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Corpus callosum differences associated with persistent stuttering in adults

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ABSTRACT

Recent studies have implicated anatomical differences in speech-relevant brain regions of adults who stutter (AWS) compared to normally fluent adults (NFA). The present study focused on the region of the corpus callosum (CC) which is involved in interhemispheric processing between the left and right cerebral hemispheres. Two-dimensional segmentation of area and voxel-based morphometry were used to evaluate the corpus callosum. Results revealed that the rostrum and anterior midbody of the CC were larger in AWS than NFA. In addition, the overall callosa area was larger in AWS than NFA. The group comparison of white matter volume showed a cluster of increased white matter volume predominantly encompassing the rostrum across the midline portion in AWS. These results potentially reflect anatomical changes associated with differences in the hemispheric distribution of language processes that have been reported previously in AWS.

Learning outcomes: After reading this article, the reader will be able to: (1) summarize research findings on functional and anatomical differences between AWS and NFA; (2) summarize research findings on anatomical anomalies observed in AWS; (3) discuss the possible relationships between functional and anatomical aberrations in AWS; and (4) discuss how the findings of the present study may support results of previous behavioral investigations (e.g. dichotic listening) in AWS.

1. Introduction

Developmental stuttering occurs in about one percent of the adult population and affects about four times as many males as females (Bloodstein, 1987; Brown, Ingham, Ingham, Laird, & Fox, 2005; Buchël & Sommer, 2004). The direct cause of stuttering remains elusive but wide ranging investigations have identified structural and functional brain differences between adults who stutter (AWS) and normally fluent adults (NFA). The overall pattern of brain differences suggest increased right hemisphere participation in speech production with particular decreases in functional and anatomical anomalies in the left hemisphere of AWS compared to NFA. Several discussions have posited that the right hemisphere

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participation may be a response to the presence of stuttering and potentially emerge from a plastic reorganization of cortical brain functions during development (Preibisch et al., 2003). A prominent structure that could mediate reorganization via interhemispheric connections is the corpus callosum (CC). This hypothesized process of interhemispheric reorganization may prompt enlargement of the CC in AWS. By contrast, the CC of NFA could remain smaller as a consequence of progressive left hemisphere specialization for language during early development. In general, an inverse relationship between callosa size and interhemispheric connectivity has been reported (Witelson, 1989; Wood, Saling, Jackson, & Reutens, 2008; Yazgan, Wexler, Kinsbourne, Peterson, & Leckman, 1995). Accordingly, we propose that the CC in AWS will be larger than NFA reflecting a process of neural reorganization of certain language functions in the right hemisphere. In this view, the presence of stuttering is expected to alter hemispheric connections contributing to an atypical distribution of brain activity for speech production across the cerebral hemispheres.

During speech production, the motor system of AWS shows overactivity that involves right lateralization of the primary motor cortex (M1) and supplementary motor area (SMA) (Fox et al., 1996). Further, left hemisphere regions associated with self-monitoring, comprehension and fluency – including the inferior frontal, primary auditory cortices and auditory association cortices – are either not activated by the task or brain activity is depressed relative to NFA (Braun et al., 1997; Ingham et al., 2004). Braun et al. reported left frontal operculum activity increases during narrative speech and sentence construction tasks in which stuttering episodes occur. In contrast, fluent speech production by AWS was shown to be correlated with increased activity in the right frontal operculum (Braun et al., 1997; Preibisch et al., 2003). Preibisch and colleagues further found the relative activity in right frontal operculum was negatively correlated with severity of stuttering indicating it might serve a compensatory function. Interestingly, in imaging studies NFA with acquired left frontal opercular damage have been observed to recruit the right frontal operculum during tasks that typically require the left hemisphere operculum (Raichle, 1996). Therefore, functional imaging studies have provided evidence that right hemisphere homologues of left hemisphere speech may be activated to a greater extent during speech in AWS and possibly serve a compensatory role in stuttering.

