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**WILLIAMS SYNDROME, DOWN SYNDROME  
AND COGNITIVE NEUROSCIENCE**

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Cognitive Neuroscience is the new research enterprise that studies the mind and its workings.<sup>1</sup> It draws on the theoretical, experimental, and analytical traditions of fields such as neurobiology, psychology, linguistics, and computational science, using results from each to constrain theories in the others. It also draws on powerful new experimental methods, such as those being developed in the field of neuroimaging. The significance of this field for pediatricians is reflected in our recent literature, which is replete with articles on the cognitive aspects of specific disease states,<sup>2, 3</sup> the cognitive effects of pharmacotherapy,<sup>4, 5</sup> and the cognitive consequences of other therapeutic interventions.<sup>6, 7</sup> It is reflected also in the increasing share of Pediatric practice that is devoted to the evaluation and management of primary cognitive disorders (e.g. attentional disorders, learning disorders, and other developmental problems). Pediatrics and pediatric patients therefore stand to benefit greatly from progress in Cognitive Neuroscience.

Some of the central issues and methods of this new field are exemplified in recent research on Williams syndrome (WS) and Down syndrome (DS). These genetic disorders result in abnormalities of language and other cognitive behavior, and of neurobiological development<sup>8, 9</sup>. In this review, we will illustrate the inter-relatedness of neuropsychological and neuroanatomic studies of WS and DS, their utility in helping us to understand the brain and the mind, and their potential utility for the practice of Pediatrics.

## Background

While DS is well-known to the medical community, WS is less so. Recognized as a distinct entity only since 1961,<sup>10</sup> it has an estimated incidence of 1 in 25,000 live births,<sup>11</sup> and was shown by Morris<sup>12</sup> to follow an autosomal

dominant pattern of inheritance. Diagnosis rests on the distinctive facies in conjunction with mental retardation and the known abnormalities of cardiac and vascular structures, calcium metabolism, growth, dentition, and the skeletal system. Culler, Jones, and Deftos<sup>13</sup> suggested that an impaired calcitonin response to calcium challenge may serve as an endocrine marker for WS, even in the absence of known hypercalcemia. Molecular geneticists are now pursuing identification of the specific defect responsible for WS.<sup>14, 15</sup>

Along with the physical stigmata of WS, observers have noted a consistent behavioral feature: language that seemed surprisingly well-developed in the face of mental retardation. Some termed WS the "Cocktail Party Syndrome," though that is a vague and impressionistic label, without precise meaning. As early as 1964, von Arnim and Engel commented on the "outstanding loquacity" of children with WS.<sup>16</sup> However, results in the literature, going across age groups and using standard educational measures such as IQ tests, were conflicting.

Bellugi and her colleagues therefore undertook a systematic set of studies on a well-defined group of WS and DS subjects. DS provides a relatively homogeneous and well-defined contrast group from the larger population of adolescents with mental retardation, and active research on the neurobiology of DS made it another exciting area for investigations of cognition. Through the Williams Syndrome Association, the national parent group, all ten adolescents with WS known to reside in San Diego and southern Orange County were contacted, and all agreed to participate. DS subjects were selected to match for age, full-scale IQ (ranging from 41 to 59), and educational background. Each of the WS and DS subjects were studied across a comprehensive series of psychological, linguistic, neuroanatomic, and neurophysiologic measures.

## **Impairment of General Cognition in WS and DS**

The general cognitive impairment of subjects with WS and DS can be demonstrated not only on IQ tests, which are known to be culture- and experience-dependent, but also on truer tests of general cognitive ability. An example of such a test, borrowed from the field of Developmental Psychology, is given in Figure 1. This task is used to probe children's understanding of the Piagetian concept of conservation, the concept that properties such as weight and volume are not changed when an object's shape, color, position, or similar properties are altered. Mastery of this concept usually is achieved by the age of 7 or 8, and is regarded as a fundamental milestone of development. However, it was found that subjects with WS and DS never mastered this or other basic cognitive concepts, even in adolescence and young adulthood.<sup>17, 18</sup>

**(Figure 1 about here)**

The adaptive functioning of subjects with WS and DS is impaired as well. Udwin<sup>19</sup> found that less than 5% of the adults with WS who were surveyed had obtained open employment or had the skills necessary to maintain an independent household. The remainder lived, worked, or studied in sheltered environments. These difficulties and the failure to understand various Piagetian concepts are consistent with marked impairment of general cognitive ability, and form the context for the comparative studies of language and other cognitive skills in WS and DS.

