Auditory Attraction: Activation of Visual Cortex by Music and Sound in Williams Syndrome

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Abstract
Williams syndrome is a genetic neurodevelopmental disorder with a distinctive phenotype, including cognitive–linguistic features, nonsocial anxiety, and a strong attraction to music. We performed functional MRI studies examining brain responses to musical and other types of auditory stimuli in young adults with Williams syndrome and typically developing controls. In Study 1, the Williams syndrome group exhibited unforeseen activations of the visual cortex to musical stimuli, and it was this novel finding that became the focus of two subsequent studies. Using retinotopy, color localizers, and additional sound conditions, we identified specific visual areas in subjects with Williams syndrome that were activated by both musical and nonmusical auditory stimuli. The results, similar to synesthetic-like experiences, have implications for cross-modal sensory processing in typical and atypical neurodevelopment.

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Williams syndrome (OMIM#194050) is a rare neurodevelopmental disorder caused by a hemizygous microdeletion on chromosome 7 (7q11.23), which contains approximately 28 genes (Bayes, Magano, River, Flores, & Perex Jurado, 2003; Strømme, Bjornstad, & Ramstad, 2002). Hypersociable and unusually empathetic, individuals with Williams syndrome exhibit relative strengths in expressive language and face processing, and their IQ tends to fall in the mild range of intellectual disability (Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999; Dykens & Rosner, 1999; Klein-Tasman & Mervis, 2003; Reilly, Losh, Bellugi, & Wulfeck, 2004). Their performance on tasks involving visuospatial cognition is often impaired relative to age-matched typically developing controls, and some show abnormal sensitivity to loud sounds, aversion to innocuous sounds, and attraction to other sounds (Klein, Armstrong, Greer, & Brown, 1990; Levitin, Cole, Lincoln, & Bellugi, 2005; Nigam & Samuel, 1994). These auditory symptoms are indicative of a more general heightened sensitivity or reactivity that might be related to increased anxiety, fear, and arousal in some persons with Williams syndrome (Blomberg, Rosander, & Angersson, 2006; Dykens, 2003).

In addition to the characteristics summarized above, individuals with Williams syndrome often exhibit a distinct musical phenotype. They show interest in music at an earlier age, spend more time listening to music, and are more emotionally responsive to music in comparison with groups of chronological age (CA) matched subjects with typically development, autism, or Down syndrome (Levitan et al., 2004). Individuals with Williams syndrome are also more likely to play a musical instrument and take music lessons compared to CA-matched subjects with Prader-Willi syndrome or Down syndrome (Dykens,

Rosner, Ly, & Sagun, 2005). Levitan (2005) showed that participants with Williams syndrome exhibited enhanced skill for rhythmic production, in particular, which is consistent with our observations, and while engaged in musical activities, they experienced unusually high levels of emotion. Caregivers have reported that these individuals seem to use music instinctively in a therapeutic manner to reduce anxiety and to increase positive affect (Dykens et al., 2005). In fact, Dykens and colleagues found that subjects with Williams syndrome who spent more time listening to music had fewer externalizing symptoms related to aggression and impulsivity, and those who had played a musical instrument for a longer duration had fewer internalizing symptoms related to anxiety (as measured using the Child Behavior Checklist–Achenbach, 1991).

Intrigued by this strong attraction to music evidenced by people with Williams syndrome, we set out to measure brain responses of individuals with this syndrome and those of matched controls in response to musical passages. From earlier work using brain imaging techniques, we knew that Williams syndrome tends to be associated with abnormalities in the corpus callosum (Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001; Wang, Doherty, Hesselink, & Bellugi, 1992) and the hippocampal formation (Meyer-Lindenberg, Mervis et al., 2005) as well as reduced cortical brain volume (Reiss et al., 2000; Thompson et al., 2005) and altered gyral patterns (Gaser et al., 2006; Kippenhan et al., 2005). Moreover, researchers who used functional MRI (fMRI) found differential activation patterns between persons with Williams syndrome and typically developing controls during the performance of tasks involving visuospatial processing (Meyer-Lindenberg et al., 2004), response inhibition (Mobbs et al., 2007), face processing (Mobbs et al., 2004), and social cognition (Meyer-Lindenberg, Hariri et al., 2005).

However, Levitan et al. (2003) were the only researchers who examined brain responses in individuals with Williams syndrome evoked by auditory stimuli including classical music. They found that in subjects with Williams syndrome relative to typically developing controls, temporal lobe activations were decreased and right amygdala activations were increased in response to musical stimuli. Although results from our initial study reported herein showed a similar trend, our measurements also revealed a remarkable pattern of auditory activations in areas of the brain conventionally associated with visual perception. Those intriguing, unanticipated results were suggestive of synesthesia, in which a person sees colors when hearing musical notes (Rizzo & Eslinger, 1989; Ward, Huckstep, & Tsakanikos, 2006). Thus, we performed two additional sets of measurements to more specifically localize the responses within each subject's visual cortex and to determine whether these responses were restricted to music or also extended to other kinds of musical and nonmusical auditory stimuli. The results of these subsequent studies confirm the presence of strong auditory activations within extrastriate visual areas. These synesthesia-like activations may well be related to the vivid visual imagery our participants with Williams syndrome describe when listening to music.

STUDY 1: BETWEEN-GROUPS ANALYSIS OF BRAIN RESPONSES TO MUSICAL STIMULI

Method

Subjects

Participants in Study 1 were 13 individuals with Williams syndrome (5 females), and 13 typically developing controls (6 females) (Table 1). We recruited typically developing controls from the local community using flyers and website postings with language approved by the Vanderbilt University Institutional Review Board. Williams syndrome participants were recruited through the Williams Syndrome Music Camp sponsored by the Vanderbilt Kennedy Center for Research on Human Development, with the assistance of the Vanderbilt Blair School of Music and the National Williams Syndrome Association. Hence, the Williams syndrome sample was biased for individuals with a talent for and/or interest in music. Therefore, typically developing controls were ascertained to have some, but not an extensive, musical background. Specifically, 10 of 13 subjects with Williams syndrome and all typically developing control subjects played one or more musical instruments (see Table 1). The individually administered Kaufman Brief Intelligence Test–K-BIT (Kaufman & Kaufman, 1990) indicated that the individuals with Williams syndrome had composite IQs that ranged from 49 to 91 ($M = 69$, $SD = 14$), indicating mild levels of intellectual disability. (See Table 1 for

Table 1. Study 1 Subject Demographics, IQ, and Musical Experience

		Sex		Verbal IQ[b]		Nonverbal IQ[c]		Subjects who have played (%)	
Group[a]	Median age[b]	M	F	Mean	*SD*	Mean	*SD*	At least one instrument	Two or more instruments
WS	25 (16–33)	8	5	80	11	65	19	77	46
TD	23 (17–27)	7	6	114	15	103	16	100	54

[a]WS = Williams syndrome. TD = typically developing. [b]Minimum–maximum ages in parentheses. [c]As determined with the Kaufman Bried Intelligence Test.

verbal and nonverbal K-BIT summary statistics.) All participants with Williams syndrome exhibited the physical, cognitive, and behavioral profile of Williams syndrome and previously had received a clinical diagnosis of Williams syndrome and confirmatory genetic testing.