In general, a degree of bilateral activation is present in both AWS and NFA during speech production, but cerebral activity is more lateralized to the left hemisphere in NFA and more right lateralized in AWS (De Nil, Kroll, Kapur, & Houle, 2000) when fluency inducing strategies are not used. A relative shift in cerebral activity is observed following certain fluency treatments with reductions in right hemisphere activation and relatively increased activity in left hemisphere frontal areas (Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983; De Nil, Kroll, Lafaille, & Houle, 2003). The mechanism and timeline of the shift are not known, but the CC is a structure that could mediate the shift.

Converging evidence from anatomical studies suggests that AWS have atypical brain symmetry and distributions of gray and white matter tissue across the cerebral hemispheres. For instance, AWS feature a larger right planum temporale (PT) and right Heschl's gyrus (HG) in contrast to NFA who feature larger left PT and left HG (Foundas, Bollich, Corey, Hurley, & Heilman, 2001; Foundas et al., 2003; Jäncke, Hanggi, & Steinmetz, 2004; Strub, Black, & Naeser, 1987). In other words, leftward asymmetry of the PT which may be a marker of left hemisphere specialization for language does not appear be present in AWS (Dorsaint-Pierre et al., 2006). Differences in cerebral tissue distribution have additionally been reported in studies using objective whole brain measures of gray and white matter volumes. One voxel-based morphometry (VBM) study (Beal, Gracco, Lafaille, & De Nil, 2007) reported increased gray matter in AWS in the right and left superior temporal gyrus (STG), left middle temporal gyrus and left inferior frontal gyrus (including the *pars opercularis*). AWS also had increased white matter in the right STG, right inferior temporal gyrus and right middle frontal gyrus, which fall within close proximity to white matter tracts that connect auditory processing and semantic retrieval regions with other language areas (Beal et al., 2007; Jäncke et al., 2004). Both VBM and diffusion tensor imaging (DTI) studies respectively indicate decreased gray matter volume and reduced fractional anisotropy of white matter tracts in the left Rolandic operculum in AWS and children who stutter (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Jäncke et al., 2004; Sommer, Koch, Paulus, Weiller, & Buchel, 2002). In addition, a recent DTI study (Cykowski, Fox, Ingham, Ingham, & Robin, 2010) reported lower white matter integrity in the callosal body in AWS. Anomalies in white matter development could particularly lead to differences in connections within and between the hemispheres. There are also higher incidences of morphometric aberrations in AWS including the existence of extra gyri and increased variability in gyri arrangement in left and right peri-sylvian regions (Cykowski et al., 2008; Foundas et al., 2001).

In addition to structural and functional brain investigations, behavioral studies indicate differences between AWS and NFA on varied tasks that implicate functional lateralization differences in AWS. In dichotic listening studies, AWS feature diminished right ear advantage or no ear advantage (Blood & Blood, 1989; Newton, Blood, & Blood, 1986; Sussman & MacNeilage, 1975), whereas NFA show right ear advantage consistent with left hemisphere lateralization for language. There are reports of poorer bimanual coordination, which Webster (1990) suggests is a reduced capacity for concurrent motor processing due to interhemispheric interference and/or reduced efficiency of the left hemisphere.

These functional and structural brain findings together with behavioral differences point to atypical development of the cerebral hemispheres, which could encompass differences in functional and structural interhemispheric connectivity. The unusual anatomical development observed in language relevant regions of the brain in AWS is also expected to be evident in the CC. As the largest white matter structure in the brain, the CC accounts for most interhemispheric transfer of information. Past studies have suggested a larger callosa could allow greater connectivity between the two hemispheres of the brain and possibly decreased functional lateralization (Aboitiz, Ide, & Olivares, 2003; Witelson, 1989; Yazgan et al., 1995). In light of the studies identifying right lateralized functional activity and increased white matter volume in the right hemisphere of

AWS, a larger CC could partially account for a lack of functional dominance in the left hemisphere, and compensatory reorganization of anatomical structures in the right hemisphere (Foundas, Corey, Hurley, & Heilman, 2004; Greiner, Fitzgerald & Cooke, 1986; Webster, 1988). The present study uses two distinct approaches to compare the anatomy of the corpus callosum in AWS and NFA.

