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“If you have to have a syndrome, Williams’ is a cool one to have<sup>\*</sup>”

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\* Comment from a 16-year-old with Williams Syndrome

Williams Syndrome (WS) is a rare neurodevelopmental genetic disorder stemming from a hemizygous deletion of about 20-28 genes from chromosome band 7.11.23q (Ewart et al., 1993) including the gene for elastin. Early estimates of incidence proposed 1 in 20,000 live births (Greenberg, 1989), but current estimates are 1:7500 (Stromme, Bjornstad, & Ramstad, 2002). Williams Syndrome was first recognized by a pediatrician, Dr. JCP Williams in 1961 who described a group of children with ‘elfin facies’ and supravalvular aortic stenosis (Williams, Barratt-Boyes, & Lowe, 1961). Shortly thereafter, Dr Alois Beuren (1962) identified another group of children with similar features including an intolerance to calcium. As such, this syndrome has also been called Williams Beuren Syndrome or infantile hypercalcemia. The early descriptions of children and adolescents with WS noted a set of characteristic facial and behavioral features: “an unusual command of language combined with an unexpectedly polite, gentle and open manner,” (von Armin & Engel 1964). Twenty years later, WS caught the interest of cognitive scientists when WS was seen as a possible case of spared language in the face of impaired cognition (Bellugi, Sabo & Vaid, 1988; Bellugi, Wang, & Jernigan, 1994). The early studies noted that in spite of IQs ranging from 40-70, with an average full scale IQ of 55 (Bellugi, Lichtenberger, Jones, Lai, & St George, 2000) and significantly impaired visuo-spatial cognition, adolescents with Williams had excellent language skills (Bellugi, Lai, & Wang, 1997; Reilly, Klima, & Bellugi, 1990). In the ensuing twenty years, recognizing Williams Syndrome as a unique opportunity to investigate genetic influences on brain development and cognitive and social processes, investigators have approached the puzzles of Williams Syndrome from multiple perspectives. In this chapter, we provide an overview of Williams Syndrome focusing on their cognitive and neuropsychological profile from a developmental perspective and where known,

the possible neural and genetic underpinnings of the Williams Syndrome profile. We close with a brief discussion of therapeutic interventions for WS.

## CLINICAL PROFILE

The WS deletion invariably includes the gene for elastin (*ELN*), which codes for an elastic protein in connective tissue that is abundant in large blood vessels such as the aorta (Lowery et al., 1995). WS is diagnosed by detecting the absence of one copy of the gene for *ELN* with the fluorescent *in situ* hybridization (FISH) test. The first deleted gene identified in the critical region of WS was *ELN*, and it has been reliably linked to the cardiac abnormalities associated with WS (Tassabehji et al., 1999, 2005). Additionally the cluster of genes *LIMK1*, *CYLN2*, *GTF2I*, and *GTF2IRD1*, has been linked to non-language cognitive features of the syndrome, as well as to craniofacial dysmorphology shared by children with Williams Syndrome. This includes a small upturned nose, full lips, a broad brow and full cheeks, as well as an elongated philtrum and small, widely spaced teeth (see Fig 1). In those with light colored eyes, a stellate or lacy patterned iris is also detectable. The gene *GTF2I* has also been linked to the intellectual impairment (Morris et al., 2003).

### **Insert Figure 1 about here**

Parents report that the first year is extremely difficult. As infants, the children frequently exhibit feeding problems including colic and reflux; hypercalcemia (high blood levels of calcium) is also common in infancy and early childhood. Thus vitamin D and calcium should be avoided. Most babies with WS are small at birth; 70% suffer from failure to thrive and generalized hypotonia characterizes these infants. Growth is slow during infancy and childhood; adults with WS are of short stature with mean adult height below the third percentile; males are less affected than females.

With respect to sensory and motor development, children and adults have difficulty with both gross and fine motor control producing an awkward gait as well as difficulty with fine motor tasks, such as writing, drawing, getting dressed, tying shoes or using tools. Sensory functions are also affected: middle ear infections are common in early childhood and most adolescents and adults with WS suffer mild to moderate sensori-neural hearing losses. Hyperacusis (sensitivity to sounds) is frequently reported in individuals with WS, as are both fears and fascinations with particular sounds. Problems with vision, such as strabismus, cataracts and visual acuity problems are reported in 50% of those with WS.

Between 50-75% of individuals with WS develop cardiovascular disease during their lifetime (Morris, Demsey, Leonard, Dilts, & Blackburn, 1988); most commonly in the form of supralvalvar aortic stenosis. In fact, the original report by J.C.P Williams (1961) is entitled “Supralvalvular Aortic Stenosis SVAS”. Additionally, reports of stenoses of the descending aorta, intracranial arteries and renal arteries also exist. The deleted ELN (elastin) gene appears to be related to these vascular problems. In discussing Williams Syndrome, it is important to keep in mind that this is a multi-system syndrome, and that because these children, like all children, are developing, the profile is dynamic. As such through childhood and adolescence, there are marked changes with development in both their clinical and neuropsychological profiles.

### **THE WILLIAMS PHENOTYPE**

A hallmark feature of those with Williams is their unusually uneven neuropsychological profile. They show strengths in language and in face processing and have very sociable personalities in concert with a strong affinity to music. These strengths contrast with significantly impaired executive functioning, problem solving abilities and visuospatial

cognition. They have difficulty with arithmetic and making change; in school, math, reading and writing present significant challenges. In spite of their sociability and affability, they have difficulty with peer relations, and non-social anxiety is common in WS, especially as they get older.

**Insert Figure 2 about here**

Much of the research to date has focused on these domains of relative strengths and weaknesses and interestingly, studies have found fractionation within, as well as across domains. In the following sections we will address overall intellectual functioning, the acquisition and use of language in WS; their visuospatial profile, their affinity for music and finally, the emergence and development of their strong sociability and attraction to others.

**THE BROAD VIEW: INTELLIGENCE AND STANDARDIZED TESTS IN WS**

Individuals with WS are classified as mildly to moderately retarded with Full Scale IQ scores ranging from 40-90 with a FSIQ mean of 55 (Bellugi et al., 2000). Verbal IQ tends to exceed Performance IQ scores with Verbal means at 63 and those for performance at 55 (Martens, Wilson, & Reutens, 2008). In spite of their higher verbal scores and facility with language, on standardized language tasks, those with Williams do poorly. For example, on the Carrow Elicited Language Inventory (CELI; Carrow, 1974) those with WS score significantly below their chronological age matched peers (see Figure 3) and some studies have found their language performance to be closer to those who are matched on mental age (Mervis & Becerra, 2007). Whereas standardized intelligence tests provide global information, it is only by looking at more targeted experimental measures that details of the phenotypic features are revealed.

**Insert Figure 3 about here**

**LANGUAGE ACQUISITION IN WS**

Consonant with initial studies of Williams, including the first reports from J.C.P. Williams, on meeting an individual with WS for the first time, one is immediately struck by their remarkable friendliness, politeness and talkativeness, as well as an apparently strong interest in their interlocutor. At the same time, one notes that the interaction is rather superficial. Current studies have gone beyond these initial impressions to reveal that the language capacities and their development in WS presents a complex picture (see Brock, 2007 for a comprehensive review); the results paint a picture of delay and perhaps an unusual route in the acquisition of language structures, but a surprisingly robust use of language for social purposes (Losh, Reilly, Bellugi & Anderson, 2000).