To optimize success and minimize anxiety with the fMRI procedures, we mailed each participant with Williams syndrome an audio CD of the sounds an MRI machine makes while scanning so that he or she could listen to them prior to attending music camp. Although typically developing control subjects were not provided such CDs, all subjects would have been exposed to the actual MRI scanner sounds prior to the acquisition of functional scans (since several structural scans precede the first functional scan). Participants also visited the scanner and interacted with imaging staff prior to their scan, and we employed a research assistant with Williams syndrome who had successfully completed previous scans with us and could talk to his peers about his experiences. The study protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. Each participant gave his or her informed assent, and the participant's parent or guardian gave informed consent prior to the experiment.

Functional Neuroimaging

MRI data acquisition. The same data acquisition parameters were used in all three studies. A Philips Achieva 3-Tesla MRI scanner (Philips Healthcare, Inc., Best, The Netherlands) was used to acquire T1-weighted anatomical volume images (time of repetition [TR] = 4.6 ms, time to encode [TE] = 9 ms, 1 × 1 × 1 mm voxels, 170 sagittal slices, 256 mm field of view) and fMRI images. A total of 31 axial slices were acquired parallel to the anterior–posterior commissural line (AC–PC), with an image matrix of 80 × 80 pixels, reconstructed to 128 × 128 pixels and a field of view of 240 mm. Slice thickness was 3.5 mm, with a 0.35 mm gap, resulting in a voxel size of 1.875 × 1.875 × 3.85 mm. We recorded fMRI images using a single-shot T2-weighted gradient-echo echo planar sequence that was sensitive to changes in blood oxygen level-dependent (BOLD) contrast with a TR of 2000 ms and a TE of 35 ms with a sensitivity encoding (SENSE) factor of 1.5. In addition, a set of high-resolution T1-weighted images, which were used for coregistration and alignment, were acquired at the same location and with the same slice thickness as the functional scans.

Stimuli and fMRI experimental design. For Study 1, we were interested in investigating how subjects responded to music with differing emotional valence. Participants passively listened to blocks of silence and blocks of instrumental music categorized as upbeat or downbeat or from an over-rehearsed song ("Happy Birthday," see Figure 1) Upbeat music included three 20-s clips from polka, jazz, and new-age genres considered to elicit a positive affect. Downbeat music included three 20-s clips from the modern classical genre considered to elicit a negative affect. A larger set of song clips was initially selected for each category and was rated by research staff; those found to elicit the desired affect most consistently were chosen for inclusion. The "Happy Birthday" (HB) song was 20-s long and was played in a big-band jazz style. The rest condition consisted of 10 s of silence. During all conditions, visual stimuli consisted of a black background with a white cross, on which subjects were instructed to fixate throughout the functional runs. We conducted two block design runs (230 s each). The upbeat and downbeat blocks each consisted of three distinct song clips (3 s × 20 s = 60-s total), whereas the HB block consisted of just one 20-s presentation of the over-rehearsed

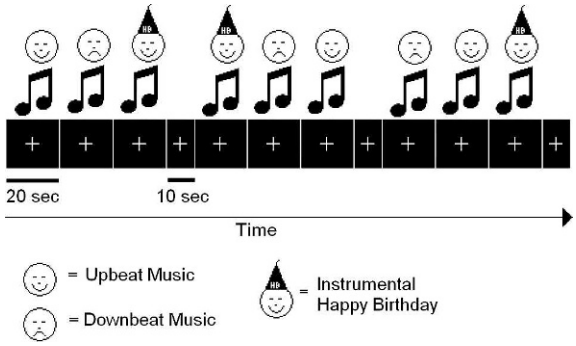

Figure 1. Study 1 fMRI experimental design for a single run. Actual order of presentation of music blocks was randomized.

song. Therefore, each run consisted of one upbeat block (60 s), one downbeat block (60 s), and one HB block (20 s). Each of these song blocks was followed by a 10-s resting block. We randomized the presentation order of the song blocks.

During scanning (in all three studies), the room lights were off and the fixation cross was projected via a rear projection system onto a translucent screen placed on the top of the head coil. Subjects viewed the screen through a double mirror attached to the head coil. Stimuli were controlled using E-Prime (Psychological Software Tools, Pittsburgh, PA). We synchronized stimulus presentation with the data acquisition by a trigger pulse delivered by the scanner console and used an fMRI-compatible pneumatic auditory stimulation system incorporated into standard Philips headphones for binaural stimulus delivery.

Statistical Analysis

We preprocessed fMRI data using slice time correction, 3D motion correction, and 3D spatial smoothing (6 mm FWHM Gaussian kernel; for Study 1 only); linear trend removal; and a high pass filter (3 cycles/time course). Scans with excessive head motion ($>$ 3 mm of translation or 3° of rotation) were removed from analysis. (Only one run from one subject was removed for excessive motion). We co-registered functional images with structural images from the same subject, and all images were transformed to Talairach space. We used brain Voyager QX (Brain Innovation, Maastricht, The Netherlands) to perform data preprocessing as well as general linear model (GLM) and regions of interest (ROI) analyses in all three studies (version 1.9) and, in Study 2, to perform color localizer and retinotopy analyses (version 1.6 and 1.9).

In Study 1, the random-effects GLM was applied to fMRI data, which measured changes in BOLD response. We conducted within- and between-group contrasts for each of the musical stimuli conditions (upbeat, downbeat, and HB) versus the silent condition; for the combined conditions (upbeat + downbeat + HB) versus the silent condition; and for upbeat versus downbeat conditions. We specified a priori anatomical ROI based on previous research (Levitan et al., 2003) and analyzed them using the Talairach-Tournoux Atlas (TTatlas+tlrc) dataset from AFNI (Cox, 1996). Whole brain analysis was focused on areas identified from between-groups statistical maps using a voxel-wise significance threshold of 0.005 and a cluster-size threshold of 50 mm^3.

Results

We conducted a whole-brain analysis, looking for areas of differential activation to music listening between groups (n = 13 per group) at a voxel-wise significance threshold of 0.005 and employed a cluster size threshold of 50 mm^3 to reduce false positive rates while maintaining power to discover moderately sized clusters of activation (Hayasaka & Nichols, 2003; Loring et al., 2002). Within-groups, activation patterns were very similar across music conditions; therefore, we report results from the contrast of combined (upbeat + downbeat + HB) music conditions versus silent fixation. There were 19 significant clusters of differential between-group activation for the combined music conditions versus silent fixation (Table 2). Sixteen of these differential activations were the result of increased activation in the Williams syndrome group, and 3 were the result of increased activation in the typically developing group. None involved significant deactivations in the respective contrast group.