2. Method

2.1. Participants

A total of eleven male AWS and twelve male NFA between 20 and 35 years of age were recruited using advertisements or by referral from the University of Illinois Speech Language Pathology Clinic. All participants were right-handed by self-report and direct observation. The mean score on the Edinburgh Handedness Inventory (Oldfield, 1971) was 80.08 (sd 13.91, $n = 8$). A diagnosis of persistent stuttering was confirmed in the experimental group by a clinically certified speech-language pathologist with expertise in stuttering. In all cases, overt stuttering was observed by one of the investigators (Ambrose or Kraft).

Participants were asked to rate the current severity of their stuttering using an 8-point scale, with 0–1 indicating normal fluency, 1–2.99 in the range of mild, 3–4.99 as moderate, and 5–7 as severe. The mean score of self-reported stuttering severity was 3.66 (sd 1.61, range 2–6). Three considered their stuttering mild, 5 moderate, and 3 severe. Each AWS reported previous therapy for stuttering, but only two individuals were receiving therapy at the time of the study. All AWS reported a history of stuttering since early childhood. Otherwise, the stuttering and normally fluent participants reported a negative history for neurological, psychiatric, speech, hearing and/or other language disorders. The methods of this study were approved by the Institutional Review Board at the University of Illinois at Urbana-Champaign.

2.2. Imaging

All images were collected on a 3 T Siemens Magnetom Allegra MR Headscanner at the Biomedical Imaging Center of the Beckman Institute at the University of Illinois, Urbana-Champaign. High resolution anatomical volumes encompassing the cerebrum, cerebellum and brainstem were collected using a T1-weighted MPRAGE (magnetization-prepared rapid acquisition gradient echo) sequence (sagittal slice volume = 196, TR = 1600 ms, TE = 2.22 ms). To minimize head movements, participants' heads were padded with foam and lightly held in place with a strap across the forehead. Participants were asked to hold their head still during the scan.

2.3. Two-dimensional segmentation of area

In the first quantitative analysis, each CC was divided into four segments and the area of each segment was calculated using MIPAV (Medical Image Processing, Analysis, and Visualization) (McAuliffe, McGarry, Gandler, Csaky, & Trus, 2001). Segmentation of the CC was performed in a similar method as described in Sullivan et al. (2001). Using MIPAV, the midline CC was visualized and subdivided into four regions in the midsagittal plane: rostrum, anterior midline body, posterior midline body and splenium (Fig. 1a and b). Before the segments were identified, each rater independently selected the sagittal slice from each participant that was considered most representative of the midsagittal plane. In 21/23 cases, both raters independently chose the same midline image. In the other two cases, there was only a difference in one anatomical slice (difference of 1 mm) and the midline image selected by rater 1 was used. As per Fig. 1, the caudal border of the rostrum was marked by a tangent line at the bend of the genu. An identical line dividing the rostral boundary of the body and splenium was placed at the concave bend of the genu. The length of the midline body between these lines was divided exactly in half to mark the anterior and posterior body. Each segment was filled manually using the MIPAV-FILL tool, which also automatically determined the area of the filled region. Ten percent of the data from each group were randomly selected and re-evaluated to measure intra-rater reliability. For inter-rater reliability, 100% of the data was re-analyzed by a second investigator using Intra-class Correlation Coefficients (ICC), who was blinded to the gender, identity and diagnosis of each participant. The t-statistic was used for planned comparisons between the absolute and relative callosa area differences between both groups. Absolute area comparisons were conducted for overall area and individual segment areas.