### **Early Language Development**

Typically, before infants begin to talk, they produce rhythmic babbling that co-occurs with other rhythmic movements, such as rhythmic hand banging. Young infants with WS follow this same developmental course. Other communicative precursors to language in typically developing children include the development of joint attention and the use of gesture, especially pointing. Pointing, which emerges in typically developing children around 9-10 months of age, serves to indicate a particular object from an array. Joint attention or the 'sharing of visual attention to a particular object or event' also plays an important role in establishing language. It is in this context, when the infant and the adult are both looking at the same toy, for example, that the adult is likely to supply a label, and the child to associate the word with the object. As such, these two communicative behaviors, pointing and joint attention, are seen as supporting language development. Interestingly, babies with WS are less likely to gesture than typically developing infants or age matched infants with Down Syndrome (with comparable mental capacity). Moreover, infants and toddlers with WS have been characterized as having 'sticky

attention' (Laing et al., 2002). That is, rather than looking at the proffered object, young children with WS are more likely to fixate on the face of the adult addressee. Such behavior also impedes their ability to follow an adult's pointing gesture.

With respect to children's first words, the first point to emphasize is that the emergence of first words is significantly delayed in children with WS, by an average of two years, compared to typically developing children (TD) children. The early lexical development of toddlers with WS is comparable to age matched toddlers with Down Syndrome and to that of typically developing children matched for mental age. For example, at 28 months, a WS toddler has about 10 words, comparable to the average vocabulary of a TD child of 12-13 months of age (Mervis, Robinson, Rowe, Becerra, & Klein-Tasman, 2003).

**Insert Figure 4 about here Figure**

Once toddlers with WS are producing their first words, in contrast to those with Down Syndrome, they begin to combine words into sentences at a comparable productive vocabulary size to typically developing children. Interestingly, although first words are initially delayed (see Figure 4, from Singer Harris et al., 1997), such words precede rather than follow the emergence of pointing (Mervis et al., 2003); this contrasts with the profile in typically developing children where pointing emerges at 9-10 months of age and is seen as a precursor to first words. In addition, children with WS continue to be drawn to others faces rather than the task at hand. These atypical early behaviors suggest that language acquisition in WS may bear a different relationship to supportive cognitive processes than in typical development.

It has also been noted that children with WS have good auditory memory which may enhance their lexical acquisition, and some researchers have suggested that children with WS depend more heavily on auditory memory than TD children in word learning (Vicari, Carlesimo,

Brizzolara, & Pezzini, 1996). In typical development, children's receptive vocabularies far outstrip their productive vocabularies. This does not seem to be the case for young children with WS: their receptive and productive vocabularies are often comparable, again suggesting that the language acquisition process in WS is atypical. The notion that language and cognitive development may have a different relation for children with WS, and that language learning is following a different route in WS, is confirmed in studies of word learning. Although their early lexicons increase, children with WS are distinctive in that such development is not followed by the accompanying cognitive changes seen in typically developing children such as categorization abilities (Nazzi, Paterson, & Karmiloff-Smith, 2003) or fast mapping (the ability to quickly deduce the object being referred to by a novel word).

Children's early sentences often are 'telegraphic', e.g., 'Where kitty? Daddy go bye bye'. Regardless of method: analyses of free speech, parental questionnaires or sentence repetition tasks, performance of children with WS is comparable in length and complexity to that of Mental Age (MA) or vocabulary matched controls, and significantly more complex than that of children with DS, but does not reach the length or complexity of age matched typically developing children. Such findings might suggest an overall delay in language development. However, Volterra and colleagues (2003) also noted that the sentences from Italian children with WS included atypical morphological or grammatical errors, not found in the data from typically developing Italian children, again suggesting the possibility of an atypical route to language (Volterra, Caselli, Capirci, Tonucci, & Vicari, 2003).

### **Later Language: Mastering the grammar**

Language comprehension has been assessed by various standardized language tests such as the Test for Reception of Grammar (TROG, Bishop, 1982) where the task is to point to the

picture described by the experimenter. Overall, school age children with WS have been found to perform better than age matched children with Down syndrome and comparably to their mental age match controls, again suggesting delay in language development. Typically developing children, acquiring English, have mastered the majority of the grammar of English by age five or six, however, in spontaneous speech, children with WS continue to make significantly more grammatical errors than their age matched peers up until adolescence. In fact in a sentence repetition task, their error rate is comparable to Children with Language Impairment (LI), who are not retarded. Reilly and colleagues (Reilly, Losh, Bellugi, & Wulfeck, 2004) found similar results regarding rates of grammatical errors comparing age matched school age children with WS and LI in a narrative task (see Figure 5).

**Insert Figure 5 about here**

As they approach adolescence, children with WS make few grammatical errors and use a range of complex sentence types. Nonetheless, even as adolescents, they make more errors than their TD peers, and at this later point in development, these errors often involve prepositions reflecting spatial relations. Similar results have been reported in tasks where participants describe filmed scenes of moving objects, particular responses on the TROG, and in narratives. Moreover, this phenomenon has been found not only in English, but also in French speaking children with WS (Reilly et al., 2005a) as well as those acquiring Hungarian, a language rich in grammatical markers expressing spatial relations. In this case, the visuo-spatial difficulties of those with WS penetrate their language, again confirming the idea that language and normally associated cognitive systems may have a unique relationship in Williams Syndrome.

**Pragmatics: Using language for social purposes**

In spite of the long developmental road for acquiring the grammatical structures of language, children and adolescents with WS are very good talkers. From their earliest utterances, they exploit language for their own social purposes. In a narrative study of WS children ages 5-10, although they made many errors and the stories were structurally poor, the stories were affectively extraordinarily rich (Losh, Reilly, Bellugi, & Anderson, 2000). Overall their narratives are characterized by an excessive use of ‘social evaluation,’ that is, language used to attract and maintain the listener’s attention. Some examples of social evaluative devices are: direct discourse, *The boy called, “Froooooog, where are you?”* intensifiers *really, very,* emotional words, *He was so very sad to lose his frog,* and sound effects, *Splash! He fell into the pond!*; in fact they use more social evaluative language than all other typical or atypical groups as shown in Figure 6.

**Insert Figure 6 about here**

In social situations where children with WS must adapt to a conversational situation or perform a specific verbal task, they have more difficulty. The Children’s Communication Checklist is a questionnaire to be completed by parents, professionals and teachers to identify communicative problems. The two areas in which the WS group had the most difficulty were: 1) inappropriate initiation of conversations and 2) conversational stereotypy’s. Their performance was below that of children with Down Syndrome and those with Language Impairment (Laws & Bishop, 2004). In conversational exchanges with an adult, they tend to speak less and their utterances contain less information than their typically developing peers. Moreover when performing a task, they have more difficulty responding to the requests of their interlocutor than either TD children or age matched children with Down Syndrome; moreover, their responses are less appropriate (Lacroix, Bernicot, & Reilly, 2007). These results are counter-intuitive as

children with Williams are usually presented as extremely expressive and sociable. Such character traits are more evident in open-ended, less constrained situations, or where the child with WS can take the social initiative, however, in more constrained contexts where the child must adapt to the interlocutor, they have more difficulty.

Using and understanding non-literal language, such as sarcasm or irony emerges in typically developing children during late school age. The single such study of children and adolescents with WS asked them to distinguish between lies and jokes (Sullivan, Winner & Tager-Flusberg, 2003). Participants listened to stories in which a participant produced an erroneous utterance that was either a joke or a lie. The WS group, similar to the other clinical groups tended to consider all the erroneous utterances to be lies, and in their justifications, they offered few mental state justifications. In line with such findings, Tager-Flusberg and colleagues tested them on 'theory of mind' tasks and the WS group failed on the false belief tasks (e.g., Does Frank know that his grandfather knows that he did not do the dishes?).

