Auditory and Visual Processing in Williams Syndrome

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ABSTRACT

Williams syndrome is a neurodevelopmental disorder caused by a deletion on chromosome 7. It is characterized by a range of medical problems in addition to severe impairments in visuospatial processing and oversensitivity to sounds, including hypersensitivity to sounds (hyperacusis) and extreme fear from sounds (phonophobia). In spite of impairments in visuospatial processing, object and face processing abilities are relatively preserved in WS. The present review discusses the growing research in the field linking the unique sensory phenotype in WS with underlying structural and functional brain abnormalities. In addition, possible associations between the genetic defect and the abnormal sensory processing are presented. Because Williams syndrome is etiologically homogeneous, it may serve as a model to promote understanding of visuospatial and auditory processing in humans. The findings may also have important implications for other developmental psychopathologies, such as autism, schizophrenia and attention deficit hyperactivity disorder.

"When I hear the sound of an electric drill, I feel as if it is drilling into my body."

Tamar is a 16-year-old girl with Williams syndrome who has had phonophobia and hyperacusis since an early age.

INTRODUCTION

Williams syndrome (WS) is a neurodevelopmental disorder caused by a hemizygous microdeletion of approximately 1.6 Mb containing ~28 genes on the long arm of chromosome 7 (7q11.23). Its estimated prevalence ranges from 1:7500 to 1:20000 live births (1). Affected subjects have a wide range of medical diseases and a unique behavioral and cognitive profile. The main physical characteristics are typical faces, supravalvular aortic stenosis, failure to thrive, short stature, transient neonatal hypercalcemia, and delayed language and motor development (2, 3). Behaviorally, WS subjects have a strong social appetite and a low level of social fear (4). The mean cognitive level is within the range of mild to moderate retardation, with some peaks and valleys in mental domains, particularly severe visuospatial construction deficits accompanied by a relative strength in expressive language (5) and relatively spared face and object recognition. In addition, subjects have a strong attraction to music and a strong auditory fascination alongside extreme hyperacusis and phonophobia.

Because WS is etiologically homogeneous, it serves as an excellent model for the study of the biological developmental processes underlying sensory processing in humans. The findings may also have important implications for other developmental psychiatric disorders associated with pathological sensory processing and sensitivity, such as autism, schizophrenia, post-traumatic stress disorder, and attention deficit hyperactivity disorder. The aim of this work was to review the current research linking the auditory and visual abnormalities in WS with underlying impairments, as seen in neuroimaging and electrophysiological findings. Possible associa-

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tions between the WS chromosomal deletion and the abnormal sensory processing are presented as well.

AUDITORY PROCESSING

PERIPHERAL FINDINGS

Middle-ear morbidity in WS is common; the reported incidence of otitis media ranges from 19% to 61% (6, 7). In the inner ear, auditory and electroacoustic findings in subjects with WS have indicated a mild cochlear hearing loss in the high frequencies, which tends to worsen with age (8-10), while prolonged cochlear nerve conduction time is indicated in brainstem auditory evoked response (BAER) (11). Findings reveal an association of cochlear hearing loss with acoustic reflex dysfunction in WS (11). Moreover, preliminary studies have suggested a deficit in the efferent auditory system which modifies cochlear function (7, 12). Acoustic reflex as well as the efferent auditory system protect against loud sound, and their dysfunction in WS may contribute to cochlear vulnerability especially to repeated exposures to high level sounds. Interestingly, the configuration of the cochlear hearing loss in WS involves the high tones, resembling a noise induced hearing loss.

CENTRAL AUDITORY PROCESSING AND AUDITORY SHORT-TERM MEMORY

The hypersensitivity to sounds in WS does not seem to be associated with peripheral mechanisms only. The diverse sensitivity to sounds as well as high interest in music (discussed broadly later) is assumed to be related to features of central auditory processing.

Central auditory processing (CAP) involves the extraction of auditory significant features by intricate processes such as analysis of the spectrum and selective amplification of important representational elements. Those processes are thought to take place in auditory centers of the thalamus and cortex. Additionally, it seems to rely on a specific short-term auditory memory module. Of the many abilities associated with CAP, only pitch perception has been investigated in WS. Pitch perception had been in the center of interest due to the perfect pitch ability reported to be very common in individuals with WS (13). Yet, on tests of pitch perception, children with WS performed worse than age-matched controls (14). In contrast, auditory short-term memory in WS, as indicated in rhythmic sequences test, was found to be a relative strength in WS (15).

Neurophysiologically, evoked response potential (ERP) studies suggested that auditory processing in individuals with WS is characterized by neural hyperexcitability and is carried out by neural systems different from those activated in typically developing subjects (16-19). Neville et al. (17, 18) reported that the auditory responses of subjects with WS were less refractory and more excitable than those of control subjects, a neural pattern which did not extend to visual modalities. Similarly, Bellugi et al. (16) reported marked increases in the amplitude of the N100 and P200 responses to auditory stimuli with fast repetition rates. Together, the findings point to cortical-level hyperactivity.