Previous studies suggest that attending to auditory stimuli results in hypoactivation of the visual cortex (Laurienti et al., 2002). Therefore, the differential activations in the occipital lobe areas that are associated with visual processing–cuneus, middle occipital gyrus, and lingual gyrus–were highly unexpected. At the within-group level of analysis, increased activation in these occipital lobe areas was significant only for the Williams syndrome group (Figure 2). Inspection of the underlying distributions of these occipital activations reveals a shift in the mean percentage of signal change from near or below zero (+0.27 to

Table 2. Significant Clusters of Activations to Music Listening in Study 1

Hemisphere[a]	Region	Subregion	Brodmann area	Cluster size[b]	Peak activation x	y	z	*T*	*p*
R	Frontal lobe	Precentral gyrus	6	108	39	−3	44	3.85	.0008
R	Frontal lobe	White matter, precentral gyrus	6	135	32	6	36	3.74	.002
R	Limbic lobe	Insula	13	1053	45	−35	19	6.01	.000003
R	Limbic lobe	Posterior cingulate	30	135	12	−47	6	4.30	.0003
R	Temporal lobe	Superior temporal gyrus	13	108	56	−41	21	3.90	.0007
R	Temporal lobe	White matter, superior temporal gyrus	13	108	55	−42	15	3.32	.003
R	Temporal lobe	Inferior temporal gyrus	37	297	45	−65	−8	4.84	.00007
L	Temporal lobe	Superior temporal gyrus	38	108	−43	9	−16	3.52	.002
L	Parietal lobe	White matter, inferior parietal lobe		135	−32	−37	26	3.70	.002
R	Occipital lobe	Cuneus	18	108	14	−68	15	4.05	.0005
R	Occipital lobe	Cuneus	18	108	1	−80	21	3.76	.001
L	Occipital lobe	White matter, middle occipital gyrus		243	−34	−82	2	4.32	.0003
R	Cerebellum, Occipital lobe	Declive, lingual gyrus		108	11	−76	−12	3.80	.0009
R	Cerebellum	Declive	9	108	31	−54	−13	3.33	.003
R	Cerebellum	Culmen		270	21	−35	−11	5.36	.00002
L	Limbic lobe	Posterior cingulate	23	135	−5	−50	23	−4.24	.0003
L	Thalamus	Medial dorsal nucleus		135	−4	−10	13	−4.51	.0002
R	Temporal lobe	Inferior temporal gyrus	20	108	62	−25	−15	−3.87	.0008

Note. The Williams syndrome (WS) group showed increased activation to music listening. Significant clusters of differential activation by group to combined (upbeat + downbeat + Happy Birthday song) music conditions versus silent fixation. Positive *t*-test values indicate activation was greater in the WS group versus typically developing (TD) group; negative *t*-test values indicate activation was greater in the TD versus the WS group. We used a cluster threshold of 50 mm^3 and a voxel-wise α of .005 to create the statistical map and resulting regions of interest.
[a]R=right, L=left. [b] In mm^3.

−0.42) for the typically developing group to approximately one percent (+0.87 to +1.00) in the Williams syndrome group, with comparable within-group variability (Figure 3). Notably, post hoc correlational analyses showed no relationship between measures of musicality and occipital lobe activations in either group. These highly unusual responses to music listening in areas of the brain known to be involved in vision motivated our subsequent two studies with subjects who had Williams syndrome, in which we aimed to better localize and characterize these activations.

In addition, as seen in a previous report (Levitan et al., 2003), the cerebellum showed increased bilateral activation in the Williams syndrome group. There were also a number of other activations in regions not previously reported to be associated with auditory perception in the Williams syndrome group (see Table 2). Some of these were in areas related to emotion processing–insula, parahippocampal gyrus, and posterior cingulate gyrus–that are consistent with increased emotional experience with music for individuals who have Williams syndrome.

We had identified the amygdala as an a priori region of interest based on previous fMRI findings (Levitan et al., 2003). Although we did discover amygdala activation to music listening, we found no significant difference in this activation between the Williams syndrome and typically developing groups using a between-groups ROI GLM. Two regions involved in audition, the

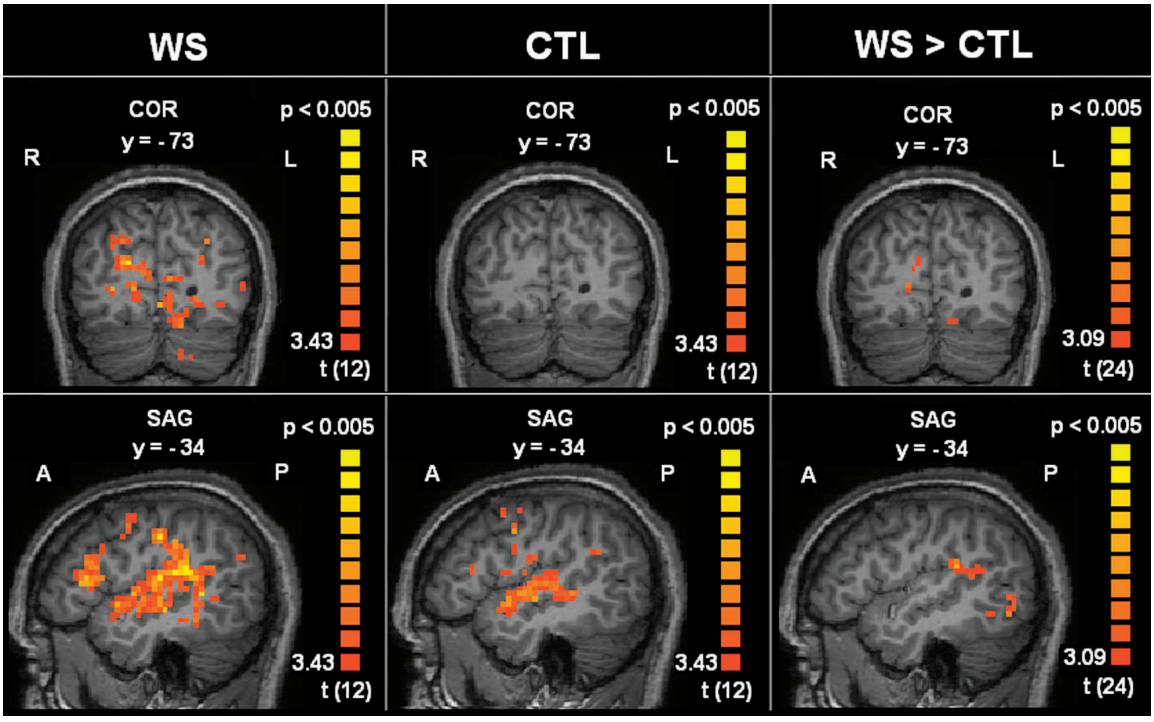

Figure 2. Occipital lobe and temporal lobe/insula activations to music listening in Williams syndrome (WS) > typical development (TD). Contrast of combined musical conditions (Upbeat + Downbeat + Happy Birthday) versus silent fixation. Within-group GLM of WS group (left) and TD control group (center). Between-groups GLM showing activations greater in the WS group versus typically developing control group (right). Statistical group maps are rendered on a representative single subject anatomical image. The top row of images shows activations in the occipital lobe. The bottom row of images shows activations in the left hemisphere.

bilateral superior and middle temporal gyri (STG and MTG, respectively), were also selected as a priori ROIs based on previous findings (Levitan et al., 2003). The STG was activated bilaterally in both Williams syndrome, $t = 6.95$, $p < 2 \times e^{-5}$) and typically developing, $t = 9.34$, $p < 5 \times e^{-6}$), and the between-groups ROI GLM was not significant (see Figure 2). Activations in the MTG were more isolated, primarily to the posterior portions of the gyrus, and only the Williams syndrome activations were significant, $t = 5.90$, $p < 8 \times e^{-5}$). Once again, using a between-groups ROI GLM, we did not find significant differences between the Williams syndrome and typically developing groups.