In summary, children with WS are characterized with a specific developmental trajectory for language that is unique to this group; the developmental delay appears more marked in the early developmental period especially up to five or six years of age. Up until age 10, there is significant heterogeneity in grammatical performance, that is, unlike in typical development, chronological age does not correlate with language development during the school years. Communicative gestures, especially pointing, are used infrequently, and the initial delay in the emergence of language is significant, yet vocabulary comprehension represents a strength as the children develop. With respect to using language, their spatial errors and excessive use of social language, especially in conversations and narratives, are characteristic of individuals with WS. The fact that children and adolescents with WS are apparently so comfortable with language in

social situations should be considered as a strength that can serve as a foundation for remediation programs and in their social integration into school and the community.

### **WILLIAMS AND MUSIC**

Another potential ‘Peak’ in the WS phenotype is music. A characteristic of many individuals with WS, but a domain that is largely unexplored, is their enhanced sensitivity and affinity for music. For example, mothers tell of their infants with WS welling up with tears at hearing Brahms’ lullaby; even the earliest reports noted that children with WS showed a strong interest in music and singing (von Armin & Engel, 1964). Attempting to characterize the WS musical profile, Levitin and colleagues (Levitin et al., 2004) administered surveys to parents of children with Williams Syndrome, Autism, and Down Syndrome as well as controls. Compared to the other three groups, the WS group showed interest in music at an earlier age, spent more hours listening to music, and displayed greater emotional responses to music.

Rhythm and timbre, as aspects of music, are viewed as strengths within the Williams Syndrome population. Levitin and Bellugi (1998) looked at rhythmic abilities using an echo clapping task and found equivalent scores in the WS group and MA controls. Looking at the errors, they found that those produced by the WS group were more rhythmically compatible than in the TD group, and the WS errors tended to be creative extensions to the reference rhythm (Levitin & Bellugi, 1998). In experimental tasks designed to test rhythm and melody in WS, Levitin and Bellugi (2006) digitally recorded stimuli and used students from the Julliard School of Music in New York as controls. The results showed that the WS group and the music students performed equivalently on the rhythm test, but when asked to complete the melody, the Williams Syndrome group struggled while the typically developing group excelled. The authors concluded that the Williams Syndrome group is better at rhythmic than melodic production. A study

investigating melodic imagery and musical expressiveness (Hopyan, Dennis, Weksberg, & Cytrynbaum, 2001) found that the WS group performed comparably to controls, suggesting that similar to rhythm, these aspects of musical production are strengths in WS.

There have been numerous reports that individuals with Williams Syndrome are fascinated by particular sounds, e.g, vacuum cleaners, and these objects of fascination frequently had previously been the target of an auditory phobia. Interestingly, the WS group is often quite skilled in identifying the timbre of particular sounds. In a timbral identification task, 12 different vacuum cleaners were digitally recorded and played back to individuals with WS and TD controls matched for chronological age from the Julliard School of Music. The WS group performed comparably to the music students demonstrating that like rhythm, timbre identification is also a strength in the WS musical profile (Levitin & Bellugi, 1998). As noted above, the auditory sensory profile of WS is atypical: estimates of hyperacusis in WS is reported at 95% (Klein, Armstrong, Greer, & Brown, 1990), although this may include other auditory anomalies. In the general population, absolute pitch is reported at the rate of 1: 10,000, whereas in WS, it occurs in 1:1,000 suggesting that overall their auditory sensitivity and processing is unusual.

Given their interest and sensitivity to music, participating in musical activities, music camp and music therapy may be a successful avenue for those with WS. In fact, in a study using parental questionnaire, researchers found lower levels of anxiety and a decrease in maladaptive behaviors when individuals with Williams Syndrome spent time engaged in musical activities (Dykens , Rosner, Ly, & Sagun, 2005; Sellinger, Hodapp, & Dykens, 2006).

### **VISUAL SPATIAL COGNITION**

A hallmark of the WS phenotype is impaired visual spatial cognition, especially in visuo-constructive tasks, such as drawing a picture or making a construction with blocks (see Farran and Jarrold, 2003 for a comprehensive and thoughtful review). Many of the initial studies noted that adolescents and adults with WS performed poorly on standardized tests, for example the five subtests of the Wechsler Intelligence Scale for Children (WISC) that constitute PIQ: Picture Arrangement, Picture Completion, Coding, Block Design and Object Assembly. Across a variety of studies, the WS group persistently demonstrates poor performance on the Block design and the Coding subtests as well as on similar pattern construction tasks. In the pioneering study of Bellugi et al (1988), they noted that although participants with either DS or WS scored well below the norm on Block Design, looking at the errors, it was clear that their performances were qualitatively different. Whereas those with DS maintained the global shape, but had difficulty with the internal pattern, the participants with WS did not maintain the overall coherence of the global configuration as exemplified in Figure 7 (Bellugi et al., 1988).

The strategy of the WS group in the construction tasks reflects a local rather than global or configural approach, and there has been much discussion as to whether this reflects a delay, as TD children show similar strategies early on, or a characteristic and atypical approach. Regardless of its underlying nature, the pervasiveness and persistence of a visuo-constructive deficit in WS as measured by the Pattern Construction subtest of the DAS or the WISC Block Design has led to these tasks being used as criterion measures for Williams Syndrome. In fact Mervis and colleagues have proposed to characterize and operationalize the WS profile using a specific pattern of performance on subtests of the DAS (Digit recall and pattern construction) (Mervis, Morris, & Bertrand, 1999).

In addition to pattern construction tasks, several studies have also looked at drawing abilities in WS. Beery's task of Visual Motor Integration (VMI) requires the participants to copy increasingly complex geometric figures. On study after study, the children, adolescents and adults with Williams Syndrome continue to perform poorly with fewer recognizable forms than either MA or CA controls; their level of performance is similar to that of preschool age children. For individuals with Williams Syndrome, there appears to be little development in this domain, and that in itself, may be deviant, and stands in striking contrast to other groups and to the developmental trajectory of language in those with WS (Stiles, Sabbadini, Capirci, & Volterra, 2000).

Another task that taps local and global processing is the Delis Hierarchical processing task or the Navon task (1977). In this task the child is presented a series of figures in which a big (global) letter is composed of smaller (local) letters, as in the Figure 7 figure below:

**Insert Figure 7 about here**

The task is to either draw or copy the figures, and for successful performance, both local and global processing systems are recruited. This task has been given to adolescents with WS with age matched TD and DS participants as controls (Birhle, Bellugi, Delis, & Marks, 1989; Rossen, Kima, Bellugi, & Birhle, 1996). In both the copy and draw from memory conditions, typically developing individuals perform comparably at both the local and global levels, similar to their performance on block design. Those with DS were significantly better at drawing global forms than local, whereas those with WS showed the opposite pattern, they were more accurate in producing local than global forms. Farran, Jarrold and Gathercole (2003) confirmed these drawing results with a larger sample of WS adults and mental age matched TD children. They also gave two perception tasks measuring divided and selective attention to the differing visual

features: local and global. In contrast to the drawing results, in the perceptual tasks, the WS participants performed like their controls, showing neither a local nor global bias. Together, these findings suggest a local bias, and a global impairment in tasks requiring visuo-spatial construction, that is, in tasks that require motor planning and an overt motor response.

