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White matter impairment in the speech network of individuals with autism spectrum disorder

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Impairments in language and communication are core features of Autism Spectrum Disorder (ASD), and a substantial percentage of children with ASD do not develop speech. ASD is often characterized as a disorder of brain connectivity, and a number of studies have identified white matter impairments in affected individuals. The current study investigated white matter integrity in the speech network of high-functioning adults with ASD. Diffusion tensor imaging (DTI) scans were collected from 18 participants with ASD and 18 neurotypical participants. Probabilistic tractography was used to estimate the connection strength between ventral premotor cortex (vPMC), a cortical region responsible for speech motor planning, and five other cortical regions in the network of areas involved in speech production. We found a weaker connection between the left vPMC and the supplementary motor area in the ASD group. This pathway has been hypothesized to underlie the initiation of speech motor programs. Our results indicate that a key pathway in the speech production network is impaired in ASD, and that this impairment can occur even in the presence of normal language abilities. Therapies that result in normalization of this pathway may hold particular promise for improving speech output in ASD.

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1. Introduction

Impairments in language and communication are core features of Autism Spectrum Disorder, or ASD (Lord and Risi, 2000; Rogers and DiLalla, 1990). In addition to deficits in higher-level language skills, children with ASD have delayed and/or impaired speech output, including phonological and articulatory problems (Bartolucci et al., 1976; Boucher, 2012; Cleland et al., 2010; Rogers and DiLalla, 1990; Shriberg et al., 2001; Wetherby et al., 1989). These impairments in speech production may be a primary deficit of ASD rather than secondary to other communication deficits. In support of this view, infants at genetic high risk for Autism produce fewer speech-like vocalizations and fewer canonical syllable shapes but more non-speech vocalizations than neurotypical (NT) infants (Paul et al., 2011). These observations suggest that the sensory-motor component of language output may be compromised at a very early stage of development in children with ASD. Even high-functioning adults with ASD process speech differently from age-matched NT participants. For example, they use less inner verbalization to solve planning tasks than NT participants (Williams et al., 2012), and use prosody differently (Depape et al., 2012). In the current study we investigate connectivity within the network of brain regions responsible for speech production (hereafter referred to as the speech network) in high-functioning adults with ASD.

The speech network includes ventral portions of the primary motor and somatosensory cortices, medial and lateral premotor cortices, auditory cortical areas in the superior temporal lobe, and posterior portions of the prefrontal cortex involved in language, working memory, and sequencing (Alario et al., 2006; Bohland and Guenther, 2006; Chen and Desmond, 2005; Gofinopoulos et al., 2010; Indefrey, 2011; Indefrey and Levelt, 2004; Krainik et al., 2003; Peeva et al., 2010; Vigneau et al., 2006). Within this network, the left ventral premotor cortex (vPMC) plays a particularly important role in the generation of speech output. Apraxia of speech, a disorder characterized by an apparent inability to access the motor programs for speech production, is associated with damage to left vPMC and/or adjacent portions of the inferior frontal gyrus (Hillis et al., 2004; Robin et al., 2007). Additionally, intraoperative brain stimulation of the vPMC disrupts speech articulation with high reliability (Duffau et al., 2003; van Geemen et al., 2013), and transcranial magnetic stimulation (TMS) applied to vPMC markedly diminishes the number of correct syllables produced during overt speech (Tandon et al., 2003). According to the Directions Into Velocities of Articulators...
(DIVA) neurocomputational model of speech production (Golfinopoulos et al., 2010; Guenther et al., 2006; Tourville and Guenther, 2011), left vPMC is the key area involved in translating the phonological content of an intended speech message into articular output.

Prior studies have noted some of the differences in neural processing of speech and language in ASD (see (Mody et al., 2013) for a review). Williams et al. (2013) used functional magnetic resonance imaging (fMRI) to investigate brain activity during language processing in ASD. The authors found lower functional connectivity in the left hemisphere language network for both children and adults with ASD compared to their respective NT groups; differences were also found in distribution of activity in the language network and dynamic recruitment of brain regions depending on text content (see also Kana and Wadsworth, 2012). Brain activity during speech and song auditory stimulation in low-functioning children with ASD and age-matched NT participants was investigated with MRI (Lai et al., 2012). Less activity was found in left inferior frontal gyrus in ASD participants compared to NT participants when listening to speech, but more activity in ASD than NT in this region when listening to song. They also found decreased white matter fractional anisotropy in the left arcuate fasciculus of the ASD group, pointing to one possible disturbance in the structural connections of the language network in individuals with ASD.