On fMRI scans, subjects with WS exhibited different patterns of neural organization from age-matched controls (20). The superior temporal and other regions that normally support music and noise processing were not consistently activated, whereas the limbic structures, particularly the right amygdala, showed above-normal activation. Furthermore, during music processing, a widely distributed network of cortical and subcortical structures, including the brain stem, was activated.

To increase our understanding of central auditory processing in WS, further investigations are needed using standardized behavioral tests – albeit difficult to administer in this population – as well as their most significant brain correlate, the Mismatch Negativity ERP.

SENSITIVITY TO SOUNDS

The hypersensitivity to sounds in WS is composed of three interacting components: hyperacusis, phonophobia and auditory fascination. Hyperacusis is the perception of common everyday sounds as unbearable, strong or painful (21, 22); it is sometimes referred to as lower uncomfortable loudness levels. Phonophobia is an aversion to or morbid fear of normal sounds (23). Whereas hyperacusis refers to loudness, a psychoacoustic aspect, phonophobia refers to the emotional perception of a sound, which is not necessarily related to its physical features (e.g., fear evoked by the sound of rain). Physiologically, hyperacusis is assumed to derive from an abnormality in the auditory pathways. By contrast, phonophobia is assumed to derive from an abnormality in the limbic and autonomic systems (24). Auditory fascination, the third prominent auditory phenomenon in WS, is defined as an above-normal attraction to or fascination with certain sounds (23).

Several surveys have been conducted to determine the prevalence of sensitivities to sound in WS. However, different questionnaires were used in the various assessments, and most of the studies did not clearly differen-

tiate hyperacusis from phonophobia (11, 25, 26). The reported prevalence of hyperacusis in WS ranged from 84% to 100%, compared to 0-12% in typically developing controls (11, 25, 26). Levitin et al. (23) used a parental questionnaire to compare the auditory hypersensitivities in subjects with WS to two other neurodevelopmentally impaired groups, patients with autism and with Down syndrome, in addition to healthy controls. Hyperacusis (which they termed odynacusis) was identified in about 80% of the WS group, 33% of the autism group, 33% of the Down syndrome group, and 4% of the normal control group. The corresponding rates for phonophobia (auditory allodynia) were 91%, 27%, 7% and 2%. Although hyperacusis and phonophobia occurred most frequently in WS, they were also common in subjects with the other neurodevelopmental disorders. The rate of auditory fascination in the WS group was about 9% compared to less than 1% in the other groups. Interestingly, in every case in which auditory fascination was identified, the same sound had previously evoked high anxiety in that subject. That is, every fascination began as an aversion (23).

The aversion of sounds in WS is present already at infancy. It peaks at around age 6 years and moderately decreases thereafter (11, 23). In typically developing children the peak age of sensitivity to sounds is between 5 to 8 years (27). When exposed to disturbing sounds, children with WS respond with avoidance and anxiety behaviors (e.g., crying, escaping from sound source) (11). The common sounds that trigger hypersensitivity are fireworks, car engines, thunder, and electric machines – all characterized by broad-band frequencies and high intensities (6, 11, 23).

To our knowledge there are no treatment studies of the sensitivity to sounds in WS. Based on our clinical experience we suggest utilizing the fascination and attraction of individuals with WS to sounds and music for behavioral treatments based on gradual exposure and extinction of the phonophobia. At the same time, because the auditory system of individuals with WS is vulnerable to the effects of loud sounds, it is important that subjects with WS will use earplugs when exposed to noisy environment. Also because of the hearing loss identified in WS all subjects with WS should be followed by audiologists.

MUSICALITY

Although it is well-established that subjects with WS are more interested in music than typically developing individuals and subjects with other neurodevelopmental disorders (14, 26, 28, 29), their musical talent is controversial. According to parental reports, subjects with WS have good musical memory and music recognition ability, and a selective pick of music (30). They also score higher on musical accomplishments and engagement than subjects with autism and Down syndrome, and equivalent on most measures to typically developing controls (28). However, on behavioral assessments, subjects with WS exhibit performances at mental age level and well below chronological age level in tasks involving pitch and rhythmic processing (14, 15, 26). At the same time, Levitin and Bellugi (15) noted a distinctive pattern of musical errors among subjects with WS. They reported that the errors made by subjects with WS were far more likely to be musically compatible with the target rhythm than the errors made by typically developing controls. However, the subjects with WS in this study were recruited from music camp, which may have created a bias.