In contrast to their difficulties with visuo-constructive tasks, researchers have reported that those with WS show relatively normal performance for object (Atkinson et al., 2006; Landau, Hoffman, & Kurz, 2006), and face recognition, (Bellugi et al., 2000, Paul, Stiles, Passarotti, Bavar, & Bellugi, 2002). Karmiloff-Smith et al. (2004) has proposed that the strength in face processing seen in WS reflects atypical processing. Whereas for typical adults, faces are processed configurally, for those with WS, she proposes that their good performance relies on using a local/featural processing strategy. Interestingly, in investigating sensory visual problems, e.g. acuity, strabismus and performance on several visuo-spatial tasks, Atkinson and colleagues (Atkinson et al., 2001) found no correlation between them suggesting that perceptual problems in WS are not predicted from sensory impairments.

The contrastive behavioral visuo-spatial profile of relatively strong facial recognition and very poor constructional abilities (which necessitate locating and placing objects in spatial arrangements) raised the hypothesis that the visual system in WS was differentially impaired. In 1982, Mishkin & Ungerleider demonstrated that the visual system included two complementary hierarchically organized processing streams; the ventral system or the 'what' system that recognizes objects, and the dorsal or 'where' system that locates objects in space. The hypothesis was that for those with WS, the ventral system functioned normally, but the dorsal system was atypical. In a clever experiment, Paul et al. (2002) tested this hypothesis with a task that used faces and scrambled black and white patterns with the same spatial frequencies as the faces, in an

object recognition and location matching task. Participants first saw one face/pattern and then a second face/pattern. In one condition, participants were asked if the 2<sup>nd</sup> face (or pattern) was the same as the first (ventral stream probe) and in the second condition, they were asked if the 2<sup>nd</sup> face (or pattern) was in the same location as the first (dorsal stream probe). Controls showed comparable performance across the conditions whereas performance by those with WS matched controls on the recognition condition, however they performed significantly worse on the location condition. Such data strongly suggest a dorsal stream deficit in WS.

As these data show, similar to language, the visuo-spatial profile of WS reflects a strikingly uneven profile both across and within this cognitive domain. Their very good performance on facial recognition tasks in the face of notably poor performance on such varied spatial tasks as drawing, VMI, block design, and Benton Line orientation has generated significant interest. Below we discuss aspects of the social profile in WS which will provide an additional perspective on WS, and may begin to explain their skill in facial recognition.

### **PERSONALITY IN WILLIAMS SYNDROME**

The WS personality is characterized by overfriendliness, a willingness to approach others, and a strong emotional and empathic response to others (Tager-Flusberg & Sullivan, 2000; for a review, see Järvinen-Pasley et al., 2008). However, in spite of this sympathetic amiability, and an unusual attraction to strangers, children with WS have difficulty forming friendships, are often socially isolated in school, exhibit substantial problems in social adjustment, including difficulties in forming and sustaining relationships with peers (Udwin & Yule, 1991; Gosch & Pankau, 1994, 1997; Jones et al., 2000). Thus, similar to the behavioral profiles in language and spatial cognition that are emerging WS, it appears that the social-behavioral profile of WS also has many paradoxes. For example, in spite of their sociability, it

has been suggested that they lack social judgment (Einfeld, Tonge, & Florio, 1997; Gosch & Pankau, 1997); and although persons with WS are socially fearless, they nevertheless show significant anxiety that has been characterized as “non-social” in nature. In particular, such anxieties tend to relate to new situations and objects. In fact, as they grow older, 57% show excessive worrying, and as many as 96% have specific phobias (Dykens, 2003). Using two standardized temperament and personality questionnaires (Children’s Behavior Questionnaire, CBQ; Rothbart, Ahadi, Hershey, & Fisher, 2001; and a parent-version of the Multidimensional Personality Questionnaire, MPQ; Tellegen, 1985), Klein-Tasman and Mervis (2003) attempted to construct an empirically derived personality profile of WS using children with other developmental disabilities as controls. They found that the characteristics that distinguished the personality of those with WS from those with other developmental disabilities included gregariousness, a lack of shyness, and high empathy. Other features that characterized the WS group were being visible, people-oriented, tense, and sensitive/anxious.

From the first reports of WS, and confirmed by recent studies, clinicians and researchers alike have noted that children and adolescents with WS are attracted to others, producing the impression that they are ‘hypersocial.’ Such interactions in older children with WS are mediated by language, so the question arises, how does this aspect of personality develop? Is it language dependent or will it be evident before language emerges? In an early case study by C. Rice (1992), a toddler with WS was followed longitudinally; on seeing the videotape of her interaction with an eight-year-old boy, viewers watched as she stared intently on his face and commented that the baby ‘looks as if her eyes are boring into him’. These initial observations of increased interest in others and the intense stare of WS infants have been confirmed. Studies of infants and toddlers with WS have noted that such babies look intently at the faces of others

(Mervis et al., 2003); in fact, as noted above, toddlers with WS have what has been labeled 'sticky attention,' that is, they evidence difficulty in shifting attention from the person to the object at hand in joint interactions. Rather, the object of fascination for these infants is the face of their interlocuter. In response to the question posed above, long before language emerges, infants and toddlers with WS, seek out others.

Looking at a large group of children with WS across childhood Doyle, Bellugi, Korenberg, & Graham (2004) used the Salk Institute Sociability Questionnaire [SISQ], a parental questionnaire, to evaluate and contrast social behavior in children with WS, DS, and typically developing controls. The SISQ Questionnaire asks questions concerning: (1) willingness to approach others (familiar and unfamiliar); (2) behavior in social settings; (3) ability to remember faces and names; (4) eagerness to please others; (5) empathy; and (6) frequency of others to approach the individual. The measure yields three composite scores: Global Sociability score (a cross-domain measure of sociability); Social Approach score, and its two sub-scores: Approach Strangers and Approach Familiars; and a Social-Emotional score. In Doyle's study, parents of 64 WS children ages 1y;1m-12y;10m completed the SISQ. Whole group analyses showed that the WS group was rated significantly higher on all aspects of sociability studied. The data were then analyzed according to three different age groups: Young (1-4 years); Intermediate (4-7 years); and Oldest (7-13 years). Comparisons among the groups at different ages revealed that heightened sociability was evident even among very young children with WS, and, significantly, children with WS exceeded typically developing controls and children with DS in every age group in Global Sociability and Approach Strangers, except for Approach Strangers in the Oldest age category. Interestingly, similar results have reported for Japanese children with WS (Zitzer-Comfort, Doyle, Masataka, Korenberg, & Bellugi, 2007). Confirming the parental

questionnaires, behavioral studies also show a profound attraction to other people and a strong preference for social over non-social stimuli among infants and toddlers with WS. Our studies using a standardized instrument for laboratory assessment of early temperament (Laboratory Temperament Assessment Battery, Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1993) highlighted clear differences in temperament and affiliative drive in toddlers with WS compared to typical controls (Jones et al., 2000). Lab-TAB comprises episodes that simulate everyday situations in which one can reliably observe individual differences in the expression of emotion, in approach/ avoidance, in activity level, and in regulatory aspects of behavior (or temperament). For example, in a task to elicit emotional reactions, specifically anger and frustration, an attractive toy is placed behind a plastic barrier before the child. We were unable to collect data on many of the children with WS because rather than looking at the toy, they instead focused on the experimenter's face. While many of the control children grabbed the barrier, those with WS tended to socially engage the experimenter, by gazing into her eyes, smiling, or otherwise initiating social interaction. This finding, that the preoccupation with the experimenter shown by toddlers with WS interfered with the administration of tasks, is in line with findings of unusually intense looking behaviors in children with WS noted above. For example, Mervis and colleagues reported that, unlike children with other neurodevelopmental disabilities, infants and toddlers with WS stared intently into the faces of strangers (Mervis et al., 2003). Interestingly, we have found evidence for a robust neurobiological marker for the increased attention to faces in individuals with WS (Mills et al., 2001). It has been suggested that this intense interest in others may result in disturbances in joint attention among young children with WS (Doyle et al., 2004a; Laing et al., 2002) and as noted above, may be a core contributor to the abnormality and/or delay of language development in WS. In sum, the drive to connect with others is a core

marker of the WS phenotype and it emerges early in infancy; from infancy through childhood, children with WS use the tools they have, be it eye gaze or language to connect with others.

