Neural Correlates of Musical Timbre Perception in Williams Syndrome

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ABSTRACT

Williams syndrome (WS) is a rare, neurodevelopmental genetic disorder. Many individuals with WS exhibit auditory aversions and attractions and are extremely emotionally affected by and interested in music. Given their auditory sensitivities, including an apparent ability to discriminate amongst particular classes of sounds (e.g., vacuum cleaners), it has been hypothesized that individuals with WS may show superior timbre discrimination abilities. However, in contrast to this anecdotal evidence, recent research reveals that individuals with WS predominantly process the fundamental frequency in complex tones rather than the spectral information, which is important for distinguishing amongst different timbres. The present study aimed to clarify timbre perception abilities in WS. Participants included 18 adults with WS and 15 typically developing (TD) controls. Participants performed a timbre detection task while EEG was recorded. Participants heard sequences of 500-ms instrumental tones (trumpet: 42% of stimuli; cello: 42%; piano: 16%). The onset and decay of the tones was replaced with a 10-ms envelope. Participants were asked to respond to the piano tones. Event-related potential (ERP) analyses revealed robust P300 responses to the target piano tones in the WS and TD groups. Individuals with WS also demonstrated differences in P300 amplitude between the non-target cello and trumpet timbres. In the WS group only, there was early and sustained increased induced alpha-band (8-12 Hz) activity to the cello vs. trumpet timbre. Thus, results indicate greater attentional and sensory processing of instrumental timbres in WS compared with TD individuals. Implications will be discussed for auditory sensitivities and musicality in WS.

I. INTRODUCTION

Williams syndrome (WS) is a neurodevelopmental genetic disorder caused by the deletion of ~28 genes on chromosome 7 (Stromme, Bjornstad, & Ramstad, 2002). WS is associated with a unique cognitive-behavioral phenotype including average IQ in the 50s-60s with greater verbal than spatial abilities, hypersociability, and anxiety and attention issues (for a review, see Martens, Wilson, & Reutens, 2008). WS has been of interest to music cognition researchers because of seemingly heightened interest and emotional reactions to music in this population (e.g., Levitin et al., 2004). It is unclear, however, to what extent the increased interest to music in WS is due to underlying low-level auditory sensitivities in this syndrome.

Indeed, questionnaire research reveals a range of auditory sensitivities in WS. For example, in one study of 118 individuals with WS, parents of nearly 5% of WS participants reported that their child experienced lowered auditory threshold for hearing, which was not reported in any of the children with autism, Down syndrome (DS), or typically developing (TD) individuals in the study (Levitin, Cole, Lincoln, & Bellugi, 2005). Parents of individuals with WS also reported greater rates of odynacusis (lowered pain threshold for loud sounds), occurring in nearly 80% of WS participants but only a third of participants with autism and DS, and fewer than 4% of TD participants. Moreover, multiple studies report markedly high rates of auditory aversions, such as being frightened or bothered by specific sounds, in WS, with approximately 90-95% of individuals having aversions to one or more sounds, including broadband, narrowband, continuous, and sudden onset sounds (Klein, Armstrong, Greer, & Brown, 1990; Levitin et al., 2005; van Borsel, Curfs, & Fryns, 1997).

For nearly 10% of individuals with WS, but none of the individuals with other disabilities in the same study, their initial auditory aversions can give rise to auditory fascinations (Levitin et al., 2005). In particular, broadband sounds, such as vacuum cleaners or electric razors, became sources of fascination to these individuals, who would insist on listening to the sounds repeatedly and became adept at distinguishing amongst particular exemplars of such sound (e.g., different makes and models of vacuum cleaners).

Based on the questionnaire studies of "soundscape sensitivity" (Levitin & Bellugi 1998) in WS, which seems to extend to the quality of the sounds and not just their loudness or pitch, researchers have hypothesized about timbre perception in WS. Timbre, or tone color, refers to the quality of sound that allows one to distinguish between two sounds when loudness, pitch, and duration are equated, such as two instruments playing the same note. However, there is only one unpublished study of timbre discrimination in WS, which reported that individuals with WS could make same/different judgments about vacuum cleaner sounds at the same level as highly trained musicians (discussed in Levitin & Bellugi, 2006).

