical profile for Williams. This sporadic disorder occurs approximately 1 in 25 000 live births and has been identified in many different countries all around the world. Molecular genetic studies have found that Williams syndrome has as its genetic basis a hemizygous deletion encompassing the elastin gene locus on chromosome 7 (i.e. one copy of a small set of genes, including elastin, LIM1-kinase, syntaxin 1a, and other surrounding genes) and this same deletion is present in 98% or more of clinically diagnosed WMS individuals [1,4,6–11]. Although medical characteristics of children with Williams syndrome had been well described, the neuropsychological characteristics of this distinctive population had been little studied until relatively recently, and have now given rise to a lively field of studies, more than we can review here [3,12–17]. Although there are some controversies, the unusual peaks and valleys of cognitive abilities we have found in Williams syndrome are generally agreed upon across investigators.

We have been engaged in a major program for investigating Williams syndrome subjects over the past decade. These studies now encompass multiple levels of investigation, and include a broad range of linguistic and cognitive capacities, as well as studies of underlying neural systems and molecular genetics [1,18–22]. Studies are underway of the functional and structural organization of the brain in subjects with Williams syndrome [3,23–25]. We are also investigating the genetic basis for the disorder in the same group of subjects.

1.1.2. Why Down syndrome?

In order to examine the neuropsychological profile of subjects with Williams syndrome, our studies compare Williams syndrome adolescents with age- and IQ-matched subjects with Down syndrome (trisomy 21), as well as with mental age matched normal controls. Subjects with Down syndrome were chosen as a contrast group for Williams syndrome because Down syndrome is a genetically identifiable chromosomal anomaly and has been relatively-well characterized in the literature. Down syndrome provides a relatively homogeneous and well-defined contrast group from the larger population of adolescents with mental retardation, and active research on the neurobiology and genetic basis of Down syndrome makes it another exciting area for investigations of the biological basis of cognition [4,26]. Since subjects with Down syndrome are generally readily available, Down and Williams syndrome subjects can be individually matched on the basis of chronological age and mental age (IQ), and form the focus of the subset of studies included here.

Individuals with Williams syndrome and Down syndrome exhibit differing linguistic, cognitive, neurodevelopmental and genetic patterns of abnormalities [1,4,9,10,17,25,27]. Molecular genetics has recently made major discoveries with respect to the pathogenesis of Williams syndrome in the identification of a major part of the specific defect responsible for Williams syndrome: a loss of one copy of a small stretch of genes including the elastin gene on chromosome 7; other genes in this stretch are Lim1Kinase, Frizzled 3, Syntaxin 1a (see Section 4). Consequently, in general, the genetic diagnosis by fluorescent in situ hybridization (FISH) is now straightforward [4,6,11].

We therefore undertook systematic sets of studies across matched subjects with Williams syndrome and Down syndrome who are contrasted with normal controls, and with children with language impairment, with early onset focal lesions, and with autism In a series of research studies, Williams syndrome and Down syndrome subjects were matched for age, full-scale intelligence quotient (IQ), and educational background. Each of the subjects was studied using a comprehensive battery of neuropsychological, linguistic, neurobiological, neuroanatomic, neurophysiological and molecular genetic probes [17].

2. Contrasting cognitive profiles in two syndromes

2.1. Equal impairment of general intellectual ability in Williams and Down

Both the Williams syndrome subjects and the comparison

cohort of Down syndrome subjects are classified as mentally retarded, as defined by the American Association on Mental Deficiency. In our subject pool, Williams syndrome subjects in our samples have a mean full scale IQ score of 55, standard deviation of 11, and range between 40 and 90 (see Fig. 2). It is important to note the variability of intellectual function within this population, as well as the relatively narrow range of scores. While one survey found that Williams syndrome adults lived or studied in sheltered environments [28], there are also, in fact, examples of individuals living autonomously or with minimal support from family members. In general, daily living problems are consistent with the continued marked impairment of general cognitive abilities observed in Williams syndrome and Down syndrome. This equal intellectual impairment forms the background context for comparative studies of language and spatial abilities in the two genetically based disorders.

On other probes of general intelligence, subjects in our studies with Williams syndrome and Down syndrome are also equally impaired, such as Piagetian conservation tasks, the Halstead Reitan Battery, a cognitive estimation task, studies of biological knowledge, etc. Across the array of conceptual and problem-solving tasks, both groups demonstrate an equivalent impairment in general intellectual functioning. For example, on Piagetian tests of conservation, including number, weight and substance, both Williams syndrome and Down syndrome adolescents fail consistently on conceptual tasks that are easily mastered by the age of eight [19,20]. In contrast, Williams subjects score at ceiling on a test of comprehension of reversible passive sentences (e.g. 'The horse is chased by the girl'), whereas Down subjects are close to chance. In general, language abilities in the two groups are dramatically different. Whereas adolescents with Williams can readily master, exhibit and use complex grammatical constructions, typically the IQ and age-matched adolescents with Down syndrome have far more difficulty with syntactic probes and expressive language tasks.

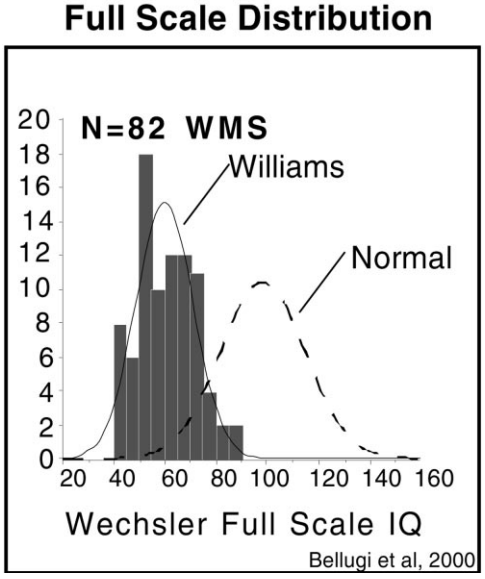

Fig. 2. Distribution of full-scale IQ in Williams syndrome sample. Wechsler full-scale IQs in the Williams syndrome subjects in our sample range from 40 to 90, and are fairly normally distributed, with a mean IQ of approximately 55 (SD = 11).