#### **PRODUCING AND UNDERSTANDING EMOTIONAL SIGNALS/EMOTION PROCESSING**

Given their high sociability and empathy, their attraction to faces coupled with good facial recognition skills, one might hypothesize that those with WS would also be skilled in emotion processing and social cognition, however an accruing literature suggests that many aspects of “social intelligence” are impaired in WS. In the first years of life, their intense staring and interest in the human face appear to contribute to their significant delay in the acquisition of joint attention as well as reducing the children’s opportunities to learn about their environment (Doyle et al., 2004b; Laing et al., 2002; Mervis et al., 2003). In experimental studies targeting recognition of both facial and vocal emotion, results show that adolescents and adults with WS perform comparably to their mental age matched controls (e.g., Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006; Plesa-Skwerer, Verbalis, Schofield, Faja, & Tager-Flusberg, 2005). It may also be the case that their social-perceptual deficits contribute to the characteristic hypersociability in WS, for example, increased approach behaviors toward strangers (Järvinen-Pasley et al., 2008). In a series of studies investigating attribution of mental state, researchers have reported significant deficits in WS for example, they are no better than mental age-matched controls in the attribution of second-order mental states (Sullivan & Tager-Flusberg, 1999). Overall, both adolescents and adults with WS show impairments in a variety of perceptual and cognitive tasks that underlie emotion processing. In an insightful paper by Tager-Flusberg and Sullivan (2000), they distinguished between social-perceptual and social-cognitive components of theory of mind, and found that individuals with WS show difficulties at both levels of social cognition. Considering these findings, the problems of those with WS to maintain friendships

and in school adjustment, in spite of their friendliness and sociability, are not so surprising. This combination of overfriendliness and lack of social judgment are of real concern to parents as children and adolescents with WS will often approach and strike up a conversation with a stranger. Even after considerable work, the social drive to make contact with a new person often overrides long practiced careful interventions.

As we noted above, in their conversations and narratives, even the youngest children with WS exploit their language abilities to connect socially with others by using what we have labeled “social evaluation devices.” To ascertain the degree to which this very social use of language was specific to American children with WS or a hallmark of Williams Syndrome, we undertook a cross-linguistic study using the same wordless picture book mentioned above, (*Frog where are you?*, Mayer, 1969) and collected stories from children and adolescents with WS and their controls in the US, France and Italy. As is evident in the Figure 9 below, in each of the three cultures, the WS far outstrip their typical counterparts in the production of social evaluation, confirming its genetic origins. Nonetheless, it is also clear that the culture in which one is raised modulates the degree to which this genetically based behavior is expressed (Reilly, Bernicot, Vicari, Lacroix, & Bellugi, 2005b).

**Insert Figure 8 about here**

#### **NEUROANATOMICAL CORRELATES OF THE WILLIAMS PHENOTYPE**

A number of laboratories have investigated brain anatomy and brain function in individuals with Williams Syndrome using structural and functional magnetic resonance imaging as well as fine grained cytoarchitectonic studies. Using structural imaging, Reiss and colleagues (2004) imaged a large group of adults with WS and TD controls and their analyses focused on brain areas associated with the cognitive strengths and weaknesses in WS. Overall they found

that the volume for overall grey matter is significantly decreased in WS versus TD controls by 11%. Others have also noted that cerebellar size is preserved in WS and this is evident even in infancy (Jones et al., 2002). In line with their deficit in visuo-spatial processing deficits, Reiss et al. (2004) found that the occipital cortex and thalamus, important in visuo- spatial cognition showed even further reductions in volume in the WS group.

Such findings have been confirmed in a group of high functioning adults with WS who showed decreased grey matter in the intraparietal sulcus (IPS), which has been implicated in the WS visuo-spatial construction deficit (Meyer-Lindenberg et al., 2004). Meyer-Lindenberg and colleagues (2004) pursued the hypothesis of differential impairments of visual spatial cognition using functional magnetic resonance imaging (fMRI). Based on the WS phenotype of relatively good facial and object processing in concert with significantly impaired visuospatial constructive abilities, they hypothesized relatively intact ventral stream processing with abnormal dorsal stream function. In the ventral stream task, including passive viewing, matching shapes and identifying pictures, functioning was normal. However, function was abnormal in the dorsal stream condition where individuals attended to shape location. Moreover, they found hypoactivity in the WS group anteriorly and adjacent to the intraparietal sulcus, where they had found decreased grey matter volume and sulcal depth. A complementary postmortem histological study by Galaburda, Holinger, Bellugi, & Shermanet (2002) found significantly smaller and more densely packed cells in the rostral striate cortex of the WS brain. The anatomical and histological anomalies in the visual cortex and visual system in WS are consistent with the decreased activation seen in visual cortices during face processing (Mobbs et al., 2004).

In contrast to the decrements found in the visual areas, Reiss et al (2004) reported that volumes of the amygdala and orbital and medial prefrontal cortices are greater, and their grey

matter denser, in WS than in controls. These brain structures play important roles in emotion and face processing as well as regulating social behavior in typical individuals; such social behaviors are hallmarks of the WS phenotype. With respect to functional aspects of these neural systems underlying social behavior, Meyer-Lindenberg et al. (2005) used negative emotional faces (scared or angry) and threatening scenes, e.g., a gun pointed at the viewer, to investigate amygdala activity and regulation in WS (such stimuli were known to activate the amygdala in TD adults). Consistent with the WS profile of increased sociability, but also increased non-social anxiety, in the WS group, they found hypoactivation of the amygdala in the face conditions, but increased amygdala activation in the scenes condition. WS attraction to faces, as we mentioned, is evident from infancy and even as children, their performance on tasks of facial recognition is within the normal range. In typical individuals, an area crucial in face recognition is the fusiform area which has become known as the fusiform face area (FFA). A recent finding from the Reiss group indicates that the fusiform is enhanced in WS; functionally, this is reflected in the signature ERP (Event related potential) response to facial stimuli characteristic in the WS group, (Mills et al., 2001).

In addition to their hypersociability, another relative strength of the WS group is language and as noted above, verbal and auditory memory may play stronger roles in the WS group than in TD children acquiring language. In line with these behavioral findings, in their postmortem histological studies, Galaburda and colleagues (Hollinger et al. 2005) have found that cell size and density in the primary auditory cortex are comparable to typical brain, in spite of a lack of asymmetry in the WS brains. Such findings are consistent with the relatively good auditory and language skills, and attraction to music characteristic of WS. To date, researchers have made important steps in mapping phenotypic features to their neural substrates. In the next

section, we will take the search a step further to review some of the studies mapping behavioral functions to their possible genetic correlates.

### **GENETIC UNDERPINNINGS**

Williams Syndrome is caused by a hemizygous deletion of ~20-28 genes from chromosome band 7.11.23q (see Figure 9). Because the etiology of WS has a clear and well-defined genetic basis, it provides a window to better understand the relation of particular genes to their developmental or behavioral function. As such, several laboratories are attempting to map certain gene(s) from the deleted region in individuals with WS to their possible function. As noted briefly above, the most common deleted gene in individuals with WS is the *ELN* gene which codes for an elastic protein called *elastin*. The deletion of the *ELN* gene is present in at least 98% of individuals with WS (Lowery et al., 1995), and its deletion causes arteries and organs to become more rigid, narrowing blood vessels and producing insufficient blood flow. Overall, about 80% of the WS population will develop some type of cardiovascular abnormality during their lifetime (Morris & Mervis, 2000).