Thus, timbre perception and discrimination remains an understudied part of the WS auditory and musical phenotype. Indeed, despite anecdotes of being able to distinguish among different sounds, there are also data that might suggest poorer timbre discrimination in WS. For example, neuroimaging research reports more diffuse activation to a wide array of music, noise, and nonspeech vocalizations in WS (Levitin et al., 2003; Thornton-Wells et al., 2010), including greater similarity of music and noise processing in WS than in TD individuals (Levitin et al., 2003). Using a behavioral paradigm, magnetoencephalography (MEG), and magnetic resonance imaging (MRI), Wengenroth et al. (2010) reported that individuals with WS are holistic or fundamental sound processors, who perceive sounds by focusing on the fundamental frequency rather than the sound's spectral or harmonic components. Though they did not report on behavioral or neural differences for different types of sounds, the finding of extreme fundamental sound processing suggests that individuals with WS may be less sensitive to timbre because they may not use the spectral components when

perceiving sound. However, timbre is a multidimensional attribute of sound, with anywhere from two to four dimensions underlying its perception (e.g., Caclin, Giard, Smith, & McAdams, 2007; McAdams et al., 1995; Samson, Zatorre, & Ramsay, 1997). For example, attack time, spectral centroid, spectral fine structure, and spectral flux have all been considered as dimensions of timbre, and these dimensions interact with each other in perception (Caclin, McAdams, Smith, & Winsberg, 2005; Caclin et al., 2007).

The current study sought to better understand timbre discrimination abilities in adults with WS through an oddball paradigm. Oddball paradigms, where participants respond to unpredictable rare target stimuli amongst more common non-target stimuli, have previously been successfully used to examine timbre perception and discrimination in TD individuals (e.g., Crummer, Walton, Wayman, Hants, & Frisina, 1994). By collecting electroencephalogram (EEG) during the oddball task, we were able to examine neural markers of timbre discrimination, specifically the P300 and alpha-band activity. The P300 is a positive event-related potential (ERP) that is evoked by the target and is thought to reflect attention and memory updating (e.g., Polich, 2007; Yordanova & Kolev, 1998). Based on questionnaire data of sensitivity to auditory stimuli in WS, we hypothesized that individuals with WS would be able to discriminate a target timbre from non-target timbres and elicit a robust P300 response, similar to TD individuals. Non-phase-locked, or induced, alpha-band activity to non-targets has been suggested to reflect sensory perception and judgment of the stimuli (Peng, Zhang, & Hu, 2012). Given their reported enhanced timbre sensitivities, we hypothesized that individuals with WS would show differential induced alpha-band activity to different timbre non-target stimuli, which would not be present in TD controls.

II. METHODS

A. Participants

Participants included 18 individuals with WS and 15 TD controls. There were no differences between the groups in age (WS: 27.2±7.3 years vs. TD: 25.2±5.7 years, t(31)=0.893, p=NS) or gender (WS: 66.7% male vs. TD: 53.3% male, χ^2=0.609, p=NS). As expected, individuals with WS had lower IQ than TD individuals (WS: 71.7±15.4 vs. TD: 109.8±15.5, t(31)=-7.053, p<.001). All participants were reported to have normal hearing and normal or corrected-to-normal vision. An additional 6 individuals with WS and 3 TD controls were excluded from analysis because they did not have usable EEG data.

The study was approved by the university IRB. Parents/guardians of individuals with WS and TD individuals provided informed written consent. Individuals with WS provided written assent.