Converging lines of evidence support the view that ASDs are disorders of connectivity, in which impairments in white matter integrity and reduced coordination of activity across brain regions give rise to core features (Casanova and Trippe, 2009; Courchesne and Pierce, 2005; Minshew and Williams, 2007; Schipul et al., 2011; Thakkar et al., 2008). An impairment of structural connectivity occurring early in neural development would very likely disrupt development of language and speech as these abilities are among the most complex human behaviors and require the coordination of a large number of brain regions.

In the present study, we investigated the integrity of white matter projections in the speech production networks of high-functioning individuals with ASD in order to identify potential causes of ASD-related speech impairments at the neuroanatomical level. Specifically, we used diffusion tensor imaging (DTI) and probabilistic tractography to identify particular tracts within the speech network that are impaired in ASD. Given the importance of vPMC for speech production, we focus our attention on tracts that project to and from this region.

2. Methods

2.1. Participants

18 high-functioning individuals with ASD (age range 16–50) and 18 neurotypical (NT) individuals (age range 19–44), recruited by poster and website advertisement, participated in the present study. ASD participants were diagnosed with Autism, Asperger’s disorder or pervasive developmental disorder, not otherwise specified, by an experienced clinician on the basis of current presentation and developmental history as determined by medical record review and clinical interview. Potential participants meeting DSM-IV criteria for co-morbid psychiatric conditions or substance abuse were excluded. ASD diagnoses were confirmed using the Autism Diagnostic Interview-Revised (Rutter et al., 2003) and the Autism Diagnostic Observation Schedule Module 4 (Lord et al., 1999) administered by trained and experienced research personnel with established reliability. Individuals with known autism-related medical conditions (e.g. Fragile-X syndrome, tuberous sclerosis) were not included.

NT participants were screened to exclude a history of autism or any other neurological or psychiatric condition. All participants were screened to exclude substance abuse or dependence within the preceding six months, and any independent condition that might affect brain function. Table 1 provides participant demographic data and statistical comparisons of group means/medians. There were no significant differences between the ASD and NT groups in age, gender, laterality as measured by the Edinburgh Handedness Inventory (scores of −100 and +100 denote exclusive use of left or right hands, respectively) (Oldfield, 1971; White and Ashton, 1976), parental socio-economic status on the Hollingshead Index (Hollingshead, 1965), and estimated verbal intelligence quotient (IQ) based on a single test of word reading (the American National Adult Reading Test (Blair and Spreen, 1989) for the first eleven subjects in each group and the reading portion of the Wide Range Achievement Test-3 (Wilkinson, 1993) for the last seven subjects in each group). The study was approved by the Partners Human Research Committee, and all participants gave written informed consent after the experimental procedures had been fully explained.

2.2. MRI data acquisition

Images were acquired with a 3.0 T Siemens Trio whole body high speed imaging device equipped for echo planar imaging and a 12-channel head coil. Head stabilization was achieved with cushioning, and all participants wore earplugs (29 dB rating) to attenuate noise. Scan sequence parameters differed slightly for the first 11 participants in each group and the last seven in each group. A high resolution structural T1 image was acquired in the sagittal plane for cortical region of interest (ROI) parcellation, using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (First 11 participants: repetition time (TR), 2530 ms; echo spacing, 7.25 ms; echo time (TE), 3 ms; flip angle 7°, 1 × 1mm in-plane resolution, 1.3 mm slice thickness; last seven participants: TR, 2530 ms; echo spacing, 7.8 ms; TE, 3.39 ms; flip angle 7°, 1.33 × 1mm in-plane resolution, 1.33 mm slice thickness). For DTI acquisition, a single-shot echo planar diffusion-weighted image of the whole brain was acquired using a twice refocused spin echo sequences (Reese et al., 2003) with the following parameters: b = 700 s/mm²; NEX = 1; 10 T2 images acquired with b = 0; 72 diffusion directions; 128 × 128 matrix; 2 × 2 mm in-plane resolution; 64 axial oblique (AC-PC) slices; 2 mm (0 mm gap) slice thickness. For the first eleven participants TR/TE = 8400/82 ms and scan duration was 12″44″, and for the last seven participants TR/TE = 7980/84 ms and scan duration was 9″44″. Diffusion directions were obtained using the electrostatic shell algorithm (Jones, 2004).

