Abnormal fMRI Activation Pattern During Story Listening in Individuals With Down Syndrome

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Abstract

Down syndrome is characterized by disproportionately severe impairments of speech and language, yet little is known about the neural underpinnings of these deficits. We compared fMRI activation patterns during passive story listening in 9 young adults with Down syndrome and 9 approximately age-matched, typically developing controls. The typically developing group exhibited greater activation than did the Down syndrome group in classical receptive language areas (superior and middle temporal gyri) for forward > backward speech; the Down syndrome group exhibited greater activation in cingulate gyrus, superior and inferior parietal lobules, and precuneus for both forward speech > rest and backward speech > rest. The Down syndrome group showed almost no difference in activation patterns between the language (forward speech) and nonlanguage (backward speech) conditions.

Down syndrome, which is caused by full trisomy of chromosome 21 in 95% of cases (Antonarkis, 1991) affects 1 in 733 live births, making it the most common genetic cause of mental retardation (Centers for Disease Control and Prevention, 2006). Although the Down syndrome cognitive profile includes global impairment, speech and language are disproportionately impacted. Short- and long-term verbal working memory are also relative weaknesses and visuospatial skills, a relative strength (Wang, 1996). Early language development in Down syndrome is characterized by relative strengths in gesture use and imitation and relative weakness in intelligibility (Abbeduto, Warren, & Conners, 2007). More profound language deficits in Down syndrome emerge later; the age of first spoken word averages 21 months in Down syndrome (Stoel-Gammon, 2001) versus 1 year in typically developing children (Tomasello, 2003). Expressive

vocabulary delays continue and often increase throughout development, whereas receptive vocabulary keeps pace with or exceeds nonverbal cognitive level (Abbeduto et al., 2007). In early adolescence, receptive and expressive syntax skills are poor relative to both nonverbal cognition and other areas of language such as receptive vocabulary (Abbeduto et al., 2007). Fortunately, there is growing evidence that expressive syntactic abilities improve in later adolescence, and these improvements continue into adulthood (Chapman, Hesketh, & Kistler, 2002).

Although language deficits in Down syndrome have been relatively well-characterized, little is known about their neural underpinnings. Dichotic listening and the measurement of mouth asymmetry during speech, techniques used to investigate hemispheric dominance for language processing, have not revealed consistent deviations from the typically developing pattern of left hemisphere language dominance. In several studies researchers have reported atypical left ear (right hemisphere) advantage in those with Down syndrome on dichotic listening tasks (Chua, Weeks, & Elliot, 1996), whereas others have found only those with relatively poorer language skills have a left ear advantage (Bunn, Walsh, Simon, Howarth, & Elliott, 2003). Still others found no evidence for a left ear advantage (Tannock, Kershner, & Oliver, 1984) or left mouth asymmetry (Heath & Elliott, 1999). Elliott, Weeks, and Chua (1994) suggested that individuals with Down syndrome may have a dissociated pattern of cerebral language lateralization, with left ear/right hemisphere specialization for speech sounds (receptive or auditory language processing), but left hemisphere lateralization for speech-related movement. Thus, it remains unclear to what extent aberrant lateralization may underlie or reflect language deficits in Down syndrome.

Structural MRI studies comparing children and adults with Down syndrome and no dementia to typically developing control subjects have produced largely convergent findings of reduced overall brain volume, with disproportionate reduction of cerebellar and hippocampal volumes, relative enlargement of the parahippocampal gyrus, and increases in subcortical gray matter (Pinter, Brown, et al., 2001; Pinter, Eliez, Schmnitt, Capone, & Reiss, 2001; Raz et al., 1995). The *planum temporale* (the posterior–superior portion of the superior temporal gyrus), a region believed to be important in auditory

processing and language comprehension, has also been noted to be smaller in adults with Down syndrome (Frangou et al., 1997). In contrast, positron emission tomography (PET) studies in which investigators measured cerebral glucose metabolism in individuals with Down syndrome have been inconclusive; although some researchers studying adult samples have found deficient cerebral glucose metabolism in areas of brain involved in language processing in Down syndrome (Azari et al., 1994), others have found cerebral glucose metabolism comparable to (Schapiro et al., 1990) or higher than (in some brain areas) (Lengyel et al., 2006) that of age-matched controls.

