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Atypical Hemispheric Asymmetry in the Perception of Negative Human Vocalizations in Individuals with Williams Syndrome

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Abstract

Williams syndrome is a neurological condition associated with high levels of auditory reactivity and emotional expression combined with impaired perception of prosody. Yet, little is currently known about the neural organization of affective auditory processing in individuals with this disorder. The current study examines auditory emotion processing in individuals with Williams syndrome.

Hemispheric organization for positive and negative human nonlinguistic sound processing was compared in participants with and without the disorder using a dichotic listening paradigm. While controls exhibited an expected right cerebral hemisphere advantage for processing negative sounds, those with Williams syndrome showed the opposite pattern. No differences between the groups emerged for the positive stimuli. The results suggest aberrant processing of negative auditory information in Williams syndrome.

Keywords

Williams syndrome; Affect; Hemispheric asymmetry; Lateralization; Prosody; Speech

INTRODUCTION

Williams syndrome (WS) is a multisystem neurogenetic disorder caused by a hemizygous deletion of 25–30 genes on chromosome 7q11.23 (Ewart, Morris, Atkinson, Jin, Sternes, Spallone, Stock, Leppert, & Keating, 1993; Korenberg, Chen, Hirota, Bellugi, Burian, Roe, & Matsuoka, 2000). It is manifested by a wide range of clinical symptoms, which includes distinct facial features and a complex profile of cognitive and behavioral characteristics, most notably hyper-sociability (see Järvinen-Pasley, Bellugi, Reilly, Mills, Galaburda, Reiss, & Korenberg,

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2008; Meyer-Lindenberg, Mervis, & Berman, 2006). Individuals with WS tend to have IQs between 40 and 90 (Searcy, Lincoln, Rose, Klima, Bavar, & Korenberg, 2004), with better performance in verbal as compared with performance tasks (e.g., Howlin, Davies, & Udwin, 1998). Moreover, in general, individuals with WS show higher levels of performance in tasks pertaining to social as compared to non-social information processing (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000; Martens, Wilson, & Reuters, 2008). The deficits in visual-spatial functions have been linked to dorsal stream dysfunction (e.g., Atkinson, Braddick, Anker, Curran, & Wattam-Bell, 2003), whereas the relatively better processing of, e.g., language functions reflect relatively less affected ventral stream function (e.g., Gothelf, Searcy, Reilly, Lai, Lanre-Amos, Mills, Korenberg, Galaburda, Bellugi, & Reiss, 2008).

A notable aspect of the WS phenotype is an unusual profile of auditory processing. Individuals with WS show a high affinity to music and musical activities (Dyken, Rosner, Ly, & Sagun, 2005; Levitin, Cole, Chiles, Lai, Lincoln, & Bellugi, 2005a). WS is also usually accompanied by hyperacusis to moderate intensity sounds, reflecting highly selective and specific sound aversions and attractions (Gothelf, Farber, Raveh, Apter, & Attias, 2006; Levitin, Cole, Lincoln, & Bellugi, 2005b). Moreover, individuals with WS are often described as very expressive, with strong abilities to socially engage the listeners through increased use of prosodic effects (Reilly, Losh, Bellugi, & Wulfeck, 2004). For example, while individuals with WS have been found to perform similarly to matched TD controls on an experimental battery involving affective prosody imitation, their spontaneous speech is characterized by increased emotionality and higher as well as wider pitch range (Setter, Stojanovic, Van Ewijk, & Moreland, 2007). A growing body of research has specifically examined receptive prosodic processing skills in individuals with WS. For example, Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg (2006) used The Diagnostic Analysis of Nonverbal Accuracy test (DANVA2; Nowicki & Duke, 1994) to evaluate recognition of happy, sad, angry, and fearful prosodic expressions. Individuals with WS exhibited poorer performance than chronological age (CA)-matched typically developing (TD) controls with all but the happy expressions. Thus, while individuals with WS exhibit greater than typical use of emotional speech effects, they have difficulties in processing such information in the speech of others.

Structural magnetic resonance imaging (MRI) evidence on the neurobiological underpinnings of auditory function in WS show that such individuals have smaller left planum temporale (part of the auditory association cortex) relative to controls (Eckert, Galaburda, Karchemskiy, Liang, Thompson, Dutton, Lee, Bellugi, Korenberg, Mills, Rose, & Reiss, 2006). Conversely, larger volumes of the ventral-orbital prefrontal region have been associated with greater use of social-affective language in individuals with WS (Gothelf et al., 2008). While cytoarchitectonic evidence has shown relative preservation in cell packing density and cell size in the primary auditory cortex in individuals with WS relative to TD controls, interesting between-group differences with implications for laterality have been reported (Holinger, Bellugi, Mills, Korenberg, Reiss, Sherman, & Galaburda, 2005). In areas associated with language function, asymmetries in neuronal packing density were found in controls, whereas they were lacking in the brains of individuals with WS. Moreover, an excessively large layer of neurons in an area receiving projections from the amygdala suggested that the auditory cortex may be more limbically connected in WS than in controls. This may underlie the heightened emotional reactivity to certain sounds in individuals with WS.

The current study is aimed at addressing the question of why individuals with WS are “hypersocial” in terms of affect production (e.g., Järvinen-Pasley et al., 2008) but impaired at affect perception. We evaluated perceptual asymmetries for the processing of positive and negative affective vocalizations in individuals with WS relative to TD controls. Thus, in the current study, the dichotic listening (DL) technique was used as a preliminary step for

elucidating the hemispheric asymmetries for the processing of affective vocalizations in individuals with WS.