2.3. Seed and target regions definitions

White matter seed and target regions of interest (ROIs) for tractography were defined in the T1 MPRAGE structural volumes using a two-step process. First, cortical ROIs were identified according to individual anatomical landmarks using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) automatic image segmentation and cortical reconstruction and labeling. Cortical ROIs were labeled on the FreeSurfer-generated white matter surface using a parcellation system tailored for studies of speech networks (Tourville, 2003). Automated parcellation was followed by review and edits by a neuroanatomical expert (J.A.T.) who was blind to group membership. Second, for each cortical ROI defined in

| Subject characteristics | NT (n = 18) | ASD (n = 18) | Test statistic | P value |
|-------------------------|------------|-------------|----------------|--------|
| Age                     | 28.5 +/- 8.7 | 25.6 +/- 9.2 | t = -0.98 | 0.33 |
| Gender                  | M/F        | M/F         | Fisher Exact  | 0.16 |
| Est. Verbal IQ           | 112.4 +/- 9.3 | 112.4 +/- 9.7 | t = 0.01 | 0.99 |
| Yrs. of Educationa      | 15.8 +/- 1.9 | 15.3 +/- 3.3 | U = 119      | 0.17 |
| Parental SESb           | 53.5 +/- 9.5 | 57.1 +/- 6.8 | U = 171      | 0.37 |
| Handedness (Edin.)      | 86.1 +/- 15.6 | 65.8 +/- 36.5 | U = 107      | 0.08 |
step one, a corresponding WM ROI comprised of the WM voxels lying up to 2 mm below the WM surface adjacent to the cortical ROI was identified. The ROI labels defined in the WM were subsequently transformed into the coordinate space of the diffusion data using FLIRT (Jenkinson and Smith, 2001) for use in tractography analyses. The a priori ROIs, six in each hemisphere, were the ventral premotor cortex (vPMC), supplementary motor area (SMA), ventral motor cortex (vMC), posterior superior temporal gyrus (pSTg), anterior supramarginal gyrus (aSMG), and posterior middle frontal gyrus (pMFG). T-tests were used to detect significant group differences in ROI size; familywise error correction (FWE) for multiple comparisons was computed using permutation tests to insure a false discovery rate of 5% over the entire family of 12 ROI size comparisons.

2.4. DTI data analysis

Diffusion data preprocessing and probabilistic tractography were done using the FMRIB Diffusion Toolbox (FDT, http://www.fmrib.ox.ac.uk/fs/ft/index.html). Preprocessing involved correction for eddy current distortions by affine registration to a non-diffusion-weighted volume (b = 0). Using the same volume, a skull-stripped brain mask was generated to exclude non-brain tissue from further processing and was manually edited for accuracy. Diffusion tensors were fitted at each voxel (Basser et al., 1994). Significant differences in motion between two participant populations can confound group comparisons of DTI data, which are known to be subject to motion artifacts (Anderson and Gore, 1994; Ling et al., 2011). Because our ASD group consisted of high-functioning adults, we did not anticipate motion differences between the ASD and NT groups. A statistical comparison of motion in the two groups was performed to verify this expectation. Motion estimation involved 3 rotational and 3 translational parameters obtained during the affine registration process. For each brain volume collected during the diffusion scan, the change in each motion parameter relative to the prior volume was calculated, and these changes were summed across all volumes to obtain a 6-dimensional motion estimate for each participant. A multivariate analysis of variance (MANOVA) was performed to compare the ASD and NT populations’ means across the six motion parameters.

2.5. Tractography

FMRIB’s Diffusion Toolbox (FDT) version 3.0 from the FMRIB Software Library (FSL) was used for tractography analyses. Probabilistic tractography was performed in each subject using the previously defined ROIs as seed and target masks (Behrens et al., 2003). Tractography was performed from all voxels of each ROI mask. For each voxel in the seed mask 5000 attempts (streamlines) at reaching a target mask was performed from all voxels of each ROI mask. For each voxel (Basser et al., 1994). Significant differences in motion between two participant populations can confound group comparisons of DTI data, which are known to be subject to motion artifacts (Anderson and Gore, 1994; Ling et al., 2011). Because our ASD group consisted of high-functioning adults, we did not anticipate motion differences between the ASD and NT groups. A statistical comparison of motion in the two groups was performed to verify this expectation. Motion estimation involved 3 rotational and 3 translational parameters obtained during the affine registration process. For each brain volume collected during the diffusion scan, the change in each motion parameter relative to the prior volume was calculated, and these changes were summed across all volumes to obtain a 6-dimensional motion estimate for each participant. A multivariate analysis of variance (MANOVA) was performed to compare the ASD and NT populations’ means across the six motion parameters.

