Genetics of Childhood Disorders: XXVI. Williams Syndrome and Brain–Behavior Relationships

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Neurodevelopmental syndromes, especially those with a clear genetic basis, present unique opportunities for understanding brain–behavior and gene–behavior relationships. Distinct aspects of cognitive and social-emotional phenotypes can be associated with their genotypic and neurofunctional foundations. Among the genetically defined neurodevelopmental disorders, perhaps none presents as compelling a case for the functional independence of select abilities as does Williams syndrome (WS). The neuropsychological profile in WS is remarkable because of the magnitude of the disparity between cognitive strengths and weaknesses, a disparity that is thought to be rooted in the functional integrity of different neural networks. In addition, WS has a striking social-emotional phenotype that includes unusually high sociability and empathy, as well as a strong attraction to music because of emotional factors. Large differences among abilities and the presence of splinter skills argue for a high degree of functional independence in underlying neural systems, and elucidation of these

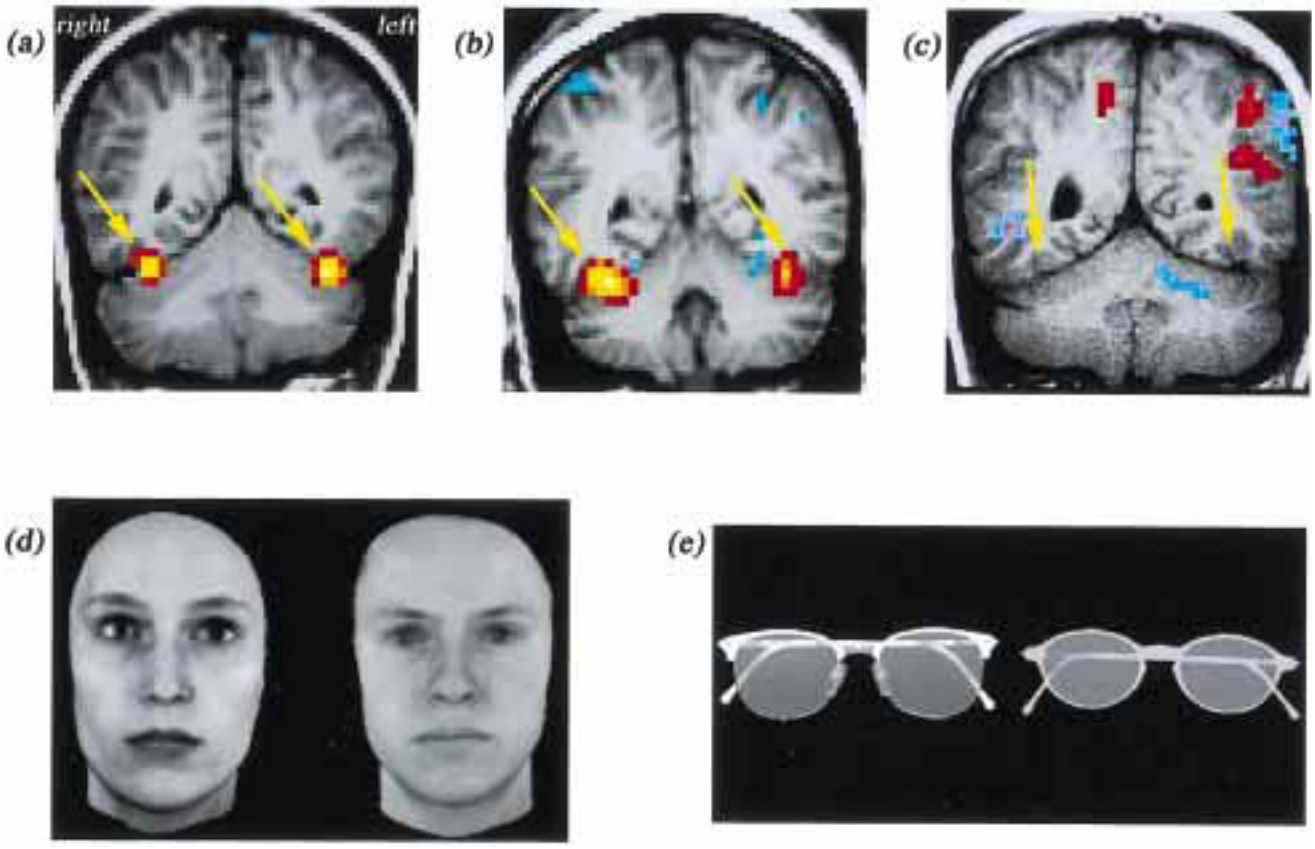

Fig. 1 Functional magnetic resonance imaging (fMRI) t-maps of the brain during face perception. The fusiform face area is shown in red/yellow (arrows) in (a) a young adult with Williams syndrome (WS) and (b) a matched normal control. In both persons, there is a clear focus of face-related activation bilaterally in the fusiform gyrus along the ventral surface of the temporal lobe. Images are in a coronal orientation, with right and left hemisphere reversed by convention, and functional data are superimposed on anatomical images for localization. Note the normal intensity and size of the fusiform face area in WS referenced to the control subject. For contrast (c), note the lack of activation in the fusiform gyrus in a young adult with autism. fMRI data are from a blocked experiment comparing face perception (d) to nonface object perception (e) during a "same/different" discrimination task on a 1.5 Tesla system. The threshold for displaying activations is set at $t = 1.5$. Object-specific areas are shown in blue on the fMRI maps.