The DL technique is a reliable method for examining hemispheric lateralization by presenting different information simultaneously to both ears. Based upon the differential temporal resolution of the left hemisphere (LH) and the right hemisphere (RH), verbal non-emotional material is typically preferentially processed through the right ear (RE, to the LH), whereas words with emotional content are preferentially processed through the left ear (LE, to the RH) reflecting each hemisphere's specialization (Bryden, 1988; Schirmer & Kotz, 2006; Voyer & Flight, 2001). The main principle underlying this procedure is that when the brain is presented with more information than can be processed the two hemispheres integrate the information received into a single percept (Hugdahl, 2000; Kimura, 1961). The DL method exploits the contralateral neural organization of the auditory pathways: that is the connection between the RE and the LH, and between the LE and the RH. The ipsilateral pathways can also transmit sensory information, albeit less efficiently. Resulting data is termed an ear asymmetry, or an index of which ear (and hence hemisphere) holds an advantage over the other in its readiness to analyze the incoming material. Thus, when an individual reports hearing the material presented to the LE, increased activation of the RH may be inferred, and likewise, attention to the message presented to the RE implicates LH activation.

The general issue to be examined in present study concerns whether individuals with WS have differential difficulty perceiving emotional information when linguistic (but not semantic) content is removed. Non-linguistic human vocalizations with either negative or positive emotional meaning, such as giggles and grunts, will be used as stimuli. A more specific hypothesis tests whether negative emotional information is particularly challenging for people with WS to perceive. This hypothesis is motivated by the Plesa-Skwerer et al.'s (2006) findings of adequate performance by individuals with WS on accurate recognition of happy prosodic information. In addition, two recent functional MRI (fMRI) studies indicate that WS individuals have reduced amygdala and orbitofrontal cortex (OFC) activation in response to negative face stimuli as compared to TD controls (Meyer-Lindenberg, Hariri, Munoz, Mervis, Mattay, Morris, & Berman, 2005). Additionally, combined event-related potentials (ERP) and fMRI evidence show that brain responses to negative facial expressions are attenuated in WS, while neural activity to positive facial expressions is enhanced (Haas, Mills, Yam, Hoeft, Bellugi, & Reiss, 2009). These data raise the possibility that the valence-specific neural activation patterns observed in the visual domain may also apply to the auditory domain.

The valence-specific hypotheses described below are consistent with the existing DL literature (e.g., Pollak, Holt, & Wismer Fries, 2004), and are based upon electroencephalographic (EEG) evidence indicating individual differences in affectivity within the TD population such that, prominent activity over the LH frontal regions is associated with positive emotional states, whereas prominent activity over the RH frontal areas is associated with negative affective states (Davidson, 2004). Further, evidence from typical adults shows that the direct communications between the anterior prefrontal cortex and the posterior regions associated with perception are mediated by the amygdala (Amaral, Price, Pitkänen, & Carmichael, 1992). These communications between the anterior and posterior affective areas are reciprocal, in that augmented activation in one area is associated with an attenuated activity of the other (e.g., Davidson & Hugdahl, 1996). Specifically, we hypothesized that the TD controls would show the normative pattern of perceptual asymmetries (e.g., Pollak et al., 2004): for positive stimuli presented to the LE a LE advantage was predicted, reflecting the RH posterior system activation; positive stimuli presented to the RE were hypothesized to activate the left anterior system, implicating a RE advantage. No ear advantage was predicted for the negative stimuli presented to the LE, as this represented the only condition implicating both anterior and posterior activation within the same hemisphere; for negative stimuli presented to the RE a LH

advantage was predicted. Finally, the presentation of neutral information to either RE or LE was predicted to activate neither anterior nor posterior emotion areas. We predicted that individuals with WS would exhibit similar processing of positively valenced auditory information to the TD controls, but reduced RH efficiency at processing negative auditory information. The rationale was that neurobiological data point to reduced leftward asymmetry in WS (Holinger et al., 2005), and decreased neural responses to negative visual stimuli in such individuals relative to TD controls (Haas et al., 2009; Meyer-Lindenberg et al., 2009). At the same time, neural activity in response to positive face stimuli is preserved or even enhanced in individuals with WS relative to TD controls (Haas et al., 2009).

METHOD

Participants

Eighteen individuals with WS (8 males) were recruited through a multicenter program based at the Salk Institute. Only right-handed participants were included in the study, and handedness was established on the basis of the hand that the individuals used for writing. For all participants, genetic diagnosis of WS was established using fluorescence in situ hybridization (FISH) probes for elastin (ELN), a gene invariably associated with the WS microdeletion (Ewart et al., 1993). In addition, all participants exhibited the medical and clinical features of the WS phenotype, including cognitive, behavioral, and physical features (Bellugi et al., 2000). Eighteen right-handed TD individuals (9 males) were matched to those with WS for CA. The participants were screened for the level of education, and those with more than two years of college-level education were excluded from this study. Each participant was screened for current and past psychiatric and/or neurological problems, and only those deemed clinically asymptomatic were included in the study. A small DD comparison group of five individuals with a learning and intellectual disability of unknown origin was included (3 males). As right-handedness was a prerequisite for being included in this study, the recruitment of the DD participants proved difficult, as a large proportion of our available population was left-handed (cf. Grouios, Sakadami, Poderi, & Alevriadou, 1999). Although the small sample size precluded inclusion in the statistical analyses, the data from this group are reported as reference. Participants with DD were recruited from the San Diego area, and were extensively screened for the absence of severe motor, visual, and auditory deficits, as well as traumatic brain injury, epilepsy and seizures, multiple sclerosis and autism spectrum disorders. Furthermore, no individuals with diagnoses of any one specific disorder (e.g., Down syndrome) were included in the study. Thus, the stringent selection criteria employed in this study were aimed at increasing the likelihood of having a comparison group with a cognitive profile characterized by developmental delay and intellectual impairment without etiology-specific or focal impairments to brain functioning.