2.2. Expressive language ability in Williams

The precise relationship between language structure (grammar) and other aspects of cognitive functions is a strongly debated theoretical issue. Major theoretical models of language acquisition present alternative views on the relationship between cognitive and linguistic domains. The study of normal development sheds little light on this issue in that linguistic and nonlinguistic cognitive functions are so intimately intertwined that it is difficult to separate these functions. Studies with atypical populations such as Williams syndrome and Down syndrome can be critical in addressing these issues that pertain to the domains of higher cognitive capacities and their underlying neural substrate [1,18].

In the context of overall cognitive impairment, the expressive language of adolescent subjects with Williams syndrome is distinct from the language of matched Down syndrome subjects. Indeed, one of the hallmarks of Williams syndrome subjects may be their relatively competent language processing, given their level of cognitive impairment. We have investigated many aspects of their linguistic abilities (phonological, morphological, syntactic, semantic, and lexical semantic, as well as discourse and narrative capacities). Our studies are also examining the interplay between language and affect [18,29,30].

2.2.1. Relative strength in grammar in Williams

The grammatical facility of adolescents with Williams syndrome, as compared to IQ- and age-matched Down syndrome subjects, is apparent on formal tests of comprehension and production as well as on their expressive language. The Williams syndrome adolescents perform much better than their Down syndrome counterparts on tests of comprehension of passive sentences, negation and conditionals [19,31]. The ability to detect and correct anomalies in the syntax of a sentence depends on knowledge of syntactic constraints and the ability to reflect upon grammatical form. These are metalinguistic abilities that are mastered considerably after the acquisition of grammar and may never fully develop in certain at-risk populations. We find that the Williams syndrome subjects' advantage in linguistic proficiency extends to some tests of metalinguistic abilities as well [18,22,29]. Moreover, analysis of the spontaneous expressive language of adolescent Williams syndrome subjects shows that they generally produce grammatically correct sentences. These individuals characteristically employ a variety of grammatically complex forms, including passive sentences, conditional clauses and

embedded relative clauses, although there are occasional errors, and even some systematic ones, e.g. spatial prepositions [30,32–34]. By contrast, the language of the matched IQ Down syndrome subjects is simplified and less varied in construction, often with errors and omissions in both morphology and syntax. These differences in linguistic competence, on both production and comprehension tasks, suggest a remarkable strength in linguistic ability in Williams syndrome, in the context of their overall cognitive impairment.

2.2.2. Unusual vocabulary: a characteristic of Williams syndrome?

Across several studies, Williams syndrome adolescents and adults show a proclivity for unusual words, not typical of normal or Down syndrome subjects. Despite their low IQ scores, adolescents with Williams syndrome were usually able to match such words as 'canine', 'abrasive', and 'solemn' with a picture on the Peabody Picture Vocabulary Test. In a task of semantic organization ('fluency'), subjects were asked to name all the animals they could think of in a minute. The Williams syndrome adolescents produced far more responses than the Down syndrome adolescents, in fact, as many as IQ-matched normal controls. The Down syndrome group gave fewer responses in different categories and sometimes strayed from the category altogether ('ice cream' for animal). Williams syndrome subjects produced many animal names, and not just typical category members but also low frequency, non-prototypical choices (see Fig. 3). Adolescent and adult subjects included choices such as 'yak', 'Chihuahua', 'ibex', 'condor', 'vulture', 'unicorn', 'saber-tooth tiger', far more often than controls matched for mental age. Thus, it appears that unusual word knowledge, processing and choice may turn out to be characteristic of adolescent and adult Williams syndrome subjects [29]. Note that this is unlike the semantic disturbances that accompany such clinical disorders (as aphasias and dementias), unlike performance errors occasionally made by normal subjects (slips of the tongue), and especially unlike the semantic limitations characteristic of other mentally retarded groups [18,35].

2.2.3. Enrichment of linguistic affect in Williams syndrome

Language may be emotionally enriched by affective prosody as well as through the use of lexically-encoded affective devices. In their narrations, Williams syndrome subjects were found to use affective prosody (pitch change, vocalic lengthening, modifications in volume) *far* more frequently than either Down syndrome matches, or even normal children. The affective richness of the Williams syndrome subjects' narratives was also reflected in their lexical choices. Their narratives included frequent comments on the affective state of the characters in the stories (e.g. 'And ah! He was amazed' or 'The dog gets worried and the boy gets mad'), as well as the use of dramatic devices such as character speech and sound effects ('And *boom*, millions of bees came out and tried to sting him'). Their use of exclamatory phrases and other audience engagement devices is evident throughout many of the stories, for example '*Suddenly splash*! The water came up'; '*Lo and behold*, they found him with a lady'; and '*Gadzooks*! The boy and the dog start flipping over'. These devices were far less frequently utilized by normal subjects and were notably absent in the Down syndrome subjects' stories. In sum, not only are the Williams syndrome adolescents' stories replete with narrative enrichment devices, they use proportionately more affective prosody and make greater use of linguistic affective devices than do Down syndrome, or even matched normal children (see Fig. 4) [36].