## **Language Ability Is Selectively Preserved in WS**

In their studies of WS and DS, Bellugi et al. were careful to examine language in isolation from other cognitive skills, and thus to avoid the

confounds found in verbal IQ scores and similar measures.<sup>17, 18, 20-22</sup> (In the case of the Wechsler Intelligence Scale for Children<sup>23</sup> for example, the verbal subtests draw on general knowledge of the world, arithmetic ability, the ability to abstract analogies, and other non-linguistic skills.) Moreover, the investigators examined abilities in each of the subdomains of language independently. These subdomains include grammar (the rules for combining words into sentences and parts of words into whole words - boy+s, see+ing), semantics (the meaning of words and sentences), affective prosody (which concerns the expression of emotion in language), and narrative abilities. Abilities in each of these subdomains will be reviewed here.

## Grammar

Consider first the spontaneous and fluent speech of an 18 year old with WS, who has a full-scale IQ of 49 and cannot read. Describing her aims in life, she said:

You are looking at a professional bookwriter. My books will be filled with drama, action, and excitement. And everyone will want to read them . . . I am going to write books, page after page, stack after stack. I'm going to start on Monday.

From the analysis of their speech, it was found that subjects with WS characteristically used well-formed, grammatical sentences, in contrast to the DS subjects, and despite their general cognitive impairments. WS speech included complex structures such as passive sentences ("The dog was chased by the bees") and conditional clauses ("If you gave him a bone he would roll over"). In sum, subjects with WS employed a rich variety of grammatical structures and did so correctly.

Adolescents with WS were tested also for grammatical comprehension ability, as shown in Figure 2. Here, subjects with WS and DS were read "semantically-reversible" passive sentences, where an understanding of the grammar is critical for the correct interpretation of the sentences. For example, in the sentence "The horse is chased by the girl," grammatical knowledge is necessary to interpret whether the horse is the "chaser" or the "chasee." Testing showed excellent comprehension of passive sentences in WS, but poor comprehension in DS.

**(Figure 2 about here)**

Subjects with WS also were much better than subjects with DS on tasks requiring the conscious manipulation of language, as in correcting ungrammatical sentences and creating "tag questions." Tag questions are questions such as "Laurie likes fish, *doesn't she*?" Even for normal children, the ability to create tag questions is acquired relatively late, because they require mastery of the rules of question formation, the auxiliary verb system, pronoun usage, negation, and more. Correspondingly, the adolescents with DS gave almost no correct responses on a test of tag question formation. The subjects with WS, however, showed excellent command of the many syntactic manipulations required by this task.

## Semantics

Early medical observers often remarked at the large vocabularies and frequent use of uncommon words by children with WS. That standardized tests did not always confirm these impressions is not surprising. For example, the Vocabulary subtest of the WISC-R demands that the subject abstract how a word is distinguished from its synonyms and construct a proper definition.

These requirements clearly are distinct from knowing the correct meaning and usage of a word. However, on a more purely linguistic instrument, the Peabody Picture Vocabulary Test, the WS group did score significantly higher than the DS group. Despite an average IQ of 51, adolescents with WS were typically correct on such words as "canine," "abrasive," and "solemn."

A "semantic fluency" task elucidated other characteristics of semantic behavior in WS. In one instance, subjects were asked to name as many animals as possible in 60 seconds. The WS group gave quantitatively more responses than the DS group, in accord with subjective impressions of their fluent speech (Figure 3). They also showed a unique deviance, peppering their responses with uncommon animals, such as "weasel," "crane," and "newt," more often than controls (second-graders) matched for mental age and number of common animal responses.<sup>22</sup> These results document objectively the anecdotes of unusual word choice in WS.

**(Figure 3 about here)**

### Narration and Affect

In addition to grammar and semantics, the core of linguistic knowledge, linguists identify a set of "paralinguistic" features. These include "discourse abilities" (e.g. narrative cohesion and good turn-taking) and "prosody" (intonation, stress, and timing). Subjective impressions of adolescents with WS suggested that they might have had relative preservation of these skills.

On a narration task,<sup>21</sup> adolescents with WS and DS were asked to tell a story from a wordless picture book which depicts a boy, a dog and their search for a lost frog.<sup>24</sup> In their stories, subjects with WS used significantly more prosody than the DS group. The WS subjects frequently used other devices



also to convey affect, including sound effects and "audience hookers" such as "suddenly" and "gadzooks." In fact, the WS narratives seemed almost aberrantly rich in affect. On a larger scale, the WS adolescents structured their narration much more cohesively than did their DS counterparts. They were far more likely to establish a clear orientation, and to state the problem ("Next morning. . .there was no frog to be found"), and the resolution ("Lo and behold, they find him, with a lady!").

### Implications for Psychology

The relevance of this Pediatric research to theoretical issues in Psychology exemplifies the cross-disciplinary nature of Cognitive Neuroscience. One such issue is the nature of the relationship between language and other cognitive functions. While some suggest that language and general cognition depend on a common set of psychological processes and neurobiological mechanisms, others argue that language is an independent process that utilizes distinct mechanisms. If the latter were true, then language and general cognitive skills should be dissociable. The selective preservation of grammar found in these studies of WS seems to support this view. Specifically, the WS findings seem inconsistent with the hypothesized link between the mastery of passive sentences and mastery of the Piagetian concept of conservation. (The two are associated in the course of normative development.<sup>25</sup>) On the other hand, the research on WS points out that language and cognition may still be related in certain places, as the unusual semantic choices of adolescents with WS may result from an aberrantly-structured knowledge base.