The participants' cognitive functioning was assessed using the Wechsler Intelligence Scale. Participants were administered either the Wechsler Adult Intelligence Scale Third Edition (WAIS-III; Wechsler, 1997) or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), depending upon time constraints. Participants were also administered a threshold audiometry test using a Welch Allyn AM232 manual audiometer, which was calibrated to ANSI s.3.21 (2004) standards. Auditory thresholds were assessed at 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz, monaurally. The hearing of all participants included in the study was within the normal range. In addition, all participants were native English speakers, and gave written informed consent before participation. Written informed assent was also obtained from participants' parents, guardians, or conservators. All experimental procedures complied with the standards of the Institutional Review Board at the Salk Institute for Biological Studies.

Table 1 shows the demographic characteristics of the three groups of participants. The participants with WS and TD were well matched in terms of CA ($F(1, 34) = .001, p = .98$). As predicted, the TD individuals had significantly higher mean VIQ ($F(1, 34) = 102.8, p < .001$) and PIQ ($F(1, 34) = 129.8, p < .001$) scores as compared to their counterparts with WS. Predictably, for participants with WS, mean VIQ scores were significantly higher than mean PIQ scores ($t(17) = 3.56, p = .002$), while this was not the case for the TD group ($t(17) = .83, p = .42$).

Dichotic Listening Stimuli

The stimuli, drawn from Pollak et al. (2004), comprised 48 positive, negative, and neutral sounds lacking in linguistic content. Non-linguistic affective vocalizations, such as laughs, gasps, and screams are important in social communication, as they represent innate behaviors to communicate affective states (Barr, Hopkins, & Greene, 2000; Kreiman, 1997). These stimuli carry semantic content without activating bilateral linguistic processes. Two sounds were compiled from the set of 48 affective stimuli to create the dichotic tokens: one sound for the presentation to the RE, and another for the presentation to the LE. For each dichotic token, the affective valence differed between the ears.

Procedure

Participants first completed the DL task and then an identification test of the DL stimuli. The rationale for administering the DL task prior to the identification subtest was to prevent familiarity effects occurring in the DL context. The stimuli were presented via circumaural noise-reducing headphones at a comfortable loudness level of approximately 75 dB SPL, using the PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1993). The DL task consisted of two blocks of stimulus trials comprising identical stimuli. Dichotic pairs were randomized and not repeated within the trial blocks. The headphones were reversed after the first block of the DL task to minimize channel effects. Each trial block consisted of four tokens of the following dichotic pairs: positive-neutral, neutral-positive, negative-neutral, neutral-negative, positive-negative, negative-positive (total of 24 trials per block). Consistent with Pollak et al. (2004), participants were not explicitly informed about the dichotic nature of the stimuli, but instead instructed that although the stimuli may sound odd, “We are interested in how you think the person making the sound probably feels.” Participants were shown three cartoon line-drawing faces (happy, sad, neutral), which represented the LE input, the RE input, and a foil. The response screen appeared on the computer screen 50 ms after the stimulus delivery, and the placement of the line-drawing faces was counterbalanced so that LE inputs, RE inputs, and foils appeared in a random order across the screen. Participants indicated their responses by pointing, and the experimenter keyed the responses into the computer on the participants’ behalf. The computer recorded the responses. After each response, a 2.5-second interstimulus interval (ISI) followed. No feedback was given during the experiment. For the identification subtest of the DL experiment, each of the 16 negative and 16 positive affective sounds was presented to both ears simultaneously via headphones, binaurally, free of the dichotic competition. Participants were asked to identify the valence of the sound as either happy, unhappy, or neither, using the three cartoon line-drawing faces (happy, sad, neutral). The response screen appeared on the computer screen 50 ms after the stimulus delivery, and procedures were as described above for the DL task.

RESULTS

Perceptual Asymmetries

Table 2 displays the percentages of the participants’ LE and RE identifications within each affect category and stimulus condition in the DL task. Consistent with Pollak et al. (2004), as the difference in accuracy for the RE and LE is correlated with the participants’ overall

performance level (Chapman & Chapman, 1988), an asymmetry score entitled the f -index, was calculated. This index is calculated as: (right ear performance–left ear performance) / (right ear performance + left ear performance). RE advantages (REA) were deemed to be present when the f -index value was positive and significantly greater than zero, whereas LE advantages (LEA) were linked to a negative, significantly below zero, f -index value (a ratio score not significantly different from zero reflects no asymmetry). The resultant f -index scores for each condition (negative to LE, negative to RE, positive to LE, negative to RE) were normally distributed (Levene's Test for Equality of Variance F statistic for all variables: $p > .11$); see Figure 1.