Despite their intellectual impairments, subjects with Williams syndrome are not only sociable and affectively sensitive, but they also appear to be able to manipulate affective linguistic devices for purposes of story-telling. However, these subjects appear to use the same level of expressivity regardless of how many times they have told the story and irrespective of their audience. This suggests that their extreme expressivity may represent a deviation from the norm [30,37]. Research suggests that the abundance of affectivity, both in prosody and in linguistic devices, may be characteristic of most subjects with Williams syndrome, distinctly different from subjects with right hemisphere damage, and markedly different from classic autistic subjects. Indeed, in some respects, individuals

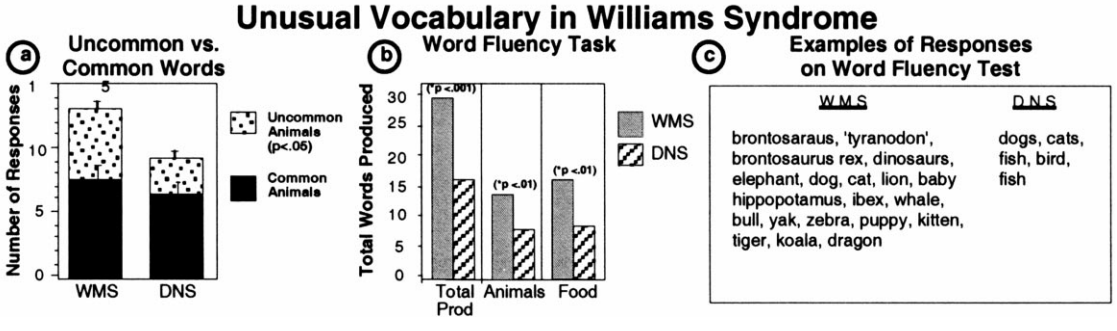

Fig. 3. Unusual vocabulary in Williams syndrome. The figure shows that there is a large proportion of uncommon names in Williams subjects' responses to a fluency probe (a); that the total number of words produced is significantly larger in Williams than in Down syndrome, regardless of category (b); and presents sample responses from a matched individual with Williams syndrome and one with Down syndrome (c).

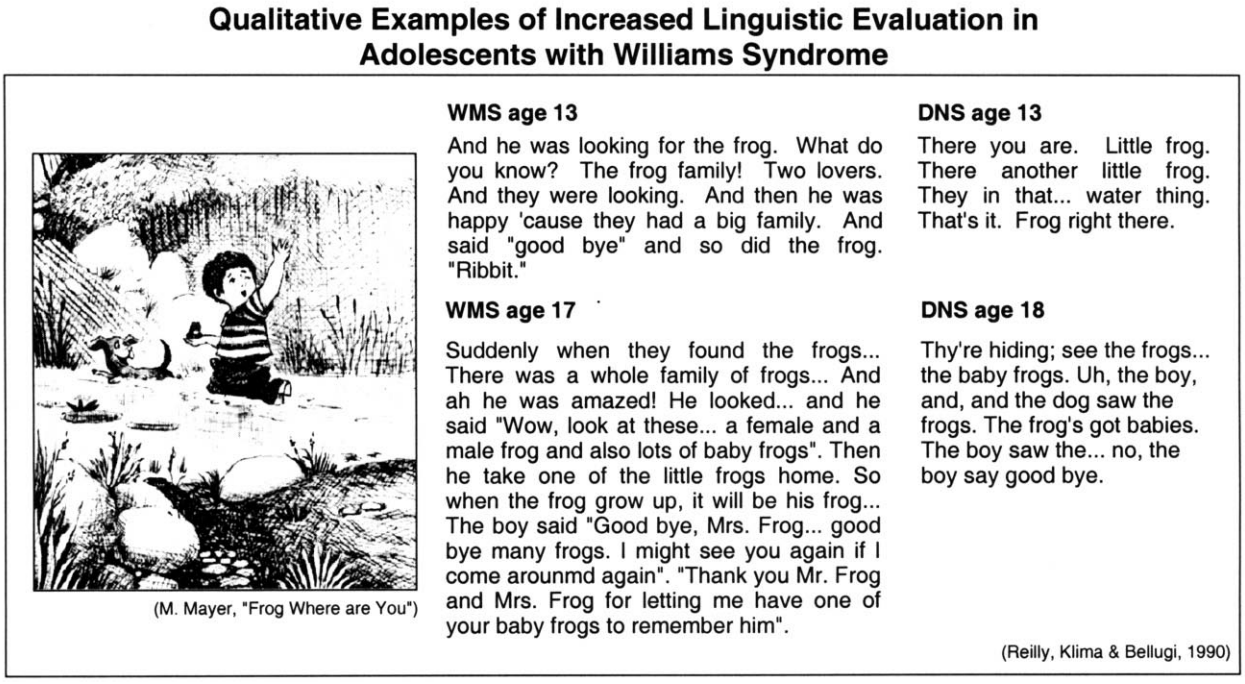

Fig. 4. Enriched linguistic affect in adolescents with Williams syndrome. Qualitative examples from narratives of the 'Frog, Where Are You?' story show the increased length of the stories and the extensive use of narrative evaluative devices made by adolescents and adults with Williams compared with matched Down syndrome individuals.

with Williams syndrome and individuals with autism appear to be socially, cognitively and neuroanatomically opposites [38]. Experimental studies of sociability measures in Williams suggest that hypersociability may turn out to be a hallmark of Williams syndrome, just the opposite of the lack of sociability in autism [37,39].

2.3. Peaks and valleys in visual-based cognition in Williams syndrome

We have shown that in language functions, Williams syndrome individuals typically show strength, whereas Down subjects exhibit weakness. When turning to the domain of spatial cognition, we find that the relations between the two syndromes are reversed. While both groups exhibit deficits in spatial cognition, they show quite diametrically opposed patterns, and overall, in Williams syndrome individuals, spatial cognition is markedly impaired, even when compared with Down syndrome subjects. By comparing the islands of spatial cognitive sparing in Williams syndrome and Down syndrome, we have been able to examine some of the differential patterns that emerge in visual-spatial cognition in these two genetic syndromes [1,18,40–42]. We review some of these results here.

2.3.1. Unique patterns of spatial deficits in Williams versus Down syndrome

Drawings by subjects with Williams syndrome often lack cohesion and overall organization. That is, a drawing of a house might include windows, a door and a roof, but the parts may not be in correct relationship to each other, that is, spatially disorganized. For example, windows and a door may be stretched outside the boundaries of the house in a drawing by a Williams adolescent. By contrast, a comparable Down syndrome subject's drawing, while simplified, often shows good closure and form, with appropriate relationships among elements (see Fig. 5).