## **Dissociations within Spatial Cognition**

Like language, spatial cognition also may be fractionated into components. However, the identity of those components has been difficult to establish. Studies of WS and DS have illuminated one way that visuospatial abilities may fractionate, as a result of genetic anomaly.<sup>17, 18, 20, 22, 26, 27</sup> We review some of these studies as a second example of the intersection between Cognitive Neuroscience and Pediatrics.

### **Unique Patterns of Spatial Deficits in WS and DS**

While a number of investigators have established that basic visual-spatial abilities are deficient in subjects with WS, a deeper understanding of visual-spatial problem-solving in WS can be obtained through a “process analysis.” This approach was developed in the field of Cognitive Psychology, and is eminently applicable to the cognitive testing of pediatric subjects.

Beginning again with subjective (but informed) impressions, it was noted that drawings by subjects with WS often seemed to lack in cohesion or gestalt organization. That is, a drawing of a house might include windows, a door, and a roof, but these parts would not be in the correct relationship to each other (Figure 4A). By contrast, a DS drawing might be very simplified, but would show the proper gestalt relationship of its elements (Figure 4B). Similar tendencies were found on the Block Design subtest of the WISC-R. Although WS and DS subjects scored equally low on that test, their incorrect responses were radically different. The DS adolescents failed to replicate the internal pattern of the blocks, but the WS subjects failed even to produce the correct

global configuration of blocks (a 2x2 square). This striking qualitative difference was evident only in the processes underlying their responses.

**(Figure 4 about here)**

An experiment which clearly separated global and local levels of organization was designed to explore this phenomenon further.<sup>26, 27</sup> Figure 5 shows the type of stimulus created for this test. When asked to copy these figures, the WS subjects drew the local features correctly, but their pictures were entirely lacking in global configuration. In contrast, the DS adolescents generally replicated the global features, but omitted the local detail. Neither group had any problem drawing either purely local or purely global figures (e.g. a large, simple diamond, or a single small plus-sign).

**(Figure 5 about here)**

#### Preservation of Facial Perception in WS

Along with their profound and idiosyncratic deficits, subjects with WS do show preservation of some visual-spatial abilities. These include abilities related to the perception of faces, such as recognizing the same face in various conditions of lighting and orientation. On such tests, subjects with WS show remarkable abilities, performing much better than subjects with DS, and no differently than normal age-matched controls! Memory for faces also may be preserved in WS.<sup>28</sup>

Thus, while subjects with WS did show gross deficits in spatial cognitive ability, it is possible to describe a specific pattern of deficits - the preference for local versus global processing - and to identify distinct domains where ability is preserved (facial perception). Further research will determine whether the local/global processing distinction is related to the processing of facial stimuli

in WS. The more general attempt to construct a unifying theory for the peaks and valleys of spatial ability in WS and DS, will contribute to the construction of a nosology for visual-spatial cognition in all people.

### **Cognitive Development: Evolving Profiles**

It is axiomatic for Pediatricians that the processes of development affect different biological systems at different ages. Cognitive studies of WS and DS reiterate this theme. Using a highly reliable parent questionnaire which inventories over 600 vocabulary items, in conjunction with laboratory measures of language and general cognitive development, it was found that early vocabulary acquisition was equivalently delayed in groups of 30 toddlers with WS and DS.<sup>29, 30</sup> Morris et al. and Trauner et al. also have reported that language and motor milestones both are late in WS, as in DS.<sup>31, 32</sup> Thus, the profile of linguistic preservation that is found in older children with WS is not evident initially. These results suggest that educational prescriptions for young children with WS must be distinct from those for adolescents. Table 1 summarizes some of the neuropsychological profile of WS and DS. Neuroanatomic studies help explicate the brain mechanisms which underlie the neuropsychology of WS and DS.

**(Table 1 about here)**

### **Studies of Neuroanatomy in WS and DS**

In addition to insights on the organization of psychological abilities, Cognitive Neuroscience seeks insight on the neurobiological bases of language and thought. This effort has been spurred recently by the development of

unprecedented methods for evaluating brain structure and function in living, thinking subjects. For the study of human subjects, the development of positron emission tomography (PET) and the refinement of magnetic resonance imaging (MRI) have been most important.

