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Neural Correlates of Auditory Perception in Williams Syndrome: An fMRI Study

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Williams syndrome (WS), a neurogenetic developmental disorder, is characterized by a rare fractionation of higher cortical functioning: selective preservation of certain complex faculties (language, music, face processing, and sociability) in contrast to marked and severe deficits in nearly every other cognitive domain (reasoning, spatial ability, motor coordination, arithmetic, problem solving). WS people are also known to suffer from hyperacusis and to experience heightened emotional reactions to music and certain classes of noise. We used functional magnetic resonance imaging to examine the neural basis of auditory processing of music and noise in WS patients and age-matched controls and found strikingly different patterns of neural organization between the groups. Those regions supporting music and noise processing in normal subjects were found not to be consistently activated in the WS participants (e.g., superior temporal and middle temporal gyri). Instead, the WS participants showed significantly reduced activation in the temporal lobes coupled with significantly greater activation in the right amygdala. In addition, WS participants (but not controls) showed a widely distributed network of activation in cortical and subcortical structures, including the brain stem, during music processing. Taken together with previous ERP and cytoarchitectonic studies, this first published report of WS using fMRI provides additional evidence of a different neurofunctional organization in WS people than normal people, which may help to explain their atypical reactions to sound. These results constitute an important first step in drawing out the links between genes, brain, cognition, and behavior in Williams syndrome. © 2002 Elsevier Science (USA)

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INTRODUCTION

Williams syndrome (WS) is a neurogenetic developmental disorder affecting some 1 in 20,000 people and presents one of the most compelling models of the relation between genes and human cognition. Individuals with WS exhibit a distinctive profile of cognitive abilities and disabilities (Bellugi *et al.,* 2000; Mervis, 1999). Specifically, WS is characterized by low IQ, ranging from 40 to 100 (mean ~ 60, SD 11; Bellugi *et al.,* 2000; Karmiloff-Smith, 1998; Mervis, 1999) with severe deficits in conceptual reasoning, problem solving, motor control, arithmetic, and spatial cognition (Bellugi *et al.,* 2000; Frangiskakis *et al.,* 1995; Mervis, 1999).

Most intriguing is that WS people present relatively *preserved* abilities in four domains: social drive, face processing, language, and music (Bellugi *et al.,* 2000). Compared to normal people, most people with WS display greater musical creativity, spend more time listening to music and certain noises that they find appealing (Levitin and Bellugi, 1999), and show stronger emotional reactions to music (Don *et al.,* 1999). Individuals with WS are not especially skillful musicians in general, but their ability to play musical instruments is quite remarkable given their general cognitive and motor impairments. Genetically, WS is defined by the hemizygous deletion of approximately 17–19 genes on chromosome 7 (band 7q11.23) between the polymorphic markers D7S1816 and D7S489B (Francke, 1999), including the gene for elastin and representing 1.6–2 million missing base pairs (Francke, 1999; Frangiskakis *et al.,* 1995). It is believed that the loss of this genetic material causes neurodevelopmental abnormalities that in turn result in this fractionation of mental abilities. Because the deletion is known in WS, and the cognitive manifestations are relatively well defined among members of the group, WS presents a unique opportunity to uncover the neurobiologic basis of complex cognitive behaviors.

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People with the WS phenotype are characterized by their exceptional receptivity to music and certain classes of noise (Levitin and Bellugi, 1999). Numerous anecdotes tell of children with WS who sit for hours entranced by music, or by the sounds of leaf blowers, automobile engines, or other noises, and who appear to derive as much pleasure and fascination from these sounds as they do from music (Lenhoff *et al.,* 1997; Levitin *et al.,* 2002). Most WS individuals also suffer from *hyperacusis* (lowered hearing thresholds) and *auditory allodynia,* a fear of sounds that others do not find fearful (Levitin *et al.,* 2002a,b). It is important to distinguish the symptoms of hyperacusis in WS—an aversion to *loud* sounds—from their attraction to a class of sounds that is best described as broad band or filtered noise. The present functional brain imaging study was conducted to learn more about the neural basis of WS participants' interest in both music and noise. We hypothesized that we would find clear differences in the functional neuroanatomy of auditory processing in WS persons versus normal controls.