#### **Insert Figure 9 about here**

With respect to cognitive performance, a promising strategy to discover the function of particular genes is to identify individuals with Williams Syndrome, who have only a partial genetic deletion. By comparing their neuro-cognitive profile to that of age matched individuals with WS who have the typical deletion, researchers can begin to isolate the role of individual genes. Such an approach was taken by Hirota and colleagues (2003) who studied 60 Japanese participants with WS, three of whom had partial deletions. Each of these three females, had retained genes at the telomeric end of the deletion, including *GTF2IRD1* and *GTF2I*. The three females lacked the characteristic facial features of those with WS, and all three of them

performed better on the WISC block design task than the comparison group of WS with full deletions. Interestingly, the errors of these three young women on the Block Design Task were qualitatively different than those seen in those with the full deletion. The researchers concluded that that *GTF2IRD1* and *GTF2I* are associated with some aspects of visual spatial function, and that in individuals with WS with full deletions, the deletion of the genes *GTF2IRD1* and *GTF2I* contribute to their impairments in visual spatial cognition.

Following this same strategy, Dai et al. (2009) have recently reported on a seven year-old girl with Williams Syndrome who has been followed longitudinally since 14 months of age. She has the typical deletion for WS, except for one preserved region, *GTF2I*. Thus, as a case study, she provides the opportunity to clarify the roles of *GTF2IRD1* and *GTF2I*. She presents with many of the characteristic physical features of WS including short stature, the specific craniofacial dysmorphology, and SVAS. However, in her cognitive testing, although she reflected deficits (Full Scale IQ of 78; Verbal IQ of 88 and Performance IQ of 71), they were much less severe than those of the comparison group children with WS who had the full deletion. In fact, rather than language delayed, she is reported as “highly talkative” at 29 months. Intriguingly, this child did not exhibit the characteristic WS social profile: unlike typical, highly sociable children with WS, this child appears reticent; in an initial session, she hid behind her mother’s skirt and held onto her mother’s leg, avoiding eye contact. Overall, she did not approach strangers; she exhibited decreased eye contact, and preferred non-social over social activities. Moreover, her performance on measures of sociability (SISQ, Doyle et al., 2004b), except the Social-emotional subscales, were significantly lower than the age matched comparison group of young children with WS. As such, Dai and colleagues propose that the *GTF2I* gene plays a role in aspects of social behavior as well as cognition. They also propose

that the gene *GTF2IRD1* plays a role in both the development of atypical facies and the visual-spatial cognition deficits in this syndrome. The authors suggest that *GTF2I* may contribute to increased function in both verbal and performance domains. However, given that poor performance was found on some spatial tests in this individual case, similar to that of typical WS, it suggests that *GTF2IRD1* may be important for specific aspects of visual-spatial cognition, such as visual-motor integration.

Another strategy to identify the role of particular genes has been to use knock-out mice where a particular gene is deleted, in combination with case studies of individuals with WS with partial deletions. A combination of approaches has been used to better understand the facial dysmorphology in WS. Williams Syndrome facial characteristics have been linked to three gene regions, *CYLN2*, *GTF2IRD1*, and *GTF2I* (Botta et al., 1999; Heller et al., 2003). When all three areas are deleted, the typical WS facial characteristic is evident. However, deletion of *CYLN2* combined with only a partial deletion of *GTF2IRD1* and with preservation of *GTF2I* has shown only mild facial features. Mild facial features have also been described when a partial deletion of *CYLN2* occurs with preservation of the two other areas (Gagliardi et al., 2003). Finally, deletions that do not affect these three areas have resulted in a lack of facial features typical of WS (Hirota et al., 2003; Tassabehji et al., 1999, 2005; Karmiloff-Smith et al., 2003; Howald et al., 2006; van Hagen et al., 2007). In the case study by Dai et al. (2009) above, the full deletion of *GTF2IRD1* is also suggested to be associated with typical WS facies. In the past ten years, with the mapping of the Human Genome, geneticists working together with physicians and neuropsychologists have made exciting progress in understanding the genetic underpinnings of Williams Syndrome, and much of this information will eventually inform our understanding of brain development and function in typical populations.

## **THERAPEUTIC INTERVENTIONS**

For families and clinicians trying to find the best way to cope with the challenges raised by having a child with Williams Syndrome, some of the basic research presented above may seem abstract and distant from the problems of everyday life. However, knowing more about the phenotype of WS and its development can help parents and pediatricians anticipate developmental milestones and work with therapists to design targeted interventions based on knowledge of the peaks and valleys of the WS profile. Since there is variability within the WS group, interventions might be based on a probabilistic model where the WS phenotype serves as the point of departure, and therapeutic programs can then be tailored to the individual child's needs at his or her particular stage of development. For parents and physicians, the Williams Syndrome Association (WSA) website is a rich resource for medical, developmental and therapeutic information as well as social support and other helpful links. With respect to specialists for different areas of remediation, WSA suggests that occupational therapists can help with fine- motor control and feeding problems; that for balance, joint-stiffness, muscle tone and gross-motor functioning, physical therapists are appropriate, and that speech language therapists can be instrumental in improving language, articulation, and as the children get older, information processing as well as in helping children to use language appropriately.

Music therapy has also been used as a means to enhance performance in children and adolescents with Williams. Music therapy is not teaching music or learning to play an instrument, but rather using music and the affinity to music characteristic of those with WS, to enhance other cognitive skills. For example, Reis and colleagues (2003) held a summer music workshop for young adults with WS and the workshop included a class on Music and Fractions. Their idea was to use a 'talent development' approach, building on the participants' musical

abilities and affinity for music to improve their math abilities, an area of deficit. Post-test results showed that 94% of the participants with WS had improved their understanding of fractions. In their recent book on Williams Syndrome designed for teachers, clinicians and parents, Semel and Rosner (2003) review the strengths and weaknesses characteristic of WS, and demonstrate how different therapeutic approaches can be used to exploit basic research findings on the WS phenotype. They present various interventions, e.g., task-specific interventions, and naturalistic training situations, and provide examples of how these might be implemented. For example, how helping in the kitchen to make cookies is a naturalistic situation where hand-eye coordination, and skills in math and measuring can be practiced. Their love of music, sociability and their proficient language provide multiple avenues to diminish the deficits in those with Williams Syndrome helping them to adapt and to find a place in the community.

### CONCLUSION

Williams Syndrome is a rare genetically based neurodevelopmental disorder that affects all aspects of the developing child. In this chapter we have reviewed the clinical, behavioral, genetic and neurological profiles of children with WS, as well as some approaches to therapeutic intervention. These children present a unique clinical and neuropsychological profile of strengths and weaknesses that changes markedly with development. While scientists look to WS as an unusual opportunity to understanding how genes interact and function in human development, parents and clinicians work to find ways to keep children, adolescents and adults with Williams Syndrome healthy and to maximize their chances for fulfilling lives. By working together across disciplines and perspectives, and by using the basic scientific findings to inform our interventions, we can improve the lives of children and families with Williams Syndrome.