Perceptual asymmetry data were analyzed by a 4×2 repeated-measures analysis of variance (ANOVA), with the f -index scores with condition (negative to LE, negative to RE, positive to LE, negative to RE) entered as a within-participants factor, and group as a between-participants factor. This analysis revealed a significant main effect of f -index ($F(3, 102) = 22.74, p < .001$), reflecting higher negative f -values for the LE presentations relative to the RE presentations. In addition, an f -index by group interaction emerged, ($F(3, 102) = 5.81, p = .001$). Follow-up Bonferroni corrected t -test analyses (significance set at $p \leq .025$) showed that the interaction effect was due to the WS group – but not the TD group – exhibiting a significantly more positive f -index value ($t(34) = 4.43, p = .001$), and thus an RE/LH advantage when participants were presented with negative stimuli. There were no other between-group differences (all $p > .21$).

As the data from the DD participants were excluded from the statistical analyses, correlations (Pearson, 2-tailed tests) were carried out between the four f -index scores and IQ for both the WS and TD groups to examine the potential contribution of intelligence upon performance. For the WS group, all correlations between the VIQ and the four f -index scores failed to reach significance (all $r < .23, p > .36$), as did all the correlations between the PIQ and the four f -index scores (all $r < .28, p > .27$). For the TD comparison group, again all correlations between the VIQ and the four f -index scores failed to reach significance (all $r < .19, p > .46$), as did all the correlations between the PIQ and the four f -index scores (all $r < .37, p > .17$).

Affect Identification Subtest of the DL Experiment

This subtest assessed each participant's ability to identify the valence of the positive and negative sounds used in the DL experiment. Instead of dichotic presentation, the stimuli were presented binaurally. Data were missing for one participant with WS, and for four participants with TD because of equipment failure. Figure 2 displays the affect identification scores that were entered into a 2×2 repeated-measures ANOVA, with affect category (positive/negative) as a within-participants factor, and group (WS/TD) as a between-participants factor. This analysis revealed a main effect of affect category ($F(1, 29) = 2.61, p = .05$), a main effect of group ($F(1, 39) = 9.80, p = .004$), and a category by group interaction ($F(1, 29) = 7.67, p = .01$.) The main effect of affect category was due to a higher overall performance with the identification of positive stimuli as compared to the negative stimuli, and the main effect of group was due to the TD group outperforming their counterparts with WS. Follow-up Bonferroni corrected t -test analyses (significance set at $p \leq .0125$) showed that the interaction effect was due to the WS group exhibiting lower recognition accuracy for negative stimuli ($t(29) = -3.59, p = .001$), while no between-group differences were in evidence for the processing of the positive stimuli ($t(29) = -.35, p = .73$). While the TD group showed similar levels of performance across the positive and negative stimuli ($t(13) = -.54, p = .60$), participants with WS were significantly better at identifying positive, as compared to negative, stimuli ($t(16) = 3.32, p = .004$).

DISCUSSION

The aim of the current study was to examine perceptual asymmetries for the processing of positive and negative affective vocalizations in individuals with WS. We also evaluated receptive affect processing abilities across positively and negatively valenced stimuli. We hypothesized that individuals with WS would show weaker perceptual asymmetries relative to the TD group. In addition, we hypothesized to observe valence-specific effects such that more marked between-group differences would be apparent with the negative, as compared to the positive stimuli (cf. Haas et al., 2009; Meyer-Lindenberg et al., 2005). As we had predicted, individuals with WS displayed a less pronounced perceptual asymmetry for the negative stimuli as compared to controls, but a similar pattern of perceptual processing as controls for positive stimuli. Consistent with our hypotheses, TD controls exhibited a LE advantage for the processing of negative sounds presented to the RH. In contrast, surprisingly, those with WS showed a RE advantage, implicating LH activation. Individuals with WS also showed poorer accuracy in identifying negative non-linguistic stimuli, while no between-group differences emerged for the positive stimuli. Taken together, the current findings highlight first known evidence within the auditory domain of significantly more aberrant processing of negative, as compared to positive, social auditory stimuli in individuals with WS, which may be linked to the atypical neurobiological characteristics (e.g., Haas et al., 2009; Holinger et al., 2005; Meyer-Lindenberg et al., 2005; Reiss, Eckert, Rose, Karchemskiy, Kesler, Chang, Reynolds, Kwon, & Galaburda, 2004). Evidence from a small group of DD participants, whose data were excluded from the statistical analyses, suggested that the pattern observed for the WS group was not accountable by intellectual impairment alone. This was supported by a correlational analysis between the IQ measures and experimental variables.