Structural neuroimaging studies have, therefore, indicated possible neuroanatomical bases for the Down syndrome cognitive phenotype, but have yet to convincingly link these structural abnormalities to functional deficits (Frangou et al., 1997). Hundreds of functional MRI (fMRI) studies have been published in which researchers evaluated children and adults with various neurodevelopmental disorders, yet to our knowledge, there have been no published studies in which fMRI was employed in Down syndrome. In this study, we used fMRI to investigate whether individuals with Down syndrome exhibit aberrant language-related activation patterns compared to an approximately age-matched typically developing control group, during an easily performed passive story-listening task. Although the use of an age-matched control group results in Down syndrome status being confounded with mental age (MA), both brain development and amount of language experience are more similar when comparing groups matched on chronological age (CA) rather than MA. Furthermore, the growing literature on language-related fMRI activations throughout typical development may help disambiguate the causes of the between-group differences in the current study (Ahmad, Balsamo, Sachs, Xu, & Gaillard, 2003; Holland et al., 2007). Therefore, we believe that the comparison of age-matched groups with and without Down syndrome will make a substantial contribution to current knowledge of the neural correlates of language deficits of individuals with Down syndrome, especially given the lack of any prior high-spatial resolution information on functional activations in the Down syndrome brain. Based on the documented language impairments, and structural and metabolic neural abnormalities in

VOLUME 114, NUMBER 5: 369–380 | SEPTEMBER 2009 AJIDD

FMRI during listening in people with Down syndrome E. A. Reynolds Losin et al.

Down syndrome, we expected that the Down syndrome group would have decreased magnitude and/or spatial extent of activations compared with the control group in receptive language regions during the story-listening task. Additionally, based on dichotic-listening studies (Chua et al., 1996), we expected that the predicted deficits in functional activations in the Down syndrome group might be greater in the left than right hemisphere, resulting in an abnormal right-dominant pattern of functional language lateralization.

Method

Participants

Nine individuals with Down syndrome (4 male, 5 female; mean age 22.0 years, range = 16.5 to 26.6) and 9 typically developing comparison participants (5 male, 4 female; mean age 17.8 years, range = 12.6 to 23.6) were studied. One participant in each group was left-handed; the remaining 8 were right-handed, according to parental and participant report. All participants with Down syndrome had characteristic facial features consistent with a diagnosis of Down syndrome, with parental report of karyotype-confirmed full trisomy 21. All of them lived at home, were able to communicate verbally, and were able to follow study directions well. None of the typically developing participants had any cognitive, language, vision, or hearing concerns.

Participants with Down syndrome were recruited through UC Davis Institutional Review Board-approved advertisements and presentations by the fifth author to local parent groups. Typically developing participants were recruited through both advertisements and a database of local families interested in psychology research at UC Davis. All potential participants were screened by phone for Down syndrome diagnosis (including parent confirmation of karyotype-confirmed full trisomy 21), handedness, adequate vision and hearing to read words on a computer screen and to follow spoken directions without glasses or hearing aids, minimum first-grade reading level by parent estimate, ability to stay still and follow directions, and any potential medical contraindications to having an MRI scan. Prior to scanning we explained the entire study to participants and parents, obtained written informed consent, written and/or oral assent of the minor or dependent participants, and completed MRI contraindication screening in accordance with the Imaging Research Center and Institutional Review Board of UC Davis.

Prescan Training

Before each scan participants completed a practice version of the listening task as well as an overt picture-naming task using line drawings (Snodgrass & Vanderwart, 1980), from which behavioral data were obtained. In each case, stimuli were distinct from those used in the scanner. For younger participants and those expressing anxiety, we mailed an instructional child-oriented DVD created at the UC Davis M.I.N.D. Institute with information about having an MRI (Day, Bacalman, & Trepagnier, 2004). Participants judged to require additional preparation then practiced lying still in a mock scanner while listening to sounds of the various pulse sequences used in the experiment.

Behavioral Language Assessment

All participants completed a picture-naming task in the scanner as a general measure of vocabulary and cognitive level. Ten sets of 8 picture stimuli (80 total images) were chosen from the original set of 260 Snodgrass-Vanderwart (1980) unambiguous line drawings of common objects. The 80 items selected were chosen for being clearly recognizable by the authors and limited to those with intended name of only one or two syllables to allow adequate time for participants to identify and speak the name within the 2-s period for which each stimulus was presented via a standard rear-projection system and a head-coil-mounted mirror. After each series of 8 pictures was presented, participants were then shown 8 pixellated images of the same line drawings for 2 s each. This control task was designed to allow subtraction of nonlanguage, visually related activations during fMRI analysis. Due to excessive participant motion when speaking during this task, however, only behavioral data could be analyzed. Preceding each block of pictures or pixellated images, participants viewed either "Name Out Loud" or "Just Look," each for 2 s. Total task time was 6 min, 8 s. Audio files were recorded and scored by one of the authors for each item as to whether the spoken word was an exact or a within-category match for the intended name of the picture. Examples of

within-category matches for pictures with intended names of *boot* and *ant* would be *shoe* and *bug*, respectively. We calculated the mean percentage correct and range of scores for each group for both exact and within-category matches and then used one-tailed *t* tests to compare the groups' performances.

