Affect, Social Behavior, and the Brain in Williams Syndrome

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ABSTRACT—*Williams syndrome (WS) is a rare genetic disorder characterized by intellectual impairment and a distinctive physical and neuropsychological profile. Relative to their level of intellectual functioning, individuals with WS exhibit strengths in language and face recognition, with deficits in visual-spatial cognition. A heightened appetitive drive toward social interaction is a strong behavioral feature. Relative to other neurodevelopmental disorders, WS has a clearly defined genetic basis, together with a consistent neurocognitive profile of strengths and deficits. Thus, this disorder offers unique opportunities for elucidating gene–brain–behavior relationships. We focus on manifestations of the unusual social profile in WS, by examining data within and across levels of cognition, brain, and molecular genetics.*

KEYWORDS—*Williams syndrome; genotype–phenotype correlations; cognition; language; sociability*

Williams syndrome (WS) is a rare genetic neurodevelopmental disorder occurring once in approximately 7,500 live births. Stemming from a deletion (a genetic aberration in which a part of a chromosome is missing) on chromosome 7q11.23, WS causes individuals to show a characteristic physical and neuropsychological profile. The deletion includes the gene ELN, which codes for an important elastic protein (elastin) in connective tissue that is particularly abundant in large blood vessels such as the aorta. Individuals with WS typically have specific cardiac abnormalities, hypersensitivity to sound, and characteristic facial features (Morris & Mervis, 2000; see Fig. 1). Most individuals have mild to moderate intellectual impairment, with more pronounced deficits in performance than verbal IQ (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000). Our 20-year program of research has outlined an unusual profile of cognitive dissociations in WS: Language represents a relative strength compared to other intellectual abilities. Within visual cognition, face recognition appears remarkably "spared," whereas other aspects of visual-spatial functioning are severely impaired (Bellugi et al., 2000). The WS personality is characterized by hypersociability, including overfriendliness and heightened approachability toward others, combined with anxiety relating to new situations and objects and a difficulty forming and maintaining friendships with peers. Although variability exists within the WS population, the clear genetic basis presents an unusual opportunity to elucidate gene–brain–behavior relations. Combining developments in human genetics and brain imaging may make it possible to trace gene–brain–cognition linkages using WS as a model. This article focuses on our across-level studies of the affiliative drive in WS.

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LANGUAGE AS AN INDEX OF SOCIABILITY

Children With WS: The Social Use of Language

Strangers are often impressed by the language proficiency and sociability of individuals with WS. Losh, Bellugi, Reilly, and Anderson (2000) asked 30 children with WS and a typically developing control group matched for gender and chronological age (4–12) to tell a story from the wordless picture book, *Frog, Where Are You?* The transcribed stories were coded separately for grammar and for the social and affective use of language (evaluative language). Evaluative language refers to language reflecting the narrator's attitude or perspective, including attributing emotions or motivations to characters, using intensifiers (*really*, *very*, *so*) and sound effects, direct quotes, and character speech. A new category called "audience hookers," referring to devices used to capture and maintain the listener's attention ("Lo and behold! There were froglets!"), was developed for the evaluative-language coding system to characterize a

Fig. 1. Children with Williams syndrome (WS). The specific facial features of WS include broad brow, full nasal tip, star-shaped or lacy iris, flat nasal bridge, prominent lips, full cheeks, and wide mouth. (Pictures used with permission.)

language function unique to WS. The findings showed that children with WS made significantly more grammatical errors than did their typical peers. In fact, their grammatical performance did not differ proportionally from that of chronological-age-matched children with specific language impairment (Reilly, Losh, Bellugi, & Wulfeck, 2004). Nonetheless, their stories contained significantly more social and affective evaluative devices (see Fig. 2). Given the high frequency of grammatical errors by the children with WS, and because evaluative devices require linguistic flexibility and presuppose a certain level of mastery, this raises interesting questions about the relationship between the acquisition of linguistic structure and the use of language for social purposes in WS.