The surprising finding that individuals with WS demonstrated a RE advantage for negative stimuli presented to the RH may be linked to the evidence indicating diminished neural activity to negative visual social stimuli (Haas et al., 2009; Meyer-Lindenberg et al., 2005). The current pattern implicated the activation of the LH anterior system, which reflects an ipsilateral pathway, linked to the processing approach-related positive emotions. It may thus be that the negative stimuli failed to activate the RH anterior affect processing system in individuals with WS, which may manifest as attenuated neural activity as measured by ERPs and fMRI (Haas et al., 2009). Consistent with the data from the controls, a LE advantage was predicted for this condition, as the RH anterior system is associated with processing of avoidance-related negative experience. As the perceptual asymmetries for the positive stimuli were similar between individuals with WS and TD, this may suggest that the hemispheric organization for the positive LH-associated processes as compared to negative RH-associated processes is relatively less affected in WS. In light of the neurobiological data indicating significantly increased neural activity to positive social stimuli in individuals with WS (Haas et al., 2009), it may thus be that such enhanced neural processing was reflected in the current results by greater behavioral accuracy in identifying positive as compared to negative non-linguistic sounds, and a relatively strong perceptual asymmetry specifically for the LH-associated positive emotional processes. However, the specific laterality effects reported by Haas et al. (2009) indicated that while participants with WS exhibited significant right amygdala activity to positive expressions, no laterality effects were observed for the controls. Whereas no laterality effects were evident for negative stimuli in the WS group, the controls displayed significantly greater right amygdala reactivity. Taken together with the current findings, the pattern of data from the TD controls indicating LE advantage for negative stimuli is consistent with that of Haas et al. (2009), showing significant right amygdala activity for such stimuli. The apparent discrepancies between the laterality effects found in the current study and those reported by Haas et al. (2009) may be due to the fact that in the latter study, only amygdala reactivity was measured while activation in the other neural structures implicated in the processing of emotion were ignored. Further, the emotions included by Haas et al. (2009) were

happy and fearful, of which the latter in particular has been linked to amygdala activation (Adolphs, 2001), while the negative stimuli in the current study included sad, angry, and fearful vocalizations. Finally, the stimuli utilized by Haas et al. (2009) were visual, while the current study used auditory material. It is also noteworthy that there is some controversy in the literature concerning the model of emotion as used for the framework for the current study, specifically with regard to the anterior/posterior divide (Murphy, Nimmo-Smith, & Lawrence, 2003; Wager, Phan, Liberzon, & Taylor, 2003; see also Barrett & Wager, 2006). More neuroimaging studies are needed to better understand the brain bases of processing positive versus negative emotion. At the same time, the current framework is consistent with those used in the existing DL literature (e.g., Pollak et al., 2004).

It is also important to consider the atypical auditory sensitivity in individuals with WS in context of the current findings. Interestingly, Marler and colleagues reported an incidence of 70–77% of mild sensorineural hearing loss in the higher frequencies (6000–8000 Hz) in their sample of individuals with WS (Marler, Elfenbein, Ryals, Urban, & Netzloff, 2005). However, a standard hearing test up to 8000 Hz was carried out as screening procedure in the current study, and all participants tested were deemed as functioning within the normal range. In the context of the Marler et al. (2005) study, the current pattern of results indicating more aberrant processing of negative than positive sounds in individuals with WS may appear surprising, as the processing of positive stimuli may have been expected to be more affected. This is because the positive stimuli (e.g., laughs and giggles) were of higher frequency in general as compared to the negative (e.g., grunts and groans) sounds.

As the differential hemispheric processing advantages are based upon differences in temporal resolution, one possibility is that the RH specialization is more aberrant in comparison to the LH specialization in individuals with WS. The LH is specialized for temporal information, and thus is well equipped for processing rapidly changing information such as speech. By contrast, the RH operates at a lower temporal resolution and is specialized in spectral processing, such as pitch (Schirmer & Kotz, 2006). In fact, investigations into musical pitch processing in individuals with WS indicate deficits in musical pitch discrimination (e.g., Don, Schellenberg, & Rourke, 1999; Deruelle, Schön, Rondan, & Mancini, 2005; Hopyan, Dennis, Weksberg, & Cytrynbaum, 2001). Thus, it is possible that these impairments may also contribute to a greater LH involvement than is typical in negative vocal affect processing in this population. A second possibility is that the perceptual processing differences reflect differences in developmental maturity of the RH (Pollak et al., 2004). On this view, the condition in which negative stimuli were presented to the RH was predicted to lead to a computational overload, resulting in increased LH involvement in child participants. Other studies utilizing more complex stimuli, such as linguistic prosody, have shown that activation of multiple specialized systems within the same hemisphere may also result in a processing advantage for the opposite hemisphere, or in bilateral processing (e.g., Banich & Belger, 1990; Pollak & Wismer Fries, 2001; Mitchell, 2006). However, as affective prosody is commonly examined within the linguistic context, the processing of such stimuli including both affective content linked to RH processes, and linguistic content associated with LH processes, would inevitably result in more bilateral processing than would be the case for non-linguistic emotion. However, the current stimuli only carried affective information in the absence of linguistic content.

Given that the majority of neuroimaging studies of individuals with WS to date have involved visual stimuli, studies examining the processing of emotion in music may provide further clues for the neuroanatomical localization of the current findings. For example, a small-scale fMRI study investigated the neural correlates of auditory processing in adults with WS and five TD controls using music and noise stimuli (Levitin, Menon, Schmitt, Eliez, White, Glover, Kadis, Korenberg, Bellugi, & Reiss, 2003). The results highlighted atypical neural activation to music in the participants with WS: while the STG and middle temporal gyri showed more activation

in response to music than to noise in controls, the only region associated with greater activity during music versus noise processing in the WS group was the right amygdala. However, as activation patterns were not analyzed by emotion, it is difficult to consolidate these findings with those from the current experiment. Nevertheless, this finding may be linked to the notion that RH dominance is linked functions that are of specific importance for processing socially relevant information (Bowers, Bauer, & Heilman, 1993), and/or to the notion that the amygdala has been suggested to activate in order to enhance the perception of emotionally salient information (Anderson, Adam, Phelps, & Elizabeth, 2001), as both social and emotional functions have been suggested to be increased in individuals with WS. Indeed, findings from a case study of a patient S.M. with complete bilateral amygdala damage have indicated that amygdala plays a necessary role specifically in the processing of fearful emotion in music (Gosselin, Peretz, Johnsen, & Adolphs, 2006). However, at the same time, S.M. shows unaffected processing of affective prosody; stimuli most similar to those used in the current experiment. The current finding of particularly aberrant perceptual asymmetry for negative auditory information in individuals with WS may thus have implications for the abnormal amygdala structure and function, as discussed above (e.g., Haas et al., 2009; Levitin et al., 2003; Reiss et al., 2004). For example, the amygdala may have atypically extensive connections to the auditory cortex (cf. Holinger et al., 2005).

