

NEW FINDINGS ON CENTRAL AUDITORY PROCESSING IN WILLIAMS SYNDROME

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Abstract

Williams syndrome (WS) is one of very few neurodevelopmental disorders associated with a well-known genetic defect, which offers an exceptional framework for understanding the relationship between genes, brain functioning and behavior. Also, this syndrome is drawing attention of the scientific community due to the unique cognitive profile of strengths and weaknesses. Despite intellectual disabilities, it is often claimed that individuals with Williams syndrome possess certain preserved cognitive abilities, such as in the domain of auditory processing. This unexpected discrepancies present seemingly paradoxical differences in high-level cortical functioning as we understand it today. The primary objective of this article is to discuss specificity of auditory processing among WS subjects by summarizing recent studies in that field, with special emphasis on its central component. Understanding how atypical populations perceive and organize auditory input could clarify the process by which higher level outcomes are achieved. Given the unusual cognitive profile, WS presents an interesting research opportunity.

KEYWORDS: auditory hyperesthesia, auditory perception, central auditory dysfunction, central auditory processing, musicality, Williams syndrome

1. INTRODUCTION

Williams syndrome (ws), also known as Williams-Beuren syndrome, was first described more than 50 years ago.¹ Since then, and especially after the discovery of its genetic basis in 1993, it has been increasingly drawing the attention of diversely specialized scientists. It offers a rare opportunity to serve as a model for the study of genotype-phenotype correlations, since it is one of very few neurodevelopmental disorders associated with a well known genetic defect.² In addition, its unique neurocognitive profile makes it an even more interesting research subject.

The underlying cause of this rare neurodevelopmental syndrome is a microdeletion on the long arm of the chromosome 7 (7q11.23) which involves approximately 26 genes.³ The results of this deletion are a number of characteristic clinical features among which cardiovascular defects and facial dysmorphism are the most prominent one. The distinctive facial appearance has been described as elfin-like and includes a broad forehead, a short upturned nose, wide mouth with full lips, and irregular dentition. The most common cardiovascular abnormality is supravalvular aortic stenosis, sometimes with additional vascular stenoses. Low muscle tone and joint laxity are

common among young children. Most children with WS experience motor developmental delay and learning disabilities. Behaviorally, WS subjects have a strong social appetite and a low level of social fear.^{2,3}

Analysis of several studies of the cognitive development of individuals with Williams syndrome has shown that the IQ scores of most patients are between 50-60, with the full range spanning 40-100, which places them in the domain of mild-to-moderate intellectual disability. However, the general IQ score is hardly representative of the unique cognitive profile of individuals with WS, which is considered to be a complex pattern of strengths and weaknesses, also described as "peaks and valleys" by some authors.^{2,3,4} These cognitive strengths and weaknesses are best demonstrated by visual, linguistic and auditory domains. For example, while general visuospatial skills in this population are proven to be significantly impaired, there is evidence of surprisingly preserved visual ability of face-processing.^{2,3,5} Auditory processing in population with WS also shows an interestingly uneven pattern. While one of the main symptoms of this syndrome is oversensitivity to sounds, which causes reactions of fear or discomfort in 90% of this population, some of the most described features of this syndrome are also fascinations with sounds and a great interest in music, along with preserved musical

skills despite the overall cognitive impairment.^{6,7,8,9,10} This unusual auditory profile has encouraged new research that is trying to get a better understanding of auditory processing.

2. MUSICALITY

Musicality is considered to be one of the strengths of the Williams syndrome cognitive profile.¹¹ The affinity towards music among children and adults with WS has been well documented and described.³ But, besides an affinity for music, several studies and anecdotal evidence have contributed to theories about outstanding musical abilities in population of people with WS.^{3,12} One of the most influential pieces of research on this topic was conducted by Lenhoff et al who found that in individuals with WS the ability to determine absolute pitch is more common than in general population.¹² These claims of preserved or extraordinary musical abilities in otherwise intellectually impaired individuals with WS have served as the evidence for the advocates of cognitive modularity (the idea that neuro-cognitive domains such as language or musicality operate independently of one another and of general intelligence) and inspired other scientists to re-evaluate the results and find out more about this intriguing phenomenon.^{3,11} Since 'musicality' is a rather abstract concept, research that is trying to evaluate musical abilities is most often based on identifying performance in pitch, rhythm and timbre perception and/or expression.