In summary, in Study 1 we investigated differences in brain responses to music in individuals with Williams syndrome versus typically developing controls. Novel activations in occipital lobe areas related to visual processing were found in the Williams syndrome group. We also found increased activation in areas related to emotion processing in the Williams syndrome group.

STUDY 2: LOCALIZATION OF WILLIAMS SYNDROME OCCIPITAL LOBE RESPONSES TO MUSICAL STIMULI USING COLOR LOCALIZER AND RETINOTOPY

Method

Subjects

Ten Williams syndrome participants in Study 1 who showed activations to musical stimuli in occipital lobe regions were asked to participate in a follow-up study. Of these, 6 participants (5 males) were available for follow-up scans. After their scans, we interviewed them about how they experienced the musical stimuli they heard as well as other music. Because individuals with Williams syndrome are highly suggestive and are very eager

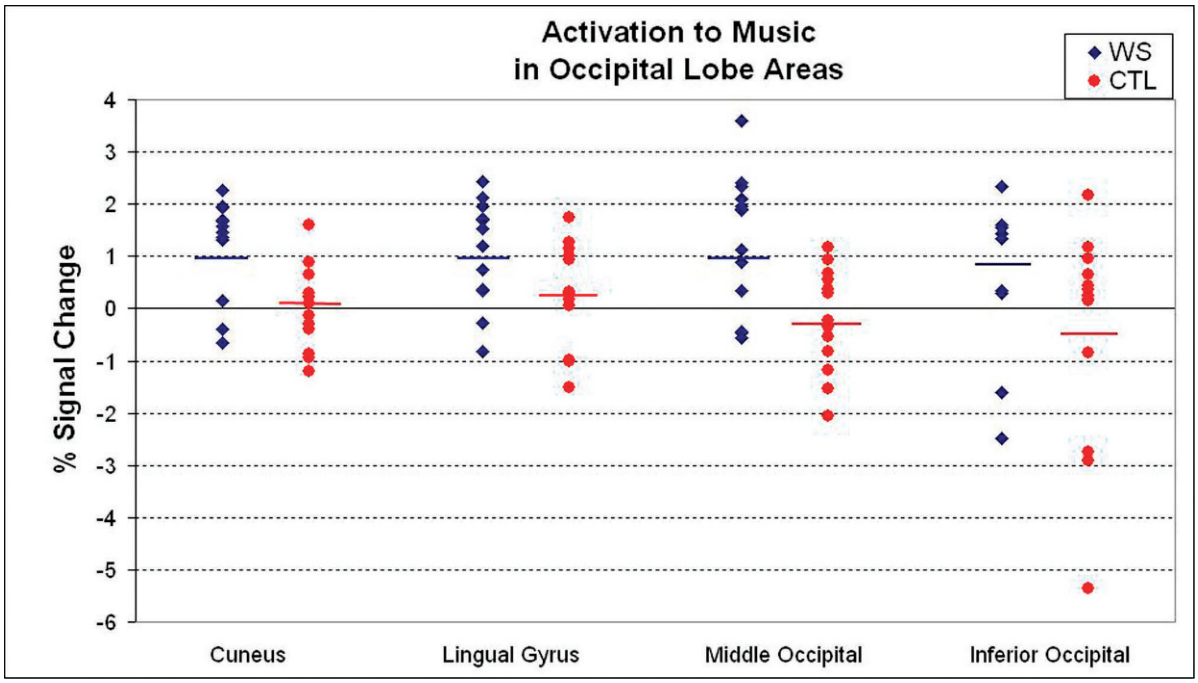

Figure 3. Distribution of occipital lobe activations to music listening by group. Contrast of combined musical conditions (Upbeat + Downbeat + Happy Birthday) versus silent fixation. Vertical bars indicate group means.

to please, we used open-ended, nonleading questions regarding how people experience music (e.g., When you listen to music, what happens to you? When you hear that song, how do you feel? What do you think about or imagine when you are listening to music?).

Functional Neuroimaging

Stimuli and fMRI experimental design. Musical stimuli used in Study 2 consisted of (a) songs and (b) musical notes and chords. Although brain responses to upbeat versus downbeat music were not consistent across subjects in Study 1, we were still interested in whether familiarity or preference for the stimuli might be important or whether auditory stimuli devoid of emotional valence might give similar brain responses. Thus, we had each participant choose songs he or she liked, and then we picked songs that all participants would hear. Song stimuli consisted of three 30-s song clips selected by the participant and three 30-s song clips selected by the researchers. All researcher songs were instrumental, but for the participant selected songs, subjects were allowed to select any songs, some of which contained vocals. We also wanted to test some more basic musical stimuli generally devoid of emotional valence, so we chose single musical notes and chords. The notes and chords were 2-s clips of a single note (A, C, or E) or chord (A, C, or E major), generated electronically to simulate either a piano or a guitar, with an equal number of clips from each instrument. There was also a silent rest condition. During all conditions, visual stimuli consisted of a black background with a white cross, on which subjects were instructed to fixate throughout the functional runs.

We conducted two block design runs (270 s each) of song stimuli (see Figure 4). Each run consisted of three blocks of participant selected songs (3×30 s $= 90$ s total), three blocks of researcher selected songs (3×30 s $= 90$ s total), and three blocks of rest (3×30 s $= 90$ s total). Each song block consisted of only one song clip. We randomized the presentation order of the song blocks, and a silent block followed every song block.

We also conducted two block design runs (360 s each) of notes and chords in Study 2 (see Figure 5). Each music block consisted of 20 clips of the 2 s long stimuli (40 s per block). Each run consisted of three blocks of notes (3×40 s $=$ 120 s), three blocks of chords (3×40 s $= 120$ s), and three blocks of silent rest (3×40 s $= 120$ s). We randomized the presentation order of the

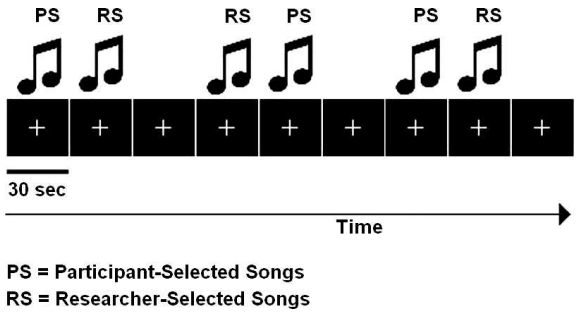

Figure 4. Study 2 block design for song stimuli runs. Actual order of presentation of sound blocks was randomized.