ERP studies have suggested that auditory processing in individuals with WS might be (1) characterized by neural hyperexcitability and (2) carried out by different neural systems than in normal people (Bellugi *et al.,* 1989, 1992; Neville *et al.,* 1989, 1994). The present work is the first known study employing functional magnetic neuroimaging in individuals with Williams. Their hyperacusis and fear of loud sounds such as those present in functional magnetic resonance imaging (fMRI) research has previously made such work impossible. To address this, we developed a systematic orientation program for persons with WS that includes a professionally produced video introduction to the procedure, samples of the scanner noises participants will encounter during the session, and an fMRI simulator. This program has successfully reduced their fear and apprehension, allowing scanning to take place.

Music and Noise in WS with fMRI

The logic of our experimental design was as follows. Previous studies have shown that particular cortical regions are associated with distinguishing music and noise in normal populations (Mirz *et al.,* 1999; Zatorre *et al.,* 1994). We played music and noise stimuli to our participants while they listened in the scanner with focused attention and compared these two conditions to each other and to a resting baseline using a standard neuroimaging subtraction procedure (Posner *et al.,* 1988). The functional neuroanatomic components related to acoustic processing, working memory, and attention were thus equivalent across experimental blocks and so any neural activity related to these components is cancelled out by the comparisons.

For normal subjects, we expected that music compared to noise processing would reveal bilateral focal activations in the superior temporal gyrus (STG) and middle temporal gyrus (MTG), regions previously shown to be associated with music processing. For WS participants, in contrast, we expected to find either different loci of activation or more diffuse cortical activation, based on our interpretation of both ERP (Bellugi *et al.,* 1992; Neville *et al.,* 1994) and cytoarchitectonic evidence (Galaburda *et al.,* 1994) of abnormal neural organization in WS. We also expected to find differences between groups in an area associated with emotional processing of music, the amygdala (Blood *et al.,* 1999; Gottselig, 2000; LeDoux, 1995), in accordance with the heightened emotional response to music associated with the WS phenotype. It is important to note that behaviorally, individuals with WS are perfectly capable of distinguishing musical pieces from one another, noises from one another, and music from noise in a manner similar to (and sometimes better than) controls (Levitin and Bellugi, 1999). It is their *polarized affect*—attraction or aversion—to certain sounds that is characteristic of their phenotype (Levitin *et al.,* 2002a).

MATERIALS AND METHODS

Participants

Five participants with WS were recruited for imaging at Stanford University (two men and three women, all right-handed; mean age 28.8 years; SD 14.6 years). All participants had been diagnosed with medical genetic testing (fluorescent *in situ* hybridization) that revealed the absence of one copy of the gene for elastin on chromosome 7, and all exhibited the associated medical and clinical phenotype including cognitive, behavioral, and physical profiles normally associated with WS (Hagerman, 1999; Hovis and Butler, 1997). Mean full-scale IQ of our sample was 63.0 (SD 17.2). The participants (and as appropriate, their guardians) gave informed consent prior to the experiment, and the protocol was approved by the Stanford University School of Medicine Human Subjects Committee. Control participants were individually matched for chronological age, handedness, gender, and musical experience.[1]

Stimuli

The stimuli for the experiment were digitized sound files taken from compact disk recordings of standard pieces in the classical repertoire. The first 23 seconds of the following pieces were used: J. S. Bach, *Jesu, Joy of Man's Desiring* and

[1] We matched for chronological age rather than mental age for four reasons. First, previous work has shown that the musical abilities of individuals with WS are commensurate with those of chronological age-matched normal IQ controls (Levitin and Bellugi, 1999, 2001). Second, control participants who are matched on IQ (e.g., individuals with Down syndrome or others with nonspecific mental retardation) generally have musical skills that are very much inferior to those of WS people and thus they do not make for a satisfactory comparison group; most individuals with Down syndrome we have tested are unable to understand the test or listening instructions. Third, full-scale IQ estimates in the case of individuals with WS are problematic, owing to the unusual cognitive fractionation of abilities; taking the average of subtests that vary widely (e.g., a high expressive verbal score and a low analytical reasoning score) is not a valid psychometric approach to IQ estimation as it tends to underestimate the operational IQ for music and verbal tasks such as those employed here. Finally, there is an emerging body of literature comparing WS individuals to chronologically age-matched normal controls on a variety of cognitive tasks (Bellugi *et al.,* 2000; Don *et al.,* 1999), and we believe that there is value in being able to integrate the present findings with those in the literature.