2.1. PITCH

Pitch refers to the property of sounds that makes it possible to evaluate them as "higher" or "lower". Absolute pitch is the ability to produce or identify the pitch without a reference tone.¹³ Although the previously mentioned study by Lenhoff et al raised a lot of interest by suggesting remarkable absolute pitch abilities in WS, subsequent research couldn't match/replicate his results.^{11,12,14} Instead, absolute pitch was proven to be as rare in WS as it is in the general population (1 in 10000).¹¹ Similarly, in relative pitch perception and discrimination abilities, individuals with WS scored lower than the control group based on chronological age.^{15,16,17} Instead, their result is mostly comparable to the result of the control group based on mental age, which would suggest that their pitch processing abilities are not extraordinary, but proportionate to their intellectual level. The opposite of absolute pitch is amusia, a term that represents a deficit in pitch processing.^{14,18} Whereas the incidence of absolute pitch in WS population is considered to be as rare as in general population, the incidence of amusia is proven to be higher (11%) than in general population (4%).⁹ But surprisingly, despite the enlarged sample of WS participants with amusia, there was approximately the same percentage of WS participants who had a near perfect score (22%) as in the age-matched control group (26%).⁹

2.2. TIMBRE

Furthermore, based on the reported ability of individuals with WS to discriminate among different classes of sounds (eg. recognition of different vacuum cleaner or lawn-mower models based only on the sound they make), it has been suggested that they may show superior timbre differencing abilities.^{10,19} Timbre, or tone color, refers to the quality of sound that allows one to distinguish between two sounds when loudness, pitch, and duration are equated, for example distinguishing between two different instruments playing the same note.¹⁹ So far, there haven't been many studies, and the results have yet again been inconsistent, with some studies confirming superior timbre differencing abilities,^{10,19} and others demonstrating poor performance.²⁰

2.3. RHYTHM

Rhythm is the aspect of music that encodes the temporal components of a music piece.¹⁰ Research has mostly shown that children with WS perform on the level expected for their mental age.^{10,17} However, the interesting thing was that the responses of participants with WS were more 'musical', even when they were not successful at reproducing the rhythmical phrase given in the task. In other words, their responses were marked incorrect when they did not match the rhythm from the task, but they were not out of rhythm either. Rather, the impression was that instead of repeating the rhythmical unit from the task, the participants with WS were, in a way, completing it.^{10,13,17} This contradictory result has once again led to an unclear conclusion about the nature of musical abilities in WS. A possible explanation for conflicting results on musicality measures in WS might lie in the heterogeneity of the population, which is in contrast to some of the previous views that found it to be very homogenous in their characteristics. But even though the results bring special musical abilities into question, some authors define musicality to be more than just musical abilities. They find that the term also encompasses interest in music, emotional reaction to music and musical expressiveness.¹³ When all this is taken into account, studies agree that there is a special importance of music in the lives of people with WS.^{2,10,13,17} The neurological reasons for this interesting and somewhat contradictory musical profile will be explained in the following passages.

