Musical Behavior in a Neurogenetic Developmental Disorder

Evidence from Williams Syndrome

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ABSTRACT: This paper reviews a series of studies performed to assess the musical abilities and behaviors of individuals with Williams syndrome, a neurogenetic developmental disorder, in the hope of eventually being able to link genes, neurodevelopment, and cognition. Two questionnaire studies addressing the role of music in everyday life, and unusual reactions to sound, are described. Additionally, the findings from two empirical behavioral studies and a neuroimaging study are reviewed. The findings show that individuals with Williams syndrome tend to be more engaged in musical activities than others, and I report a possible neuroanatomical correlate of this engagement, with increased activation in the right amygdala to music and to noise. Williams syndrome represents a compelling model of the relationship between genes, brains, and such complex cognitive behaviors as music.

KEYWORDS: Williams syndrome; Williams-Beuren syndrome; neurodevelopmental disorders; neurogenetic disorders; music cognition

The study of distinct, well-defined, and atypical populations is of increasing importance to cognitive neuroscientists because it offers a unique window into specific aspects of cognition, and to establish the degree to which various cognitive abilities are correlated with, or can be decoupled from, one another.[1–3] Williams syndrome (WS, also referred to as Williams-Beuren syndrome), a neurogenetic developmental disorder, offers one of the most compelling human models of the links between genes, neurological function, cognition, and behavior.[4] This article does not present any new data, nor does it attempt to provide an integrative review or synthesis of the excellent work done by colleagues on WS. Rather, the purpose of this paper is to summarize a series of studies my collaborators and I have performed over the past 10 years on music and WS. Excellent work is being conducted in other laboratories as well, as attested to in a number of recent papers.[5–8]

A diagnosis of WS is generally made in one of three ways: physician diagnosis; a score of 3 or more points on the Williams syndrome diagnostic score sheet;[9,10] or confirmation of a microdeletion on chromosome 7, including the gene for elastin

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Ann. N.Y. Acad. Sci. 1060: 1–10 (2005).
doi: 10.1196/annals.1360.027

(ELN), following application of the fluorescent *in situ* hybridization (FISH) test. It was recently discovered that some individuals lack the full, previously documented deletion associated with WS.[11] With these cases of partial deletion, the diagnostic situation has become somewhat muddied; some individuals with partial deletions present the WS phenotype and some do not. In the work reported here, we have followed the more conservative and exclusive criterion, and we report results from only those individuals who have met the stricter criterion of the hemizygous deletion of 17–20 genes on the long arm of chromosome 7, in region 7q11.23 and including the ELN gene and approximately 50,000 base pairs.[12]

The physical manifestations of WS include supravalvular aortic stenosis (narrowing of the aorta), a deficit in the elastin production, hypercalcemia, scoliosis, and elfin or "pixie-like" facial features.[13–15] Cognitive manifestations include generally impaired cognitive function (mean full scale IQ = 58–61); poor spatial, quantitative, and reasoning abilities; distractibility; poor attention span; poor eye–hand coordination; and delayed acquisition of reading (if reading is acquired at all).[16–18] What has made the study of WS so interesting is the finding of relatively spared ability in four cognitive domains: face processing, sociability, language, and music. However, there exists a great deal of variability within the group. IQs can range from near 40 to over 100, and competencies in all domains can vary from one individual to another. Although it is a characteristic of WS that they tend toward being hypersocial and hypermusical, this is a general tendency, and individuals do show variation.

With respect to their oral language skills, individuals with WS tend to have fluent speech, good phonology, preserved morphology and syntax, and a good vocabulary. However, we have encountered many persons in which their expressive vocabulary tends toward low-frequency and unusual words. For example, on the name-as-many-animals-as-you-can test, one child responded with "newt, saber-tooth tiger, ibex, antelope" as her first responses. Individuals with WS are also prone toward using exaggerated prosody in their speech, and attention getters during story-telling, such as "all-of-a-sudden" or "lo-and-behold!" We've also encountered children with linguistic preservation problems. For example, when I first met child CB, all he could say was *Tchaikovsky's 1812 Overture* over and over again, with different prosody and emotional presentation. The following day, he could speak more fluently but could only speak about the musical instrument steel drums: "I'd like to play—to play steel drums. Do you have any steel drums? Steel drums? Are *those* steel drums over there? I wanna get some steel drums."