Sicilienne; Beethoven, *Fifth Symphony* and *First Symphony;* Mozart, *Eine Kleine Nachtmusic;* Strauss, *Blue Danube* and *Wine, Women, and Song;* and Tchaikovsky, *March from the Nutcracker Suite* and *First Symphony.* Noise samples were taken from sound effects compact disks and included the types of sounds in which individuals with WS are typically interested (Levitin *et al.,* 2002a), including water running, broad-band filtered noise, sounds recorded at a construction site, noise from motors, and a telephone dial tone. Participants listened to the sounds at a comfortable listening level over headphones employing an fMRI-compatible pneumatic delivery system. Pilot testing with a separate group of six participants established that the stimuli were equally matched for loudness.

Experimental Design

Twenty-three epochs of 23 s each were randomly presented: 10 epochs each of music and noise and three baseline "silent" epochs.

fMRI Acquisition

Structural and functional images were acquired in the same session on a 1.5-T GE Signa scanner with echospeed gradients using a custom-built whole head coil with an integral head holder to prevent head movement. Eighteen axial slices (6 mm thick, 1 mm skip) were imaged with a temporal resolution of 2 s. The field of view was 240 mm, and the effective in-plane spatial resolution was 3.75 mm. Further details are provided in Adleman *et al.* (2002) and Kwon *et al.* (2001).

Image Preprocessing

Images were reconstructed by inverse Fourier transform, for each of the 225 time points into $64 \times 64 \times 18$ image matrices (voxel size $3.75 \times 3.75 \times 7$ mm). fMRI data were preprocessed using SPM99 (Friston, 1999). Although the head coil dramatically reduces movement, we also employed motion correction. We analyzed the displacement values (six altogether: the three axes of rotation and three axes of translation) for the average displacement from the mean during the functional scan for each subjects and found no significant difference in displacement values between the controls and the WS participants ($P = 0.16$). Nevertheless, all images were corrected for movement using least square minimization without higher-order corrections for spin history and normalized to stereotaxic Talairach coordinates. Images were then resampled every 2 mm using sync interpolation and smoothed with a 4-mm Gaussian kernel to decrease spatial noise. The image coregistration reduced displacement of the images from the mean so that the final values were not significantly different from 0 displacement (by t test, $P = 0.2$).

Statistical Analysis

The individual anatomic data set for each participant was used to overlie the functional images. Statistical analysis was performed on individual and group data using the general linear model and the theory of Gaussian random fields as implemented in SPM99 (Friston *et al.,* 1995; Friston, 1999) [see Adleman *et al.* (2002) and Kwon *et al.* (2001) for additional details].

A within-subjects procedure was used to model all the effects of interest for each participant. Individual subject models were identical across participants (i.e., a balanced design was used). For each participant, voxelwise t statistics during each of the contrasts of interest were determined using multivariate regression analysis (Friston *et al.,* 1995; Friston, 1999). Finally, the t statistics were normalized to Z scores, and significant clusters of activation were determined using the joint expected probability distribution of height and extent thresholds ($Z > 1.67$, $P < 0.05$). Activation maps were determined for the following comparisons: (1) Music minus Noise, (2) Music minus Rest, and (3) Noise minus Rest (where "Rest" refers to the silent baseline condition). For tests of intergroup differences, we did not use parametric tests since the small number of subjects per group would render such tests invalid (due to insufficient degrees of freedom), so we instead tested intergroup differences with the nonparametric Mann-Whitney U test (see, for example, Kuehl, 2000).

We also tested for intergroup differences in overall brain activation patterns, in an effort to confirm previous speculation that auditory processing in WS people might be characterized by wholly different neural circuitry. Such an analysis is especially revealing since it is independent of any a priori theories we might have had about which specific regions might show activation differences. To accomplish this we employed the technique of Bharucha *et al.* (2001) of using multidimensional scaling analysis (Kruskal and Wish, 1990; Shepard, 1980). We first selected those brain regions that showed activation levels of $P < 0.001$ or better for the music and noise conditions combined, compared to rest—this served as a test of acoustic processing versus resting state in the whole brain. The regions thus selected were superior temporal gyrus, middle frontal gyrus, superior frontal gyrus, cerebellum, amygdala, and cingulate gyrus (all bilateral), plus the pons. The data were analyzed using ALSCAL, creating a multidimensional similarity map based on pairwise comparisons of all subjects. The resulting two-dimensional solution represents subjects who are similar on all 13 dimensions (or parameters) in spatially proximal positions on the resulting plot, as an easy way to visualize any intergroup differences that may exist.

RESULTS

Our analyses were aimed at addressing any functional neuroanatomic differences between the two groups of subjects, individuals with WS and normal, age-matched controls. We sought to address three hypothesis-driven questions: what if any differences in activation exist in the brain as a whole and in subregions of the temporal lobe and the amygdala?