The reason for the discrepancy between the parental reports and the behavioral measures may be attributed to the earlier development of the interest in and emotional response to music in children with WS compared to children with autism and normal controls, as well as to the tendency of the emotional effects (positive or negative) from music to last longer (28). Brain fMRI findings of enhanced activation of the amygdala coupled with inconsistent activation of regions in temporal lobe in response to music, support the presence of a unique neural music-processing in WS population which may alter their experience of music.

Overall, the cumulative data suggest that whereas subjects with WS lack analytical skills in the formal aspects of music, they possess unique strengths in engaging music as a means of expression, play and, perhaps, improvisation.

VISUAL PROCESSING

PERIPHERAL FINDINGS

Peripheral dysfunctions in the visual system are common in WS. Reported rates of strabismus, mainly esotropia, range from 29% to 79% (31-34), and the rate of visual acuity deficit and amblyopia is about 50% (35). Unique abnormalities in the anatomy of the eye have also been reported, including white satellites or incomplete anterior irises and bright irises (usually blue) (31). No association has been found between the ocular abnormalities and the visuospatial deficits (35).

PRIMARY VISUAL PROCESSING

There is little evidence of primary visual abnormalities in WS. Neurophysiological studies reported atypical neural functioning during perceptual contour square completion (36). Additionally, findings of cytoarchitectonic abnormalities of the primary visual cortex, including abnormal tissue density and neural organization (37), were later supported by structural MRI studies (38, 39). Whereas some visual fMRI studies reported hypoactivation in the primary and secondary visual cortices (40), others failed to detect primary visual abnormalities (1). The structural and functional visual cortex abnormalities may contribute to the higher incidence of visual-perceptual problems in WS, including reduced stereopsis and visual acuity.

VISUOSPATIAL PROCESSING

A major feature of the cognitive profile in WS is the marked impairment of visuospatial abilities as demonstrated on drawing or copying tasks (41, 42) and on motor tasks requiring visuospatial guidance, such as walking over uneven surfaces or down steps (43). By contrast, face processing and object recognition are relatively spared (19, 44). Form-, color- and face-processing functions are associated with the ventral ("what") visual stream, with predominant input from the parvocellular pathway; spatial-integrative and motion-processing functions are associated with the dorsal ("where") extrastriatal stream linked to the magnocellular pathway. Thus, the split in WS between the extremely poor visuospatial abilities and the relatively preserved face and object processing skills suggests a neural processing abnormality limited to the dorsal stream (35, 45). This assumption was supported by the study of Meyer-Lindenberg et al. (45) wherein high-functioning subjects with WS performed similarly well to controls in matching shapes, but significantly worse in assembling the shapes into squares. On fMRI, the ventral stream was equally activated in both groups. However, subjects with WS showed hypoactivation in the dorsal stream areas adjacent to the intraparietal sulcus, which takes part in perceptual-motor coordination and visual attention control. Accordingly, on tasks of attention to objects vs. location (45), brain structure analyses revealed reduced gray matter volume in the intraparietal sulcus. It is suggested from path analysis that the structural anomaly in the intraparietal sulcus may be responsible for the deficits in dorsal stream of the visual system (45).

Subjects with WS are also characterized by a deficiency in perception of global spatial arrangements, with relatively preserved perception of local spatial arrangements. This pattern can explain their poor drawing abilities (46) as well as their poor performance on block design task, in which the subject is required to organize blocks into a global pattern (47). For instance, when children with WS are asked to draw a house, they tend to place the windows and doors as separate entities from the house itself. By contrast, in a typical drawing of a child with Down syndrome, the house elements will be simplified, but there will be a better gestalt relationship among them (47).

In summary, the main cognitive phenotype of WS consists of impairment in most visuospatial abilities with a local bias and deficiency in the perception of global spatial arrangements; face processing and object recognition are relatively spared. The phenotype is attributed in part to a deficiency in the dorsal visual stream alongside a relatively intact ventral visual stream.

VISUOSPATIAL SHORT-TERM MEMORY

Subjects with WS have visuospatial short-term memory deficits compared to typically developing controls and to subjects with Down syndrome (19, 48, 49). Physiologically, there is a reduction in the volume of the parahippocampal gyrus, an essential component of the neural system underlying visuospatial memory (39). The short-term memory deficit might be partly explained by the impaired visuospatial perception typical of these children, but it apparently extends beyond it (50). Whether the deficit is related to coding, storage or retrieval processes is not yet known.