Story-Listening Task Development and Presentation

The fMRI task was created using Presentation® software (Neurobehavioral Systems, Inc., Albany, CA) on a PC computer. During imaging, participants wore MRI-compatible headphones (MR Confon, Magdeburg, Germany), through which we presented a passive story-listening task consisting of ten 20-s blocks of a female voice reading a novel children's story (written by the fifth author), alternating with ten 20-s blocks of the same passages played backward as the comparison condition, intended as a control for nonlanguage aspects of story stimuli. The children's story was written to always include full sentences of equal length during each block and to be very simple, as reflected by the Flesch-Kincaid grade level (an approximation of number of years of education required to read the text) of 2.6, calculated by the formula (0.39 × average words per sentence) + 11.8 × average syllables per word) − 15.59 (Kincaid, Fishburne, Rogers, & Chissom, 1975) by use of an online calculator (Child, 2008). A similar task has been used in a number of other studies and has been shown to produce reliable activations in classical receptive language areas (Harrington, Buonocore, & Farias, 2006). In order to decrease attempts to decipher the backward speech, we applied a 100–1600 MHz Butterworth bandpass filter to these passages, reducing the prominence of fricatives and harsh consonants. We performed speech recording and manipulation using Adobe Audition 2.0 software (Adobe Systems, Inc., San Jose, CA). Between the forward and backward speech blocks, participants viewed "Listen to the Story" (preceding blocks of forward speech) or "Rest" (preceding blocks of backward speech), each for 2 s, via a standard rear-projection system and a head-coil-mounted mirror. Immediately after scanning, participants' responses to several comprehension questions (e.g., "What was the boy's name?" "What kind of pet did the boy have?" and "What did the dog do?") were obtained in order to confirm that they had been able to hear and attended to the task.

fMRI Image Acquisition

The fMRI data were collected on a 3T Siemens Trio scanner using a Siemens 8 channel phase array head coil (Siemens Medical Solutions, Erlangen, Germany). During scanning each participant's head was packed into the head coil snugly using foam padding in order to minimize head movement. Thirty-four interleaved axial images (4 mm thick) covering the entire brain were acquired parallel to the anterior commissure–posterior commissure line with a T2-weighted fast gradient echoplanar imaging (EPI) sequence with the following parameters: TR = 2000 ms, TE = 25 ms, flip angle = 90°, field of view = 220 mm, voxel size = 3.4 × 3.4 × 4.0 mm, and total scan time of 7 min, 28 s. To aid in anatomic localization of functional data, we acquired a magnetization-prepared rapid gradient echo (MPRAGE) scan in the same scan session with the following parameters: TR = 200 ms, TE = 3.49 ms, flip angle = 12°, field of view = 220 mm, 176 slices (1 mm thick), voxel size = 0.9 × 0.9 × 1.0 mm, and total scan time of 4 min, 42 s.

fMRI Analysis

Functional MRI data were analyzed using the FMRIB software library (FSL) (Release 4.1, Copyright 2008, the University of Oxford, http://www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004). We preprocessed the functional time-series data from each participant using several steps, including slice timing correction, motion parameter estimation, and correction using FMRIB's motion correction linear registration tool (MCFLIRT) (Jenkinson, Bannister, Brady, & Smith, 2002), application of a high-pass filter with a cutoff of 84 s, and spatial smoothing with a 6 mm Gaussian smoothing kernel. Subsequent to motion parameter estimation, any images that exceeded 2 mm of movement were removed (typically developing = 26 volumes removed from 1 participant, Down syndrome = 262 volumes removed from a total of 4 participants). The groups did not differ significantly in number of volumes, with over 2 mm of head movement, $t(16) = -1.59$, $p = .133$ (two-tailed), suggesting that the groups did not differ significantly on their head motion. All participants included in the

VOLUME 114, NUMBER 5: 369–380 | SEPTEMBER 2009 AJIDD

FMRI during listening in people with Down syndrome E. A. Reynolds Losin et al.

analysis retained at least 40 volumes of each condition (forward and backward speech) after motion correction, and major activation patterns were qualitatively unchanged by the motion correction procedure.