Preliminary Analyses

We examined brain activations for the difference between music processing and noise processing (the *Music minus Noise* or M − N condition). To clarify these findings, we

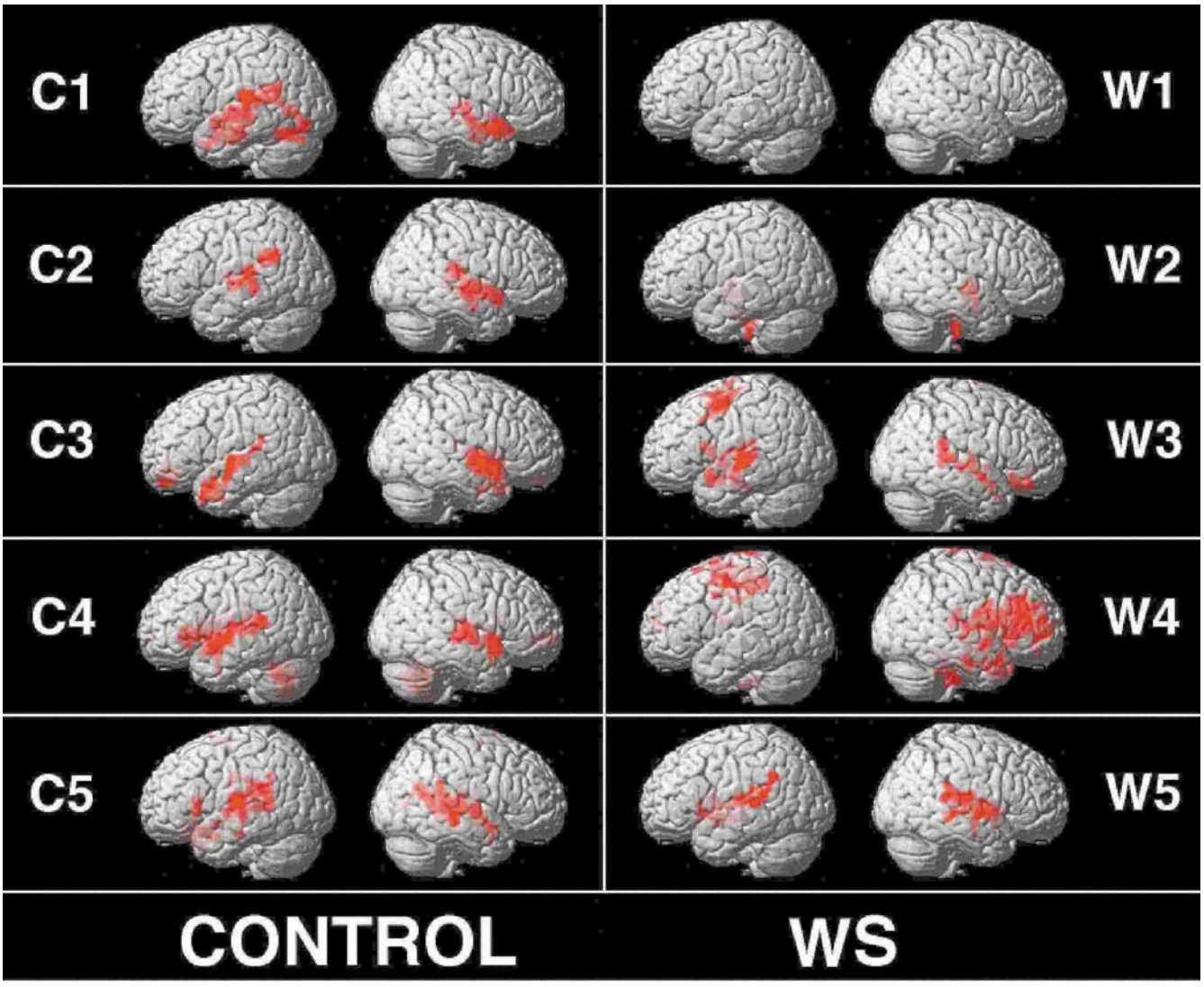

FIG. 1. Left and right lateral views of whole brain activations for five age- and sex-matched typically developing controls (C1–C5) and five participants with Williams syndrome (W1–W5) in the music minus noise (M − N) comparison. Red regions are surface projections of statistically significant clusters of activation at $P < 0.05$. Control participants showed consistent bilateral activation in the superior temporal gyrus and middle temporal gyrus. No WS participant showed significant activation in both of these regions, and other WS activations were more widespread and diffuse, recruiting regions in the amygdala and cerebellum.