## MRI Studies

Morphometric MRI studies of the brain in WS and DS were performed on the same group of adolescents and young adults in which Bellugi et al. studied psychological functions.<sup>9, 33, 34</sup> Using state-of-the-art volumetric techniques, Jernigan et al. found comparable overall reductions of cerebral volume in both syndromes, in comparison to age-matched normal controls. Further analyses revealed important regional differences in brain volume between WS and DS. First, anterior brain volume was proportionately preserved in WS but not in DS. Second, limbic structures in the temporal lobe showed essentially equal volumes in WS and control subjects, but were significantly reduced in DS. On the other hand, the volume of the thalamus and lenticular nuclei were much better preserved in DS than in WS. Wang et al. found that the anterior parts of the corpus callosum, like the anterior hemispheres, were preserved in WS, but diminished in DS.

Quantitative analysis of cerebellar volumes also yielded intriguing results. Whereas the DS group showed comparable diminutions of volume in cerebrum and cerebellum, cerebellar volume was well-preserved in WS. Again, closer regional analyses were enlightening: it was found that the locus of preservation in WS was the neo-cerebellum. Of the two parts of the neo-cerebellum that were subjected to scrutiny, the neo-cerebellar vermis and the neo-cerebellar tonsils<sup>35</sup>, both showed volumetric preservation or even increases

in WS, whereas both were volumetrically-diminished in DS. These results are summarized in Table 2.

**(Table 2 about here)**

### Implications for Developmental Neurobiology

Results of other research have suggested that ~~the~~ expansive pre-frontal cortex and the neo-cerebellum, both selectively preserved in WS, are thought to be closely related.<sup>36, 37</sup> These two regions of the brain achieve their large extent only in *homo sapiens*, and are thought to have evolved contemporaneously. Furthermore, the neo-cerebellum has more extensive connections to pre-frontal and other association areas of cortex, than do the older parts of the cerebellum. The third area of preservation in WS, mesial temporal lobe, may include portions of auditory association cortex, which also projects to Broca's and other pre-frontal areas.<sup>38</sup>

The neuroanatomic profile of WS thus contributes to the understanding of the brain's organization, by demonstrating a morphological pattern that can result from genetic anomaly. The finding that anterior, temporal limbic, and neo-cerebellar regions are selectively preserved in WS suggests that they all may come under the influence of a single genetic, developmental factor, or that their development is mutually interactive, or both. Conversely, the previously accumulated evidence that these regions are closely related lends plausibility to the findings in WS. These hypotheses also are consistent with the selective preservation of the basal ganglia and thalamus in DS, since they are less well-connected to the regions that are preserved in WS.<sup>39</sup> Future MRI studies of younger children with WS and DS will address the relationship between their evolving cognitive profiles and their profiles of brain development. Such

questions on the relationship of brain to behavior bring us back to the issues of Cognitive Neuroscience.

### **Implications for Brain-Behavior Relationships**

A number of insights on the relationship of the brain to cognitive behavior are gained from the juxtaposition of neuropsychological and neuroanatomic findings in WS and DS. One of these insights regards the specialization of the two hemispheres. At a first approximation, the preservation of linguistic skills and the poor visual-spatial function in WS is very similar to the pattern found in non-syndromic adults with lesions of the right hemisphere.<sup>40</sup> The WS bias for a local (not global) mode of processing of hierarchical stimuli also is seen in right hemisphere-damaged adults. However, the absence of focal lesions or lateralized dysplasias in MR imaging studies demonstrates that the dissociations between and within language and spatial cognition, which are found in WS and DS, can arise as a result of genetically-determined defects of neurodevelopment, even in the absence of lateralized brain lesions.

In fact, studies of genetic syndromes such as WS and DS may provide new clues about the behavioral patterns that can arise as a result of aberrant neurodevelopment. The relatively good semantic fluency, affective prosody, and narrative abilities that are found in WS would be unexpected in right hemisphere-damaged adults, who typically show deficits in these skills. Face perception abilities also are thought to depend more heavily on right than left hemisphere integrity. The preservation of these abilities in WS, along with the preservation of grammar, implies then that higher cortical function can break down, neurobiologically, along lines other than the lines of cerebral laterality.

For WS, an alternative to this “right vs. left” biological scheme may be found in the MRI demonstration of frontal/limbic/neo-cerebellar preservation vs. overall cerebral volume reduction.

The finding of neo-cerebellar preservation in WS is another intriguing piece of data for Cognitive Neuroscience. Until recently, it had been thought that the cerebellum was concerned with motor function exclusively. However, a recent study employing PET techniques with normal subjects showed activation of the neo-cerebellum only when semantic reasoning was required.<sup>41</sup> Detailed studies of patients with pure cerebellar lesions also have shown deficits in cognitive function.<sup>42</sup> Moreover, MRI and pathological studies have shown that the neocerebellum is selectively hypoplastic in autism, a pervasive disorder of cognition. The neuroanatomic connections of the neo-cerebellum, discussed above, furnish a basis for cerebellar participation in higher cortical function. The findings that semantic fluency, other linguistic functions, and neo-cerebellar volume all are preserved in WS adds to the body of evidence that the neo-cerebellum may subserve more than motor function.