Anecdotal reports over the past decade suggested that individuals with WS might be more musical than others, although what is meant by "musical" can vary from description to description. On the basis of our own observations, claims of musicality involve a range of proclivities, including being drawn toward frequent music listening, music performance (in spite of a general eye–hand coordination deficit), a deep emotional engagement with music, or an above-average musical memory. Alongside such anecdotal reports we also heard many reports of unusual sensitivity to sound, including being able to hear sounds other can't, being able to categorize or label sounds that other can't (such as the make and model of a vacuum cleaner, based on the sound of its motor), or being fearful of sounds that others don't find aversive. Collectively, these sound sensitivities were being referred to under an umbrella term, *hyperacusis*, in a way that was at odds with its precise medical definition. A fundamental task, as my collaborators and I saw it, would be to attempt to quantify these

anecdotal claims of musicality and of sound sensitivities, and document them in a systematic fashion.

What can the uneven cognitive profile in WS teach us about intelligence and independence of mental faculties? Although recent years have seen most cognitive neuroscientists shying away from claims of strong modularity, it nevertheless goes against traditional neurological understanding that motor action plans could be so domain specific: how can we account for individuals who can play the clarinet or piano but cannot button their shirts or tie their shoes? What does it say about the motor system and about motor action planning circuits that they function in a musical context, but not in others? How can we quantify "musicality" in WS? How can we assess perception and performance in this population? Because the genetic profile in WS is well known, WS can help us to better understand the links between genes, brain, and musical behaviors. It has further been speculated that their hypersociability and lack of social inhibitions might be related to their musicality, a notion that I will take up later.

CHARACTERIZING THE MUSICAL PHENOTYPE IN WILLIAMS SYNDROME

To better understand and to systematically document the nature of musical behaviors in individuals with WS, we administered a questionnaire to the caregivers of 130 individuals with WS (age = 5–50, M = 20.4, S.D. = 10.4), and to comparison groups of individuals with Down syndrome (DS, $n = 30$, age = 5–51, M = 17.2, S.D. = 9.2), individuals with autism (AUT, $n = 40$; age = 9–39, M = 18.2, S.D. = 7.7), and a group of typically developing normal controls (NC, $n = 130$, age = 5–44, M = 20.9, S.D. = 7.4), all matched for chronological age.[19] The questionnaire contained 46 items: 33 multiple choice items (including Likert-like scales) and 13 free-response items. The questionnaires gathered information about physical variables (age, sex, handedness, hearing loss, physical deficits), interest in music, emotional responses to music, musical training, the amount of time engaged in various musical activities, and the age of onset of musical activities. The reliability of the questionnaire was established using split-subjects analysis, and we found no significant differences between the halves (F (1,305) = 0.16, $P \sim .69$).

Individuals with WS showed a significantly younger age of onset of musical interest, spent a greater number of hours per week listening to and playing music, and were reported to experience higher levels of emotion while listening to music (by ANOVA, all $P < .05$ and adjusted for multiple comparisons).

A principal components analysis revealed seven underlying orthogonal factors (FIG. 1) that contributed to the profile we obtained from the questionnaire. A recent reanalysis of our data by Goldberg[20] shows the derivational tree for the seven factors. At the seven-factor level, the components include content related to musical complexity, reproduction, sensitivity, musical theory and achievement, listening habits, positivity, and emotions. The reproduction factor splits off at the second level, staying virtually unchanged all the way down the hierarchy. What is particularly important about this representation is that factors at different levels are able to differentiate between the four populations studied: Williams syndrome, autism, Down syndrome, and the normal controls. A discriminant function analysis predicted