looked at two additional conditions, *Music minus Rest* (M − R) and *Noise minus Rest* (N − R), where "Rest" refers to a baseline condition during which no stimuli were presented. One a priori concern in interpreting the results that follow is that individuals with WS and normal individuals may exhibit differential baseline responses. This might occur, for example, if the WS participants found the acoustic properties (similar to pulsed FM modulations) of the spiral pulse sequence used for the fMRI scans during rest and "task" periods similar to the "noise" stimuli used during the task periods. If this were the case, differences between groups in the degree of activation analyses would be driven by differences in the baseline rest condition. To address this issue, we conducted a group comparison of (Noise in WS − Rest in WS) − (Noise in Controls − Rest in controls) and found no significant difference (by t test, $P = 0.6$). This confirms that the baseline activations levels between the groups were similar to begin with.

Whole Brain Analysis

Our most intriguing finding was that the overall pattern of activation in the whole brain was markedly different between the two groups. An analysis of whole brain activation patterns revealed that all five control participants showed consistent and overlapping patterns of activation bilaterally in extended areas of the STG, MTG, and superior temporal sulcus (STS) for the M − N condition, with no other brain regions showing consistent activation among the control participants (Fig. 1). In contrast, the WS participants showed

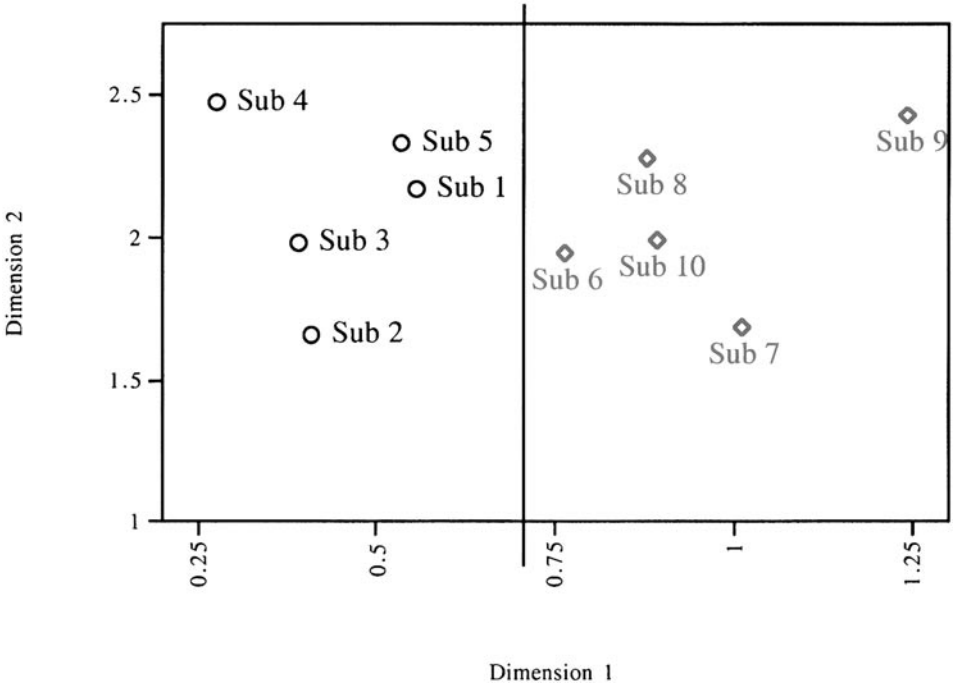

FIG. 2. Multidimensional scaling (MDS) solution in two dimensions illustrating the significant differences in the pattern of brain activation between control (○) and WS (◇) participants. The MDS procedure determined pairwise similarity ratings between subjects assessed on activation levels in thirteen key regions; similarity between subjects is represented as spatial proximities, showing the clear differentiation between the two groups.

substantially decreased activation in these regions, accompanied by more variable patterns of activation throughout the neocortex, and higher activation levels than controls in the paleocortical amygdaloid complex. Unlike the controls, the WS participants showed consistent cerebellar activation as well as activation in the pons and brain stem. In the M − N and M − R conditions, temporal lobe activation levels were also lower for WS participants than controls. The relatively well-defined activation pattern in neocortex among the normal participants, and the relatively dispersed activation in WS participants involving both neo- and paleocortical regions, is the first indication of a different neurofunctional basis for auditory processing between the two groups.