### **Cognitive Neuroscience and Pediatrics**

The particular strengths of Cognitive Neuroscience stem from its multi-disciplinary approach. By drawing on cognitive psychology, this research has shown that meticulous testing of cognitive domains in WS and DS may reveal important dissociations among them. By drawing on neuroimaging techniques, this research has identified certain parts of the brain that may be related developmentally, as evinced by their common preservation in a genetic disease.

Even more instructive are the insights drawn by looking across levels of neuroscience. In the research on WS, this approach is shedding light on neo-



cerebellar function and on the organization of higher cortical functions that previously have been mapped according to hemispheric specialization. Studies of memory provide another example of the benefits of a cross-level approach. Cognitive neuroscientists are studying memory on the molecular, synaptic, and neural system levels, as well as at the behavioral level. Research on memory in WS and DS, not reviewed here, is beginning to contribute to this enterprise.<sup>43</sup> Preliminary findings on spatial memory in DS and WS are opening a window onto the investigation of the brain substrate for spatial memory, imagery, and perception.

It is important to remember, in addition, that the research presented here also is motivated by its potential benefit to Pediatric patients. For diagnostic purposes, it has been suggested that the specific cognitive or behavioral profiles can be just as helpful as physical signs are: both may be characteristic, though neither is invariant.<sup>44</sup> Hand-wringing in Rett syndrome and self-mutilating behavior in Lesch-Nyhan are characteristic behavioral phenotypes. Characteristic cognitive phenotypes have been proposed for neurofibromatosis type I<sup>45</sup> and for Fragile X,<sup>46</sup> as well as for WS.

For therapeutic purposes, it is obvious that educational interventions and job placements must be guided by a precise knowledge of patients' psychological strengths and weaknesses. So too, the medical management of attention deficit, learning, and other cognitive disorders must be guided by a precise knowledge of (neuro)pathophysiology. The research on WS and DS strives toward such an explication of cognitive disease processes and their behavioral expression. We anticipate that the future will bring a precise understanding of brain development and of how the brain accomplishes cognitive functions. Then, our therapeutic interventions might be more efficacious than we can now imagine.

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## FIGURE LEGENDS

**Figure 1. Piagetian Concept of Conservation.** A. According to the concept of conservation, the volume of water remains constant, regardless of the shape of its container. B. Subjects with Williams syndrome and with Down syndrome both score very poorly on a test of understanding of the concept of conservation.

**Figure 2. Grammatical Understanding of Passive Sentences.** A. In order to decide which picture matches the sentence, the child must understand the grammar of passive sentences. B. Subjects with Williams syndrome perform almost perfectly on tests of passive sentence comprehension, whereas those with DS perform at chance levels.

**Figure 3. Semantic Fluency.** When asked to name as many animals as they can in 60 seconds, subjects with Williams syndrome give the same number of common responses, but significantly more uncommon responses than either subjects with Down syndrome or control subjects matched for the number of common responses.

**Figure 4. Free Drawing.** Drawings of a house by a subject with Williams syndrome (A) and a subject with Down syndrome (B). The Williams drawing contains many parts of houses, but the parts are not coherently organized. The Down drawing is simplified but has the correct gestalt of a house.

**Figure 5. Hierarchical Processing.** When asked to draw a diamond made up of small plus-signs, the subjects with Williams syndrome (A) draw plus-signs without a global configuration, and the subjects with Down syndrome (B) draw a diamond without local detail.