systems can help characterize more precisely the modular organization of large-scale networks in the brain. Thus, WS is often held as a model disorder that can teach us about the nature of parallel functional networks within the brain and the manner by which these are instantiated by genetic processes during neurodevelopment.

WS is a genetic disorder caused by a hemizygous "microdeletion" on the long arm of chromosome 7 (7q.11.23) affecting multiple organ systems (Pober and Dykens, 1996). The syndrome was first characterized in the early 1960s by cardiologists who noted a particular constellation of abnormalities. These included supravalvular aortic stenosis, distinctive facial features, and cognitive impairment. Over the subsequent decades, the full clinical manifestations of the disorder were well described, but it was not until the early 1990s that the genetic deletion responsible for WS was discovered. Current research shows that the WS deletion spans a 1.5 megabase chromosomal segment, and codes for an estimated 17 genes, including elastin (*ELN*) and four genes that are highly expressed in the brain (*FZD9, STXIA, LIMK1, CYLN2*). WS occurs at a rate of about 1 in 20,000, and the mechanism thought to cause the deletion is unequal recombination during meiosis.

WS is associated with distinctive physical characteristics, including unique facial features that may include a stellate iris, periorbital fullness, full nasal tip and flattened nasal bridge, wide mouth with full lips, long philtrum, full cheeks, and a small jaw. Facial appearance can change dramatically with age. Other physical manifestations of the disorder include short stature, dental malocclusion, hypercalcemia, hyperacusis, lower-extremity hyperreflexia, a premature and abbreviated pubertal growth spurt, and cardiovascular abnormalities, especially supravalvular aortic stenosis. The deletion of the *ELN* gene is believed to cause the cardiac abnormalities and possibly some of the connective tissue problems, such as lax joints, premature aging of the skin, joint contractures, a hoarse voice, and hernias.

One of the more intriguing features of WS is its distinct social-affective profile. WS is associated with an engaging personality and excessive sociability with strangers, an increased frequency of affective prosody, strengths in face perception and face recognition memory, and an increased interest in music, especially the rhythm and emotional flavor of music. Most individuals with WS function in the mild range of mental retardation, with IQs averaging about 60. A modest percentage of cases have IQs greater than 70, with an upper limit of perhaps 100. Against this backdrop of mild mental retardation, persons with WS have a distinctive neuropsychological profile that includes strengths in face perception, affective attunement, short-term auditory memory and select aspects of language, along with weaknesses in visuospatial, motor, visuomotor integration, and arithmetic skills. The differences between peak and trough in the WS neuropsychological profile can be extreme, and, therefore, this syndrome offers unique leverage for understanding better the modular nature of neurocognitive and neuroaffective systems within the brain.

Persons with WS show a strong dissociation between relatively preserved language abilities and profound deficits in visuospatial functions. Whereas most people without WS might show some pattern of strengths and weaknesses, the difference between abilities for the average person is typically modest. Persons with WS, on the other hand, show differences between verbal and nonverbal abilities that can exceed two or three standard deviations on standardized measures. Upon meeting a person with WS for the first time, one might not immediately guess that the person has developmental cognitive delays. They frequently show "cocktail party" verbal abilities—language abilities that are superficially quite intact, coupled with good adherence to social conventions and mores and a rather intense social interest. Formal assessment of language abilities, however, yields a somewhat mixed picture (Karmiloff-Smith et al., 1998). There are strengths in the areas of phonological processing, verbal fluency, vocabulary, and select aspects of morphosyntax, but overall language abilities are delayed for chronological age. Thus, while some language skills might venture into the normal range despite a mean IQ in the mildly retarded range, other language skills are only slightly elevated compared to overall IQ.