To further establish that strong intergroup differences exist in whole brain activation patterns, we performed a multidimensional scaling analysis (see Methods). This served as a test of acoustic processing versus resting state in the whole brain. In the resulting plot (Fig. 2), subjects with activation patterns that are similar are represented as being spatially proximal, whereas subjects who exhibited different neural activation patterns are proportionally farther apart in the plot. As Fig. 2 clearly shows, the subjects cluster within groups, confirming that WS participants and control participants are readily distinguished on the basis of their brain activations to acoustic stimuli ($r^2 = 0.97$, $P < 0.001$).[2]

[2] The r^2 value reported represents the proportion of variance of the multiple dimensionally scaled data (disparities) in the partition which is accounted for by their corresponding distances in the model.

Temporal Lobes

To address the question of temporal lobe activation, we defined a functional volume of interest (fVOI) localized to the left and right STG and MTG and adjoining STS based on pilot data from our laboratory and prior research (Mirz *et al.*, 1999; Peretz, 1985; Zatorre *et al.*, 1994). In this and the analyses that follow, we examined differences in brain activation between the two groups of participants and between experimental conditions by calculating the average voxel intensity level (AVI).

Both groups of subjects displayed statistically significant activation for music compared to noise (by t test, $P < 0.01$, and as indicated by the Z scores in Fig. 3, which are all greater than 2.33). But we found significantly higher levels of task-related activation in both hemispheres of the fVOI for the control participants compared to the WS participants (left hemisphere, $P < 0.02$; right hemisphere, $P < 0.01$); this is an additional indication that the neurofunctional basis of music versus noise processing is markedly different between the two groups of participants.

The comparatively reduced activation in WS participants for this particular analysis could be interpreted as indicating that music and noise are processed more similarly in WS than they are in controls. To pursue this possibility, we then looked at the Music minus Rest (M − R) and Noise minus Rest (N − R) contrasts (see Fig. 4). These analyses confirm that music and noise stimuli are treated as more similar to one another by WS participants than by control participants.

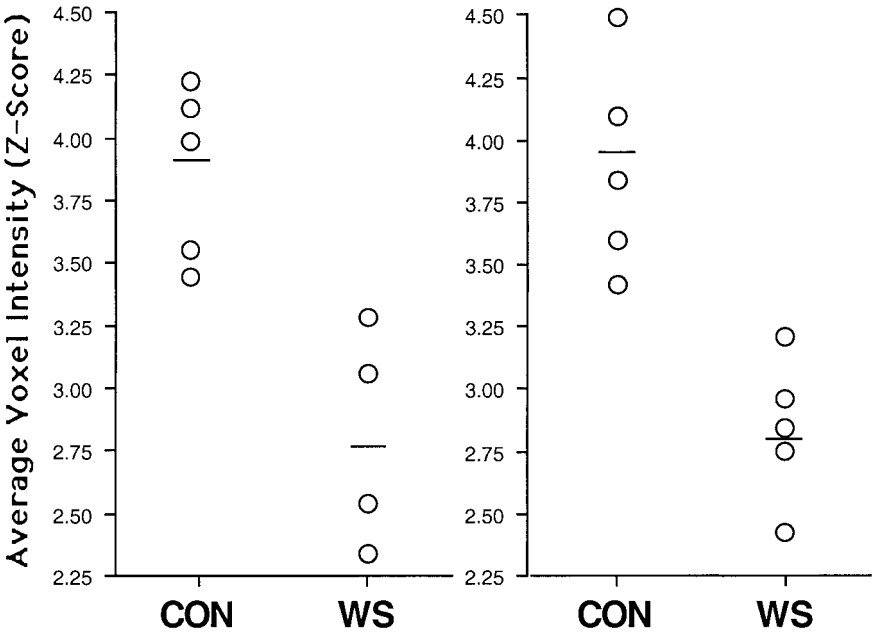

FIG. 3. Results of the music minus noise contrast. Average voxel intensity for control (CON) and WS participants in the functional volume of interest (fVOI) localized around the superior temporal and middle temporal gyri and superior temporal sulcus. Control participants as a group showed significantly higher activations than WS participants in this contrast in both hemispheres. The *y* axis indicates *z* scores; accordingly, all points above 1.67 are statistically significant at $P < 0.05$, and points above 2.33 represent $P < 0.01$. The horizontal bars represent group means within each condition. Left, left fVOI; right, right fVOI.