Adolescents With WS: The Social Use of Language

In one of the first language studies on WS (Reilly, Klima, & Bellugi, 1990), we asked adolescents with WS (aged 10–18 years), age- and IQ-matched adolescents with Down syndrome, and mental-age-matched typically developing children to narrate the *Frog* story. Stories were analyzed for grammar and evaluative language. The adolescents with WS were relatively proficient, specifically in their use of grammar. The WS group used evaluative language significantly more frequently than did the typically developing controls or the adolescents with Down syndrome. Consistent with the child study (Losh et al., 2000), these results demonstrate the excessively social use of language in WS. Participants with WS exceed their typically developing peers in the use of social evaluation at all ages, and this effect has also been observed across different languages and cultures.

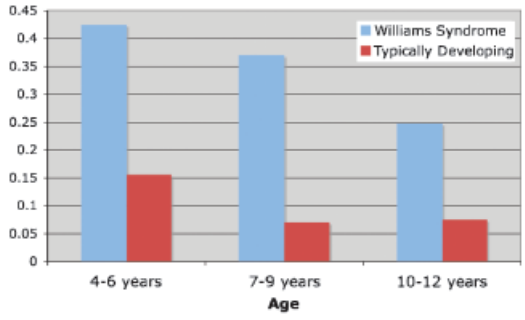

Fig. 2. Frequency of social-evaluation devices (expressive language reflecting the narrator's attitude or perspective) in narratives from typically developing children and children with Williams syndrome (aged 4–12 years). Individuals with WS use social evaluation significantly more frequently than controls, at all ages studied.

Table 1 includes examples from both WS and typically developing children to illustrate how the use of social evaluation differs qualitatively between the groups. For individuals with WS, structural language proficiency is not necessary for extensive use of social evaluation. Indeed, as soon as children with WS are able to produce simple narratives, they exploit their linguistic abilities maximally for social purposes.

NONLINGUISTIC SOCIAL-BEHAVIORAL PROFILE IN WS

At the heart of the enigma surrounding WS is the enhanced drive toward social interaction. We elucidate its nature by examining data from three sources: (a) parental report forms, (b) an experiment assessing willingness to approach strangers, and (c) social interaction of toddlers with WS.

Sociability in WS Using Parental Questionnaire

The Salk Institute Sociability Questionnaire (SISQ) solicits information from parents of children with WS concerning their child's (a) willingness to approach other people (familiar and unfamiliar), (b) behavior in social settings, (c) ability to remember faces and names, (d) eagerness to please other people, (e) empathy, and (f) frequency with which others approach the individual. The analysis produces three composite scores: Global Sociability (a cross-domain measure of sociability); Social Approach and its two sub-scores, Approach Strangers and Approach Familiars; and Social-Emotional. Doyle, Bellugi, Korenberg, and Graham (2004) used the SISQ to examine social behaviors in children with WS and Down syndrome and typically developing children matched for chronological age. Findings showed that the WS group was rated significantly higher than typically developing controls on all aspects of sociability. Moreover, children with WS significantly exceeded the Down syndrome group on nearly every rating, even when the data were analyzed by age category (Fig. 3).

Consistent with the child study, findings from another study utilizing the SISQ showed that adults and adolescents with WS were rated significantly higher on all aspects of sociability, compared to chronological-age-matched typically developing individuals and those with Down syndrome (Jones et al.,

TABLE 1

Evaluative Language in Narratives of Children With Williams Syndrome (WS) and Typically Developing (TD) Controls

Group	Age (year;month)	Narrative excerpt
WS	6;8	"'I'm lookin' for . . . a frog', said the little boy." "'Oh . . . here froggie froggie!', he said."
WS	9;11	"The boy says, 'Froooog, come out here, you little bitsy frog!' "
TD	5;4	"The boy thinks that the frog is inside that hole but he isn't."
TD	10;3	". . . and the boy said 'quiet' to the dog because the boy was going to look in a log for the frog."

Note. All of the excerpts pertain to the search for the frog in the book *Frog, Where Are You?* When the controls discussed the boy's and the dog's behavior, they often included motivation for the character's behaviors. However, when the participants with WS discussed the same event, they often used evaluative devices to perform as the character, thereby engaging the audience in the performance.