3. HYPERSENSITIVITY TO SOUNDS

Some recent work suggests that hypersensitivity to sounds in WS is reflected in three interacting auditory phenomena- hyperacusis, auditory fascinations and phonophobia.^{6,5} The reported prevalence in all three aspects of sound hypersensitivity was substantially higher in WS not only relative to healthy controls, but also relative to other developmental disorders such as autism and Down syndrome.⁸ As much as 90% of the WS children exhibited overt behavioral reactivity to mild intensity sounds, compared to only 20% in children with other developmental disabilities.²¹

The term hyperacusis mainly refers to oversensitivity or intolerance to common environmental sounds.⁶

Hyperacusis in WS has an early onset, within the first year of life and generally tends to decrease in severity during adolescence.^{6,22} In a large study, 83,7% of WS participants reported being bothered and/or frightened by normal environmental sounds.⁶ Phonophobia is defined as an aversion to, or morbid fear of, everyday sounds.⁸ Like hyperacusis, it is also very common in WS population.¹⁰ It is interesting to note that the sounds that cause phonophobia in WS, often end up evolving into auditory fascinations, the third specific auditory phenomena associated with WS.^{6,10} These marked fascinations with sound are reported to appear ten times more frequently in individuals with WS than in general population.^{6,10} This phenomena is described as a particular interest and affinity for a certain type of sounds, usually broad-band noises (such as humming, buzzing, motor noises and thunder).⁸ Furthermore, numerous reports show that these attractions go far beyond merely wanting to hear the sound, and extend to fascinations

with the sources

of the sounds like collecting the pictures and learning as much as they could about the objects that are producing these sounds.⁸ The potential neurological reasons for these common aversions and fascinations with sound in WS will be further discussed and explained.

QEWCENTRAL AUDITORY PROCESSING

Neurophysiologic encoding of auditory signals takes place in the central auditory nervous system.²³ All the operations executed on peripheral auditory inputs which are required for the successful generation, resolution, differentiation and identification of auditory precepts are defined by the umbrella term central auditory processing (CAP).²⁴ CAP involves the extraction of significant auditory features by intricate processes such as analysis of the spectrum and selective amplification of important representational elements. These processes are thought to take place in auditory centers of the thalamus and cortex⁵ and result in the perception of sound.

4.1. MUSICALITY

The perception of music in the general population is evenly distributed into two variations, that are independent of age, gender or degree of musical training: holistic listeners perceive the sound as a whole with emphasis on the fundamental tone, whereas spectral listeners decompose the sound into its single harmonic constituents.²⁵ For example, spectral listeners favor overtone-rich instruments such as organ and saxophone, as well as opera and jazz music. Dominant holistic listeners prefer high-pitched and/or percussive instruments (drums) and rhythmic beats.²⁵ But whereas this distribution is even in the general population, the population of WS perceives sound almost exclusively in the extremely holistic manner, which is a significant and noticeable deviation from the general population (*Figure 1*).²⁵ The holistic type of processing, when considering its preference for percussive instruments and its prevalence in WS, could be a possible explanation for reports of a great sense of rhythm and rhythmic abilities in WS population.

Extreme holistic processing is combined with functional and structural leftward asymmetry of auditory cortex (AC).²⁵ AC is located in the superior temporal gyrus and comprises the primary auditory cortex, located within the medial portion of Heschl's gyrus (HG) and the association auditory cortex, located in the planum temporale (PT).¹⁶ The primary auditory cortex is a sensory region that is thought to encode a range of auditory stimuli, including pitch, loudness, duration, and spatial location and is shown to be enlarged in musicians.¹⁶

In analyzing AC with an MRI, it was found that in spectral-processing listeners HG is larger in the right hemisphere, whereas in holistic-processing listeners it was more pronounced in the left hemisphere.²⁵ Consistent with this finding, HG in WS was almost exclusively larger in the left hemisphere, correlating with the extreme holistic sound processing.²⁵ Besides the atypical lateralization of HG, its size in WS is also surprising. Despite their overall smaller