We conducted statistical analysis of the blood oxygen level dependant (BOLD) signal differences between the forward and backward speech condition for each participant using FMRIB's improved linear model (FILM), which uses the general linear model with voxel prewhitening to correct for time-series autocorrelation. The results of the single-subject analysis were used to create Z-statistic images of whole-brain activation with a cluster threshold of $Z > 1.7$ and a corrected cluster threshold of $p < .05$. We registered each participant's low resolution functional data to his or her own high resolution structural image using a 6 parameter transformation, which we then registered to a standard image (Montreal Neurological Institute 152 template, MNI152) using a 12 parameter transformation.

Higher level analyses were carried out using FMRIB's local analysis of mixed effects (FLAME). We averaged differences in functional activity between the forward and backward speech condition for the Down syndrome and the typically developing groups; the resulting Z-statistic images were generated with a cluster threshold of $Z > 1.7$ and a corrected cluster threshold of $p < .05$. Both within- and between-group comparisons in these analyses were one-tailed. We used linear regression analyses to investigate the effects of age on activation because of a significant age difference between groups, $t(16) = 2.42$, $p = .03$; however, virtually no age-related activations were found in either group.

Three contrasts of interest were examined in single-subject and higher level analyses: forward speech > rest, backward speech > rest, and forward speech > backward speech. The forward speech > rest contrast was intended to identify all activations related to receptive language processing, which typically includes large areas of left-biased bilateral activations in superior and middle temporal gyri as well as smaller foci of activation in frontal, parietal, and cerebellar cortices in some tasks. The backward speech > rest contrast was intended to target nonlanguage-specific aspects of receptive language processing, such as auditory processing, that are typically associated with activations in primary auditory cortex (superior temporal gyrus) that are not left-lateralized.

Finally, the forward speech > backward speech contrast was intended to isolate the language-specific aspects of receptive language processing, typically left-lateralized areas of superior temporal gyrus extending beyond primary auditory cortex (Ahmad et al., 2003; Harrington et al., 2006)

Results

Behavioral Measures

All participants were able to recall story details immediately after scanning, indicating a basic level of task compliance and comprehension for all participants. One with Down syndrome was unable to answer any questions about the story on the first scan attempt but admitted to falling asleep, so no behavioral or fMRI data were used from that scan session. A repeat scan was scheduled when she was well-rested, and she had no difficulty answering basic questions regarding the story. Visual monitoring of participants during scanning by the fifth author in all cases except for this one revealed that all participants were awake and alert throughout the task and displayed minimal movement.

Behavioral data from the picture-naming tasks were obtained for all typically developing participants and for 7 of 9 participants with Down syndrome. Of the 2 participants for whom no auditory data were obtained, one was due to failure of recording equipment for a participant who was visually observed participating very well on the task. Although the other participant did provide spoken responses to each picture stimulus presented, because he had articulation problems we were unable to understand his speech for analysis. We were not able to reschedule either of these participants for a repeat scan. Mean percentage of exact matches for the typically developing group was 89.3 (range = 80.8 to 95.0) and for the Down syndrome group, 81.1 (range = 62.2 to 93.1). Mean percentage of within-category matches for the typically developing group was 99.9 (range = 98.7 to 100), and for the Down syndrome group, 98.1 (range = 91.9 to 100). Scores for both exact matches, $t(14) = -1.89$, $p = .04$, and within-category matches, $t(14) = -1.78$, $p = .05$, were significantly lower in the Down syndrome group.

fMRI Results

The Montreal Neurological Institute (MNI) coordinates and anatomic locations of maximum

VOLUME 114, NUMBER 5: 369–380 | SEPTEMBER 2009   AJIDD

FMRI during listening in people with Down syndrome   E. A. Reynolds Losin et al.