FACE PROCESSING

As mentioned before, face processing, being part of the ventral visual stream, is relatively preserved in WS. On various standardized tests of facial perception, discrimination, recognition and memory, subjects with WS performed significantly better than subjects with Down syndrome and nearly equal to typically developing controls (51, 52). However, more recent studies indicated an abnormal pattern of face processing in WS (53). These authors noted that the overall performance of individuals with WS on face recognition tasks was below that of controls matched for chronological age but similar to that of controls matched for mental age. Yet, they did not show the bias toward a global mode of facial and geometric-

shape processing that was characteristic of the typically developing controls (54). These findings suggest that the face-processing domain in subjects with WS undergoes an abnormal developmental trajectory, so that they rely mainly on components or features of objects and faces for processing and less on configural or holistic elements. This assumption has been supported by neurophysiological and neuroimaging studies. Mills et al. (55) measured ERPs (N320) in adults with WS during a face-matching task and found that the subjects employed a similar neural network for recognizing upright vs. inverted faces, much like typically developing young children. Additionally, there was an abnormal early ERP pattern in the match-mismatch face condition (decreased N100 and robust N200 amplitudes), apparently owing to the subjects' increased attention to faces. This might explain the spared facial perception function in WS. Since the unique ERP pattern was found in all subjects with WS and in none of the typically developing controls or subjects with other impairments, the authors suggested that it might serve as an electrophysiological marker of WS (55).

Structurally, high-resolution MRI studies revealed that subjects with WS have a disproportionately large volume and increased density of gray matter in areas known to be important for face processing (39). The larger the gray matter volume in the fusiform gyrus area, the better their face recognition on the Benetton test (56).

Functional MRI neural activation studies during tasks of face and eye-gaze direction processing demonstrated preserved neural functioning in the frontal and temporal regions, including the fusiform gyrus, coupled with impairments in visual regions (40). It is possible that the preserved functioning of the fusiform and frontal regions, including the anterior cingulate cortex, which has strong connections to the limbic system, may mediate the increased social interest and attention to faces characteristic of subjects with WS. This assumption is in line with the robust ERP N200 amplitudes found in scalp regions adjacent to the anterior cingulate cortex during face-processing tasks (55). The impairments in the visual cortical regions may account for the disrupted global-coherence and visuospatial aspects of face and gaze processing in WS, as manifested by diminished accuracy and longer response time on behavioral measures (40).

In summary, although face processing is relatively spared in WS and may indicate an intact ventral stream, it is apparently executed via atypical neural processing mechanisms that rely on component strategies instead of holistic ones. The face processing in subjects with WS benefited from the high attention resources which may be associated with the increased social appetite typical of the syndrome.

GENOTYPE-PHENOTYPE LINK

The pervasiveness of hyperacusis and exaggerated startle response in WS suggests that one or more of the 28 genes from the deleted 7q11 region are pivotal in auditory processing. So far, only the elastin gene (ELN) has been definitely associated with the WS phenotype of supravalvular aortic stenosis (57). Studies have suggested that a haploinsufficiency of the ELN gene may also be involved in the peripheral impairments mediating hyperacusis. Since the elastase enzyme disintegrates the stereocilia tip links (58), an elastin deficiency could lead to a desynchronized movement of the stereocilia, resulting in hearing loss and delayed cochlear nerve activation. This would, in turn, adversely affect the acoustic reflex and lead to hyperacusis (11).

Another candidate gene that may be responsible for the auditory phenotype in WS is LIMK1, which encodes for a serine/threonine kinase that is specifically expressed in neuronal tissue and regulates actin reorganization (59). LIMK1 knockout mice subjected to a fear-conditioning test showed significantly longer and more constant freezing than wild-type mice when exposed to certain sounds (60). It remained unclear, however, if the aggravated response was specific to auditory stimuli.

The possible contribution of CYLN2 haploinsufficiency to the visuospatial deficits in WS comes from reports of individuals with atypical deletion who had clinical features of WS, but without the specific spatial and constructive impairment (57). Studies conducted in CYLN2 knockout mice revealed features resembling WS, such as particular deficits in motor coordination coupled with hippocampal dysfunction, but no specific spatial deficit (61).

Other genes from the critical region, such as GTF2IRD1 and GTF2I, which encode for transcription factors, may also contribute to the mental and cognitive aspects of the WS phenotype (57). Additional in-depth studies are needed to clarify these issues.

CONCLUSIONS AND REMARKS

WS is a homogeneous genetically based syndrome and as such may serve as an excellent model to promote our understanding of visual and auditory process-

ing, as well as their underlying brain mechanisms in humans. Particularly, findings from research on WS greatly enhanced our knowledge on the function of the ventral and dorsal visual streams in human. Moreover, the research conducted to date has shed light on the dissociation of local and global perception and the partial distinction of face processing from other visuospatial and object processing. Furthermore, the findings in WS have important implications for the development of treatments to alleviate the adverse impact of the auditory hypersensitivity symptoms on the subjects' quality of life. They might also be extendable to other genetic syndromes with a similar neurocognitive profile, such as velocardiofacial syndrome, fragile X syndrome, and Turner syndrome (62). At present, less is known about the atypical auditory processing mechanism than the visual processing mechanism in WS, and future research needs to focus on this area.

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