B. Stimuli

Timbre stimuli were created from the University of Iowa Musical Instrument Samples (http//:theremin.music.uiowa. edu). These musical samples are recorded in an anechoic chamber and sampled at 44.1 kHz. 500-ms excerpts from stable portions in the middle of the samples were taken for cello, trumpet, and piano stimuli on C4 and E4 pitches. The

cello and trumpet stimuli are recorded in mono while the piano is recorded in stereo. For purposes of another study, stimuli were presented in blocks of either long-short or short-long timbre stimuli. Long-short stimuli were edited in Audacity to contain a 326-ms tone followed by 12 ms of silence and then a 162-ms tone, while short-long stimuli were created in the reverse (see Figure 1 for examples). The start and end of each tone was replaced with 10 ms envelope rise and fall time to prevent onset/offset clicks. Stimuli were presented from a speaker approximately 60 cm above the participant's head at ~70 dB. For the current study, results across the long-short and short-long stimuli, and C4 and E4 pitches, were collapsed.
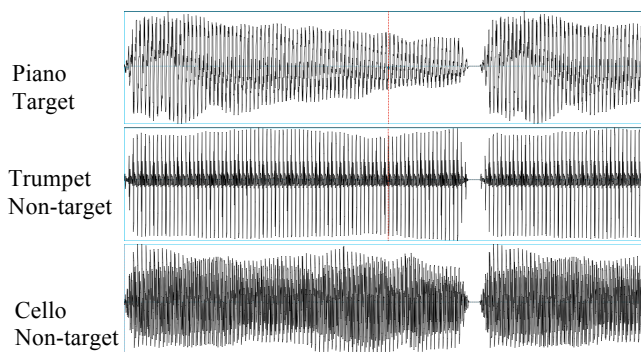

Figure 1. Waveforms of the timbre stimuli in the long-short, C4 block.

C. Procedure

Participants were instructed that they would hear different sounds and their task was to identify the piano sound. When they heard a piano sound, they were to press the response box, which was made to look like a piano keyboard, with both of their thumbs. To be sure that participants could identify the different instrumental timbres, they first completed a practice block of 10 trials during which they heard the instrumental timbre stimuli and were instructed whether it was or was not a piano tone and whether they should respond. Following the practice block, they completed 24 blocks of an oddball paradigm, with each block containing, in random order, 2 piano tones and 10 cello or trumpet tones. Thus, they heard a total of 288 instrumental tones (42% cello, 42% trumpet, 16% piano) over the course of the experiment. The SOA between tones was 1.3s. In each block the tones were either short-long or long-short and at the same pitch (E4 or C4). Blocks were evenly split between the pitches and short-long and long-short timbre stimuli. (For purposes of another study, participants also heard 4 spoken words within each block as well, but these were not analyzed as part of the current study.) Between blocks was a 2-s rest period. The order of blocks was randomly set by the computer. Stimuli presentation and response collection was done in E-prime 2.0. A research assistant sat with all participants to answer any questions and make sure the participant stayed on task.

D. EEG Collection and Preprocessing

EEG was recorded using a high-density array of 128 Ag/AgCl electrodes embedded in soft sponges (Geodesic Sensor Net, EGI, Inc., Eugene, OR, USA). Data was collected

at 500 Hz with a 0.1-200 Hz filter and a vertex reference. Impedance was kept below 40 kohm. After the session, data was low-pass filtered at 25 Hz and re-referenced to an average reference. EEG was epoched separately for the three instrumental timbres from 100 ms before tone onset to 800 ms post tone for the ERP analyses, and from 500 ms before to 1000 ms post for the time frequency analyses (the longer epochs were required for the wavelet analyses). Epochs with ocular artifacts or other movement were excluded from analysis.

E. Data Analysis

1) *ERPs:* The primary purpose of the ERP analysis was to evaluate the P300 response to the target piano vs. non-target timbre (trumpet, cello) stimuli. 14 of the 18 WS participants, and 15 of 15 TD participants had enough good EEG epochs to be included in these analyses. The 4 remaining WS participants did not have enough usable piano epochs, but did have enough trumpet and cello epochs, so they were only included in the time frequency analyses focusing on the non-target tones (see below; results were similar when these individuals were excluded from time frequency analyses, as well).