2.6. Estimation of tract volume

The number of successful streamlines between two regions estimates the likelihood that a white matter connection between these two regions exists (Behrens et al., 2003; Hagmann et al., 2003; Parker and Alexander, 2003; Tournier et al., 2003). This number reflects not only the microstructural integrity of the white matter, but also the number of voxels in the seed region, as tractography is run from each voxel. Due to inter-individual variability in brain anatomy, the same ROI may differ between two participant populations can confound group comparisons of DTI data, which are known to be subject to motion artifacts (Anderson and Gore, 1994; Ling et al., 2011). Because our ASD group consisted of high-functioning adults, we did not anticipate motion differences between the ASD and NT groups. A statistical comparison of motion in the two groups was performed to verify this expectation. Motion estimation involved 3 rotational and 3 translational parameters obtained during the affine registration process. For each brain volume collected during the diffusion scan, the change in each motion parameter relative to the prior volume was calculated, and these changes were summed across all volumes to obtain a 6-dimensional motion estimate for each participant. A multivariate analysis of variance (MANOVA) was performed to compare the ASD and NT populations’ means across the six motion parameters.

2.7. Estimation of mean fractional anisotropy

Fractional anisotropy (FA) is a measure of the directionality of water diffusion within a voxel. An FA of 0 corresponds to an isotropic distribution while an FA of 1 corresponds to water diffusion only along one axis. Voxels with higher FA values are likely to contain many axons coursing in the same direction, a higher rate of axonal packing, and/or better axonal fiber myelination (Beaulieu, 2002). For each tract, the mean FA for all voxels in the tract was calculated for each participant. A voxel was considered part of the tract if at least 10 successful streamlines (out of hundreds of thousands of attempts) passed through the voxel. This was done to exclude improbable voxels from further analysis. Group means were then calculated, and t-tests were performed to detect significant group differences in mean FA for each tract. FWE correction for multiple comparisons was computed using permutation tests to insure a false discovery rate of 5% over the entire family of 10 comparisons.

2.8. Estimation of tract volume

An estimation of tract volume was calculated for each tract in each subject. Tract volume was defined as the number of voxels through which at least 10 successful streamlines had passed. Group means were then calculated, and t-tests were performed to detect significant group differences in tract volume for each tract. FWE correction for multiple comparisons was computed using permutation tests to insure a false discovery rate of 5% over the entire family of 10 comparisons.
2.9. Canonical tracts

To qualitatively compare group differences in the spatial distribution of successful streamlines between seed and target regions we constructed canonical tracts, which represent the spatial overlap of streamlines across participants in each group. These tracts are primarily used for qualitative comparison and visualization as they are not amenable to rigorous statistical comparisons between groups. Prior to constructing the canonical tracts, the NT and ASD data were registered to a standard brain provided by the FMRIB Library (FMRIB58_FA_1mm). We then binarized the individual subject tracts, setting voxels containing at least 10 successful streamlines to 1 and the remaining voxels to 0. In this manner a voxel value represented only whether a tract was passing through it (1) or not (0). The binarized voxels belonging to individual tracts were then summed across all subjects within each group to obtain the canonical tract for that group. Canonical tracts were then thresholded to include only voxels where at least 12 out of the 18 participants (>60%) had a tract passing through the voxel. For display purposes, the canonical tracts of the two groups were projected onto the standard brain used to coregister the NT and ASD data.