This is most clearly seen in the interaction between group and condition for the M − R analysis, in which controls reveal significantly greater bilateral activation than WS participants (left hemisphere, $P < 0.01$; right hemisphere, $P < 0.03$). We found no statistically significant difference between the two groups in the N − R condition in this fVOI, nor between the M − R and N − R conditions within the WS group. Taken together, these results point to the neurofunctional correlate of the similar behavioral responses elicited by music and noise for individuals with WS.

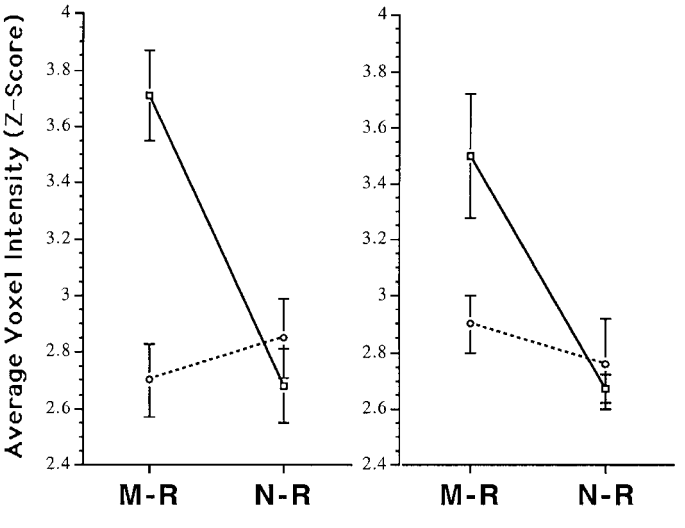

FIG. 4. Average voxel intensity within the fVOI for control (□) and WS (○) participants in the music minus rest (M − R) and noise minus rest (N − R) contrasts. Note the overall higher activation levels for controls (as seen in the previous figure) and the interaction effect of group and condition: WS are apparently unable to modulate neural activity in the temporal cortex in response to music and noise in a manner similar to controls. Axes the same as in Fig. 3. Left, left fVOI; right, right fVOI.

Amygdala

Our third research question concerned activation differences in amygdala (Fig. 5), a region known to be associated with emotional processing in music. For the Music − Noise comparison, we found evidence of significantly greater activation in the *right amygdala* for the WS group than the control group ($P < 0.04$). We found no significant differences in the left hemisphere in this same comparison, nor were there differences in amygdala activation in either hemisphere for the M − R and N − R analyses.

DISCUSSION

WS participants showed significant differences from normal control participants in their neural processing of music and noise stimuli. Both groups displayed significant bilateral temporal lobe activation for music compared to noise and rest, indicating that their music processing can be neuroanatomically distinguished from their noise processing. However, these activations were at significantly lower levels for the WS participants versus the control participants, indicating a different neurofunctional basis for music and noise processing between the groups.

For the control subjects, musical processing was found to occur in particular regions of the temporal lobe (the STG,

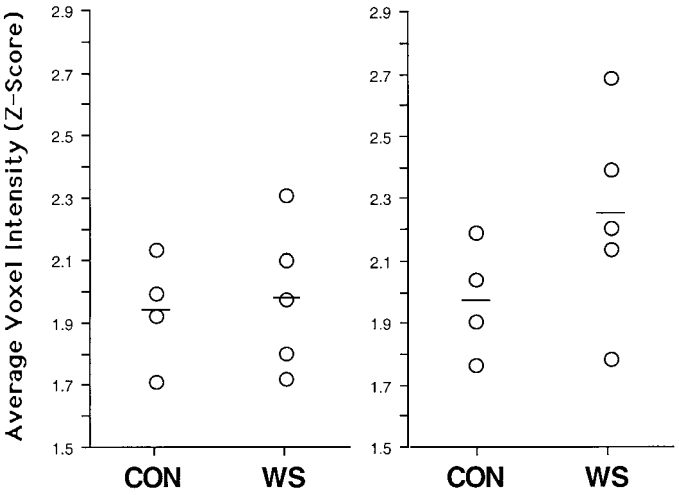

FIG. 5. Average voxel intensity within the amygdala for control (CON) and WS participants in the music minus noise contrast. Note the overall higher activation levels for WS in the right amygdala ($P < 0.04$). Axes the same as in Fig. 3. Left, left amygdala; right, right amygdala.

MTG, and STS) previously associated with music versus noise. In contrast to this, our second major finding was that the WS participants failed to show the type of well-defined and consistent focal activations seen in control participants. WS participants processed music by employing a wider set of neural structures, exhibiting more variable and diffuse activation than control subjects, recruiting subregions of the amygdala, cerebellum, and brain stem. This further suggests that the underlying neural substrates for music and noise processing are different between the two groups. We believe that the additional regions recruited in WS participants form the functional basis for their increased orientation toward acoustic stimuli.