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## Figures

**Figure 1: Photographs of Children with Williams Syndrome**



**Figure 2: The Uneven Cognitive Profile in Williams Syndrome**

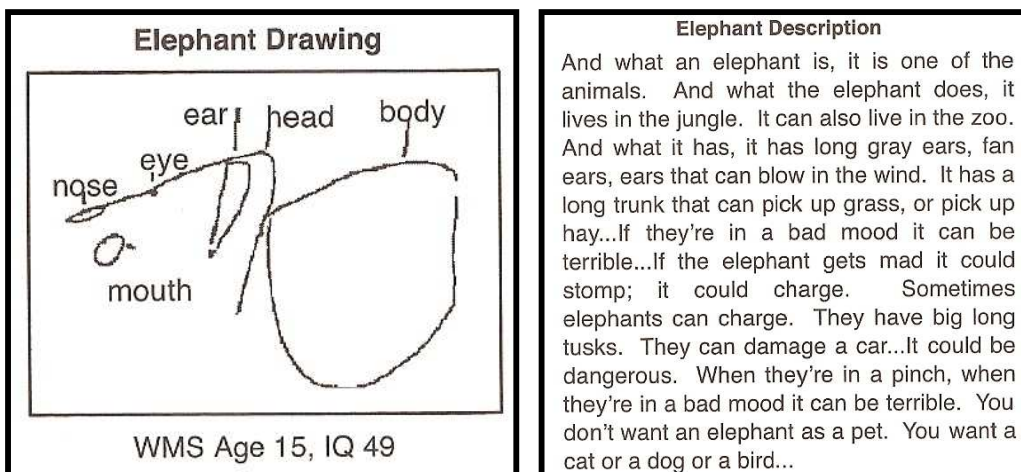


Figure 3: Morphological Errors in Sentence Repetition

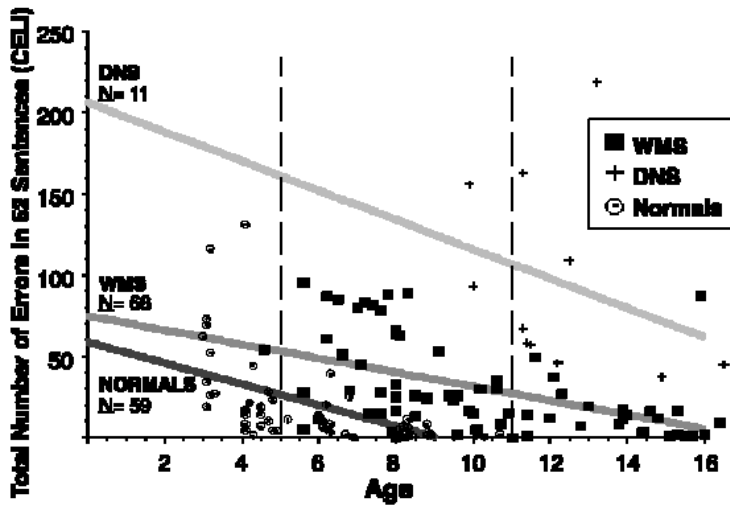


Figure 4: CDI performance

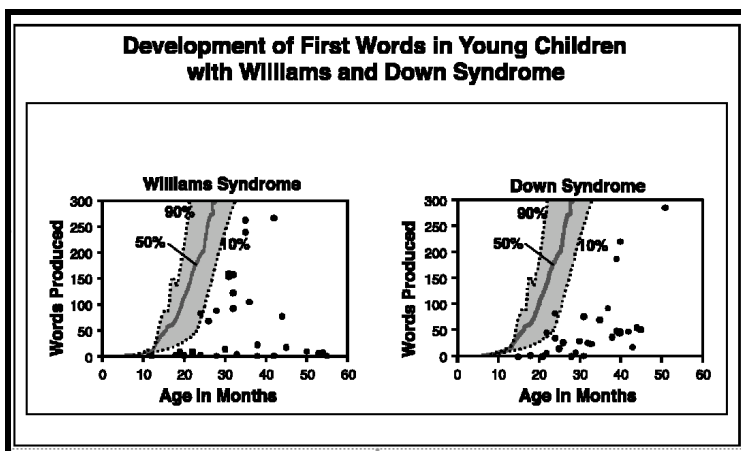


Figure 5: WS/LI Morphosyntactic Errors in a Spoken Narrative

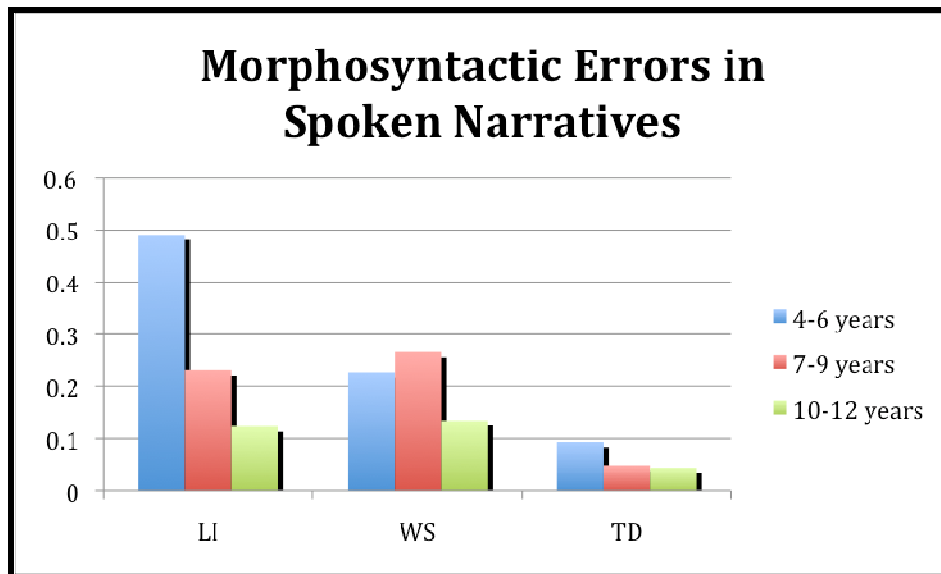


Figure 6: Evaluation in the Frog stories: WS with LI, PL ,HFA

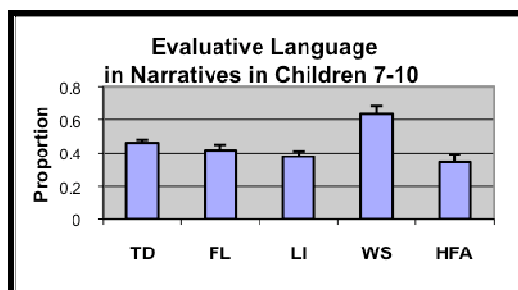


Figure 7: Local Global-WS and DS

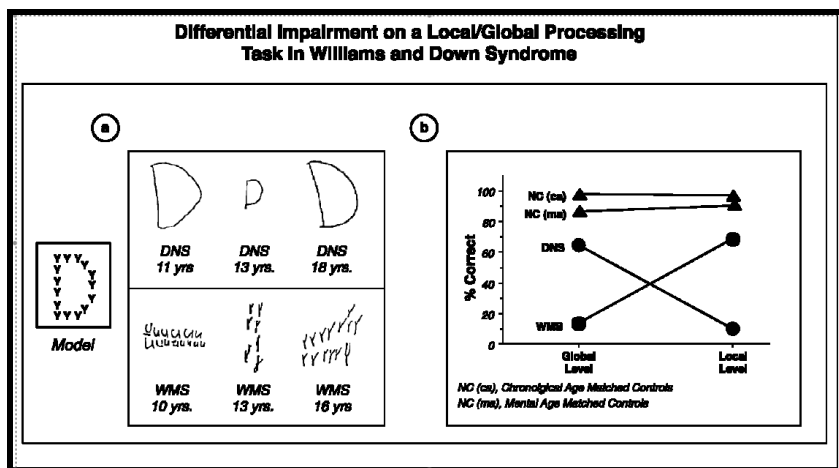
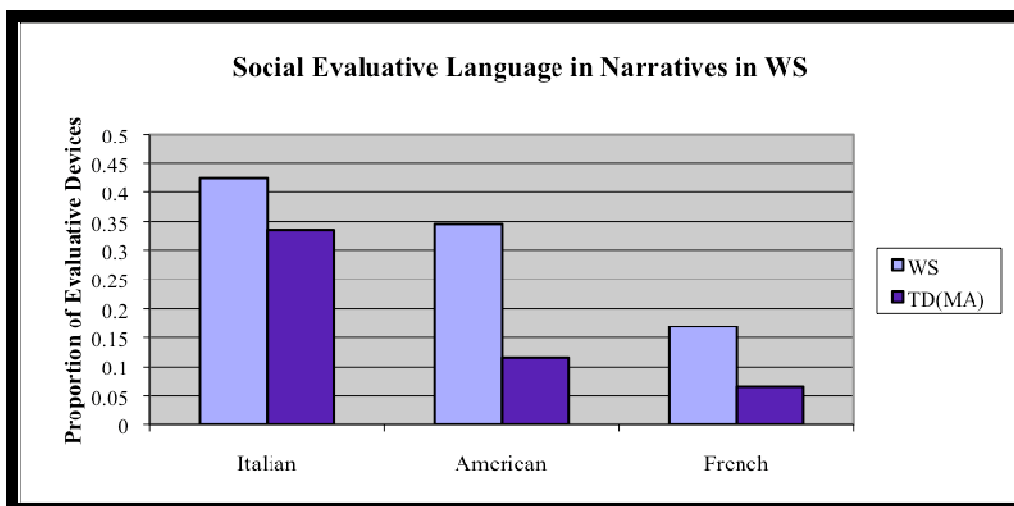
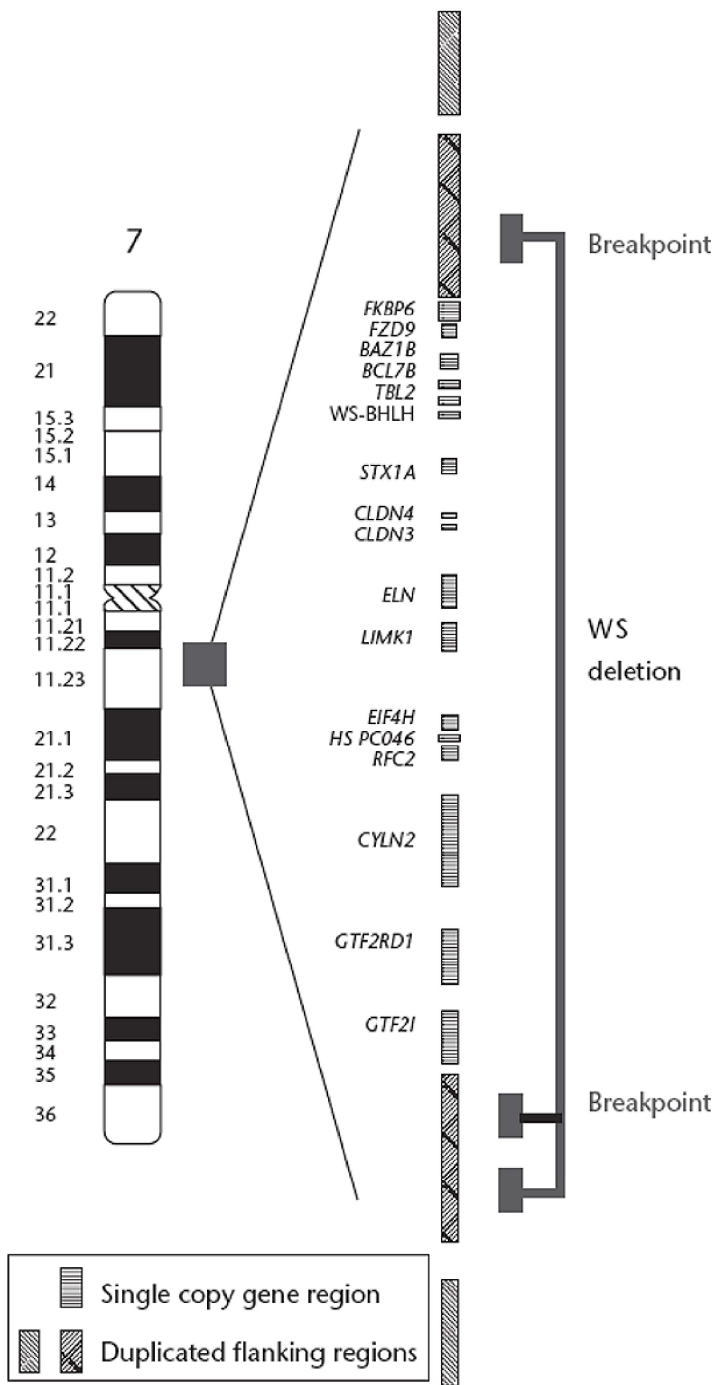


Figure 8: Cross-Cultural Use of Social Evaluation in Narratives



**Figure 9: WS Deletion**



## Figure Captions

**Figure 1.** Photographs of children with Williams Syndrome

**Figure 2.** The dissociation between spatial cognition and linguistic abilities, characteristic of WS, is clearly evident in the drawing and verbal description of an elephant by this young woman with Williams, (age 15; her Full scale IQ is 49; Verbal IQ is 52 and Performance IQ of 54). From Bellugi & St George, 2000..

**Figure 3.** In a standardized sentence repetition task, TD children are making no errors by age 8 whereas in the Williams group there is a persistent decline in the number or errors from 5-16, broadly mirroring the profile of younger controls. Those with Down Syndrome appear to plateau.

**Figure 4.** The number of words produced by young children on the MacArthur-Bates Communicative Development Inventory (CDI) for children with WS and with DS shows variability, but also comparably delayed onset of first words for both groups (from Singer-Harris et al, 1997). The shaded areas represent a normative sample (Fenson et al., 1993).