2000). Individuals with WS appear to show little variability in sociability throughout their lifespan, and they differ from the other populations by showing generally heightened sociability, including an increased tendency to approach strangers.

Experimental Approach Characterizing Sociability in WS

Evidence from an experiment in which participants were asked to judge their willingness to approach unfamiliar people converges with our questionnaire data. Adolescents and adults with WS rated unfamiliar faces as significantly more approachable than did controls matched for mental age or chronological age (Bellugi, Adolphs, Cassady, & Chiles, 1999). Black-and-white photographs of unfamiliar adults, which had previously been rated by typical adults as the most, or the least, approachable, were presented. The task was to indicate willingness to approach and converse with the person in the photograph. Although the control groups performed comparably with each other, those with WS displayed a positive bias, rating positive and negative unfamiliar faces as significantly more approachable than did the controls. Thus, an abnormally positive assessment of unfamiliar

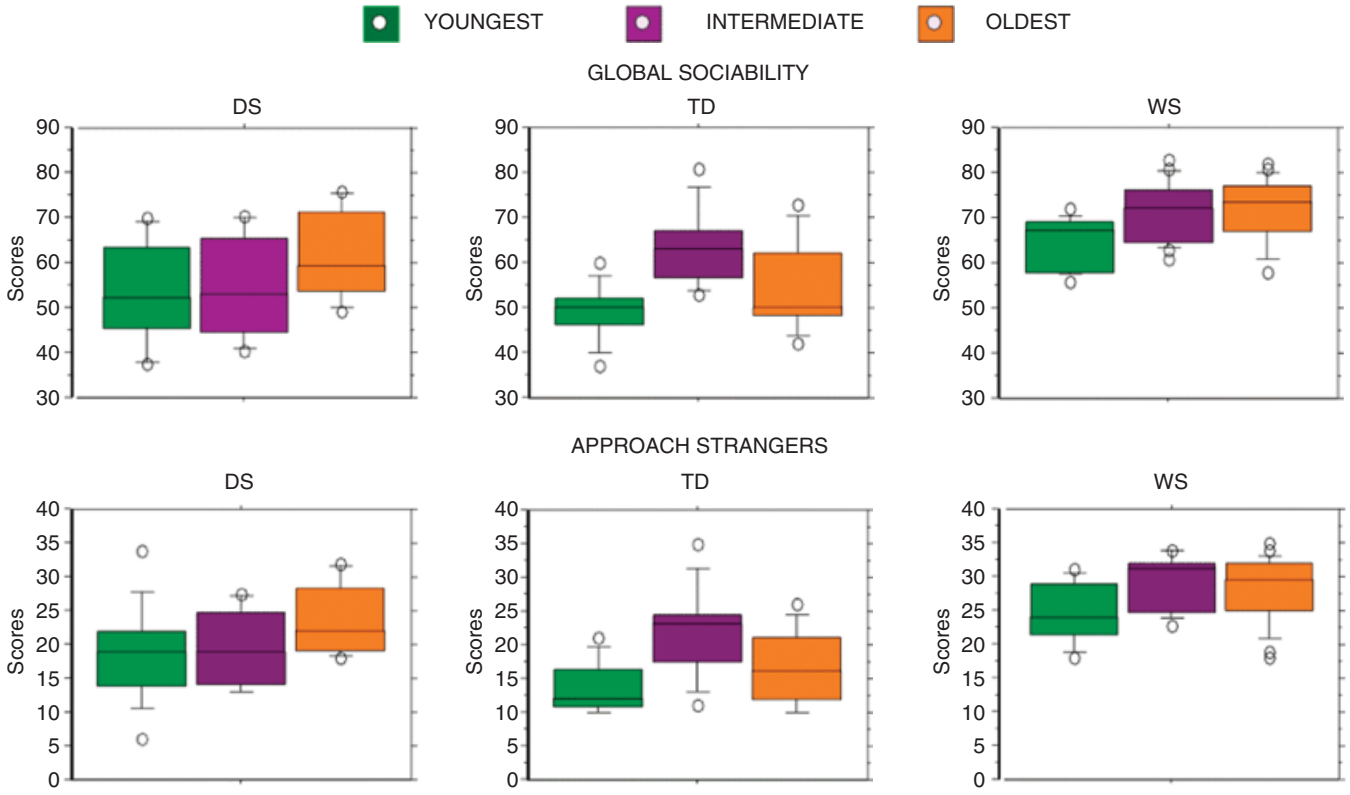

Fig. 3. Age-related developmental changes in global sociability and willingness to approach strangers for individuals with Down syndrome (DS), typically developing individuals (TD), and individuals with Williams syndrome (WS; adapted from Doyle, Bellugi, Korenberg, & Graham, 2004). (Age categories: youngest = 1–4 years, intermediate = 4–7 years, and oldest = 7–13 years). For all ages, children with WS were rated significantly higher than children with DS or TD for Global Sociability and Approach Strangers. Whereas for the TD group overall sociability and willingness to approach strangers peaked in the intermediate category and decreased for the oldest group, the approach behaviors for the WS group increased with age.

faces by individuals with WS closely reflects their real-life social behaviors (Doyle et al., 2004; Jones et al., 2000). Subsequent analyses of these data indicate that, in individuals with WS, a self-rated high degree of willingness to approach strangers may be specifically associated with poor ability to recognize facial affect (Järvinen-Pasley et al., 2006), which may indicate a dissociation between social-perceptual abilities and expressive social tendencies in this population.

Observations of Social-Interaction Behaviors of Toddlers With WS

Our studies show clear differences in temperament and affiliative drive in toddlers with WS compared to typical controls (Jones et al., 2000). 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. Whereas many of the controls grabbed the barrier, those with WS tended to socially engage the experimenter by gazing into her eyes, smiling, or otherwise initiating social interaction. Similar findings of atypically intense staring at the faces of strangers in children with WS have been reported elsewhere. The findings in this section demonstrate that the atypically strong affiliative drive is evident throughout development in WS.