In the context of the clinical presentation of WS, the current findings of relatively preserved processing of positive affect coupled with atypical processing of negative affect suggest that the well-documented receptive affect processing impairments (e.g., Plesa-Skwerer et al., 2006) and hypersociability (e.g., Järvinen-Pasley et al., 2008) may at least partially stem from deficits in detecting negative affective states, within both the visual and auditory domains. Indeed, a failure to process negative signals in the context of social interaction may result in both socially inappropriate and overly social behavior, both of which are characteristics of WS. However, further studies are needed to establish the processing of both linguistic and non-linguistic auditory aspects of social interaction in this population. Limitations of the current study include the small size of the DD comparison group; however, the performance profile of these participants as well as data from child participants reported by Pollak et al. (2004) suggest that the processing pattern of individuals with WS was markedly different from these groups.

In conclusion, the current study provided first known evidence on the processing of auditory aspects of social interaction in individuals with WS. Specifically, present results extend the existing literature on WS by providing initial evidence of atypical processing of negative affect within the auditory domain. The results implicated a reduced RH involvement in the processing of negative affective vocalizations in these individuals, as well as behavioral identification deficits in the processing of such stimuli. The pattern of results fits in well with current neurobiological evidence from the visual domain indicating attenuated neural activity to negative, and increased neural activity to positive, social stimuli in individuals with WS, relative to TD controls (Haas et al., 2009; Meyer-Lindenberg et al., 2005). Future research should be directed towards further elucidating the neural correlates of auditory affect processing in individuals with WS. These questions aimed at illuminating the complex neurobiology underlying the aberrant, albeit highly intriguing, profile of social functioning in WS would be ideally addressed experimentally using fMRI.

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REFERENCES

- Adolphs R. Cognitive neuroscience of human social behavior. *Nature Reviews Neuroscience* 2003;165–178.
- Amaral, DG.; Price, JL.; Pitkänen, A.; Carmichael, ST. Anatomical organization of the primate amygdaloid complex. In: Aggleton, JP., editor. *The amygdala: Neurobiological aspects of emotion, memory and mental dysfunction*. New York: Wiley; 1992. p. 1-66.
- Anderson AK, Adam K, Phelps EA, Elizabeth A. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Letters to Nature* 2001;41:17.
- Atkinson J, Braddick O, Anker S, Curran W, Andrew R, Wattam-Bell J, Braddick F. Neurobiological models of visuospatial cognition in children with Williams syndrome: measures of dorsal-stream and frontal function. *Developmental Neuropsychology* 2003;23:139–172. [PubMed: 12730023]
- Banich MT, Belger A. Interhemispheric interaction: how do the hemispheres divide and conquer a task? *Cortex* 1990;26:77–94. [PubMed: 2354647]
- Barr, RG.; Hopkins, B.; Greene, JA. *Crying as a sign, a symptom, and a signal*. New York, NY: Cambridge University Press; 2000.
- Bellugi U, Lichtenberger L, Jones W, Lai Z, St. George M. The neurocognitive profile of Williams syndrome: A complex pattern of strengths and weaknesses. *Journal of Cognitive Neuroscience* 2000;12:7–29. [PubMed: 10953231]
- Bowers D, Bauer RM, Heilman KM. The nonverbal affect lexicon: Theoretical perspectives from neuropsychological studies of affect perception. *Neuropsychology* 1993;7:433–444.
- Bryden, MP. An overview of the dichotic listening procedure and its relation to hemispheric organization. In: Hugdahl, K., editor. *Handbook of Dichotic Listening: Theory, methods, and research*. Oxford, England: John Wiley & Sons; 1988. p. 1-43.
- Chapman LJ, Chapman JP. Artfactual and genuine relationships of lateral difference scores to overall accuracy in studies of laterality. *Psychological Bulletin* 1988;104:127–136. [PubMed: 3043525]
- Cohen JD, MacWhinney B, Flatt M, Provost J. PsyScope: A new graphic interactive environment for designing psychology experiments. *Behavioral Research Methods, Instruments, and Computers* 1993;25:257–271.
- Davidson RJ. What does the prefrontal cortex "do" in affect: perspectives on frontal EEG asymmetry research. *Biological Psychology* 2004;67:219–233. [PubMed: 15130532]
- Davidson RJ, Hugdahl K. Baseline asymmetries in brain electrical activity predict dichotic listening performance. *Neuropsychology* 1996;10:241–246.
- Deruelle C, Schön D, Rondan C, Mancini J. Global and local music perception in children with Williams syndrome. *Neuroreport* 2005;16:631–634. [PubMed: 15812322]
- Don A, Schellenberg EG, Rourke BP. Music and language skills of children with Williams syndrome. *Child Neuropsychology* 1999;5:154–170.
- Dykens EM, Rosner BA, Ly T, Sagun J. Music and anxiety in Williams syndrome: a harmonious or discordant relationship? *American Journal of Mental Retardation* 2005;110:346–358. [PubMed: 16080773]
- Eckert MA, Galaburda AM, Karchemskiy A, Liang A, Thompson P, Dutton RA, Lee AD, Bellugi U, Korenberg JR, Mills D, Rose FE, Reiss AL. Anomalous sylvian fissure morphology in Williams syndrome. *NeuroImage* 2006;33:39–45. [PubMed: 16876437]
- Ewart AK, Morris CA, Atkinson D, Jin W, Sternes K, Spallone P, Stock AD, Leppert M, Keating MT. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nature Genetics* 1993;5:11–16. [PubMed: 7693128]
- Barrett LF, Wager TD. The structure of emotion: evidence from neuroimaging studies. *Current Directions in Psychological Science* 2006;15:79–83.
- Gosselin N, Peretz I, Johnson E, Adolphs R. Amygdala damage impairs emotion recognition from music. *Neuropsychologia* 2007;45:236–244. [PubMed: 16970965]
- Gothelf D, Farber N, Raveh E, Apter A, Attias J. Hyperacusis in Williams syndrome: characteristics and associated neuroaudiologic abnormalities. *Neurology* 2006;66:390–395. [PubMed: 16476938]