Z values within each significant cluster for each group's average and group comparison statistical maps are listed in Table 1. In order to examine all activations underlying significant between-group differences, we did not correct within-group statistical maps for multiple comparisons. Note that major clusters of BOLD activation in the typically developing group forward speech > backward speech contrast did survive correction for multiple comparisons (Figure 1c) while statistical activity in the other within-group contrasts presented in Figure 1 (forward speech > rest and

Table 1. Montreal Neurological Institute (MNI) Coordinates, Anatomic Locations, and Volume in Voxels of Significant Clusters of BOLD Activation During Listening by Group

Anatomic location of maximum Z value within each significant (Z > 1.7) cluster	MNI coordinates			Max Z	Voxels
	X	Y	Z		
TD[a] group average					
Forward > rest[b]					
Left superior temporal gyrus	−50	−18	4	5.55	6579
Right superior temporal gyrus	54	−24	0	5.01	5431
Left superior frontal gyrus	−6	10	68	3.75	1859
Backward > rest[b]					
Right middle temporal gyrus	66	−18	−10	4.36	3832
Left superior temporal gyrus	−50	−18	6	4.91	3056
Left superior frontal gyrus	−10	20	62	3.31	1113
Forward > backward					
Left middle temporal gyrus	−50	12	−22	6.53***	21686
DS[c] group average					
Forward > backward[b]					
Left superior temporal gyrus	−46	16	−28	2.07	103
Left middle temporal gyrus	−52	−12	−16	2.28	102
Left middle frontal gyrus	−56	10	38	1.96	30
Forward > rest[b]					
Left middle temporal gyrus	−58	4	−14	3.79	2706
Right medial frontal gyrus	4	48	−8	3.24	2282
Left superior temporal gyrus	−40	14	−38	2.97	615
Backward > rest[b]					
Left medial frontal gyrus	−2	50	−8	3.27	2825
Left superior temporal gyrus	−54	0	−6	3.9	2205
Right superior temporal gyrus	48	−2	−8	3.09	1288
TD > DS					
Forward > backward					
Right middle temporal gyrus	52	−30	0	5.21**	4629
DS > TD					
Forward > rest					
Right precuneus	16	−64	50	3.84	11643
Backward > rest					
Right precuneus	4	−72	50	3.72*	15787

[a]Typically developing. [b]Activation only significant at $p < .05$ uncorrected for multiple comparisons. For each of these contrasts, the three clusters with lowest p values are displayed. [c]Down syndrome.
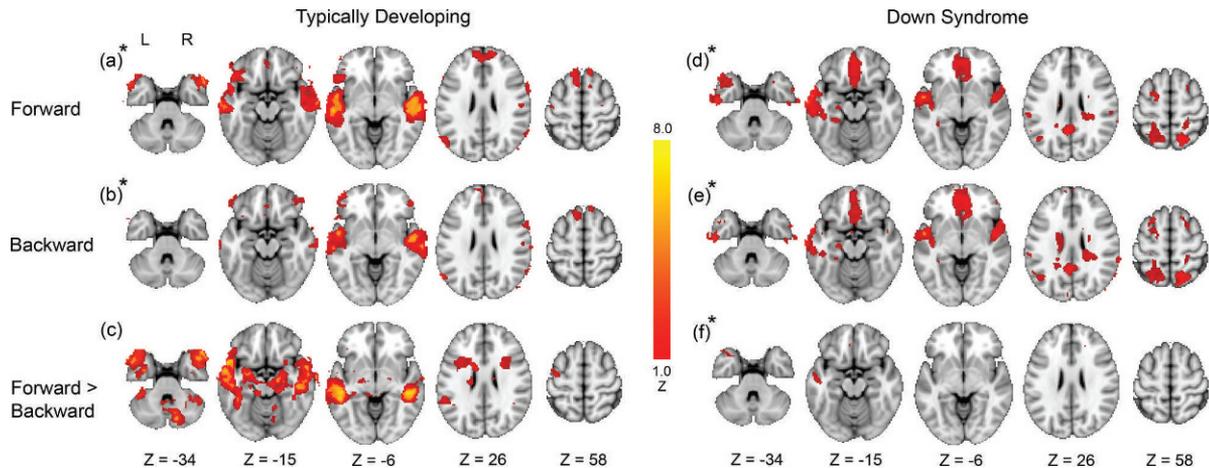*$p < .05$. **$p < .01$. ***$p < .001$.

Figure 1. Statistical maps of significant clusters of fMRI BOLD activation for typically developing and Down syndrome within-group averages for forward speech > rest (top row, a and d), backward speech > rest (middle row, b and e), and forward speech > backward speech (bottom row, c and f) contrasts. Functional activations are displayed on axial slices of the Montreal Neurological Institute (MNI) 152 brain. Activations shown in the typically developing group average for the forward speech > backward speech contrast (c) have a threshold of $Z > 1.7$ for clusters and a cluster threshold of $p < .05$ after correction for multiple comparisons. All other contrasts have a threshold of $Z > 1.7$ for clusters and are not corrected for multiple comparisons (indicated by an asterisk [*] in order to show potential subthreshold effects.

backward speech > rest for both groups, and forward speech > backward speech for the Down syndrome group) did not; see Figure 1a, 1b, and 1d–1f for uncorrected statistical maps of these contrasts. Statistical maps of between-group comparisons described were all corrected for multiple comparisons with a corrected cluster threshold of $p < .05$.