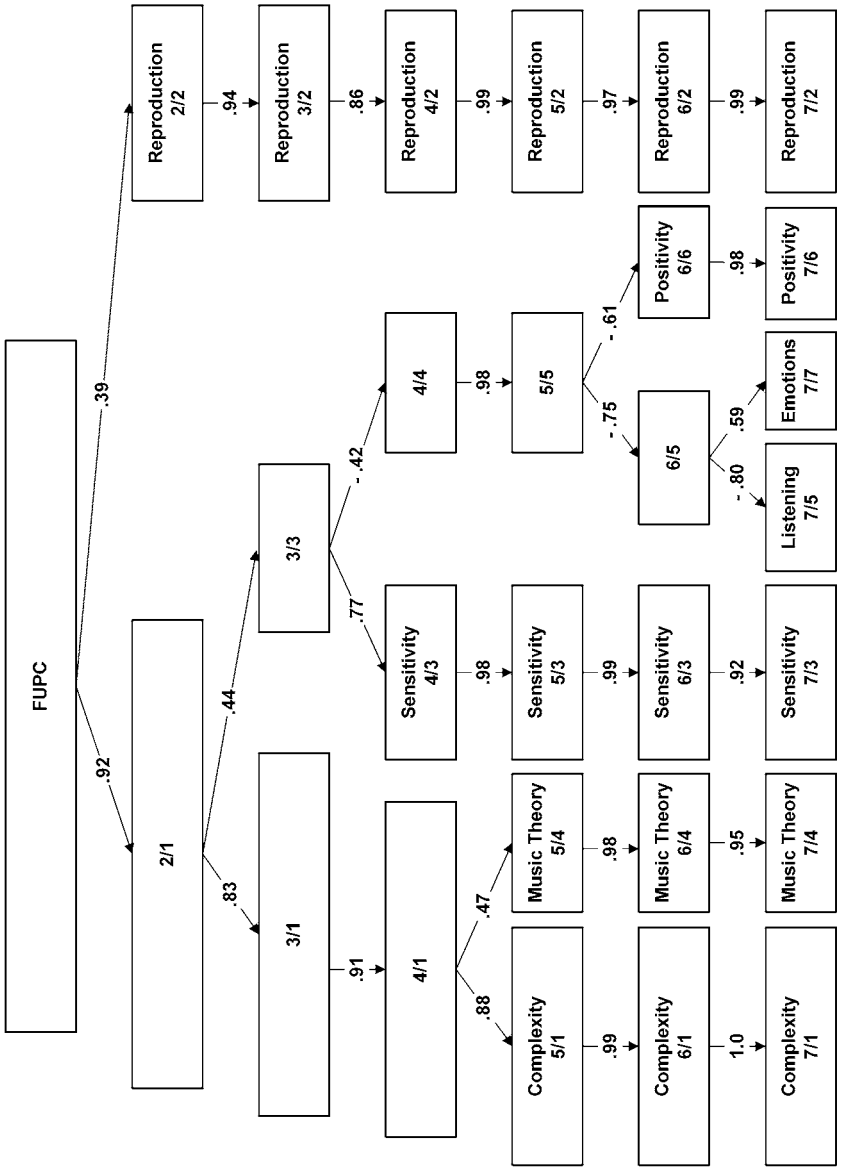

FIGURE 1. Varimax-rotated components derived from 33 kinds of musical bahaviors and experiences.

group membership for 70% of the cases ($P < .01$). Next, to control for age and sex, we performed stepwise linear regressions of age and sex against the seven factors, and found that neither factor resulted in a statistically significant improvement in the model.

UNDERSTANDING CLAIMS OF HYPERACUSIS IN WS

A careful reading of the literature suggested that both caregivers and medical/research professionals were using the term *hyperacusis* in an inconsistent fashion. The medical definition of hyperacusis (also known as oxyacusis) is that it is an "abnormal sensitivity to sound,"[21,22] where sensitivity is meant in its psychophysical, not psychiatric connotation; in other words, as an ability to hear soft sounds that others cannot. Yet published and anecdotal accounts were reporting a host of other auditory abnormalities, including people with WS who report that some normal sounds are uncomfortabe for them, some normal sounds are simply annoying or aversive to them, and some sounds are especially attractive, what Bellugi has referred to as "auditory fetishes." Amy Bihrle referred to this cluster of behaviors as "aversion, awareness, and attraction," which became the title of the paper in which we investigated this phenomenon.[23]

On the basis of a questionnaire that we administered to the same caregivers as for the musical phenotype study, we found that the incidence of *true hyperacusis*, or lowered-hearing thresholds, was just under 5% for people with WS, and there were no reports of it among our sample of people with AUT, DS, or NC. Three other categories of auditory anomalies emerged: *odynacusis* (a lowered-pain threshold for loud sounds, also known as lowered uncomfortable loudness levels, or LULLs[24]); *auditory allodyni*a, also referred to as *phonophobia* (an aversion to sounds not normally found aversive), and *auditory fascinations* (a substantial attraction to certain sounds. Persons with WS were significantly more likely to experience all three of these symptoms, or behaviors, than the other groups. Interestingly, we discovered that many WS children outgrew their fear of certain sounds, and those same sounds subsequently became objects of intense fascination. We heard many stories of children who would sit for hours listening to leaf blowers outdoors, or who loved the sounds of vacuum cleaners. One child had a collection of vacuum cleaners, and every year at Christmas he would ask for a new one.