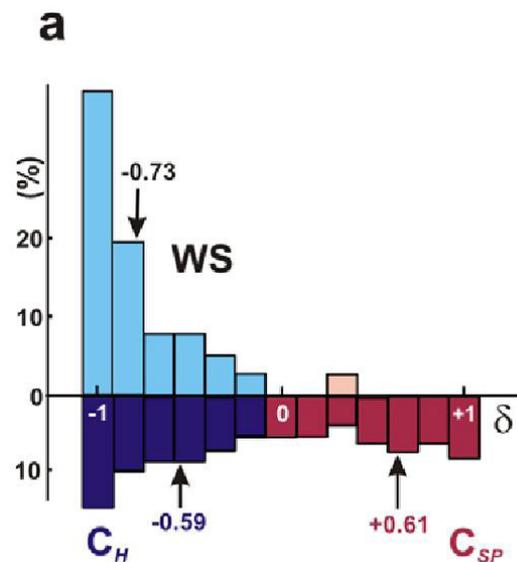


Figure 1. Perception of music in general and WS population. The control group (dark colors) of this experiment showed an even distribution of holistic (CH) and spectral (CSP) listeners (CH: mean $\delta = -0.59 \pm 0.06$; CSP: mean $\delta = 0.61 \pm 0.05$). In striking contrast to the even distribution of CH and CSP listeners within the control group, WS subjects (light colors) showed extreme and almost exclusive holistic sound perception. (all controls: mean $\delta = -0.11$ vs. WS: mean $\delta = -0.73 \pm 0.07$; $p < 0.0001$). Mean δ of groups are indicated (arrows).

Source:
 Wengenroth M, Blatow M, Bendszus M, Schneider P. Leftward Lateralization of Auditory Cortex Underlies Holistic Sound Perception in Williams Syndrome. Yan J, ed. *PLoS ONE*. 2010;5(8):e12326. doi:10.1371/journal.pone.0012326. Copyright © 2010 Wengenroth et al. Available under the CC BY 4.0 International license (<https://creativecommons.org/licenses/by/4.0/>).

brain volumes, the volumes of HG exceed those of controls, identifying a very probable neural basis of the distinctive auditory skills of ws individuals.²⁵ Such overproportional HG volumes can be typically encountered in professional musicians and talented music students.²⁵ Besides greater HG volume, MRI studies found also increased gyrification of the HG, a higher occurrence of complete posterior HG duplications (*Figure 2*).²⁵ The exact meaning of this gyrification is yet unknown, but some studies indicate that it is active during early auditory processing.²⁵

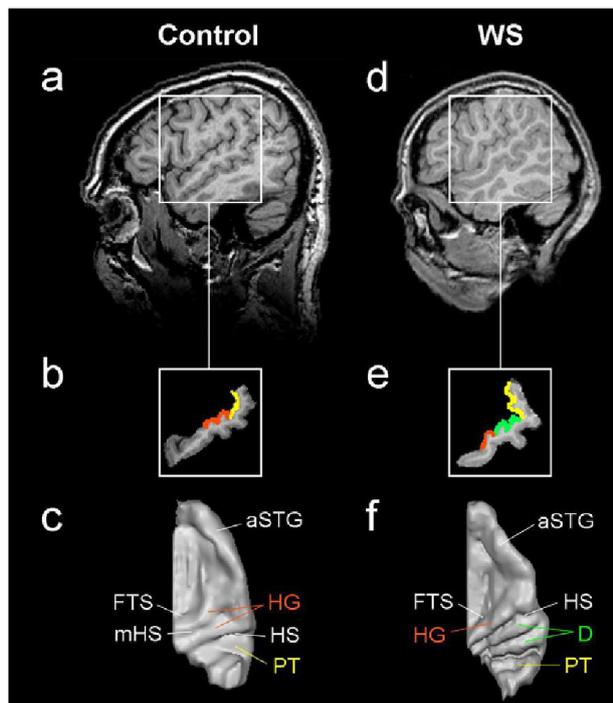


Figure 2. Anatomical landmarks of the auditory cortex. Auditory cortex (AC) of one control person (a–c) and one WS subject (d–e). Sagittal MR image. Segmented STG (b,e) including Heschl's gyrus (HG; marked orange), planum temporale (PT; marked yellow) and two posterior duplications of HG in the WS subject (D; marked green). Three-dimensional surface reconstruction of right AC (c,f) reveals anatomical features and individual peculiarities such as D (f) or medial Heschl's sulcus (mHS; c). FTS = first transverse sulcus; HS = Heschl's sulcus; aSTG = anterior superior temporal gyrus.