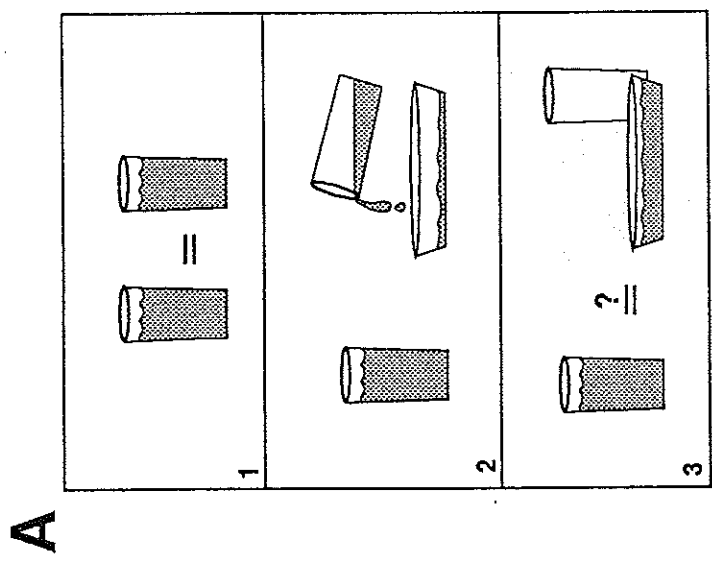
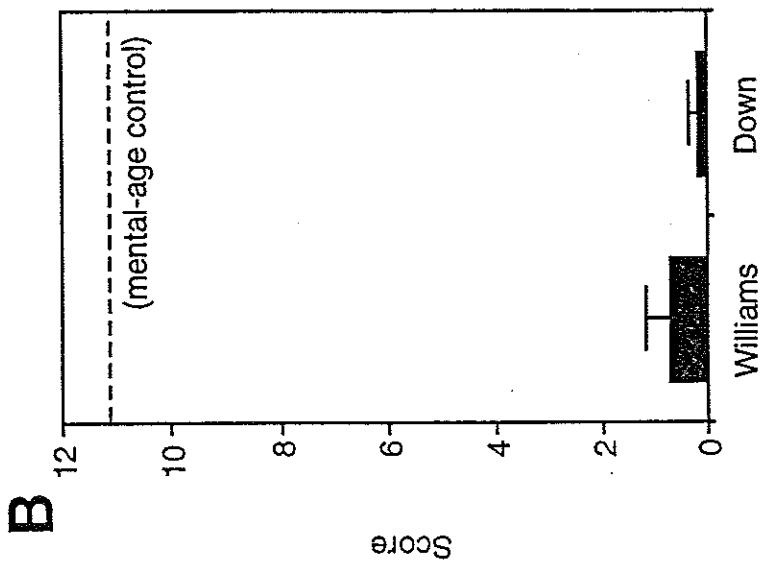
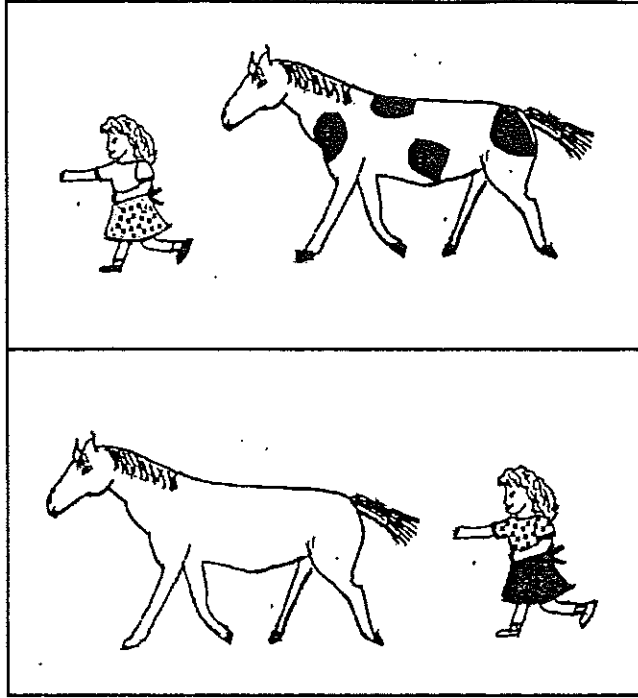


Figure 1