Consistent with previous research (e.g., Crummer et al., 1994), the Pz electrode was chosen for P300 analyses because it is the site of maximal P300 amplitude. Using Matlab, P300 response for each timbre was determined as the maximal amplitude between 300-500 ms post stimulus onset, while P300 latency was the time post-stimulus onset that maximal amplitude occurred. A 2 (group: WS vs. TD) x 3 (timbre: piano vs. trumpet vs. cello) repeated measures ANOVA was conducted on the P300 amplitude and latency. Preliminary analyses revealed no effects of age, gender, or IQ so they were not included as covariates in the analysis.

2) *Time Frequency*: The primary purpose of the time frequency (TF) analysis was to examine differences in alpha-band activity to the non-target tones (trumpet vs. cello). All 18 WS and 15 TD participants had enough usable data to be included in the analysis. The open source Fieldtrip Toolbox was used for the wavelet-based time frequency decomposition (http://www.ru.nl/neuroimaging/fieldtrip; Oostenveld et al., 2011). For induced (non-phase-locked) TF analysis, single trial data was convolved with a Morlet waveform with a width of 5 cycles (standard deviation of frequency resolution equals $f/5$; standard deviation of temporal resolution equals $1/(f/5)$). Convolution occurred from 8-12 Hz with a frequency step of 1 Hz and a time step of 2 ms within the segment length for the trumpet and cello conditions (see Herrmann, Grigutsch, & Busch, 2005 for more information on EEG wavelet analysis). Single trial data power was then averaged within the trumpet and cello timbres for each participant.

To control for absolute power differences between individuals, TFs were normalized by averaging the spectra across the trumpet and cello timbres for each participant, resulting in a baseline frequency at each electrode. For each participant, relative percent change in power spectra from the averaged baseline was calculated, thus normalizing power across conditions and individuals.

Electrode cluster randomization (Maris & Oostenveld, 2007) was used to examine differences in normalized power between the trumpet and cello timbres for the WS and TD groups. This is a data-driven method that identifies clusters of electrodes, which show similar power differences between the two timbres over each frequency and time point. The significance of the power differences in these data driven clusters is compared with randomly partitioned clusters via Monte Carlo methods. P-values were set at 0.05.

III. RESULTS

A. ERP

Grand average waveforms for the piano, trumpet, and cello timbres at electrode Pz are presented in Figure 1 (top: WS; bottom: TD). The target piano timbre elicited a P300 component in both the WS and TD groups. The repeated measures ANOVA for P300 amplitude revealed a main effect of Timbre (F(2,26)=68.025, p<.001, partial eta^2=0.840), showing that, as expected, the P300 amplitude was significantly greater to the target piano than the non-target timbres. There was also a main effect of Group (F(1,27)=5.585, p=.026, partial eta^2=0.171). Specifically, follow-up t-tests revealed that the P300 amplitude to the target piano timbre was significantly greater in the TD than the WS group (t(27)=-3.943, p=.001) while the P300 amplitudes to the non-target timbres did not differ between groups (p's=NS). Finally, there was a significant Group x Timbre interaction (F(2,26)=11.432, p<.001, partial eta^2=0.468). In the TD group, the piano tone elicited a greater P300 amplitude than either the trumpet (t(14)=10.287, p<.001) or cello (t(14)=9.300, p<.001) timbres, which did not differ from each other (t(14)=0.031, p=0.976). In contrast, in the WS group, the P300 amplitudes differed amongst all three timbres (piano vs. trumpet: t(13)=6.212, p<.001; piano vs. cello: t(13)=3.526, p=.004; trumpet vs. cello: t(13)=-2.159, p=.05). Thus, though both groups showed the expected larger P300 to the target piano vs. non-target stimuli, the target elicited a larger P300 response in the TD vs. WS group. Additionally, the P300 response differentiated amongst the non-target trumpet and cello stimuli in the WS group but not in the TD group.