- Gothelf D, Searcy YM, Reilly J, Lai PT, Lanre-Amos T, Mills D, Korenberg JR, Galaburda A, Bellugi U, Reiss AL. Association between cerebral shape and social use of language in Williams syndrome. *American Journal of Medical Genetics A* 2008;146A:2753–2761.
- Grouios G, Sakadami N, Poderi A, Alevriadou A. Excess of non-right handedness among individuals with intellectual disability: experimental evidence and possible explanations. *Journal of Intellectual Disability Research* 1999;43:306–313. [PubMed: 10466869]
- Haas BW, Mills D, Yam A, Hoeft F, Bellugi U, Reiss A. Genetic influences on sociability: Heightened amygdala reactivity and event-related responses to positive social stimuli in Williams syndrome. *Journal of Neuroscience* 2009;29:1132–1139. [PubMed: 19176822]
- Holinger DP, Bellugi U, Mills DM, Korenberg JR, Reiss AL, Sherman GF, Galaburda AM. Relative sparing of primary auditory cortex in Williams syndrome. *Brain Research* 2005;1037:35–42. [PubMed: 15777750]
- Hopyan T, Dennis M, Weksberg R, Cytrynbaum C. Music skills and the expressive interpretation of music in children with Williams-Beuren syndrome: pitch, rhythm, melodic imagery, phrasing, and musical affect. *Child Neuropsychology* 2001;7:42–53. [PubMed: 11815880]
- Howlin P, Davies M, Udwin O. Cognitive functioning in adults with Williams syndrome. *Journal of Child Psychology and Psychiatry* 1998;39:183–189. [PubMed: 9669231]
- Hugdahl K. Lateralization of cognitive processes in the brain. *Acta Psychologica* 2000;105:211–235. [PubMed: 11194413]
- Järvinen-Pasley A, Bellugi U, Reilly J, Mills DL, Galaburda A, Reiss AL, Korenberg JR. Defining the social phenotype in Williams syndrome: A model for linking gene, brain, and cognition. *Development and Psychopathology* 2008;20:1–35. [PubMed: 18211726]
- Kimura D. Cerebral dominance and the perception of verbal stimuli. *Canadian Journal of Psychology* 1961;15:166–171.
- Korenberg JR, Chen X-N, Hirota H, Lai Z, Bellugi U, Burian D, Roe B, Matsuoka R. VI. Genome structure and cognitive map of Williams syndrome. *Journal of Cognitive Neuroscience* 2000;12:89–107. [PubMed: 10953236]
- Kreiman, J. Listening to voices: theory and practice in voice perception research. In: Johnson, K.; Mullenix, J., editors. *Talker variability in speech research*. New York, NY: Academic Press; 1997. p. 85-108.
- Levitin DJ, Menon V, Schmitt JE, Eliez S, White CD, Glover GH, Kadis J, Korenberg JR, Bellugi U, Reiss AL. Neural correlates of auditory perception in Williams syndrome: an fMRI study. *Neuroimage* 2003;18:74–82. [PubMed: 12507445]
- Levitin DJ, Cole K, Chiles M, Lai Z, Lincoln A, Bellugi U. Characterizing the musical phenotype in individuals with Williams Syndrome. *Child Neuropsychology* 2005a;104:223–247.
- Levitin DJ, Cole K, Lincoln A, Bellugi U. Aversion, awareness, and attraction: investigating claims of hyperacusis in the Williams syndrome phenotype. *Journal of Child Psychology and Psychiatry* 2005b; 46:514–523. [PubMed: 15845131]
- Marler JA, Elfenbein JL, Ryals BM, Urban Z, Netzloff ML. Sensorineural hearing loss in children and adults with Williams syndrome. *American Journal of Medical Genetics A* 2005;138:318–327.
- Martens MA, Wilson SJ, Reuters DC. Research Review: Williams syndrome: A critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry* 2008;49:576–608. [PubMed: 18489677]
- Meyer-Lindenberg A, Hariri AR, Munoz KE, Mervis CB, Mattay VS, Morris CA, Berman KF. Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nature Neuroscience* 2005;8:991–993.
- Meyer-Lindenberg A, Mervis CB, Berman KF. Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nature Reviews Neuroscience* 2006;7:380–393.
- Mitchell RC. How does the brain mediate interpretation of incongruent auditory conditions? The neural responses to prosody in the presence of conflicting lexico-semantic cues. *European Journal of Neuroscience* 2006;24:3611–3618. [PubMed: 17229109]
- Murphy FC, Nimmo-Smith I, Lawrence AD. Functional neuroanatomy of emotion: A meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience* 2003;3:207–233.