Typically Developing Within-Group Analysis

The typically developing group exhibited BOLD activation in the forward speech > rest contrast in bilateral temporal pole, bilateral superior and middle temporal gyri, left inferior frontal gyrus (BA 47), left angular gyrus, and right posterior lobe of the cerebellum (Figure 1a). The backward speech > rest contrast again revealed bitemporal activation, but this was greatly reduced compared to the forward speech > rest contrast, especially in more anterior temporal areas. Additionally, the left inferior frontal activation was virtually absent, and right cerebellar activation was completely absent (Figure 1b). BOLD activation was greater during forward speech than backward speech (Figure 1c) bilaterally in middle and superior temporal gyri surrounding the superior temporal sulcus (BA 38 and 21), extending from the temporal pole posterior into the angular gyrus and inferior parietal lobule. Significant clusters of activation were also present bilaterally in the superior cerebellum, right posterior cerebellum, bilaterally in the parahippocampal gyrus, and in the left precentral gyrus.

Down Syndrome Within-Group Analysis

The Down syndrome group exhibited BOLD activation in the forward speech > rest contrast (Figure 1d) in left temporal pole, bilateral inferior and superior temporal gyri, left middle temporal gyrus, left angular gyrus, right fusiform gyrus, left parahippocampal gyrus, and left anterior cerebellum. Additionally, prominent clusters of activation were present in bilateral superior and inferior parietal lobule and precuneus, and bilateral anterior and posterior cingulate gyrus, all quite distinct from the pattern seen in the typically developing group for the backward speech > rest contrast (Figure 1e). A virtually identical activation pattern to the forward speech > rest contrast was seen in the backward speech > rest contrast. In the forward speech > backward speech contrast (Figure 1f), only small clusters of BOLD activation were present in left temporal pole, bilateral middle temporal gyrus (left predominant), left superior temporal gyrus, left orbitofrontal cortex, bilateral postcentral gyrus, and left middle frontal gyrus (BA9).

Between-Group Analysis

The typically developing group exhibited significantly larger magnitude activations than the Down syndrome group in the right superior and middle temporal gyri extending from the temporal pole to the angular gyrus in the forward speech > backward speech contrast (Figure 2a). The typically developing group did not have any areas of greater activation than did the Down syndrome group for either the forward speech > rest or backward speech > rest contrasts at the $p <$ .05 corrected threshold.

The Down syndrome group did not have any activation that was greater magnitude than that of the typically developing group in the forward speech > backward speech contrast at the $p < .05$ corrected threshold. The Down syndrome group had greater magnitude activations than did the typically developing group in the forward speech > rest contrast (Figure 2b) in a cluster in the superior parietal lobule and precuneus regions bilaterally that was borderline significant, $p =$ .053, after correction for multiple comparisons.
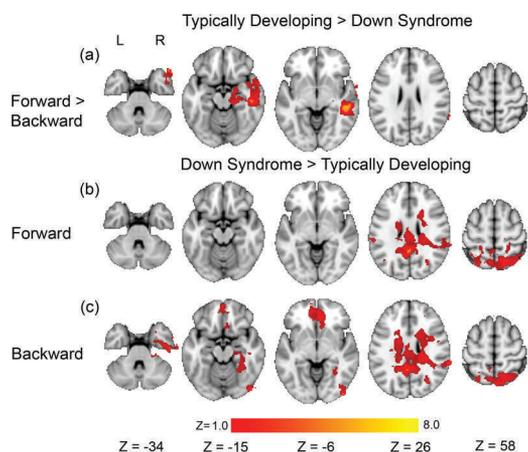

Figure 2. Statistical maps of significant clusters of fMRI BOLD activation for intergroup comparisons, displayed on axial slices of the Montreal Neurological Institute (MNI) 152 brain. (a) Typically developing > Down syndrome, forward speech > backward speech contrast. (b, c) Down syndrome > typically developing, (b) forward speech > rest and (c) backward speech > rest. Activations shown have a threshold of Z > 1.7 for clusters, and a cluster threshold of $p < .05$ after correction for multiple comparisons except for the cluster shown in the forward speech > rest contrast (b), which was marginally significant, $p =$ .053.