In contrast to the P300 amplitude effects, the repeated measures ANOVA for P300 latency revealed only a marginal effect of Timbre (F(2,26)=3.172, p=.059), with follow-up tests showing that P300 latency was longer in the piano than the cello conditions (p=.021) but there were no differences in latency between piano and trumpet or trumpet and cello timbres. There was no difference in latency between the WS and TD groups (F(1,27)=0.392, p=0.537), and no Group x Timbre interaction (F(2,26)=0.849, p=0.439). Thus, overall, there were no differences in latency to the target piano vs. non-target timbres in the WS vs. TD groups, nor was there a

WS

TD
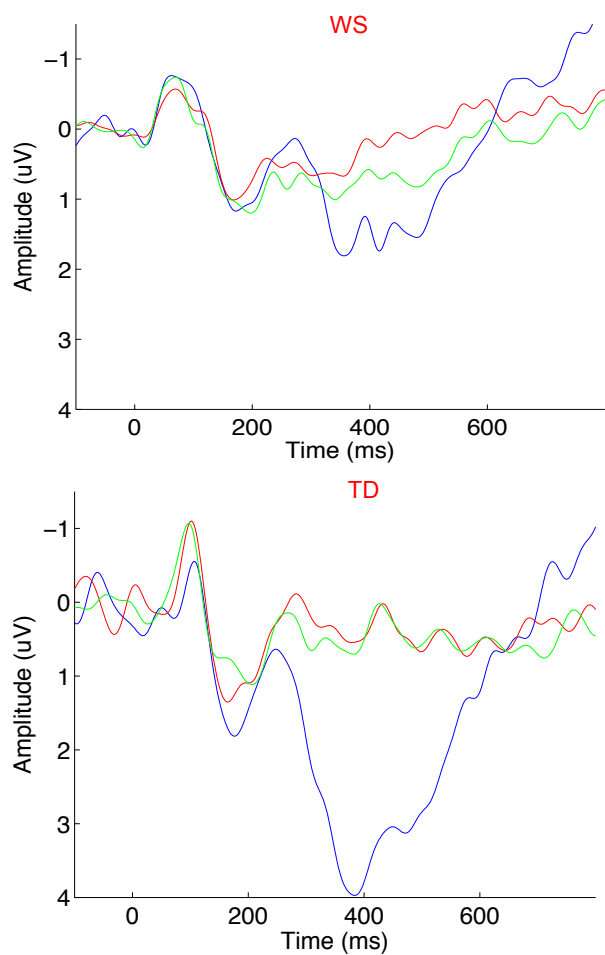
Figure 2. Grand average waveforms at electrode Pz in WS (top) and TD (bottom) groups. In both the WS and TD groups, the target piano elicited a larger P300 response compared to the non-target timbres (F(2,26)=68.025, p<.001, partial eta^2=0.840). In the WS group only, the amplitude to the non-target trumpet and cello timbres also differ (trumpet vs. cello: t(13)=-2.159, p=.05).

difference in latency between the non-target timbres in either group.

B. Time Frequency

Time frequency analysis of the EEG data revealed a marginal difference in induced alpha-band power to the trumpet vs. cello timbres in the WS but not the TD group. Specifically, as depicted in Figure 3, in the WS group only there was greater induced alpha power to the cello vs. trumpet timbre over a central and frontal, as well as right temporal, cluster of electrodes from 200-662 ms (p=0.052).