THE NEURAL CORRELATES OF AUDITORY PERCEPTION IN WS

In trying to understand the pattern of auditory anomalies we observed, as well as the intense involvement with music and sound experienced by many people with WS, we hypothesized that we would find differences in brain activation between people with WS and NCs. On the basis of cytoarchitectonic studies, Galaburda and his colleagues[25–27] have shown morphological and neurophysiological differences between people with WS and normals, including differences in cell-packing density, cortical layering, and gray matter to white matter ratios. We hypothesized in particular that individuals with WS would show a wider and more diffuse pattern of activation to music and noise stimuli than NCs, and that they would show a greater

amygdaloidal activation, indexing their heightened emotional reactions to music and noise.

We were initially pessimistic about being able to perform any neuroimaging studies, however, based on the high incidence of LULLs and overall aversion to loud noises: the noisy environment of the scanner and its relatively confined space would have made it frightening to most individuals with WS. Positron emission tomography (PET), while quieter than functional magnetic resonance imaging (fMRI) would have required injection of radioactive tracers, and individuals with WS are known to hate needles even more than normal children. In response to these concerns, Allan Reiss developed a desensitization program that involved a professionally produced video introduction to the fMRI scanning procedure, using a child's-eye-view of the facility and a child's narration. This was followed by a visit to an fMRI simulator in which the participants could become acclimated to the noises and enclosed space. In the end we were able to recruit five participants with WS for an fMRI study of differential processing of music and noise, and five age- and sex-matched controls.[28]

Participants listened to excerpts from familiar and unfamiliar classical music, as well as the types of noisy sounds that individuals with WS are often sensitive to, such as fans, motors, and leaf blowers. For our analyses, we examined brain activations from the blood oxygenation level–dependent (BOLD) signal for music compared to rest, noise compared to rest, and music compared to noise. Our hypotheses were confirmed. Comparing music to noise, WS individuals showed a significantly lower voxel intensity bilaterally in the superior temporal cortex, middle temporal gyri, and superior temporal sulcus. In a comparison of responses to music-minus-rest versus noise-minus-rest, control participants showed significantly higher temporal lobe activations to the music than the noise, while the WS participants showed virtually indistinguishable activation levels. Persons with WS are apparently unable to modulate neural activity in the temporal cortex in response to music and noise in a manner similar to that of controls. We also observed marked differences between WS patients and controls in the right amygdala, with WS patients exhibiting far greater activation intensity in the music-minus-noise contrast. This amygdala result points to a possible neural basis for the unusual acoustical and musical sensitivities observed in affected individuals. Overall, WS participants displayed more variable and diffuse activations throughout the brain, and they showed increased activation in the amygdala and cerebellum, thus providing new and converging evidence that their neural organization may differ from that of normal individuals.

RHYTHMIC PRODUCTION ABILITY

In an effort to better understand the music production facility of individuals with WS, we separately tested rhythmic production, pitch production, and song production. To test rhythm, we presented eight WS individuals and eight mentally age-matched controls with a set of clapped rhythms in increasing complexity.[29] The task of the participant was to clap back the rhythm as accurately as possible. Independent coders, blind to hypothesis, and group membership, analyzed audio tapes of the test sessions and scored each trial as correct or incorrect. Part of the way through the coding process, the two coders, both professional musicians, independently reported that some of the trials contained responses that were clearly not replications of the

presented rhythm, but that they felt bad marking them "incorrect" because they seemed to be musically compatible with the target phrase; that is, a subset of the incorrect answers struck the coders as completing a musical phrase, and as "musical," though clearly not straight repetitions. The coders were instructed to then go back and assign trials to one of three categories: "right," "wrong," or "wrong, but very musical nonetheless."

The results showed that the WS and NC participants obtained an equal number of correct trials, approximately 66%. However, WS individuals were three times more likely when incorrect to supply a musically compatible rhythm. We interpreted this as a marker of rhythmic ability or creative rhythmicity among the WS participants.