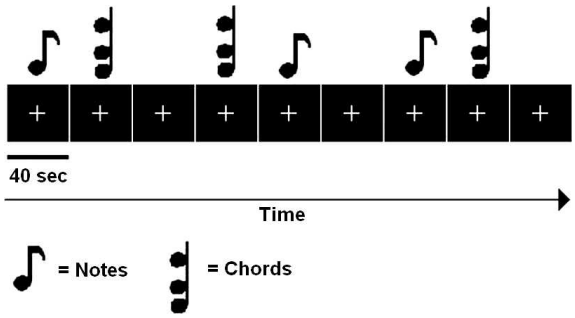

Figure 5. Study 2 fMRI experimental design for notes and chords runs. Actual order of presentation of musical sound blocks was randomized.

music blocks and the presentation order of the stimuli (notes/chords) within a block. A silent block followed every music block.

Retinotopy and color localizer experiments. In Study 2, retinotopically organized visual areas V1, V2, V3, and V4v were identified using conventional phase-encoded retinotopic mapping methods (DeYoe et al., 1996; Engel, Glover, & Wandell, 1997; Sereno, McDonald, & Allman, 1994). Functional MRI were acquired while participants viewed a slowly rotating, contrast-reversing checkerboard wedge subtending 22.5° in polar angle while fixating on the center cross. The wedge started at the lower right visual field and slowly rotated counter-clockwise. After 8 s, the wedge was at the lower vertical meridian and kept rotating counter-clockwise for a full cycle of 360° thereafter (within 64 s). Each retinotopic mapping run consisted of 4 repetitions of this rotation. Each of two color localizer scans lasted 4 min 32 s, the initial 8 s (4 volumes) of which were discarded prior to analysis to allow magnetic resonance stabilization.

Color-selective areas were also defined by a conventional color area localizer that contrasts viewing of partially overlapping chromatic rectangles (i.e., chromatic Mondrians) with viewing of achromatic, luminance-varied Mondrians (Howard et al., 1998). Each of two color localizer scans lasted 5 min 4 s, the initial 8 s (4 volumes) of which were discarded prior to analysis to allow for magnetic resonance stabilization. The scan was divided into 6 blocks of chromatic Mondrians and 6 blocks of achromatic Mondrians, with interspersed fixation baseline blocks.

Functional MRI data from the retinotopic mapping and color localizer scans were registered with the subject's high-resolution anatomical images, providing a subject-specific mapping of visual area ROIs at the voxel level. These ROIs were used for analyzing the fMRI images corresponding to the music-listening conditions.

Statistical Analysis

We applied a fixed-effects GLM with separate study predictors (for multiple runs) to each subject's fMRI data from the music stimuli experiments. Statistical maps of BOLD activation were generated for music conditions; and due to the highly constrained nature of our hypothesis to determine whether activations were present within visual cortex, we used a slightly more liberal significance threshold of .01. We identified retinotopically defined visual areas using cross-correlation analysis on the retinotopic mapping data. Data from two separate functional runs were averaged for statistical analysis. We used the predicted hemodynamic signal time course for the first half of a stimulation cycle (corresponding to 180° visual angle in the polar mapping experiment) and shifted this reference function successively in time. Sites activated at particular polar angles were identified through selection of the lag value that resulted in the highest cross-correlation value for a particular voxel (Muckli, Kohler, Kriegeskorte, & Singer, 2005). Color-selective ROIs were defined as the clusters of voxels that showed significantly higher BOLD response (multi-study GLM on two scans, $p < .05$ (false discovery rate [FDR] corrected) to colored Mondrians than to achromatic Mondrians. In subjects whose color localizer or retinotopy data did not permit adequate localization, we made extra efforts to identify early visual, including color-selective, areas from each subject's anatomy.

For example, the calcarine sulcus (whose banks are V1 areas) of a subject was examined to see whether any of voxels activated by auditory stimulation fell on or around this region. We note that each subject had good localization on one or both of the color localizer and retinotopy scans. For Subjects 2 and 5, functional runs using the participant selected and researcher selected songs were incomplete and could not be analyzed.

Results

Because individuals with Williams syndrome are known to have decreased cortical volume in posterior occipital and parietal areas, it was important to test whether such differences in anatomy across groups, which can result in poor coregistration of images, was responsible for the novel occipital lobe activations found in Study 1. In Study 2 we assessed whether within-subject occipital lobe activations to music were located in areas related to visual processing, as initially expected from Study 1 based on anatomy and how areas of activation to music related spatially to visual cortical areas.

Within-subject functional ROIs were identified based on color localizer and retinotopy scans. All 6 subjects with Williams syndrome showed activation, $p < .01$, to one or more musical conditions in areas that were identified by color localizer, retinotopy, and/or anatomy as being visual areas, including V1, V1 and V4v (Table 3). The contrasts involving simple chords consistently activated early visual areas, including color-selective areas, across all 6 subjects. Contrasts involving the participant- or researcher-selected songs showed activation in visual area ROIs in 3 of the 4 subjects for whom there were complete data.

We also used more stringent subject-specific ROI GLM analyses to determine whether the activation across the entire volume of a given visual ROI was significantly different for a music condition versus silent fixation. All 6 subjects had at least one color localizer ROI that was significantly activated by either the notes or the chords condition versus silent fixation contrast. In contrast, only 1 subject had activation to the participant-selected song that was significant by ROI GLM analysis. Figure 6 shows intrasubject activations to the chords condition in visual areas identified using their respective color localizer ROIs. Table 3 summarizes data from color localizer and retinotopy analyses, indicating which visual areas (denoted by an asterisk) were activated significantly (by ROI GLM analysis) to which conditions in which subjects. We note that hypoactivations, indicating lower BOLD response than during silent fixation, were also observed in visual areas to some conditions in 5 of 6 subjects, as would be more typical of (inhibitory) brain responses to auditory perception tasks (Laurienti et al., 2002).

In summary, Study 2 demonstrated that early visual areas, including color-selective areas, were

Table 3. Visual Areas by Musical Condition for Subjects With Williams Syndrome in Study 2

	Early visual areas[a]			
	Color selective		Noncolor selective	
Subject	LH	RH	LH	RH
1	N, C*, RS	N, C*, RS	N, C*	N, C*
2	N*, C*	N, C	—	N, C*
3	C*	C	C*	C*
4	N*, C*, PS*	N	N, C*, PS*, RS	N, C*
5	N	C	N, C*	C*
6	C	C*, RS		RS

Note. Blood oxygen level-dependent (BOLD) activations, $p < .01$, to contrasts of musical condition versus silent fixation that overlap with color localizer regions of interest for each subject. Color-selective areas were areas that showed greater response to colored Mondrians than to achromatic Mondrians. These areas included V4v. Noncolor-selective areas were V1 and V2 that were not identified by the color localizer.