**A**



"The horse is chased by the girl."

**B**

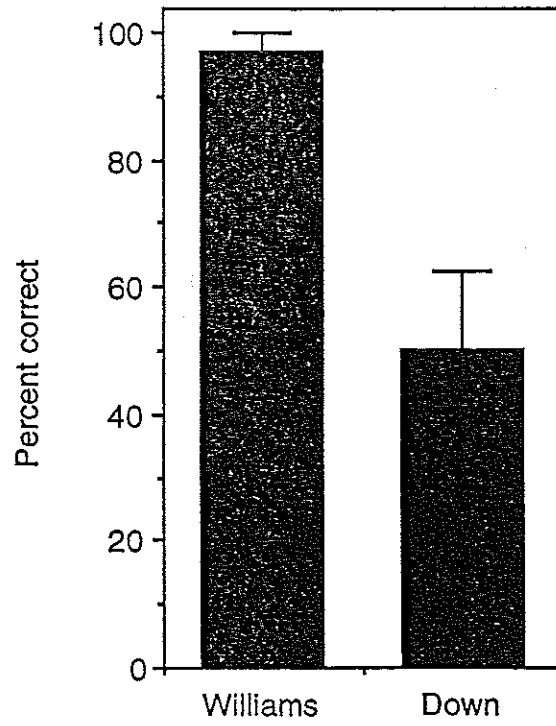
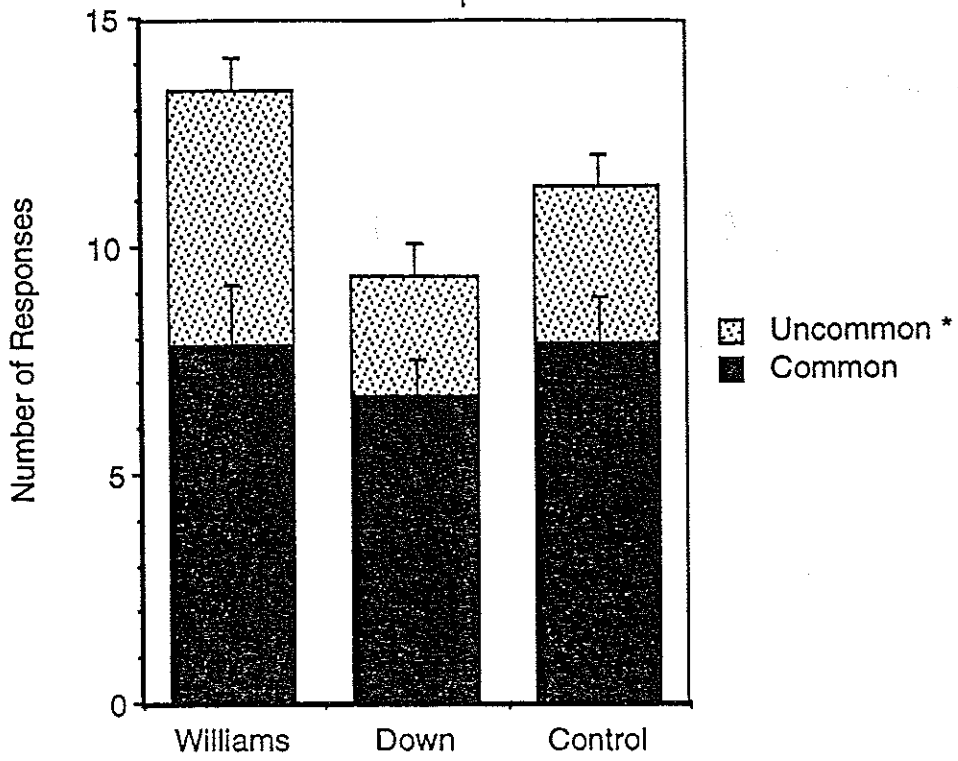