3. Results

Table 2 provides mean ROI sizes, measured as the number of voxels in the ROI, for the ASD and NT groups, along with \( p \) values for differences in ROI size between groups. None of the 12 ROIs showed a statistically significant size difference between the NT and ASD groups. Table 3 provides mean tract strengths for the ASD and NT groups, along with \( p \) values for differences in tract strengths between the groups. Of the 10 tracks analyzed, only the tract between left SMA and left vPMC showed a significant between-group difference in tract strength, with the ASD group having a weaker tract strength between these regions. A MANOVA comparing head motion parameters between the two groups found no significant difference (Wilks’ \( \Lambda = 0.737; p = 0.150 \)), indicating that the difference in the left SMA–vPMC tract strength was unlikely to be the result of motion artifacts. Fig. 2 shows the left SMA–vPMC tract for 5 subjects from each group (randomly chosen) to give a sense of variability across individuals.

To verify that handedness differences between the two groups (which were borderline significant; see Table 1) did not contribute substantially to the finding of reduced left SMA–vPMC tract strength in ASD participants, we performed three linear regressions to examine the relationship between handedness (Edinburgh score) and the strength of this tract in each group separately and both groups combined. None of these regressions were significant (NT: \( F = 771, p = 0.39; \) ASD: \( F = 0.34, p = 0.56; \) NT and ASD combined: \( F = 2.30, p = 0.14)\), suggesting that the between-group laterality difference was not responsible for the group difference in left SMA–vPMC tract strength.

Table 3 Mean tract strengths for each subject group and \( p \) values for between-group differences in tract strength. Boldface indicates a statistically significant difference in tract strength between the ASD and NT groups. \( P \)-uncorr: uncorrected \( p \) value for difference in tract strength between groups. \( P \)-FWE: \( p \) value for difference in tract strength between groups corrected for multiple comparisons at a familywise error rate of 0.05. SD: standard deviation.

| Hemisphere | Tract   | NT tract strength (SD) | ASD tract strength (SD) | \( P \)-uncorr | \( P \)-FWE |
|------------|---------|------------------------|-------------------------|---------------|------------|
| Left       | SMA–vPMC| 0.0059 (0.0070)        | 0.0008 (0.0014)         | 0.005         | 0.031      |
|            | pMFg–vPMC| 0.0848 (0.0378)        | 0.0589 (0.0318)         | 0.033         | 0.236      |
|            | vMC–vPMC| 0.3588 (0.0590)        | 0.3661 (0.0563)         | 0.707         | 1.000      |
|            | aSMg–vPMC| 0.0194 (0.0165)        | 0.0222 (0.0176)         | 0.670         | 1.000      |
| Right      | SMA–vPMC| 0.0046 (0.0066)        | 0.0156 (0.0175)         | 0.018         | 0.128      |
|            | pMFg–vPMC| 0.0038 (0.0061)        | 0.0021 (0.0036)         | 0.315         | 0.968      |
|            | vMC–vPMC| 0.0469 (0.0399)        | 0.0376 (0.0293)         | 0.432         | 0.599      |
|            | aSMg–vPMC| 0.3516 (0.0790)        | 0.3113 (0.0896)         | 0.161         | 0.760      |
|            | pSTg–vPMC| 0.0255 (0.0140)        | 0.0207 (0.0148)         | 0.326         | 0.974      |

Fig. 3 illustrates canonical tracts for each subject group formed by including only voxels that contain the tract in at least 12 of 18 subjects from that group. For the most part, the canonical tracts appear to follow the same routes in the ASD and NT groups. However, the left hemisphere SMA–vPMC canonical tract for the ASD group is visibly smaller in the 2D cross-sections (upper left panel) and 3D rendering (bottom right panel). This canonical tract had over 50% fewer voxels in the ASD group than in the NT group. This finding, combined with the finding of no significant volume differences between the individual participant’s tracts in the two groups, suggests that in addition to a weaker left vPMC–SMA tract strength, ASD participants also showed more variation in the spatial location of the tract than NT participants.

4. Discussion

A detailed understanding of the neural basis of abnormal speech production in individuals with ASD is key to understanding the nature of their communication deficits and to the development of more effective therapies. In this study we examined structural connectivity of the speech production network in high-functioning adults with ASD using DTI and probabilistic tractography. Specifically, we studied connectivity between ventral premotor cortex, which is a key processing center for speech production (Bohland and Guenther, 2006; Chen and Desmond, 2005; Peeva et al., 2010; Williams et al., 2012), and other regions within the speech production network. Connection strength between two anatomically defined regions of interest was estimated as the proportion of the number of streamlines from the seed region that successfully reached the target region. We also calculated the mean FA values for the voxels in each tract and tract volumes as additional measures of connection integrity. Tract strength, FA, and tract volume all can be affected by a number of factors related to white matter structure and integrity (Beaulieu, 2002; Harari et al., 2006). For example, reduced connection strength between two regions could...
SMA axons, or disturbance in the pattern of axonal branching (Zikopoulos et al., 2010). However, any of these factors would be expected to result in reduced communication efficacy between the two regions.