This group had greater activation than did the typically developing group in the backward speech > rest contrast (Figure 2c) in the right inferior temporal gyrus, right parahippocampal gyrus, right fusiform gyrus, bilateral anterior and posterior cingulate, bilateral inferior and superior parietal lobules, and bilateral precuneus.

Discussion

In this study, individuals with Down syndrome exhibited differences in BOLD activation patterns compared to a typically developing group during an fMRI story-listening task. Consistent with our predictions, these differences included a significantly lower magnitude of temporal activations when the groups were directly compared. Although the typically developing group showed greater activation in temporal language regions to forward than backward speech, in contrast, the Down syndrome group showed virtually identical activation patterns during these two conditions (Figure 1d and 1e). This finding is confirmed by the presence of very few significant group effects for the forward speech > backward speech contrast even without using correction for multiple comparisons (Figure 1f). Finally, when compared directly, the Down syndrome group exhibited greater activation than did the typically developing group in the anterior and posterior cingulate gyrus in the forward speech > rest contrast (Figure 2b) as well as in the bilateral superior and inferior parietal lobule and bilateral precuneus in both the forward speech > rest and backward speech > rest contrasts (Figure 2b–c). Although the activation pattern in the Down syndrome group forward speech > rest and forward speech > backward speech contrasts was clearly different than that seen in our typically developing controls and that of typically developing groups reported in the literature, our data provide no direct evidence, based on qualitative image assessment, of aberrant right hemisphere language lateralization in the Down syndrome group, as has been suggested by some dichotic listening researchers (Bunn et al., 2003; Chua et al., 1996).

In previous structural (MRI) and functional (PET) imaging studies, researchers have found evidence for reduced volumes (Pinter, Brown, et al., 2001; Pinter, Eliez, et al., 2001; Raz et al., 1995) or aberrant cerebral glucose metabolism (Lengyel et al., 2006) in the brains of individuals

VOLUME 114, NUMBER 5: 369–380 | SEPTEMBER 2009   AJIDD

FMRI during listening in people with Down syndrome   E. A. Reynolds Losin et al.

with Down syndrome, including in classical receptive language areas (Azari et al., 1994; Frangou et al., 1997). Thus, the reduced activations in the Down syndrome group in the superior and middle temporal gyrus during forward speech listening compared to the typically developing group may reflect deficits in connectivity or cellular brain function, which in turn may contribute to their behavioral language deficits.

It is particularly interesting that, in contrast to the typically developing group who showed clear and significant differences in both the magnitude and spatial extent of activations between forward and backward speech listening compared to rest (Figure 1c), participants with Down syndrome showed almost no difference in activation patterns between the language (forward speech) and nonlanguage (backward speech) conditions (Figure 1f). Highly congruent activations in superior and middle temporal gyri during these two conditions in the Down syndrome group suggests that rather than simply having reduced functional activity in receptive language regions, the brains of individuals with Down syndrome may be failing to discriminately activate distinct brain networks to process speech (forward) and nonspeech (backward) sounds typically.

Although the Down syndrome group did exhibit some activation in classical receptive language areas at the $p < .05$ uncorrected threshold in forward speech > rest (Figure 1a) and backward speech > rest (Figure 1b) contrasts, they also exhibited activations in additional areas not seen in the typically developing group. These unique regions of activation are evident both in the within-group averages (Figure 1) and in the intergroup comparisons (Figure 2), including bilateral anterior and posterior cingulate gyrus and bilateral superior parietal lobule and precuneus. The cingulate cortex is known to play an important role in attention (Sarter, Gehring, & Kozak, 2006). Increased cingulate activations in the Down syndrome group could represent a greater attentional requirement to stay focused on the task, given that it may have been more difficult for them as compared with typically developing subjects. Although our story was written at a very basic level and Down syndrome and typically developing participants performed equally well on simple comprehension questions, it is possible that a more sensitive measure would have revealed poorer comprehension, presumably

reflecting greater task difficulty, for the Down syndrome group. Their behavioral performance on the picture-naming task (mean percentage of exact matches) was 81.1, which was significantly lower than the typically developing group mean of 89.3, but fell roughly between typical 6-year-old (72.15) and 8- to 10-year-old (83.65) children's mean performance on normative studies using the full picture set from which the stimuli used in this study were taken (Cycowicz, Friedman, Rothstein, & Snodgress, 1997), indicating at least that the story was written at an appropriate cognitive/age level. Future studies are required for evaluation of whether higher magnitude cingulate activations in Down syndrome (compared with typical development) accompany nonlanguage cognitive tasks as well and whether they are related to task difficulty.