- Nowicki S Jr, Duke MP. Individual differences in the nonverbal communication of affect: The Diagnostic Analysis of Nonverbal Accuracy Scale. *Journal of Nonverbal Behavior* 1994;18:9–35.
- Plesa-Skwerer D, Faja S, Schofield C, Verbalis A, Tager-Flusberg H. Perceiving facial and vocal expressions of emotion in individuals with Williams syndrome. *American Journal of Mental Retardation* 2006;111:15–26. [PubMed: 16332153]
- Pollak SD, Wismer Fries AB. Perceptual asymmetries reflect developmental changes in the neuropsychological mechanisms of emotion perception. *Emotion* 2001;1:84–98. [PubMed: 12894813]
- Pollak SD, Holt LL, Wismer Fries AB. Hemispheric asymmetries in children's perception of nonlinguistic human affective sounds. *Developmental Science* 2004;7:10–18. [PubMed: 15323113]
- Reilly J, Losh M, Bellugi U, Wulfeck B. Frog, where are you? Narratives in children with specific language impairment, early focal brain injury, and Williams syndrome. *Brain and Language* 2004;88 (Special Issue):229–247. [PubMed: 14965544]
- Reiss AL, Eckert MA, Rose FE, Karchemskiy A, Kesler S, Chang M, Reynolds MF, Kwon H, Galaburda A. An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. *Journal of Neuroscience* 2004;24:5009–5015. [PubMed: 15163693]
- Schirmer A, Kotz SA. Beyond the right hemisphere: brain mechanisms mediating vocal emotional processing. *Trends in Cognitive Sciences* 2006;10:24–30. [PubMed: 16321562]
- Setter J, Stojanovic V, Van Ewijk L, Moreland M. Affective prosody in Williams syndrome. *Clinical Linguistics & Phonetics* 2007;21:659–672. [PubMed: 17701754]
- Searcy YM, Lincoln AJ, Rose FE, Klima ES, Bavar N, Korenberg JR. The relationship between age and IQ in adults with Williams syndrome. *American Journal of Mental Retardation* 2004;109:231–236. [PubMed: 15072519]
- Voyer D, Flight J. Reliability and magnitude of auditory laterality effects: The influence of attention. *Brain and Cognition* 2001;46:397–413. [PubMed: 11487289]
- Wager TD, Phan KL, Liberzon I, Taylor SF. Valence, gender, and lateralization of functional neuroanatomy in emotion: A meta-analysis of findings from neuroimaging. *Neuroimage* 2003;19:513–531. [PubMed: 12880784]
- Wechsler, D. San Antonio, TX: Psychological Corporation; 1997. Wechsler Adult Intelligence Scale – Third Edition (WAIS-III).
- Wechsler, D. San Antonio, TX: Psychological Corporation; 1999. Wechsler Abbreviated Scale of Intelligence.

Figure 1.

Mean f-index values for participants with WS, TD, and DD across the negative and positive affective stimuli and ear of presentation (LE/RH and RE/LH). Negative f-index values indicate an LEA, whereas positive f-index values indicate a REA (Error bars represent ± 1 standard error mean (SEM)).

Figure 2. Accuracy of participants' ability to identify the binaurally presented individual negative and positive non-linguistic affective sounds used in the DL experiment (Error bars represent ± 1 SEM).

Table 1

Mean characteristics of the three participant groups (SD; range in parentheses)

	CA (SD; range)	VIQ (SD; range)	PIQ (SD; range)
WS (n=18)	27.8 (7.4; 18–42)	71 (9.5; 55–91)	62 (8.1; 44–78)
TD (n=18)	27.7 (9.1; 19–49)	108 (11.8; 88–139)	105 (13.9; 87–125)
DD (n=5)	24.1 (4.4; 21–31)	62 (6.3; 55–70)	57 (4.3; 53–62)

Table 2

Asymmetry values for DL experiment by affect and stimulus conditions, for individuals with WS, TD (in parentheses), and DD (italics).

Stimulus condition	% RE identification	% LE identification	Error	f-index
Negative to LE/RH	.44 (.30) .27	.36 (.69) .53	0.20 (.01) .20	.19* (−.38*) −.40
Negative to RE/LH	.40 (.62) .45	.35 (.35) .32	0.25 (.03) .23	.11 (.32*) .25
Positive to LE/RH	.20 (.30) .27	.59 (.67) .60	0.21 (.03) .13	−.34* (−.37*) −.30
Positive to RE/LH	.60 (.67) .48	.21 (.29) .37	0.19 (.04) .15	.42* (.32*) .11

* denotes difference from zero is significant at $p < .05$;

LE = left ear; RE = right ear; LH = left hemisphere; RH = right hemisphere