Our primary finding was that connection strength between vPMC and SMA in the left hemisphere is lower in adults with ASD compared to matched neurotypical participants. This was the only significant difference between the ASD and NT groups in any of the tracts, including the left SMA–vPMC tract. The finding of lower tract strength with no mean FA difference in left SMA–vPMC suggests that, although the anisotropies of the diffusion tensors within each voxel of a tract were similar in the two groups, the main axes of diffusion were less aligned between voxels in the ASD group than the NT group. Further study into this issue is warranted in order to verify this interpretation. The finding of no significant differences in individual tract volumes, but a large difference in the left SMA–vPMC canonical tract volume, indicates that the individual left SMA–vPMC tracts in the ASD participants were more variable in their spatial locations than the NT tracts.

The left vPMC has been identified as the primary cortical site for the motor programs that underlie syllable production (Bohland et al., 2010; Guenther et al., 2006; Peeva et al., 2010). Accordingly, damage to this region in the left, but not the right, hemisphere is associated with apraxia of speech (Hillis et al., 2004; Robin et al., 2007). Like vPMC, SMA is consistently active in speech neuroimaging studies (Bohland and Guenther, 2006; Indefrey, 2011; Indefrey and Levelt, 2004; Peeva et al., 2010; Williams et al., 2012), as well as studies of non-speech motor control tasks (Amador and Fried, 2004; Hoshi and Tanji, 2004; Shima and Tanji, 2000). Lesions to the medial wall are associated with speech output deficits (Jonas, 1981, 1987; Pain, 1999; Ziegler et al., 1997), including reduced propositional speech with non-propositional speech (e.g., counting, repeating words) largely intact.

Bohland et al. proposed that the pathway from left SMA to left vPMC is responsible for initiating speech motor programs (Bohland et al., 2010). According to this account, articulation requires activation of neurons in SMA corresponding to the sounds to be produced. Signals from these SMA neurons in turn activate neurons in vPMC via the SMA–vPMC tract. The connection distribution of the vPMC tract is illustrated for 5 NT participants (left column) and 5 ASD participants (right column). Lighter shades represent voxels with more successful streamlines passing through them (see Methods for details). For each subject, the Y coordinate was chosen to highlight the largest cross-section of the tract. L: left hemisphere; R: right hemisphere; Y: location of the slice along the anterior–posterior axis of the Montreal neurological Institute coordinate frame.

Unlike tract strength, mean FA values and tract volumes did not differ between the ASD and NT groups in any of the tracts, including the left SMA–vPMC tract. The finding of lower tract strength with no mean FA difference in left SMA–vPMC suggests that, although the anisotropies of the diffusion tensors within each voxel of a tract were similar in the two groups, the main axes of diffusion were less aligned between voxels in the ASD group than the NT group. Further study into this issue is warranted in order to verify this interpretation. The finding of no significant differences in individual tract volumes, but a large difference in the left SMA–vPMC canonical tract volume, indicates that the individual left SMA–vPMC tracts in the ASD participants were more variable in their spatial locations than the NT tracts.

### Table 4
Mean fractional anisotropy (FA) values for each subject group and p values for between-group differences in FA. P-uncorr: uncorrected p value for difference in FA between groups. P-FWE: p value for difference in FA between groups corrected for multiple comparisons at a familywise error rate of 0.05. SD: standard deviation.