IV. CONCLUSION

To our knowledge, this is the first study to directly examine neural correlates of timbre perception to musical instrument tones in WS. We found that similar to TD participants, individuals with WS were able to detect a target timbre from non-target timbres, as indexed by a P300 component to the target piano timbre. However, individuals with WS, but not TD individuals, also showed signs of neural
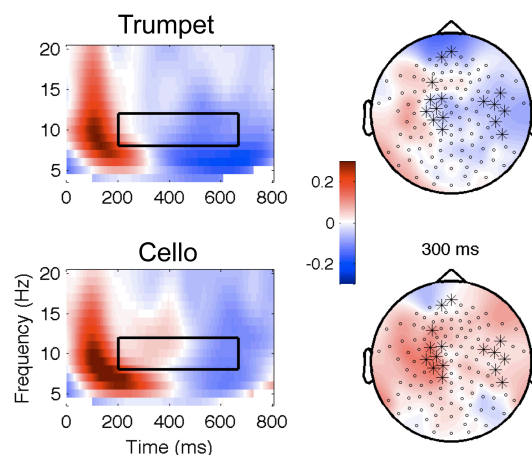
Figure 3. Time frequency representations (left) and topographic plots (right, at 300 ms) of grand average induced alpha-band (8-12 Hz) power to the non-target timbres in the WS group. In the WS group, but not the TD group, greater induced alpha power was seen to the cello vs. trumpet timbre (200-662 ms, p=0.052). Electrodes belonging to the significant cluster are marked with *. The black box depicts the time and frequency of the significant cluster. The same scale applies to all plots.

discrimination of non-target timbres, both in P300 amplitude and induced alpha activity to two non-target timbres. Thus, results provide the first neural evidence for prior anecdotal reports of enhanced timbre sensitivity in WS.

Timbre perception is believed to rely on multiple areas within the brain. Though there is evidence for bilateral timbre processing (Menon et al., 2002), the anterior part of the right temporal lobe appears to be particularly important (Samson, 2003; Samson & Zatorre, 1994). Neuroimaging studies in WS reveal relative preservation of the temporal lobes bilaterally despite overall reduction in cortical volume (e.g., Chiang et al., 2007; Martens, Reutens, & Wilson, 2010; Reiss et al., 2000; Reiss et al., 2004). Some studies have reported a relative increase in the right planum temporale in WS leading to a lack of typical left>right asymmetry (Eckert et al., 2006; Galaburda & Bellugi, 2000), while others have reported no difference in asymmetry (Martens et al., 2010) or even greater left asymmetry (Wengenroth et al., 2010). Histological analysis of three brains from individuals with WS reported larger cells in bilateral primary auditory cortex (Holinger et al., 2005). Thus, the structural differences of proportionally larger temporal lobe structures and cells may underlie enhanced timbre perception in WS.

The difference in P300 amplitudes to the target vs. non-target timbres and between the non-target timbres, as well as the differential alpha-band activity to the non-target timbres in WS may reflect differences in sensory and attentional auditory processes in persons with WS. They may be more sensitive to the psychoacoustic, including temporal and spectral, qualities of sounds, which may affect their ability to appropriately attend to elements in their auditory environment. Indeed, in a survey study of 78 children with WS, approximately two thirds were rated by their parents as displaying definite abnormalities, and another quarter were rated as having probable abnormalities, in auditory filtering, or the ability to select versus ignore sounds appropriately (John & Mervis, 2010). The P300 indexes both attention and

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memory updating of the target stimulus, and its amplitude decreases as task demands (e.g., available attention) increase (Polich, 2007). The overall lower amplitude of the P300 response across timbres in WS may reflect the greater difficulty they have in focusing their attention on a specific target auditory stimulus amongst auditory distractors. Additionally, the presence of, albeit smaller, P300-like responses in WS to the non-target timbres may reflect their broad attentional focus on all the timbre stimuli and a concomitant difficulty with categorizing targets vs. non-targets.