Source:

Wengenroth M, Blatow M, Bendszus M, Schneider P. Leftward Lateralization of Auditory Cortex Underlies Holistic Sound Perception in Williams Syndrome. Yan J, ed. *PLoS ONE*. 2010;5(8):e12326. doi:10.1371/journal.pone.0012326.

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Functionally, lateralization measured by magnetoencephalography (MEG) on auditory evoked fields (AEF), was consistent with the structural findings - activation in the control group was equally divided between the right and left hemisphere, depending on sound processing preferences. In the ws group, MEG confirmed leftward lateralization, consistent with holistic perception and structural MRI findings of leftward asymmetry.²⁵ Amplitudes of left AEF in WS subjects were increased to almost twice the size compared to normal controls.

Planum temporale (PT) contains the association auditory cortex, a secondary, higher order auditory area that has been linked with music processing, including absolute pitch ability. Some studies found its volume in relation to total brain volume to be larger in ws compared to general population.¹⁶ In a study where participants with ws were divided into subgroups by their musical abilities, the small group with higher musical abilities was found to have a larger left planum temporale volume, as shown by an MRI analysis.¹⁶ When conducting a more thorough statistical analysis, it was discovered that the increased volume of left PT was correlated to pitch abilities.¹⁶ These results lend support to previous findings that the superior temporal region, which includes the planum temporale, contains specialized neural tissue for processing pitch and melodies.¹⁶

As opposed to studying the part of ws population with good musical ability, a recent study tried to find neural correlates of amusia, a specific disability in pitch processing.¹⁸ Unlike the studies that focused only on regions associated with the auditory cortex, this study included the MRI analysis of the entire network involved in auditory processing. They discovered that amusia is due to disconnectivity in the right fronto-temporal pathway connecting the right auditory cortex and inferior frontal lobe rather than isolated dysfunction in the primary auditory cortex.¹⁸ A major right fronto-temporal pathway is the right superior longitudinal fasciculus (SLF), which connects the parieto-temporal association areas and the frontal lobe.¹⁸ It includes the arcuate fasciculus (AF), which connects the right inferior frontal gyrus (IFG) and the right AC.¹⁸ While the relationship between amusia and right fronto-temporal disconnectivity was present for both the inferior and superior components of the SLF in the present study, it was particularly strong for the inferior SLF.¹⁸ Interestingly, the volume of the right superior portion of the AF correlated with pitch perception thresholds, while the volume of the right portion of the AF correlated with the degree of mismatch in auditory perception and vocal production.¹⁸ By involving other parts of auditory network, these results helped explain the reason for the disproportion between preserved sizes of the AC in ws and low pitch processing abilities.

Neural correlates of musical timbre perception in ws were studied only recently and in one study so far. In this study, the participants had to recognize the target timbre (piano) among three options (piano, cello and trumpet).¹⁹ The results showed that the participants with WS were as successful as the control group in discriminating timbre, but in addition, their EEG results showed a greater activation in neural discrimination between the non-target timbers, which wasn't present in the control group. Besides neural activity when hearing the piano contrasted to the other two timbers, event-related potentials (ERP) in participants with ws revealed early and increased discriminatory activity in response to the timbers of cello and trumpet, even though they were not the target of the task. In contrast, participants in the control group perceived the difference only when presented with the piano timbre, without spontaneously perceiving

the difference between the non-target timbers as well. The authors suggest that these are the first evidence of previously anecdotal enhanced timbre sensitivity in WS, which also may begin to explain the process behind greater auditory sensitivities to psychoacoustic features as is normally observed.