| Hemisphere | Tract            | NT tract FA (SD) | ASD tract FA (SD) | P-uncorr | P-FWE |
|------------|------------------|------------------|-------------------|----------|-------|
| Left       | SMA–vPMC         | 0.417 (0.03)     | 0.412 (0.10)      | 0.876    | 1.000 |
|            | pMFg–vPMC        | 0.319 (0.02)     | 0.325 (0.01)      | 0.333    | 0.964 |
|            | vPMC–vPMC        | 0.310 (0.01)     | 0.321 (0.01)      | 0.798    | 1.000 |
|            | aSMg–vPMC        | 0.338 (0.02)     | 0.322 (0.02)      | 0.050    | 0.282 |
|            | pSTg–vPMC        | 0.354 (0.03)     | 0.335 (0.03)      | 0.080    | 0.452 |
| Right      | SMA–vPMC         | 0.414 (0.03)     | 0.424 (0.03)      | 0.276    | 0.923 |
|            | pMFg–vPMC        | 0.322 (0.02)     | 0.329 (0.02)      | 0.272    | 0.950 |
|            | vPMC–vPMC        | 0.312 (0.02)     | 0.310 (0.02)      | 0.825    | 1.000 |
|            | aSMg–vPMC        | 0.324 (0.02)     | 0.322 (0.02)      | 0.812    | 1.000 |
|            | pSTg–vPMC        | 0.344 (0.02)     | 0.340 (0.02)      | 0.605    | 1.000 |

### Table 5
Mean tract volumes (in voxels) for each subject group and p values for between-group differences in tract volume. P-uncorr: uncorrected p value for difference in FA between groups. P-FWE: p value for difference in tract volume between groups corrected for multiple comparisons at a familywise error rate of 0.05. SD: standard deviation.

| Hemisphere | Tract       | NT tract volume (SD) | ASD Tract volume (SD) | P-uncorr | P-FWE |
|------------|-------------|----------------------|-----------------------|----------|-------|
| Left       | SMA–vPMC    | 1773 (1221)          | 1196 (1092)           | 0.145    | 0.515 |
|            | pMFg–vPMC   | 5438 (2143)          | 5359 (1794)           | 0.906    | 1.000 |
|            | vPMC–vPMC   | 3468 (1012)          | 3694 (1215)           | 0.549    | 0.985 |
|            | aSMg–vPMC   | 5022 (1932)          | 5359 (2402)           | 0.651    | 0.987 |
|            | pSTg–vPMC   | 4750 (2465)          | 5230 (2336)           | 0.553    | 0.985 |
| Right      | SMA–vPMC    | 1630 (821)           | 1153 (652)            | 0.062    | 0.269 |
|            | pMFg–vPMC   | 5096 (1544)          | 5166 (1603)           | 0.894    | 1.000 |
|            | vPMC–vPMC   | 3397 (932)           | 3407 (1102)           | 0.578    | 1.000 |
|            | aSMg–vPMC   | 5395 (1988)          | 5354 (1961)           | 0.951    | 1.000 |
|            | pSTg–vPMC   | 4997 (1887)          | 5142 (2076)           | 0.682    | 1.000 |
commands for the coming utterance, and activation of these neurons sends these commands to the motor cortex and onward to the speech articulators. In keeping with this account, increased activity has been identified in SMA during overt speaking relative to preparing to speak without actually initiating speech output (Bohland and Guenther, 2006). Furthermore, increased effective connectivity between the left SMA and vPMC was found using structural equation modeling of fMRI data collected while participants produce a series of different words compared to when they produce the same word repeatedly (Peeva, 2010).

In this context, the current results suggest that individuals with ASD may have reduced speech output due to impaired SMA–vPMC connectivity in the left hemisphere. Whether the abnormal connectivity between vPMC–SMA is inherent to ASD or instead results from reduced or impaired use of the speech network for communication cannot be established by the present study, which is limited to high-functioning adult participants in whom speech output was not measured. Neuroimaging studies of young children with ASD can more definitively answer this question. The ASD group in the current study was also limited to high-functioning individuals with normal verbal IQ. Our results thus raise the possibility that impaired speech output could occur in ASD in the absence of marked impairments to higher-level language skills, and raise the question of whether nonverbal or minimally verbal individuals with ASD might show an even greater impairment in the left SMA–vPMC pathway.

The current results also shed light on the hypothesis that a dysfunctional mirror neuron system is partially responsible for language deficits in ASD (Iacoboni and Dapretto, 2006). Mirror neurons are cells in premotor cortical areas that respond during both the perception and production of an action (Rizzolatti et al., 1996), and vPMC has been proposed as the location of mirror neurons for speech (Wilson et al., 2004). Our findings raise the possibility that impaired activity of mirror neurons may occur as a result of impaired influence of SMA on vPMC, though further research will be necessary to determine whether impaired SMA–vPMC connectivity is the source of impairment of the mirror neuron system or a consequence of other impairments in that system.

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