Recent magnetic resonance imaging (MRI) morphometric evidence provides a possible physiological basis for strengths in language and also for the heightened interest in music and, in some cases, savant-like musical skill. Despite whole brain volumes that are about 15% smaller than normal, the superior temporal gyrus, an area that encompasses primary auditory cortex and association regions important for the elaboration of auditory inputs necessary for both language and music processing, is of approximately normal volume in people with WS (Reiss et al., 2000). To date there have been no published functional neuroimaging studies in WS, although a small study using auditory event-related potentials found increased amplitude of early endogenous components suggesting hyperexcitability of the primary auditory cortex. Alterations of function in this brain region may subserve the high rate of hyperacusis in WS and could also be related to language and music perceptual processes. In addition, preliminary structural MRI evidence suggests an exaggerated leftward asymmetry of the planum temporale, a cortical region buried in the depth of the sylvian fissure along the posterior aspect of the superior temporal gyrus. A leftward asymmetry of planum temporale has been linked to normal hemispheric dominance for language, and in musicians with perfect pitch there appears to be even more pronounced leftward asymmetry of this region than is typical. The associations between language, music, and superior aspects of the temporal lobe may be just one of many examples of this nature in the brains of people with WS. A more general hypothesis is that

variations in the integrity of diverse brain regions, each with discrete functions within larger networks, provide the physiological bases for the specific strengths and weaknesses in WS.

In addition to areas of preserved skill, WS is associated with profound visuospatial weaknesses. Scores on tasks requiring judgments of positional relationships between lines or objects are frequently several standard deviations below IQ. Most individuals with WS have profound difficulties visualizing the spatial relationships between objects, their distances and overall configuration, skills critical for movement in a three-dimensional world. Moreover, some evidence has linked the spatial deficits in WS to one of the four brain-expressed genes in the deleted region. An association between the deletion of *LIMK1* and deficits in visuospatial abilities was reported in the mid-1990s in a family with a smaller than typical deletion involving only *LIMK1* and *ELN*. Affected members were noted to be of average IQ but with select deficits in spatial abilities. More recently, this association has been challenged by several cases with similar small deletions involving *LIMK1* but intact spatial abilities (Tassabehji et al., 1999). It may be that no one gene acts alone to influence spatial functions, but rather specific combinations are important. While more work is needed to clarify this problem, these case studies highlight the potential power that rare deletions in the WS critical region have for elucidating specific gene–behavior associations.

Much is known about functional segregation of visual processes in the brain. Processing is split by visual domain (visuospatial versus visuofeature) into a dorsal stream that connects the occipital cortices and the parietal lobe (the "where pathway"), and a ventral stream of information flow from the occipital to the temporal cortices (the "what pathway"). The large skill difference in the perception of faces and spatial material seen in WS suggests that these two pathways are quite dissimilar in their functionality, and perhaps also in their neuroanatomical integrity. However, there have been no direct neuroimaging assessments of this functional discontinuity. A group of investigators at the Salk Institute led by Ursula Bellugi have reported in a small sample of patients that the posterior width of the brain is reduced in WS, and more recently that the total gray matter volume in the occipital cortex may be disproportionately reduced in WS (Reiss et al., 2000). This could have relevance to the duality in functioning in "face and space" in WS.

The processing of objects and faces has been extensively studied with functional imaging methodologies in typically developing individuals. Indeed, one region on the underside of the temporal lobes, the fusiform gyrus (FG), has a specific role in face perception. It is likely that face perception and related functions such as understanding the emotional states of others through facial cues are closely tied to social-cognitive skills and the ability to form and maintain social relationships. The presence of anatomical connections between the FG and limbic areas of the brain that are responsible for many emotional processes supports this conjecture. Thus workers in this field have been eager to relate the perceptual expertise for faces seen in WS to their hypersociability and prosocial orientation.

A similar comparison is frequently made in the study of an unrelated disorder: autism. In many ways, autism is the polar opposite of WS. Whereas autism is defined by low sociability, lessened empathy, and deficits in face recognition and nonverbal aspects of communication (prosody and pragmatic aspects of language), these are all areas of strength in WS. Studies by our group have shown that persons with autism spectrum conditions fail to engage the FG during face perception tasks (Schultz et al., 2000), perhaps because of their unique developmental history marked by the lack of interest in social relationships. We have now extended this work to a sample of persons with WS. Figure 1 shows the similarity in FG activation to faces in a person with WS and a matched control. It includes a comparison to a typical person with autism for whom there is no activation of this region at this threshold level. Preliminary results such as these suggest that individuals with WS are normal in their use of the FG for face perception. Moreover, we believe that levels of FG activation can be related to levels of social relatedness. Thus, similar to the connection between language and intact superior temporal gyrus morphology, our initial results are showing intact face recognition representation in the temporal cortex in the context of intact social relatedness.

There is converging evidence to suggest that the WS brain is a mosaic of spared and affected systems and that the pattern of spared and affected brain networks will correlate and predict the WS cognitive and social-affective profile. This not only serves as a model for understanding the functional and structural independence of discrete brain systems, but as more is learned about the functions of genes in the WS critical region, there is the promise of being able to delineate the ontological progression of genes to brain organization to phenotypic function.

WEB SITES OF INTEREST

http://www.williams-syndrome.org/
http://www.neosoft.com/~rlpierce/wgene.htm
http://www.geocities.com/HotSprings/8172/
http://info.med.yale.edu/chldstdy/wspws

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