4.2. HYPERSENSITIVITY TO SOUND

Hypersensitive auditory processing, frequently observed in WS, can also be linked to CAP. Findings that could relate it to CAP, could help in understanding other disorders associated with pathological auditory perception and processing, such as autism, schizophrenia, posttraumatic stress disorder, Down syndrome, and attention-deficit hyperactivity disorder.^{6,26}

Some argue that while impairments of cochlea, efferent auditory system or acoustic reflex in WS may account for some of the auditory intolerance due to deficient protection against excessive auditory input, these peripheral impairments cannot fully explain the WS auditory phenotype.^{5,26} Accumulated findings propose an involvement of central mechanisms in auditory hyperactivity, specifically in the stages of auditory sensory encoding.^{5,6,26,27} Neurophysiologically, evoked response potential (ERP) studies suggest that auditory processing in individuals with WS is characterized by neural hyperexcitability and abnormality in different places along the auditory path.⁵ A recent study found evidence of hyperactive CAP in WS, by finding enhanced brain responses in early stages of sound encoding and deviance detection.²⁶ Atypical hyperactive processes of tonal encoding and auditory preattentive deviance detection were identified by higher amplitudes of the mismatch negativity response (MMN) and a P1-N1-P2 obligatory complex (MMN and P1-N1-P2 complex are electrophysiological indicators of preattentive pitch discrimination and involuntary attention change).²⁶ From the developmental point of view, the amplitudes of the P1-N1-P2 complex usually decrease as children grow up, but in WS this doesn't happen.²⁶ This could be linked to the prevalence of hyperacusis that is normally higher in children, but decreases over time, whereas in WS it stays high, as well as the amplitudes of P1-N1-P2.²⁶

Another study of hyperacusis in WS, tested the medial olivocochlear (MOC) efferent system.²⁷ MOC fibers act through synapses on outer hair cells to reduce the gain of the cochlear amplifier and reduce basilar membrane motion, thereby protecting the auditory system from excessively loud sounds. The results showed that patients with WS had a significantly higher suppression effect of the MOC reflex on the measure of otoacoustic emission (OAE).^{27,28} Ipsilateral and contralateral acoustic reflex reactions to tonal and broadband stimuli presented at maximum stimulus intensities were absent in 62-86% of the patients with WS and in the rest, acoustic reflexes were elicited at lower auditory sensation thresholds than in controls.²⁷ Findings of abnormal MOC and acoustic reflexes were described by several authors and could lead to the identification of the possible cause of hyperacusis and phonophobia in WS.^{6,27}

However, as mentioned before, whereas hyperacusis refers to loudness, a psychoacoustic aspect, phonophobia mainly refers to non-physical features of sound perception, based on intense emotional experience. Therefore, explanation of hyperacusis are mainly related to abnormalities found in the auditory system, whereas the explanation of phonophobia lies primarily in abnormal emotional perception of a sound which primary derives from the limbic and autonomic system.⁵ It is still not well-defined if the medial olivocochlear efferent system is hyperactive by itself or if its hyperactivity is mediated by abnormal loudness information sent through the afferent auditory pathways. These abnormalities, in conjunction with frequent absence or deficiency in acoustic reflex can enhance hyperacusis in WS subjects.^{2,11,27,29} Non-auditory factors such as fear, anxiety, aversion related to specific sounds are mostly considered underlying causes of phonophobia. But, despite phonophobia and hyperacusis, individuals with WS also display a heightened interest in music. Their musical engagement and receptivity almost uniformly surpasses that of typically developing age peers.²⁵ Similarly to phonophobia, auditory fascinations are probably related with recruitment of emotional centers of the brain after particular auditory stimuli.³ The amygdala, part of the brain related to experiencing fear and other emotions, is among the isolated areas with preserved volume in WS (along with auditory regions in the STG).^{25, 30} Beside the preserved volume, these auditory and limbic areas in participants with WS also show an excessive and atypical activation on fMRI when exposed to sound stimuli (especially in response to emotional music), which could very well explain heightened emotional reactivity to music in this population.^{26, 19,18} These findings support the theory of a unique music-processing pathway in WS population which may alter their experience of music.⁵