[a]LH=left hemisphere; RH=right hemisphere. N=notes, C=chords, PS=participant-selected song, RS=researcher-selected song.

*Activation significant, $p<.01$, according to ROI GLM using subject-specific color localizer regions of interest. No early visual regions of interest could be identified in this area for Subject 2.

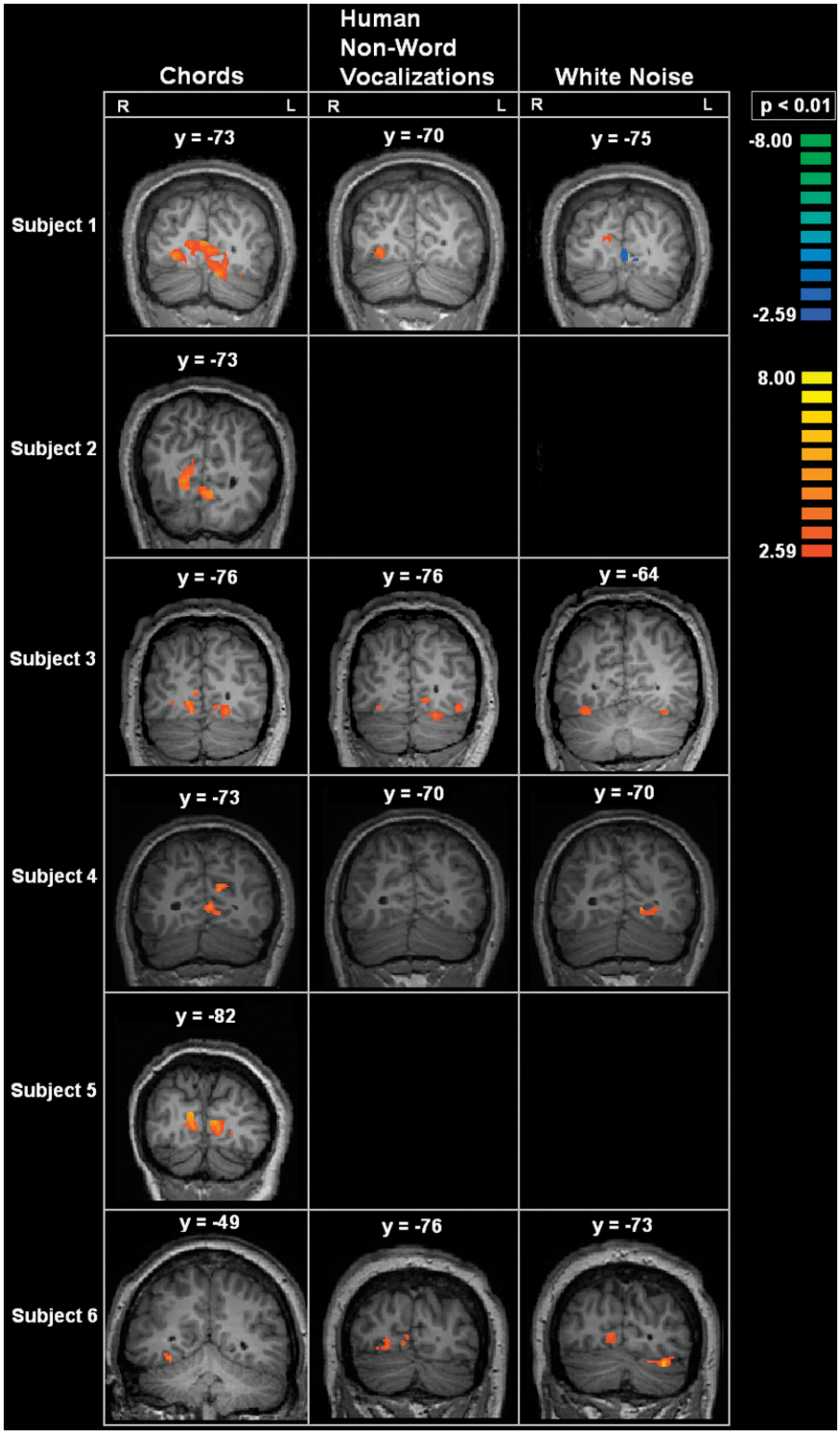

Figure 6. Listening to musical and nonmusical sounds activates early visual areas. Intrasubject activations to chords (Study 2), human nonword vocalizations (Study 3), and white noise conditions (Study 3) versus silent fixation in early visual areas identified by color localizer runs. Subjects 2 and 5 did not participate in Study 3.

being activated to music in individuals with Williams syndrome. Notably, visual cortex responses were more consistent across subjects for the simple musical stimuli of notes and chords than to songs.

STUDY 3: CHARACTERIZATION AND LOCALIZATION OF WILLIAMS SYNDROME OCCIPITAL LOBE RESPONSES TO NONMUSICAL STIMULI

Method

Subjects

All 6 subjects from Study 2 were asked to participate in a third MRI scan for Study 3; of these, 4 (all males) were available. After their scans, participants were re-interviewed with open-ended questions regarding how they experienced the same songs involved in Study 2, as well as notes, chords, and other music.

Functional Neuroimaging

Sound stimuli and fMRI experimental design. We were interested in whether brain responses observed in Studies 1 and 2 were specific to musical stimuli or whether other nonmusical auditory stimuli could elicit similar responses. Stimuli in Study 3 consisted of (a) musical notes and chords similar to those in Study 2, (b) human nonword vocalizations, and (c) different frequency bands of white noise. All sound stimuli were 2- s clips, and there were six unique clips per sound condition. The human nonword vocalizations were selected from a library of such sounds used in previous brain imaging work on voice perception (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000). We created the white noise clips using commercially available sound-editing software (Sound Studio 3.0©) running on a Macintosh© G4 Power PC computer. Each sound was created from white noise that was bandpass-filtered at three center frequencies: 256, 512, or 1024 Hz. Three of the six sounds consisted of these three bandpass noise samples, and the other three consisted of weighted combinations of these three components. Each sound clip was audibly distinct from the others, none were judged aversive among researchers involved, and all were adjusted to be equal in volume. The rest condition consisted of 24 s of silence. During all conditions, visual stimuli consisted of a black background with a white cross, on which subjects were instructed to fixate throughout the functional runs.

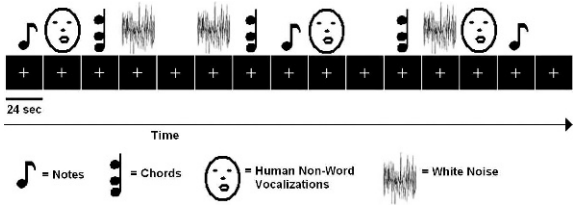

Figure 7. Study 3 block design for a sing run. Actual order of presentation of sound blocks was randomized.