2.4. VBM analysis–regions of interest

A voxel-based morphometry analysis of the corpus callosum was conducted with SPM5 using the default options recommended for this version (Wellcome Trust Centre for Neuroimaging, London, UK). Spatial normalization, segmentation and modulation were performed with the unified segmentation algorithm in SPM5. Our approach to the whole brain processing follows Beal et al. (2007) exactly for the initial processing except where we focused on a region of interest (ROI) of the corpus callosum, rather than a whole-brain comparison. For our purposes, only the white matter images were retained and then smoothed with a 10 mm full-width-half-maximum filter. The normalized white matter images of each subject were then masked with the corpus callosum region-of-interest (ROI) mask from the WFU PickAtlas toolbox developed by the ANSIR laboratory at Wake Forest University (Department of Radiology, Wake Forest University School of Medicine, Winston-

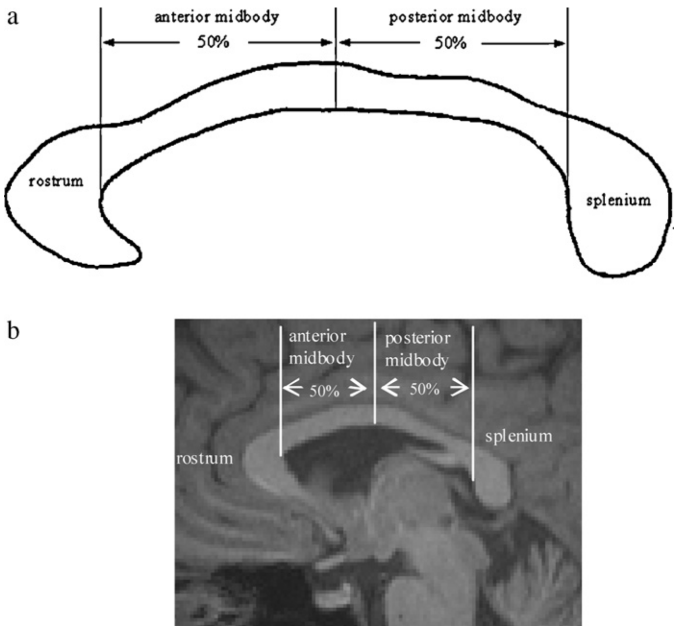

Fig. 1. (a) Schematic midsagittal corpus callosum indicating the division into four subregions: the rostrum, anterior midbody, posterior midbody and splenium. The caudal border of the rostrum was marked by a tangent line at the bend of the genu. An identical line dividing the rostral boundary of the body and splenium was placed at the concave bend of the genu. The length of the midline body between these lines was divided exactly in half to mark the anterior and posterior body. (b) Midsagittal corpus callosum MR images of a participant showing the callosal subdivisions.

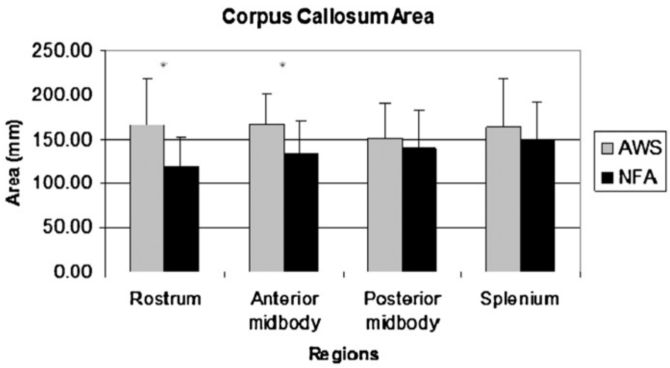

Fig. 2. The average area for subregions of the corpus callosum are shown for AWS and NFA. Error bars indicate standard deviations and the asterisks denote significant results.

Salem, NC). A voxel-wise two-sample *t*-test was used to compare white matter volume in the corpus callosum between the two groups ($p = 0.01$, uncorrected).

3. Results

3.1. Corpus callosum area

An intra-class correlation analysis indicated high intra-rater reliability for all segments including the rostrum (ICC = 0.99), anterior midbody (ICC = 0.99), posterior midbody (ICC = 0.99) and splenium (ICC = 0.99). Intra-class correlations for inter-rater reliability were also high for the rostrum (ICC = 0.93), anterior midbody (ICC = 0.70), posterior midbody (ICC = 0.88) and splenium (ICC = 0.99).