In conclusion, the characteristics of CAP in WS very distinctive when compared to the general population. The almost exclusively leftward (and therefore holistic) auditory processing is probably one of the most prominent differences. Another difference is that, while structural brain findings show decreased brain volume in WS, the volume of auditory centers remains the same, or even bigger relative to control groups. Even though this interesting finding at first glance imply greater auditory (or musical) abilities in individuals with WS, newer research tends to show the opposite. This is possibly due to the disconnectivity of auditory pathways that connect auditory centers to frontal lobes, which demonstrates the complexity of networks involved in auditory processing. Another reason is probably atypical activation of auditory areas, which explains their increased sensitivity to sound as well. Abnormal activity in response to auditory stimuli has also been found in the limbic system, which could be the basis for increased emotional reactions (phobias and fascinations) to sound and music in this population.

CONCLUSION

Williams syndrome is characterized by seemingly paradoxical differences in high-level cortical functioning: some faculties are relatively preserved (music, language, facial processing and social drive), while others show severe deficits (conceptual reasoning, spatial ability, motor coordination, problem solving, arithmetic processing). This discrepancy, which can be observed in a lot of different cognitive and behavioural areas in Williams syndrome, presents a good opportunity for scientists to study and understand the mechanisms that underlie these areas of functioning, especially when taking into account the possibility to relate these cognitive differences to the exact genes responsible for them.

Even though the previous findings of superior musical abilities in WS were generally not confirmed by newer studies, auditory processing in WS is definitely proven to be unique. This authenticity is valuable for science of CAP, because understanding how atypical populations perceive and organize auditory input, and what alternative constraints govern this specific organization, could clarify the process by which higher level outcomes are achieved.¹⁴ Because of its interesting auditory profile, Williams syndrome serves as a tempting potential source of information about CAP that is waiting to be further discovered.

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NOVE SPOZNAJE O CENTRALNOM AUDITIVNOM PROCESIRANJU KOD WILLIAMSOVOG SINDROMA

Sažetak

Williamsov sindrom (WS) jedan je od rijetkih neurorazvojnih poremećaja s poznatim genetičkim uzrokom, što pruža izvrstan temelj za razumijevanje odnosa između gena, moždanih procesa i ponašanja. Uz to, ovaj sindrom privlači pozornost i zbog jedinstvenog kognitivnog profila karakteriziranog neobičnim jakim i slabim stranama. Unatoč intelektualnim teškoćama, često se tvrdi kako su odlika sindroma određene očuvane kognitivne sposobnosti, kao što je auditivno procesiranje. Takve neobične neujednačenosti predstavljaju naizgledno paradoksalnu razliku u odnosu na način na koji trenutno shvaćamo više razine kortikalnog funkcioniranja. Primarni cilj ovog članka je opisati specifičnost auditivnog procesiranja među populacijom s WS-om kroz pregled novih istraživanja iz tog područja, s posebnim naglaskom na razumijevanje neurološke pozadine, odnosno centralne komponente auditivnog procesiranja. Razumijevanje načina na koji atipične populacije percipiraju i organiziraju ulazne slušne informacije, moglo bi omogućiti bolje razumijevanje procesa kojima se postižu viši kognitivni ishodi. S obzirom na neobičan kognitivni profil, WS predstavlja zanimljivu priliku za istraživanje.

KLJUČNE RIJEČI: centralna slušna disfunkcija, centralno slušno procesuiranje, glazbene sposobnosti, slušna percepcija, slušna preosjetljivost, Williamsov sindrom

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