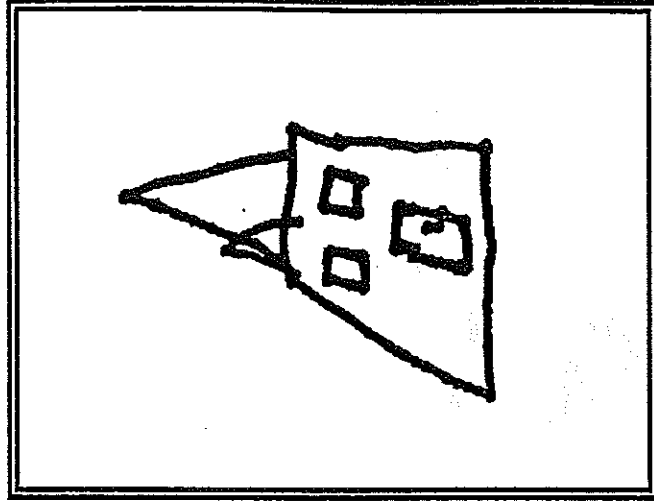
Figure 2



\*  $p < .05$ , Williams vs. Down and Williams vs. Control

Figure 3

B



A

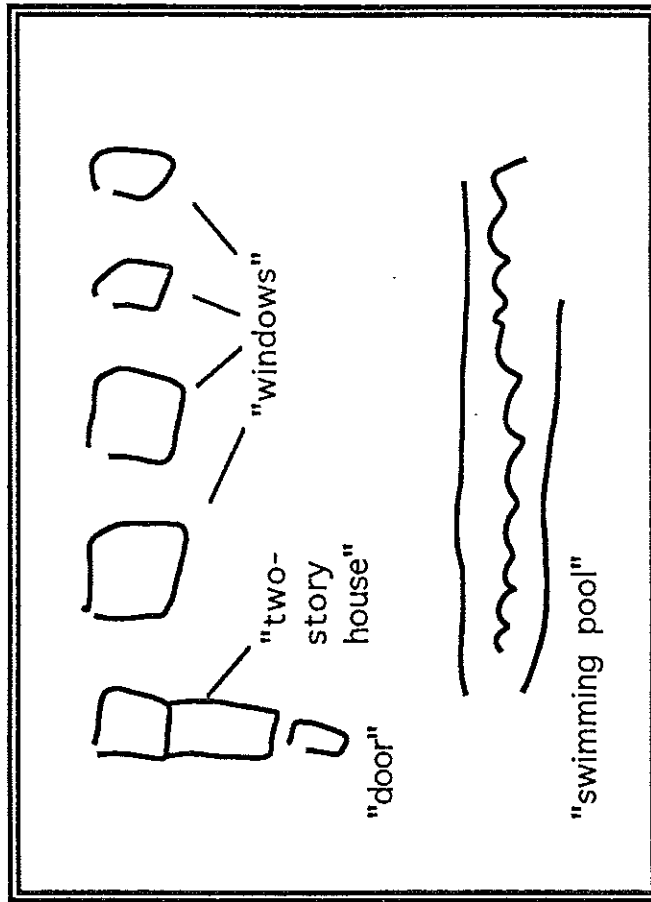
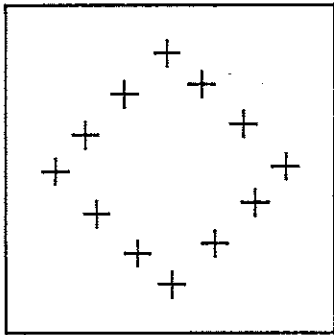
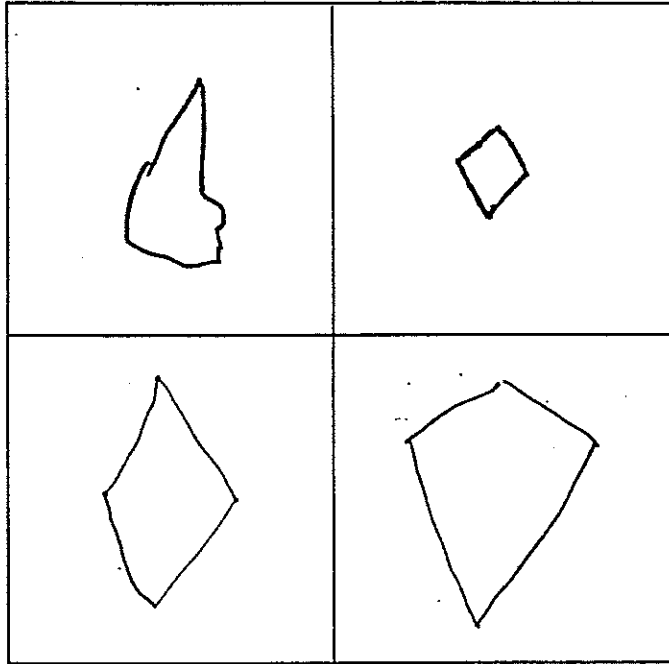


Figure 4

Model



Down



Williams

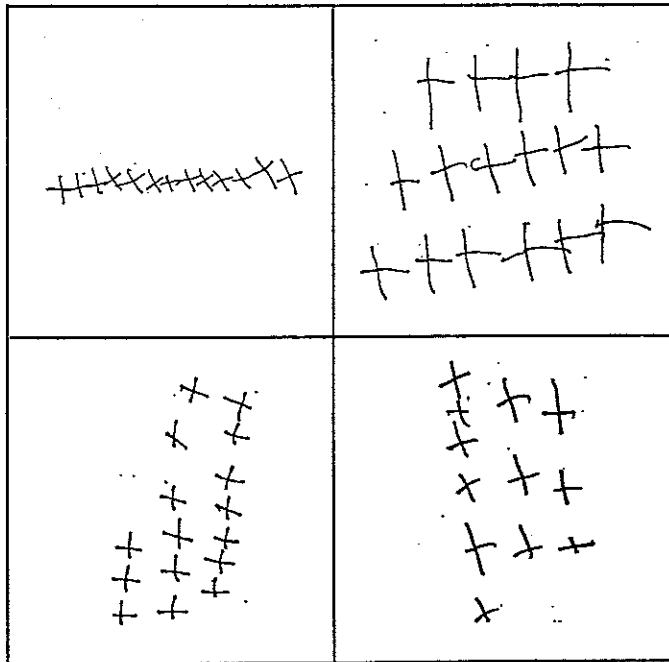


Figure 5

**Table 1. Neuropsychological Profiles in Williams and Down Syndromes**

Age group:	Williams	Down
<b>Pre-Schoolers</b>		
Vocabulary Acquisition	Delayed	Delayed
Motor Milestones	Delayed	Delayed
<b>Adolescents/Young Adults</b>		
Grammar	Correct, complex	Poor, simple
Semantics	Larger vocabulary Uncommon word choices	Smaller vocabulary
Linguistic Affect	Rich	Diminished
Visuomotor Ability	Poor, fragmented	Simple, cohesive
Hierarchical processing	Local	Global
Processing of Faces	Remarkably strong	Impaired

**Table 2. Brain Morphometry in Williams and Down Syndromes**

Brain region:	Williams	Down
<b>Cerebrum (and regional proportions)</b>		
Overall volume	↓	↓
Anterior cerebrum	↔	↓
Temporal limbic	↔	↓
<b>Subcortical nuclei (proportional sizes)</b>		
Caudate	↔	↔
Lenticular	↔	↑
Diencephalon	↔	↑
<b>Cerebellum (volumes)</b>		
Overall	↔	↓
Paleocerebellar vermis	↔	↓
Neocerebellar vermis	↑	↔
Neocerebellar tonsils	↔	↓

↔ indicates "similar to controls"

↑ indicates "greater than in controls"

↓ indicates "less than in controls"