The parietal activations uniquely observed in the Down syndrome group are also intriguing because previous volumetric MRI data have revealed relative preservation of parietal lobe gray matter in Down syndrome (Pinter, Eliez, et al., 2001). Furthermore, both imaging and lesion-based studies have shown the parietal lobes, especially the superior parietal lobule, to be heavily involved in visuospatial processing and visual attention (for a review see Husain & Nachev, 2007) areas of relative strength in Down syndrome (Wang, 1996). It is possible that the inferior and superior parietal lobules are compensatorily active in the performance of this listening task for individuals with Down syndrome, perhaps due to an increased reliance on visualization of the auditorily presented story or to increased use (compared to typically developing participants) of these relatively preserved regions specifically for auditory language processing as a result of abnormal functional connectivity during brain development.

Because we did not find significant differences in the pattern of lateralization of activations between typically developing and Down syndrome groups, this study does not provide evidence for aberrant rightward lateralization of language-related brain activity, as has been suggested in previous dichotic listening studies (Chua et al., 1996). However, in one of these studies, Bunn et al. (2003) indicated that aberrant lateralization was restricted to those individuals with Down syndrome who had more severe language impairments, so perhaps inclusion of such subjects in future fMRI studies using the current paradigm will show a spectrum of severity-

associated lateralization abnormalities. Future fMRI studies of expressive language (i.e., speech) or other specific aspects of language (e.g., syntax, semantics) may reveal abnormal lateralization. Our participants with Down syndrome did show good ability to successfully complete a picture-naming (expressive language) task, but, unfortunately, their speech-related movement was excessive and prevented analysis of the fMRI data. We expect that future, larger fMRI studies of both receptive and expressive language will be able to overcome these problems with longer periods of training and a possible change to a covert (silent) naming task to decrease movement, as well as with utilization of expected advances in motion correction software.

An important limitation of our study is that our comparison group was not matched for MA. We chose a CA-matched comparison group primarily because matching for MA would have resulted in some individuals in a typically developing comparison group being too young to reliably cooperate with the scanning procedure. In addition, we believe that trying to compare very young children to young adults with Down syndrome is problematic because it would result in major differences in brain development and years of language experience between groups that could also have represented a major confound to interpretation. Data suggesting that the differences between the typically developing and Down syndrome groups might indeed be due to Down syndrome status rather than the MA difference between groups come from a large story-processing fMRI study of 5- to 18-year-old typically developing children ($N = 269$), including the age group of typically developing children most closely matching Down syndrome picture-naming performance in the current study (Holland et al., 2007). The activation pattern reported (left-biased bilateral superior and middle temporal activations) was similar to those noted in both previous fMRI studies of receptive-language-related tasks in adults (Harrington et al., 2006) and to those in the typically developing group in our study and dissimilar from the Down syndrome group in our study. However, it will be very important in future studies to include a comparison group of individuals with intellectual disability other than Down syndrome, but with comparable verbal IQ (or other measures of language performance), to truly determine whether the pattern seen here is syndrome-specific.

Another question that we did not address in this study is whether there are differences in resting state fMRI activations between typically developing individuals and those with Down syndrome. Resting state abnormalities in Down syndrome are of particular interest for future researchers because the pattern of activations in the Down syndrome group in our study during both forward and backward speech is very similar to that of the default mode network, a network of regions, including the posterior cingulate, ventral anterior cingulate, and inferior parietal lobes, that in typically developing individuals has been found to be active during rest and to deactivate during task performance (Greicius, Krasnow, Reiss, & Menon, 2003). In our data, it appears that this network may not be deactivating during the listening task in the Down syndrome group as it is in the typically developing comparison group. Abnormalities in default state fMRI activations have been found in individuals with other neurological disorders, including Alzheimer's disease (Greicius, Srivastava, Reiss, Menon, & Raichle, 2004), schizophrenia (Garrity et al., 2007), and attention deficit hyperactivity disorder (Uddin et al., 2008). Thus, resting state analyses in individuals with Down syndrome represent another important future research direction that may help us better understand the observed fMRI activation differences.

Although this study represents a starting point for identifying evidence for functional differences related to language in Down syndrome, it is not clear whether the abnormal patterns noted represent dysfunctional activity that higher function or training can normalize, or whether this (particularly the anterior cingulate and parietal activations) represents the best compensatory strategy for brains with unique structural and connectivity deficits.

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