On Block Design, a subtest of the WISC-R that requires visual-spatial and visual-motor capacities, the two groups scored equally poor. However, examination of the *process* by which they arrived at their scores reveals striking differences. Although they failed to copy the stimuli correctly, the subjects with Down syndrome generally produced the global configuration of the block arrangements, although the internal aspects were often incorrect. Williams subjects, by contrast, typically failed to produce the global configuration of the designs, and were biased to the details of the designs. They placed the blocks in apparently haphazard, non-contiguous arrangements. In a process analysis comparing Williams syndrome and Down syndrome adolescents, we found that Williams syndrome subjects used more steps to achieve the end product, and almost invariably moved in continuously fragmented patterns (see Fig. 6, top).

An experimental task that distinguishes local and global features more rigorously was employed to investigate and characterize these different visual cognitive impairments. Items were composed of local components that together constituted a global form (i.e. a big *D* constituted of little *Y*s). In these tasks, we found characteristic deficits in Williams syndrome versus Down syndrome that superfi-

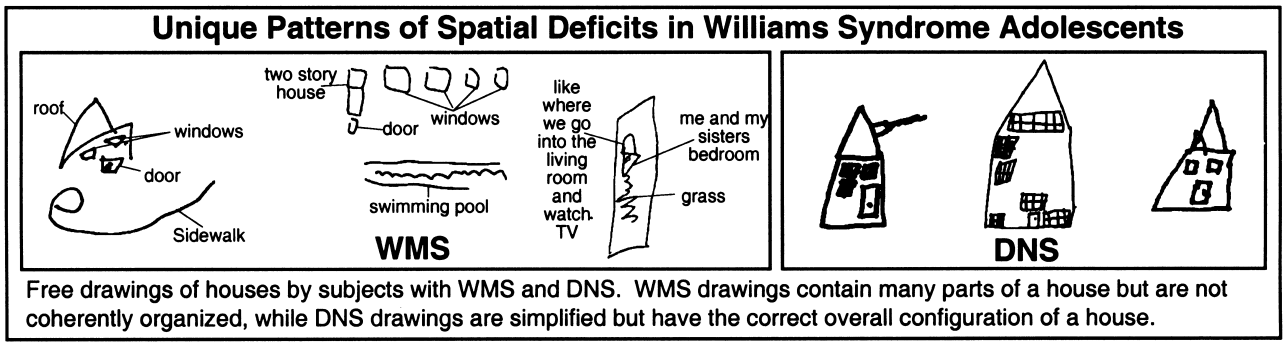

Fig. 5. Different patterns of spatial deficits in Williams versus Down syndrome adolescents (free drawings). Free drawings of houses by age- and IQ-matched adolescents with Williams and Down syndrome show different spatial deficits. The drawings by subjects with Williams syndrome contain many parts of houses but the parts are incoherently organized. In contrast, the Down subjects' drawings are highly simplified but have the correct overall configuration of houses.

cially mirrored differences between right- and left-lesioned brain damaged subjects. When asked to draw the designs, both groups failed, but in distinctively different ways. In these paradigms, Williams syndrome subjects typically produced only the local forms sprinkled across the page and were impaired at producing the global forms. Subjects with Down syndrome showed the opposite pattern; they tended to produce the global forms without the local forms (see Fig. 6, bottom). This was true whether subjects reproduced forms from memory (after a five-second delay) or whether they were asked to copy the form placed in front of them. In perceptual matching tasks as well, Williams syndrome subjects showed a local bias. These results suggest an unusual visuospatial processing pattern in Williams syndrome, a bias toward attention to detail at the expense of the whole [1].

2.3.2. Preservation of face processing in Williams syndrome

Despite their severe spatial cognitive dysfunctions, there are domains of visual-based cognition where Williams syndrome subjects display selective sparing of abilities. The Williams subjects (but not the Down subjects) demonstrate a dramatic ability at recognizing, discriminating, and remembering unfamiliar and familiar faces [29]. This includes abilities related to the perception of faces, such as the ability to recognize faces when seen in various lighting conditions and orientations. Despite their marked visuospatial deficits, subjects with Williams syndrome perform remarkably well, far better than Down syndrome subjects and as proficiently as normal age-matched controls on face recognition tasks. Thus, while there are gross deficits in intellectual ability, subjects with Williams syndrome exhibit a distinctive pattern of peaks and valleys in spatial cognition: an emphasis on local over global processing; extreme fractionation in drawing; yet an island of sparing for processing, recognizing and remembering faces [18,43–46].

2.4. Different stages of development in Williams syndrome

Interestingly, the neurocognitive profile we find in adolescent and adult Williams and Down syndrome subjects is in some ways quite different from that exhibited during development. Studies of the acquisition of first words and grammar in large groups of subjects with Williams syndrome and Down syndrome reveal that aspects of the

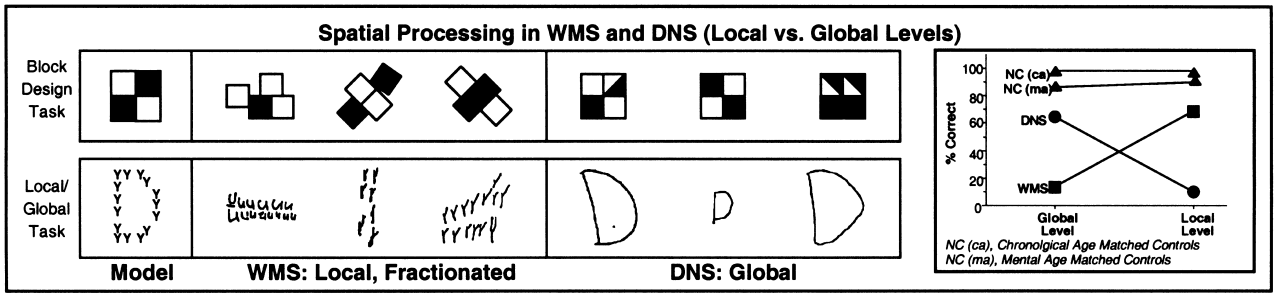

Fig. 6. Spatial processing in Williams and Down syndrome (block design and hierarchical processing). (Top) Although Williams and Down syndrome subjects score equally poorly in the Block Design subtest of the WISC-R (scaled scores more than 2 SD below normal, not shown), they fail in very different ways. Subject 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. (Bottom) 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, where as age and IQ matched DNS subjects tend to produce only the global forms. Normal chronological age-matched subjects reproduce both levels of the figure with approximately equal accuracy.