MELODIC PRODUCTION ABILITY

We presented 12 WS individuals, 12 chronologically age-matched normal controls, and 12 individuals with DS a set of melodies increasing in complexity, to assess their melodic reproduction ability. WS and NC were statistically better at melodic repetition than the DS, and not significantly different from one another. We then presented all participants with a set of melodic fragments and instructed them to complete the melodies. As FIGURE 2 shows, the WS individuals were *not* as good at melodic completion as the NCs. Thus, WS individuals are better at rhythmic production than melodic production.

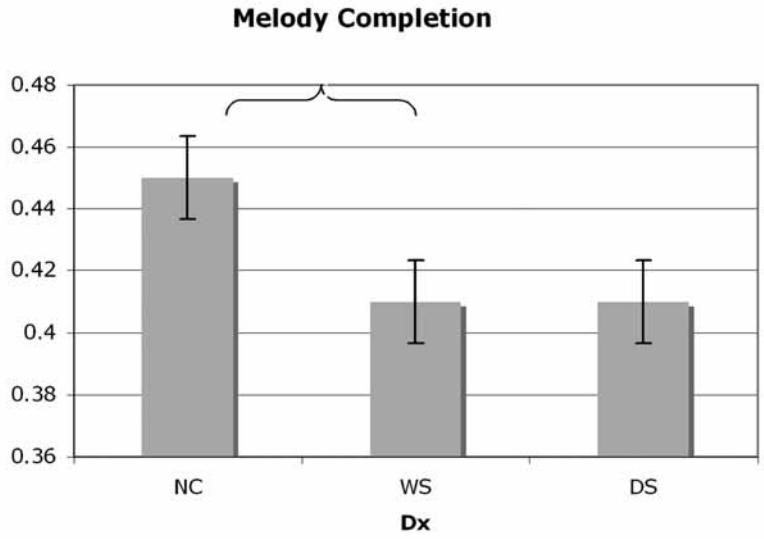

FIGURE 2.

TABLE 1. An opposite pattern of phenotypic traits and brain volumes obtains for individuals with autism and Williams syndrome

	Autism	Williams
Sociability	low	high
Musical engagement	typically low	high
Empathy	low	high
Cerebral volume	normal	small
Paleocerebellar volume (vermal I–IV)	normal	small
Neocerebellar volume (vermal V–VI)	small	large

RHYTHMIC AND MELODIC PERCEPTION

In a study currently underway, we presented 20 individuals with WS and 20 Julliard students with the Gordon Primary Measures of Musical Audiation rhythm and tonal tests. These tests probe the ability of participants to detect differences in the rhythm or pitch in pairs of sequences that are either the same or different. We found that the WS and NC participants performed equivalently. Thus, the disparity between rhythm and melodic *production* does not carry over to the *perception* of rhythm and production.

HYPERSOCIABILITY AND MUSICALITY: A POSSIBLE CONNECTION?

David Huron[30] has noted that autism and Williams syndrome present some interesting double dissociations, diagrammed in TABLE 1. Huron suggests this as evidence for a possible genetic link between sociability and musicality, speculating that during our evolutionary history, music played a role in social bonding and social communication, and thus those same genes that were selected for sociability were those involved in musical behaviors.

CONCLUSIONS

We have documented that individuals with WS are more engaged with music than members of other groups. Their music perceptual abilities are equivalent to those of typical developing normal individuals, as is their rhythmic (but not their melodic) production abilities. Neural activations in individuals with WS are marked by distinctive differences from normal individuals, including more widespread and diffuse activation to music and noise, and greater right lateralized amygdala activation.

ACKNOWLEGMENTS

I am grateful to the Fondazione Pierfranco e Luisa Mariani and the Max Planck Institute for funding my participation in the Neurosciences and Music II meeting, at

which a version of this paper was originally presented, and at which I received helpful feedback from many colleagues, including Angela Friederici, Stefan Koelsch, Sandra Trehub, and Dennis Drayna. I am grateful also to the following collaborators for their participation in the work reported herein: Ursula Bellugi, Albert Galaburda, Julie Korenberg, Vinod Menon, and Allan Reiss. Thanks also go to the following for helpful comments on previous versions of this paper: Jamshed Bharucha, Carolyn Drake, Francesca Happé, Pamela Heaton, Donald Hodges, Carolyn Mervis, Helen Neville, Isabelle Peretz, Mike Posner, John Sloboda, and William F. Thompson. The preparation of this report was supported by a grant from the Social Sciences and Humanities Research Council of Canada (SSHRC) to DJL.

[Competing interests: The author declares that he has no competing financial interests.]

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