THE SOCIAL BRAIN IN WS

Here we address whether behavioral components of heightened sociability in WS might be linked to aberrant brain structure and function. Recent findings highlight that, in typically developing individuals, cortical regions in the temporal lobe are involved in the perception of social stimuli, and the amygdala, orbitofrontal cortices (OFCs), cingulate cortices, and right somatosensory cortices connect such stimuli to emotion, motivation, and cognition (Adolphs, 2001).

Brain Structure and Function in WS

An important anatomical finding using structural magnetic resonance imaging is that individuals with WS have disproportionately large volumes of the amygdala (Reiss et al., 2004). Given the amygdala's critical role in the processing of social-emotional stimuli such as faces and in the subsequent regulation of appropriate behavioral and autonomic responses (Adolphs, 2001), this anatomical anomaly may either underlie, or be the result of, the enhanced sociability in people with WS. It is noteworthy that emerging evidence from typically developing individuals highlights important gender- and age-related changes in amygdala size.

A recent functional magnetic resonance imaging (fMRI) study compared amygdala activation in response to threatening faces and scenes in unusually high-functioning individuals with WS and typically developing controls (Meyer-Lindenberg et al., 2005). Both groups exhibited comparable behavioral performance. Whereas the controls showed greater amygdala activation in response to threatening faces than to threatening scenes, participants with WS exhibited the opposite pattern. Individuals with WS showed significantly diminished amygdala reactivity to faces compared to the controls, and the controls exhibited significantly decreased amygdala activity to scenes.

Furthermore, during exposure to faces and scenes, individuals with WS exhibited a lack of OFC activation. The amygdala is anatomically connected to the OFC via robust, reciprocal pathways, which are hypothesized to play a role in connecting sensory representations with social judgments. Because the fear response is also regulated by the amygdala, the abnormally reduced activation in this region in individuals with WS in response to threatening faces might contribute to their positive perceptual bias to unfamiliar faces and the subsequently heightened approachability toward strangers (Bellugi et al., 1999). Together, these findings point to abnormal neural circuitry underlying social-emotional information processing in individuals with WS: Although the findings do not implicate a deficit in amygdala function per se, amygdala interactions with the prefrontal regions (e.g., the OFC) are clearly abnormal.