**Figure 5.** The proportion of morphological errors in an oral narrative for the children with Williams Syndrome is comparable to that of children with Language Impairment (LI) in the two older age groups (from Reilly et al. 2004).

**Figure 6.** Comparing the use of evaluative language across groups: Typically Developing (TD), children with early unilateral focal lesions (FL), children with Language Impairment (LI), children with Williams Syndrome (WS) and those who are high functioning with Autism (HFA), the children with WS use significantly more evaluative language their narratives than any other group.

**Figure 7. (a)** On the Navon figure (model to the left: a large global figure composed of smaller local forms), children are asked to copy the figure. With participants matched for age and IQ both the WS and DS group are impaired, but in qualitatively different ways; those with DS tend to produce the global figure, while those with WS tend to produce the smaller local forms, ignoring the global

configuration. (b) In both copying the forms or drawing from memory, the WS group is more accurate on the local forms whereas the DS group is more accurate on the global forms; typically developing controls perform comparably on both conditions (From Bellugi et al., 2000).

**Figure 8:** In all three countries, children with WS use more evaluation in their stories than their typically developing peers, yet the effect of the culture in which they are raised also plays a role (from Reilly et al, 2005).

**Figure 9.** The solid square represents region of chromosome 7, band 7q11.23, which is commonly deleted in WS. An expansion of this area is shown on the right (from Korenberg et al., 2003).