Table 1
Developmental neuropsychological profiles in Williams and Down syndrome

	Williams syndrome	Down syndrome
Preschoolers		
Vocabulary acquisition	Delayed	Delayed
Motor Milestone	Delayed	Delayed
Adolescents/young adults		
Grammar	Correct, complex	Poor, simple
Semantics	Larger vocabulary, uncommon word choices	Small vocabulary
Linguistic affect	Rich	Diminished
Visuomotor ability	Poor, fragmented	Simple, cohesive
Hierarchical processing	Local	Global
Processing of faces	Remarkably strong	Impaired

acquisition of first words are quite delayed in both cohorts. However, we note that children with Down syndrome exhibit an early advantage for communicative gestures, while children with Williams syndrome display an advantage for grammar later in development [47]. Other differences emerge in a comparison of three domains across developmental ages (vocabulary, visuospatial abilities, and face processing). Down syndrome children showed similar low scores across the three domains. In contrast, the Williams syndrome developmental profile is different across the three domains: visuospatial functions are significantly below the Down syndrome level at all ages and seldom develop beyond the normal five-year level. Face processing is strong from very early on, with Williams syndrome subjects tending to score above their mental age regardless of chronological age. In language development there is an initial delay in development of words in Williams syndrome subjects equivalent to that of the Down syndrome subjects, and followed by a later continuing rise in linguistic processing as grammar emerges [48,49]. Thus the profile of linguistic preservation found in older children is not evident initially. Table 1 provides a summary of developmental neurocognitive features of Williams syndrome, contrasting Williams and Down syndromes. Performances on neurocognitive measures suggest that individuals with Williams syndrome, but not Down syndrome, show an uneven neurobehavioral profile of specific deficits, with preservations and anomalies both within and across domains of higher cognitive functioning. Furthermore, the early stages in Williams syndrome do not necessarily predict the later stages. Williams syndrome thus presents a rare pattern of dissociations providing an unusual opportunity to forge links to neural substrates and to the genetic basis of the syndrome, and we turn to these issues next.

3. The neurobiological profile of Williams syndrome

The neurobiological profile of individuals with Williams syndrome is being revealed through studies of brain function (event-related potentials, or ERPs), brain structure (thre-dimensional computer-graphic analyses of magnetic resonance images, or MRI) and brain cytoarchitectonics in autopsy brains. Initial proposals about how the cognitive and brain profiles might be linked are presented here. Studies using event-related potential (ERP) techniques are useful in assessing the timing and organization of the neural systems that are active during sensory, cognitive and linguistic processing in subjects with Williams syndrome. Event-related potentials provide information about the timing and temporal sequence of neural events and, to some extent, the location of neural activity. Electrodes are placed on the scalp over specific brain areas while subjects are processing information, thus allowing the monitoring of the time course of neural activation on a ms-to-ms basis.

Studies of brain wave activity during language and face processing paradigms in individuals with Williams syndrome and normal individuals are reported here. The characterization of these neurophysiological results for Williams syndrome individuals represents one of the most enticing findings to date, and the first to provide 'brain markers' for Williams syndrome as they are not seen in other studied populations including children with language impairments, focal lesions, Down syndrome, and normal controls.

3.1. Neurophysiological characteristics of Williams syndrome

3.1.1. A neurophysiological marker for language processing

The morphology of ERP components to auditory words was dramatically different in individuals with Williams syndrome compared to normal controls. ERPs were recorded as subjects listened to sentences presented one word at a time. The final word in each sentence provided good closure or was semantically anomalous (for example, 'I have five fingers on my moon'). The results revealed that the morphology of Williams syndrome individuals' ERP components to auditory words were different from that of normal controls. The unique pattern of ERPs in Williams includes prominent positivities at 50 and 200 ms, and a smaller than normal negativity at 100 ms which was most striking over temporal brain regions. This pattern of components (see Fig. 7a) was not evident in normal school-age children or adults-or any other group examined, which suggests that this might emerge as a marker for Williams syndrome.

In age-matched normal controls, there are differences in ERPs to open and closed class words. In normals, open class words which typically convey specific referential meaning (e.g. nouns, verbs, and adjectives), elicit a negativity at 400 ms that tends to be larger from posterior regions of the *right* hemisphere. Closed class words, which typically convey information about grammatical relations (e.g. articles, prepositions, conjunctions), elicit a negativity that peaks

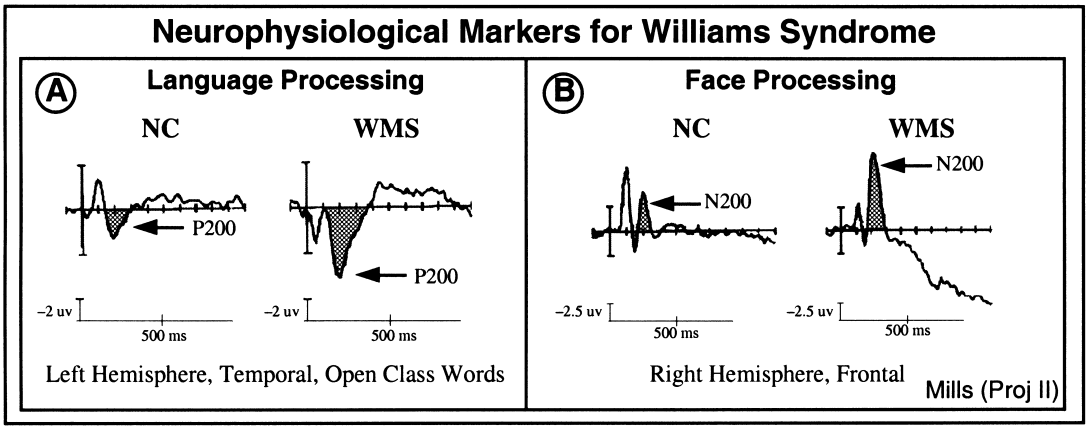

Fig. 7. Neurophysiological markers for Williams syndrome. Shown on the left is the unusual wave form to language (auditory words) exhibited by all subjects with Williams and none of the normal controls. This is a candidate neurophysiological marker for Williams. Shown on the right is the abnormally large negativity at 200 ms in subjects with Williams but not in normal controls or other groups tested, occurring over multiple brain regions. This is another candidate neurophysiological marker for Williams.