In contrast to the P300 response, which requires conscious attending to a target, alpha-band activity is thought to reflect both attentional and sensory-specific processing (e.g,. Banerjee, Snyder, Molhom, & Foxe, 2011; Peng et al., 2012; Schurmann & Basar, 2001). Recently, Peng et al. (2012) reported that induced alpha-band activity to targets was due to top-down attention-directed mechanisms, while for the non-targets, it appeared to result from specific sensory processing of the stimuli. In the current study, we found differential alpha-band activity to the non-targets in the WS group. Thus, consistent with anecdotal reports and questionnaire studies of auditory sensitivities in WS, this may reflect greater auditory sensitivity to psychoacoustic features of the two non-target timbres. In line with previous studies (Peng et al., 2012), the alpha-band power differences were long-lasting and preceded the P300 component. Thus, it is plausible that sensory sensitivities to the non-target timbres in persons with WS relate to their difficulties allocating attention only to the target timbre and away from the non-target timbres.

In the WS group only, the non-target cello timbre, relative to the non-target trumpet timbre, elicited greater P300 amplitude and had greater induced alpha-band power. Most oddball studies of timbre perception in TD individuals do not report direct comparisons among the non-target stimuli but there is some precedence for the string instrument timbre being associated with greater neural response than the brass instrument timbre. Crummer et al. (1994) reported greater P300 amplitudes in an oddball task of discriminating between two string instrument timbres (cello vs. viola) than between two brass instrument timbres (B-flat vs. F tubas). Levy and colleagues (2003) report a greater P300-like component in response to non-target string instrument timbres (particularly cello) in comparison to non-target brass or woodwind timbres. The authors suggest this may be due to string instruments' perceptual similarity to the human voice, which may be particularly salient to listeners.

Future research should examine how this musical timbre sensitivity affects the auditory and musical phenotype of WS. For example, it is plausible that their sensitivity to timbre relates to their increased emotional responsiveness to music. In TD individuals, timbre manipulations within and across instruments changes emotional tone (Goydke, Altenmuller, Moller, & Munte, 2004). A recent EEG study found that individuals with WS, but not TD individuals, showed differential alpha-band power to task-irrelevant 500 ms happy or sad musical excerpts (Lense, Gordon, Key, & Dykens, 2012). Timbre was one way in which the happy and sad musical excerpts differed, though other musical characteristics (e.g., number of notes) also differentiated the emotional excerpts.

There are limitations to the current study, which point toward directions for future research. The sample size was relatively small, though it was larger or similar to samples in previous studies examining the neural underpinning of auditory processing in WS (e.g., Levitin et al., 2003; Thornton-Wells et al., 2010). It will be important to examine the role of musical training and musical listening habits in timbre sensitivity in WS. Previous research suggests that individuals with WS spend more time playing and listening to music than TD controls (Levitin et al., 2005). Timbre differentiation may improve in individuals with musical training (Chartrand & Belin, 2006). However, as timbre perception tends to be enhanced specifically for the instrument of training (Pantev, Roberts, Schulz, Engelien, & Ross, 2001), and individuals with WS most typically play percussion instruments and not the cello or trumpet (Levitin & Bellugi, 2006), concerns about musical training confounds are somewhat attenuated in the current context. Based on prior research of an emphasis on temporal versus spectral cues when processing auditory information in WS (Wengenroth et al., 2010), research should examine how perceptual processing style affects timbre perception. Given the seeming increased noticing of and interest in specific timbres in WS (Levitin & Bellugi, 1998, 2006), it would be of interest to examine the breadth and depth of timbre processing in WS. For example, do individuals with auditory fascinations (Levitin et al., 2005) have greater timbre sensitivities than those without? Is this specific to their class of auditory fascinations (e.g., vacuum cleaners) or does it generalize to a wide array of timbres? Finally, given the overlap in music and language processing (e.g., Lima & Castro, 2011), do the timbre sensitivities in WS also occur in the vocal domain to help them distinguish between different speakers?

In summary, using an EEG paradigm, the current study found physiological support for the anecdotal reports of greater timbre sensitivity in WS. Their timbre perception abilities appear to be due to both auditory sensitivity and auditory attention differences. Future research can examine timbre in the context of real music to explore how timbre perception relates to the increased interest and emotional responsiveness to music that are hallmarks of the WS phenotype.

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