Two block design runs (360 s each) were conducted (see Figure 7). Each sound block consisted of 12 clips of the 2-sound stimuli (12 × 2 s = 24 s per block). Each run consisted of three blocks of notes (3 × 24 s = 72 s), three blocks of chords (3 × 24 s = 72 s), three blocks of human nonword vocalizations (3 × 24 s = 72 s), three blocks of white noise (3 × 24 s = 72 s), and three blocks of silent rest (3 × 24 s = 72 s). The presentation order of the sound blocks and the presentation order of the stimuli within a block were randomized. A silent rest block followed each repetition of the four sound blocks.

Statistical Analysis

We applied a fixed-effects GLM with separate study predictors to each subject's fMRI data from the sound stimuli experiments. Statistical maps of BOLD activation were generated for each sound condition, and due to the highly constrained nature of our hypothesis to determine whether activations were present within visual cortex, we used a slightly more liberal significance threshold of .01. Each subject's anatomical images from Study 3 were co-registered with those from Study 2, and then functional data were registered with the subject's high-resolution anatomical images, providing a subject-specific mapping of visual area ROIs at the voxel level. These ROIs were used for analyzing the auditory condition fMRI images.

Results

In a final study, we assessed whether nonmusical auditory stimuli could also elicit activation in areas of the brain involved in visual processing. The same within-subject functional ROIs that we identified using color localizer and retinotopy scans in Study 2 were used in Study 3. All 4

Table 4. Visual Areas Activated by Sound Condition for Subjects With Williams Syndrome in Study 3

	Early visual areas[a]			
	Color selective		Noncolor selective	
Subject	LH	RH	LH	RH
1	C	N, C, H, W	N, C, W	N, C, H, W
3	N*, C*, H*, W*	N*, C, H*, W*	N*, H*, W*	N*, C*, W*
4	W*	N, W	W	N, W
6	W	H*, W*	H	H

Note. Blood oxygen level-dependent (BOLD) activations, $p < .01$, to contrasts of sound condition versus silent fixation that overlap with color localizer region of interest (ROIs) for all subjects in Study 3. Color-selective areas were areas that showed greater response to colored Mondrians than to achromatic Mondrians. These areas included V4v. Noncolor-selective areas were V1 and V2 that were not identified by the color localizer.
[a]LH = left hemisphere, RH = right hemisphere, N=notes, C=chords, H=human nonword vocalizations, W=white noise.
*Activations significant, $p<.01$, according to ROI GLM using intrasubject color localizer ROIs.

subjects showed activation, $p < .01$, to one or more sound conditions in areas that were identified by color localizer, retinotopy, and/or anatomy as being visual areas (Table 4). Brain responses to notes and chords were not as consistent as they were in Study 2, perhaps due to lower power (fewer data points) per condition; however, each subject showed activation in visual areas to one or both of these conditions versus silent fixation. Three of 4 subjects showed activation to the human nonword vocalization condition versus silent fixation (Figure 6). All 4 subjects showed activation to the white noise condition versus silent fixation (Figure 6). As in Study 2, we observed hypoactivations, indicating lower BOLD response than during silent fixation, in early visual areas to some auditory conditions in each of the subjects, as would be more typical of (inhibitory) brain responses to auditory perception tasks (Laurienti et al., 2002).

GENERAL DISCUSSION

In this three-part study, we examined the neural correlates of the unique auditory and musical phenotype of individuals with Williams syndrome. Previous work was focused on differential activation of the amygdala and temporal lobes in music perception in subjects with Williams syndrome versus typically developing controls (Levitan et al., 2003). Although we did observe a trend toward weaker but more widespread activation of temporal lobe areas in people with Williams syndrome versus those who were typically developing, these results were not significant in our larger sample using more conservative ROI GLM analyses. Instead, we found compelling evidence that some persons with Williams syndrome activate occipital and early visual areas in response to musical and other auditory stimuli. These novel findings have implications for current views of cross-modal processing in the general population and may help explain the unusually strong attraction to music and sounds often seen in people with Williams syndrome.

At first glance, these cross-sensory activations of visual cortical areas are reminiscent of brain activations in synesthetic individuals who report seeing colors when listening to musical notes (Rizzo & Eslinger, 1989) or spoken words (Nunn et al., 2002). Indeed, upon repeated interviews, our participants with Williams syndrome reported vivid, detailed, colorful imagery in response to listening to music, including favorite songs, and these images often contained strong affective connotation (see sample excerpt in the Appendix). However, unlike individuals with classical synesthesia, subjects with Williams syndrome did not describe experiencing the exact same visual sensations in response to specific notes, chords, or songs; consistent, repeatable sensory experience is another defining characteristic of synesthesia. In this respect, the visual experiences of the subjects with Williams syndrome depart from those of people with classic synesthesia.

Nonetheless, the finding that simple notes and chords and two types of nonmusical stimuli (chosen because they seemed unlikely to produce visual imagery) activated early visual areas strongly

suggests that the responses in participants with Williams syndrome might be stimulus-driven and not–at least not exclusively–the result of top-down feedback or association pathways. Likewise, the fact that all types of auditory stimuli we presented elicited these responses, albeit to varying degrees in different individuals, suggests that they were likely not being filtered for salience and, therefore, might be the result of bottom-up, or automatic, processes. Thus, it perhaps is worthwhile to consider possible common mechanisms that might underlie both synesthesia and the phenomenon we observe in individuals with Williams syndrome. One mechanism posited by the cross-activation theory of synesthesia is that functionally distinct brain regions, such as the auditory and visual cortices, possess aberrant neural connections in individuals with synesthesia, as the result of failure of pruning at some point in development (Baron-Cohen, Harrison, Goldstein, & Wyke, 1993; Maurer, 1993). A second theory posits disinhibited feedback, whereby functional segregation of brain regions (due to top-down inhibitory processes that strengthen during the course of development) is unusually weak in individuals with synesthesia (Grossenbacher & Lovelace, 2001). Although these theories are often treated as competing, they need not be mutually exclusive; indeed, both of these processes could be at work in the same individual or in a group that shares similar sensory phenomena.

In this vein, growing evidence indicates that cross-modal integration of information from two or more sensory modalities is the norm rather than the exception and that sensory cortical areas are not as isolated from each other as previously thought. Both animal and human studies suggest that we all have, to some degree, feedback pathways from areas of the brain that respond to multiple sensory modalities, for example, auditory and visual (Calvert et al., 1999; Driver & Spence, 2000; Macaluso, Frith, & Druver, 2001). In at least one study researchers found that synesthetic experience exploits the same neural connections that enable cross-modal mechanisms, suggesting that these pathways are not privileged to synesthetes (Ward et al., 2006). These shared neural connections lend support for the disinhibited feedback (reduced top-down inhibition) theory of synesthesia playing a role in the unique auditory–visual phenomenon observed in participants with Williams syndrome.