somewhat earlier and is largest over anterior regions of the *left* hemisphere. Unlike normals, individuals with Williams syndrome do not show ERP differences to open and closed class words, nor do they show the normal right and left hemispheres asymmetries. In normal controls, the semantically anomalous final word elicits an N400 component (negativity that peaks at 400 ms) that is larger from the left than the right hemisphere. The N400 effect is larger in individuals with Williams syndrome than in normal control individuals over the left hemisphere. This larger semantic anomaly may be related to the unusual semantic proclivities shown by subjects with Williams syndrome in lexical tasks. Thus, the results showing ERP differences between subjects with Williams and normal subjects in language processing suggest that the neural organization of these aspects of language might be different in subjects with Williams syndrome compared to normal controls. [1,2,50,51].

3.1.2. A neurophysiological marker for face processing

ERP recordings were made as subjects watched photographic pairs of faces presented sequentially on the computer monitor. The subjects' task was to indicate whether or not the pairs of faces matched. Face processing ERP data on subjects with Williams syndrome and normal controls were obtained; the results showed that both individuals with Williams syndrome and normal control groups showed ERP differences to matched versus mismatched upright faces. The normal subjects showed the largest component over anterior regions which was greater over the right hemisphere than the left; however, the subjects with Williams syndrome did *not* show this right greater than left asymmetry. In contrast to the normal adults, the subjects with Williams syndrome also displayed an abnormally large negativity at 200 ms to upright faces (see Fig. 7b), but not to pictures of objects. These results appear to be specific to individuals with Williams syndrome and might well be related to *their increased attention to faces.* The abnormally large negativity at 200 ms, which occurred in all subjects with Williams syndrome subjects but not in any other groups studied, is suggestive of a brain activity marker that is linked to the noted strength in face processing abilities found in individuals with Williams syndrome. Neurophysiological indices that relate brain and behavior and that might be phenotypic markers for Williams syndrome are suggested by these neurophysiological studies. The distinctive brain wave markers, one found during face processing and a different one found during language processing, could be characteristic of individuals with Williams syndrome but not of other groups. Taken together, these findings suggest that the neural systems subserving higher cognitive functions such as language and face processing are different in individuals with Williams syndrome than in normal individuals [1,2].

3.2. Neuromorphological characteristics of Williams syndrome

New techniques of brain imaging permit visualization and analysis of structures within the brain that were not possible in the past. Techniques developed by Reiss, by Damasio, and others [3,52,53], now permit an unprecedented visualization and three-dimensional analysis of the living brain of subjects. Initial studies revealed that both Williams and Down syndrome leave a distinctive morphological stamp on specific brain regions. MRI studies of brain volumes were performed on a group of matched adolescents and young adults with Williams and Down syndrome [24,54,55]. Neuromorphological characterization of Williams and Down syndrome subjects by magnetic resonance imaging showed that the cerebral volume in both groups was smaller than that of age-matched normal controls. Analyses revealed important regional differences in brain volume between the two groups of subjects. First, anterior-brain volume was found to be disproportionally reduced in Down syndrome subjects but proportionately

preserved in subjects with Williams. Secondly, limbic structures in the temporal lobe showed essentially equal volumes in Williams and control subjects, but were significantly reduced in Down subjects. On the other hand, the volume of the thalamus and lenticular nuclei were seen to be much better preserved in subjects with Down syndrome than those with Williams. We also found that the anterior parts of the corpus callosum, like the anterior hemispheres, were preserved in Williams subjects, but diminished in Down subjects [56].

Quantitative analysis of cerebellar volumes also suggested differences, with cerebellar volume well preserved in Williams subjects but diminished in Down subjects. Closer regional analyses were enlightening: Jernigan and Bellugi [24] found that the locus of preservation in Williams was the neocerebellum. Of the two parts of the neocerebellum that were subjected to analysis, the neocerebellar tonsils and the neocerebellar vermis both showed volumetric preservation or even *increases* in Williams as compared to controls, whereas both were found to be volumetrically diminished in Down syndrome. Importantly, the specific regions of the neocerebellum that may be enlarged in Williams were shown to be dysplagic in autism [24,38,57].

More recently, Reiss and his brain imaging group [3,25,53,58] carried out MRI studies with higher resolution techniques. In 14 young adult subjects with Williams and an aged-matched control group, the decrease in total brain volume was confirmed, as well as the relative preservation of the cerebellum. The superior temporal gyrus was also found to be relatively preserved, an area that contains the auditory system and those auditory association areas that form part of language networks. There was also a significant curtailment of the volume of the brainstem. A greater ratio of frontal to parieto-occipital forebrain volume was also found, and there was reduction of the forebrain white matter, with relative preservation of the cerebrocortical volume. Nonetheless, regionally, the right-occipital lobe showed excessive volume loss.

Results of related research suggest that the expansive prefrontal cortex and the neocerebellum, both selectively (relatively) preserved in Williams, are thought to be closely related. These two regions of the brain are most highly developed in *Homo sapiens,* and are thought to have evolved contemporaneously [59]. Furthermore, the neocerebellum has more extensive connections to prefrontal and other association areas of the cortex than do the older parts of the cerebellum. On the other hand, the reduction in the forebrain white matter may explain the curtailment of the brainstem, but it may be relevant to note that FZD3, which is one of the deleted genes, is associated with hindbrain segmentation, which could also explain, in part, the brainstem changes in Williams. The neuroanatomic profile of Williams emerging from neuroimaging is beginning to contribute to the understanding of the brain's organization by exhibiting a morphological pattern that can result from genetic bias. The finding that frontal and neocerebellar regions are selectively preserved in Williams suggests that they all may come under the influence of a single genetic developmental factor, or that their development is mutually interactive, or both. These issues bearing on the relationship of brain to behavior are fundamental to central questions of cognitive neuroscience.