Our findings of amygdala activation in the WS group are interesting in the context of recent findings that the human amygdala triggers socially and emotionally relevant information *in the visual domain* (Adolphs *et al.*, 1998). In this study, patients with bilateral amygdala damage showed abnormal responses to unfamiliar faces with a threatening appearance; the patients tended to rate all faces as friendly and in particular showed a disproportionate impairment in judging negative faces. WS individuals also display this behavior—they are socially outgoing and tend to be utterly unable to judge if a stranger is trustworthy or untrustworthy—acting in these ways like amygdala-damaged patients. The abnormal emotional responses to sound we observe phenotypically in WS appear to correlate with abnormal amygdala activation in the present study. This suggests a larger role for the amygdala in judgments of threatening or unthreatening stimuli. Indeed, we observe here unusual amygdala activation for *auditory stimuli*, in a subject group whose social behavior is consistent with amygdala damage. The precise way in which the amygdala mediates fear and attraction in normal people and in persons with WS will require further investigation.

For both groups of participants, we found specific evidence that music processing is characterized by greater temporal lobe activations than is noise processing, which in turn is characterized by greater temporal lobe activations than the resting condition, but we also found important intergroup differences: music and noise processing together were characterized by a much more similar pattern of activation in the WS participants than in the controls. The results of music minus rest and noise minus rest revealed a significant interaction effect indicating that in control subjects, the difference between music and rest activations is much greater than for WS. Taken in the context of the series of analyses we performed, we interpret this as evidence that the processing of music and noise among individuals with WS shows greater neuroanatomic similarity than in control participants, while still showing significant differences from the resting state.

One might wonder if the intergroup differences were the simple result of different mental processes employed during the task. All our subjects reported engaging in the same mental processes during the task, focused listening, and this was verified by the experimenters at the time of testing. In addition, we conducted a short debriefing session after the trials during which the subjects reported to the experimenters which sounds were familiar or unfamiliar. From this debriefing, we found no evidence of differential mind set or attention during the scanning.

We discovered greater activation in the right amygdala for the WS group compared to the control group, pointing to a potential dissociation: control subjects show greater activation in the temporal lobes, and WS participants (who have a known affinity for music) have greater activation in the amygdala. Although the full function of the amygdala is not entirely known and may involve processing of cognition, emotion, and motivation, previous work has demonstrated its role in the mediation of emotional aspects of music (Blood *et al.*, 1999), and this may extend to auditory stimuli in general.

Our findings of functional neuroanatomic differences between WS and controls participants provides converging evidence with previous ERP, cytoarchitectonic, and morphometric MRI studies documenting morphologic and neural organization irregularities in brains, which may be in part due to characteristic deficits in elastin production and hypercalcemia (Galaburda *et al.*, 1994). WS brains show a pattern of region-specific sparing in the context of overall reduction in cerebral volumes: for example, although the cerebrum is volumetrically reduced in WS, the relative size of the temporal lobe is preserved bilaterally (Reiss *et al.*, 2000). Moreover, the amygdala appears to be relatively spared in volume, as does the STS (Jernigan *et al.*, 1993; Reiss *et al.*, 2000). Although we are not yet able to determine how the present findings might be influenced by abnormal temporal and temprolimbic morphology, these structural data indicate that the functional differences we observe may have a neurodevelopmental etiology. As we have noted elsewhere, perhaps a neurodevelopmental course favoring certain limbic structures over other cortical and subcortical structures has resulted in relative prominence of affective strategies in perception, cognition, and communication (Jernigan *et al.*, 1993).

CONCLUSION

In this first fMRI study of Williams syndrome, we report a possible neural basis for the unusual acoustical and musical sensitivities observed in affected individuals. WS participants displayed more variable and diffuse activations throughout the brain, and they showed increased activation in the amygdala and cerebellum, thus providing new and converging evidence that their neural organization may differ from that of normal people (Galaburda *et al.,* 1994; Neville *et al.,* 1994).

The present findings shed new light on the neuroanatomic underpinnings of musical experience, as well as the functional architecture of the temporal lobes and related regions. The WS population is especially valuable in understanding auditory processing by virtue of the several distinct sensory and cognitive functions that are affected in them. Moreover, the very nature of WS as a neurogenetic developmental disorder with a known genetic etiology permits a rare opportunity to advance our understanding the relation between genes, brain development, and cognition.

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