Our analysis of the underlying distribution of visual activations to sound (Figure 3) lends further support to the idea that cross-modal processing might not be unique to synesthetes but that there is a wide distribution of ability and that individuals with synesthesia are at one end of the spectrum and that, on average, individuals with Williams syndrome are also near the end of that spectrum, but to a lesser degree than those with synesthesia. Activations that extend beyond the boundaries of visual areas mapped by retinotopy and color localizer might also implicate association pathways. Although the literature on auditory processing in typically developing individuals does not include reports of visual activation to auditory stimuli, most investigators simply do not look for them and possibly dismiss them as spurious when they are found, because they do not conform to the dogma that sensory systems are hard-wired and functionally distinct. The literature on auditory processing in persons with congenital blindness, however, shows extensive plasticity of sensory cortices and the recruitment of occipital lobe areas for the processing of auditory stimuli (Collignon, Voss, Lassonde, & Lepore, 2009; Hertrich, Dietrich, Moos, Trouvain, & Ackermann, 2009).

Although under some debate, a developmental approach suggests that multisensory processing, and perhaps synesthesia, might be the norm in infancy, with perceptual systems becoming more specialized throughout development (Baron-Cohen et al., 1993; Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996; Harrison, 2001; Maurer, 1993). It is not clear what developmental features in Williams syndrome might contribute to altered sensory processing, but one study implicates aberrant neurotrophin nerve growth factor (NGF) levels. Calamandrei et al. (2000) examined hyperacusis and other auditory abnormalities in Williams syndrome and found that while NGF levels were elevated in typically developing children from 2 to 6 years of age, individuals with Williams syndrome had high NGF levels from 2 to 20 years of age–more than four times as long as in controls (Calamandrei et al., 2000). This extended window of prolonged, high NGF could be responsible, in part, for the abnormal development of cortical regions and/or the white matter tracts that connect them. This would lend support for the cross-activation (reduced pruning) theory of synesthesia playing a role in the unique visual experience to sound in individuals with Williams syndrome.

Preliminary findings from diffusion tensor imaging (DTI) studies shed some light on altered fiber tracts in Williams syndrome. Marenco et al. recently used DTI to examine white matter architecture in high-functioning adults with Williams syndrome and IQ-matched typical controls (Marenco et al., 2007). Subjects with Williams syndrome showed increases in longitudinal tracts, coursing along the anterior–posterior axis, and decreases in transverse fibers, coursing right-to-left. Further, compared to controls, the longitudinal fiber tracts in those with Williams syndrome, including the inferior longitudinal fasciculus (ILF) that connects the temporal and occipital lobes, had increased fiber coherence (anisotropy), skewness, and lattice index values. Also, fiber tracts of subjects with Williams syndrome diverged from those of controls at the junction between the medial temporal and occipital lobes. Hoeft et al. (2007) also found evidence of increased fractional anisotropy (FA) in the ILF, particularly in the right ILF, which these authors suggest might be related to relative strengths in face recognition. Marenco et al. speculated that these findings might be related to the relatively spared verbal abilities in Williams syndrome (Marenco et al., 2007). Although it is unclear whether these findings will generalize to a Williams syndrome cohort with more variable IQs, DTI findings may also relate to the unique visual activations to auditory stimuli we are reporting here.

In future studies researchers should also investigate the genetic basis of this unusual cross-sensory hyperconnectivity in Williams syndrome. Almost all persons with this syndrome have the same chromosomal microdeletion, with the same breakpoints; however, the identification of atypical cases of Williams syndrome with shorter or longer deletions, translocations, or inversions has aided in the ongoing attempts to map specific genes to particular parts of the Williams syndrome phenotype, including cardiac defects, visuospatial deficits, hypersociability, and intellectual disability, in general (Bellugi et al., 1999; Borg, Delhanty, & Baraitser, 1995; Doyle, Bellugi, Korenberg, & Graham, 2004; Frangiskakis et al., 1996; Gray, Karmiloff-Smith, Funnell, & Tassabehji, 2006; Morris et al., 2003; Tassabehji et al., 1999, 2005; Young et al., 2007). Thus far, no genes in the chromosome 7 deletion region have been associated with differences in auditory perception, musicality, or affective response to music. Within-group variability in the cross-modal connectivity or musical phenotype of persons with Williams syndrome could be due to other genetic factors or environmental exposures, such as musical training, neither of which has been fully explored in the literature.

Despite the challenge of recruiting adequate numbers of participants with rare disorders such as Williams syndrome, we included in Study 1 a sample size (13 with Williams syndrome; 13 controls) that represents the largest fMRI study to date on auditory processing in Williams syndrome. Future researchers should strive to increase these numbers further and should include a wider range of auditory stimuli, including sounds with positive or negative emotional valence or those that are encountered in everyday life.

The choice of an appropriate control group and matching criteria is very important and often controversial. In the current study, we were primarily interested in understanding how individuals with Williams syndrome differ from those with typical development. However, it would also be interesting to now investigate these same phenomena in other neurodevelopmental groups, such as Down syndrome or autism, whose neuropsychological profiles are very different from that of people with Williams syndrome. Given the wide range of intellectual disability in our Williams syndrome group and our choice to use typically developing controls, we did not try match subjects on mental age. Hence, intellectual ability is a potential confounder in this study. Finally, although we did not find evidence for a relationship between musicality and cross-modal activity, perhaps other musically enriched samples, such as professional musicians or individuals with perfect pitch, would show evidence of cross-modal processing similar to that seen in Williams syndrome. Ideally, future investigators would try to control for musical interest (regardless of talent) as well as for musical talent.

This study is among the first in which brain responses to music and auditory stimuli in Williams syndrome was examined. Musicality remains a less-well understood, but prominent feature of the Williams syndrome behavioral phenotype, and findings from this three-part study have led to new hypotheses regarding multisensory processing in this population. Not all persons with Williams syndrome have a passion for music, and it is unclear if only certain subsets of those with this syndrome respond to auditory stimuli with visual activation. Our ongoing analyses of structural and functional connectivity, especially connections

between auditory and visual cortical regions are promising ways to shed light on this question.

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Appendix

The following is a sample excerpt from one of the interviews with a participant who has Williams syndrome about his experience listening to music. I = interviewer. P = participant.

I: "She's Gonna Make It" by Garth Brooks. Did you see anything when you heard that song?
P: Mountain…with stairs on the mountain.
I: So tell me about the mountain. Did it have a color?
P: Orange.
I: All right. So the stairs, what did the stairs look like?
P: Like an escalator.
I: Anything else beside the mountain and the stairs?
P: It had roses on the steps.
I: What color were they?
P: Red.
I: They were red? Anything else can you tell me?
P: It was a wedding type thing.
I: Any people?
P: Just the bride and the bridesmaids were going upstairs.
I: What was the bride wearing?
P: She was wearing a white gown with a silver necklace with a diamond shape
I: What was the diamond shape?
P: The necklace. And she was wearing sandals.
I: Sandals?
P: Yeah, this is kinda weird.
I: So tell me about her sandals.
P: They were crocs.
I: Did the crocs have a color?
P: White, so they could match.
I: At least she was matching.
P: Yeah.