3.3. Brain cytoarchitectonic characteristics of Williams syndrome

Anatomy is the logical link between genes and behavior. The purpose of our research on the neuroanatomy of Williams is to help link the anatomical findings to the genetic/molecular disorder on the one hand and to the behavior disorder on the other, thus helping to link genes to cognition and emotion. Specifically, an anatomical research program in Williams must ultimately be able to explain the relationship between the deleted genes in region 7q11.23 [4,9,11,23,60–62] and the building and maintenance of brain structures, on the one hand, and, on the other hand, the abnormal behaviors, consisting of mental retardation, visuo-spatial deficits, relatively good linguistic abilities, an unusual personality, and good facial recognition and musical abilities [7,18–20,37,63–65].

Williams syndrome involves selective rather than generalized cognitive deficits, and offers an important opportunity for linking brain findings to specific atypical cognitive profiles. Four autopsy brains of individuals with Williams syndrome have been studied by Galaburda and colleagues [23,60,62]. Microencephaly and the relative curtailment of the occipital and posterior-parietal areas were evident in three of the brains. One of the four brains showed a marked reduction in the size of the parietal, posterior-temporal and occipital regions in comparison with the more rostral portions of the hemispheres. These abrupt and dramatic reductions led to the brain appearing as if a band had constricted its posterior portions. MRI data also corroborated the general finding of a reduction in posterior areas. Curtailment of the dorsal-parietal regions and posterior-temporal areas might indeed be relevant to the extreme visuospatial deficits seen in individuals with Williams syndrome (see Fig. 8). One brain showed dramatic reduction in the size of the amygdala, which could be associated with the hypersocial behavior that occurs in subjects with Williams syndrome. The four brains show largely normal overall sulcal patterns, except for some simplification of tertiary sulcation and a consistently non-opercularized dorsal central sulcus. The central sulci in normal brains reach all the way to the interhemispheric fissure and then a short distance further onto the medial surfaces of the hemispheres, but in all the available Williams syndrome cases the central sulcus ends no less than a centimeter lateral to the interhemispheric fissure. This finding could indicate abnormal development of the medio-dorsal cortices, which have been associated with visuospatial functions (see Fig. 8b) [60,62].

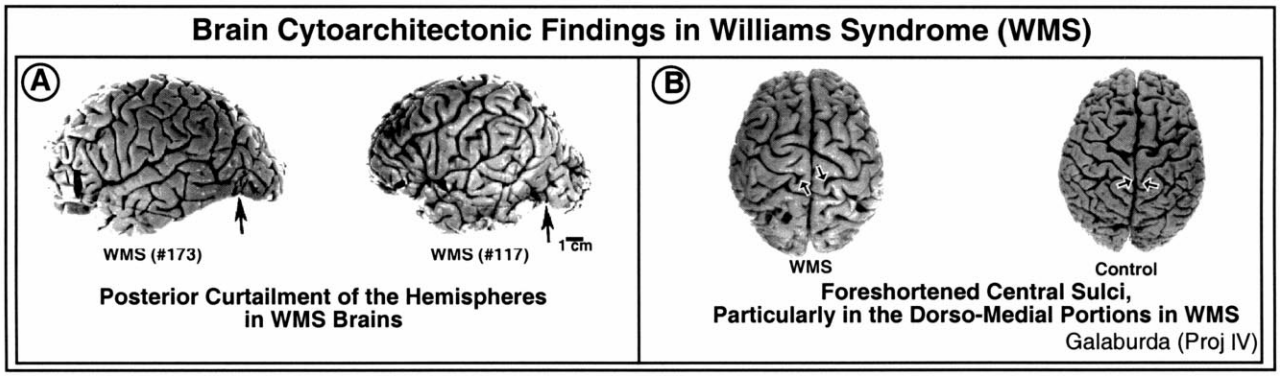

Fig. 8. Brain cytoarchitectonic findings in Williams syndrome. The arrows point to a marked indentation of the temporoparietal region and to posterior curtailment of the hemispheres in Williams' brains, consistent with their spatial deficit. (left). Note the difference in the medial reach (arrows) of the central sulci between the Williams and controls subjects/brains, particularly in the dorsomedial portions of the hemispheres, again consistent with the visuo-spatial deficit in Williams syndrome (right).

The observed cell numbers and cell-packing densities suggest early developmental arrest (for example, prenatally or before the second year of age), or regressive events occurring postnatally into the middle of the first decade of life. Galaburda and colleagues are currently examining gene expression in comparative Williams and normal brains with respect to elastin, syntaxin 1A and other genes in the Williams region [60]. Research that involves links between genomic changes, messenger and product expression leading to the unusual development of the Williams syndrome brain, will shed light on normal brain and behavioral development. The results may relate to the peaks and valleys of cognitive abilities in Williams syndrome. These analyses provide opportunities for linking brain findings to cognitive deficits and their genetic underpinnings [66].

4. The molecular genetic profile of Williams

The unusual neurocognitive profile of Williams syndrome makes it a compelling model of the pathways between genes and human cognition. It is becoming clear that the syndrome's unique genomic organization may also make it an important model of human chromosomal evolution and disease [4,9]. Williams syndrome is known to be caused by a deletion that includes the gene encoding elastin (ELN), Frizzled, Syntaxin 1a, Lim1 Kinase and other genes on chromosome 7 [4]. Studies are underway seeking to identify the genes and elucidate the chromosomal mechanisms responsible for Williams syndrome, in order to relate these to the cognitive and neural characteristics of the population [4]. Fig. 9 shows the molecular genetic basis for Williams, specifically, the area of the hemideletion in Williams on chromosome 7 affecting approximately 20 genes, some of which are indicated on the genetic map.