In another fMRI study elucidating the neural mechanisms underlying face and eye-gaze processing (Mobbs et al., 2004), individuals with WS and typically developing controls were presented with images of neutral faces and were asked to judge eye-gaze direction. The aim was to disentangle the cognitive versus social-emotional aspects of face processing in WS. Behaviorally, participants with WS exhibited delayed response latencies and a trend toward poorer accuracy for the gaze judgments. Whereas individuals with WS showed a marked decrease in activation of posterior visual-spatial brain regions and heightened frontal activation, the controls exhibited the opposite pattern. Activation in the brain structures typically associated with face processing did not differ between groups. The frontal regions showing heightened activation in WS are implicated in the processing of social-affective stimuli. Mobbs et al. hypothesized that the unusual pattern of increased frontal activation in people with WS may underpin their social-emotional behavior rather than their general face-processing skills and that the atypical frontal activation may be compensatory—namely, the reorganization of cognitive processes in frontal/limbic areas due to aberrant development in the posterior regions. Taken together, the exaggerated social-affective behaviors in individuals with WS appear to be associated with abnormalities in brain structure as well as in brain function, as contrasted with the brains of typically developing individuals.

MOLECULAR-GENETIC BASIS OF SOCIABILITY IN WS

We are currently addressing the following questions in our program of studies: How can WS help provide clues to some of

the mysteries of the genetic bases of behavior? How can knowledge of the genes responsible for the alterations of behavior in people with WS point toward the discovery of neural systems underlying human cognition? How can molecular biology be used to refine knowledge of the underpinnings of human social behavior and social characteristics—for example, trust and friendliness? Because of the well-defined genetic basis of WS—a deletion of the gene coding for elastin and approximately 20 surrounding genes on chromosome 7q11.23 (Korenberg, Bellugi, Salandanan, Mills, & Reiss, 2003; Korenberg et al., 2000; Morris & Mervis, 2000)—researchers are in the position to begin to answer such questions.

We compared individuals with the typical WS gene deletion to the very rare individuals who have atypical deletions, a crucial step in elucidating gene–behavior relations. We reported a case of a child with a clinical diagnosis of WS but with an unusually small gene deletion (see Doyle et al., 2004, for discussion). Unlike the typical hypersocial children with WS, this child appeared reticent; she hid behind her mother's skirt and held on to her mother's leg, avoiding eye contact. These findings support the hypothesis that the tendency of children with WS to excessively engage with strangers socially may be influenced by the genes at the end regions of the deletion for WS, and provide important clues to the role of specific genes in the sociability of WS.

FUTURE DIRECTIONS

The social phenotype of WS, robustly established through multiple measures (parental questionnaires, experiments, narrative and prosody analyses, and behavioral observations), is characterized by unusually high motivation to socially interact, particularly with strangers; overfriendliness; and gregariousness. Yet major questions remain to be explored in depth. What do the paradoxes in the WS social-behavioral profile tell us? Why are individuals with WS highly social yet have difficulty sustaining friendships, specifically with peers? Growing evidence suggests that WS is linked with a dissociation between social-perceptual abilities and social-expressive behaviors; and although individuals with WS are socially fearless, they show strong undercurrents of nonsocial anxiety.

Defining the specific genetic basis of the WS social-affective phenotype presents a major challenge. Careful study of small-deletion cases, specific gene families, gene expression in brain autopsies, primate studies, and mouse models may all provide important converging evidence.

Recommended Reading

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Acknowledgments—This research is based largely on our studies stemming from a National Institutes of Health–funded Program Project: "Williams Syndrome: Linking Cognition, Brain and Gene," PO1 NICHD 33113. Projects include: I. Molecular Genetics, Julie R. Korenberg; II. Neurophysiology, Debra Mills; III. Functional Neuroanatomy, Allan L. Reiss; IV. Cellular Architectonics, Albert Galaburda; and V. Neurocognitive Characterization, Ursula Bellugi. Anna Järvinen-Pasley, Teresa F. Doyle, and Judy Reilly are associated with Bellugi on Project V.

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