Molecular genetic studies [4] are involved in constructing a physical map of the deleted region of chromosome 7 band q11.23 by using multi-color fluorescence in situ hybridization (FISH) of bacterial artificial chromosomes (BACs) on metaphase and interphase chromosomes, large-fragment library screening, genomic Southern blot and pulsed field gel analyses, STS (sequence tagged site) and polymorphic marker analyses. BACs were chosen to construct the physical map because they are cloned in a stable vector and contain large genomic fragments of up to 300 kb that are stable and readily manipulated and are therefore suitable for gene isolation and DNA sequencing. These map reagents were used to investigate the size and extent of the deletions in individuals with Williams syndrome in whom subsets of features including neurocognitive profiles, brain structures and functions were simultaneously determined [1,9–11].

A working model of the genome organization characterizing chromosome band 7q11.2 that incorporates other maps was developed, which suggested that the region includes highly homologous chromosomal duplications which are also characterized by a number of repeat sequence families, genes and pseudogenes, the totality of which is organized as

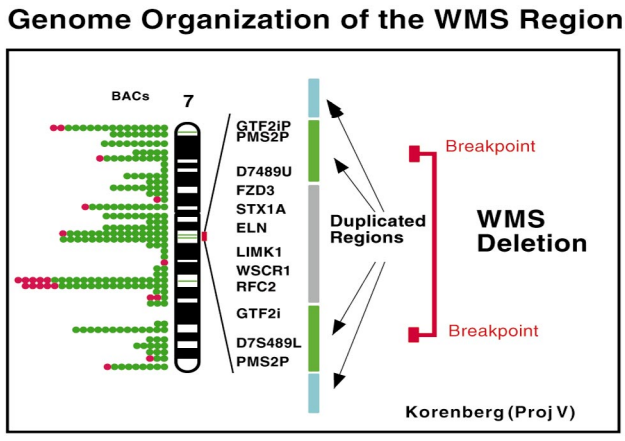

Fig. 9. Genome organization of the Williams region. A genetic marker for WMS is the deletion of one copy of a small set of genes on chromosome 7, band 7q1123, shown in the ideogram. This region is expanded to the right to illustrate genes that are missing one copy in WMS, including the gene for elastin. The region involving the common breakpoints in WMS are also illustrated.

a nested repeated structure that surrounds the largely unique region occupied by elastin and the other deleted genes. This suggests that the Williams syndrome deletion is located within an apparently single copy region of chromosome 7 that appears to be surrounded by a series of genomic duplications, some of which must be recent and others of which might have been duplicated earlier in primate evolution. Meiotic mispairing of subsets of the numerous repeated sequences might ultimately contribute to the deletion. Therefore, it is not unexpected that the deletion breakpoints in Williams syndrome occur largely in common regions and most, though not all, individuals with Williams syndrome are deleted for the same genes [1,4].

However, it is studies of the uncommon individuals with smaller deletions that are beginning to provide clues to the genes responsible for subsets of Williams syndrome features. For example, from studies of individuals with isolated deletions and mutations of the elastin gene, it appears that the absence of one copy of the gene is probably responsible for the heart defect, supravalvular aortic stenosis (SVAS), typically found in Williams syndrome. However, although absence of one copy of LIMK1 had been implicated in the spatial deficit characteristic of Williams syndrome, recent work revealed that the deletion of this gene and others in the region was compatible with normal function. Further, preliminary analyses of individuals with the facial, cardiac and mental retardation of Williams syndrome but with a smaller deletion, indicate that the region of the frizzled (FZD3) gene may not be essential for the development of these typical diagnostic features. In summary, using this approach, it is now becoming possible to link aspects of the phenotypic profile (specific cognitive functions, facial features, hypersociability, and spatial deficits) to their genetic origins. [4,9–11].

Important issues revolve around the definition of the remaining genes in the common deleted region. Furthermore, it is essential to further dissect Williams syndrome cognitive features and to determine the contributions of single genes and their interactions with others in the deleted regions, to each of these features and to the other characteristic embryological, neuroanatomical, physiological and functional landmarks of Williams syndrome and to the genetic origins of variability in these phenotypes. Studies will focus on those genes mapping in regions that when deleted are not compatible with normal phenotypes, but rather, generate subsets of the features of particular interest in Williams syndrome. Animal models of the Williams syndrome deletion will be useful but it is expected that understanding many aspects of human cognition and its genetic underpinnings will ultimately rest on further studies of humans. Such human studies might depend on the need to define further rare individuals with Williams syndrome and small deletions and to combine their molecular structures with a sophisticated understanding of their neurocognitive and behavioral phenotypes. Although many genes probably contribute to the mental retardation, it will without doubt be of interest to determine if specific genes could be responsible for hypersociability, visual-spatial deficits, or to the characteristic event-related potentials patterns that may be markers for Williams. Hopefully, these new studies will provide the tools for investigating human evolution as well as for identifying the regions, the genes, and ultimately clues to the pathways leading to the cognitive features of Williams and underlying normal human cognition [67].

5. Summary

In the studies reported here, we have undertaken a line of investigation in cognitive neuroscience that provides clues to long-standing theoretical issues in language and brain organization, and additionally may forge links between specific metabolic disorders, neuropsychological profiles, abnormal brain organization, and their genetic underpinnings. We investigated a major dissociation between language and other cognitive functions in Williams syndrome subjects who exhibit selectively spared grammatical capacity in the face of marked intellectual deficits. Furthermore, we report that Williams syndrome results in a distinctive cleavage *within* visual/spatial cognition, in which there is selective attention to details of a configuration at the expense of the whole. These dissociations are explored in terms of their implications for the understanding of normal language and other cognitive functions and their underlying neural networks, allowing us to address issues such as the basis for cerebral specialization in humans. Our studies combine several approaches that include the interrelationship of neurolinguistics, neuropsychology, cognitive psychology and studies of brain structure and brain function as well as molecular genetic studies. One of the greatest challenges faced in understanding the brain and cognition is the need to link investigations across disciplines within the neurosciences. Until now, this goal has remained elusive. These studies using a specific neurogenetic disorder, which presents unusual dissociations in higher cortical functioning, might provide opportunities to explore some of the central issues of cognitive neuroscience that tie cognitive functions to brain organization and ultimately to the human genome.

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