The planned comparisons of the overall area and individual segment area between the NFA and AWS groups indicated significant group differences in CC area. The absolute area analyses revealed that the CC of the AWS was significantly larger compared to NFA in the rostrum ($t(21) = 2.67$, $p = 0.014$) and anterior midbody ($t(21) = 2.25$, $p = 0.036$) (see Fig. 2). No significant differences were found for the posterior midbody ($t(21) = 0.64$, $p = 0.53$) and splenium ($t(21) = 0.78$, $p = 0.44$). AWS also featured a larger overall CC area ($t(21) = 11.10$ $p < .0001$). The Cohen's *d* test revealed a large effect size for the rostrum

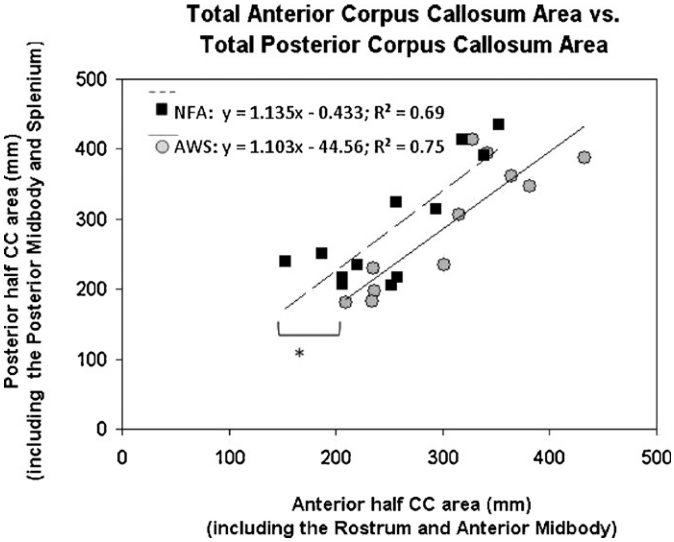

Fig. 3. Scatter plot showing the relationship between the area of the total anterior half of the corpus callosum including the rostrum and anterior midbody, and the area of the total posterior half of the corpus callosum including the posterior midbody and splenium. The asterisk denotes a significant difference in midsagittal corpus callosum size between AWS and NFA for the anterior and posterior callosal segments.

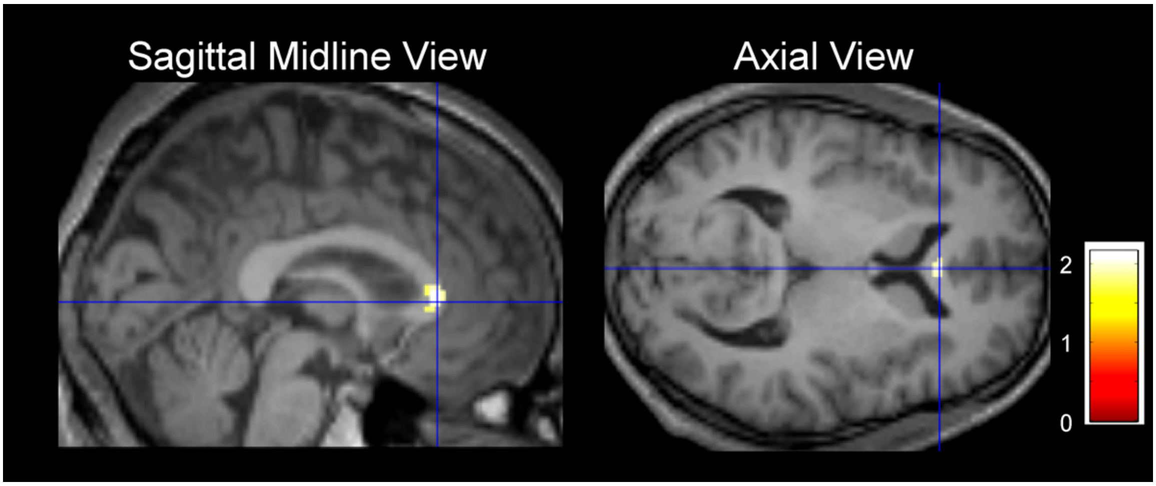

Fig. 4. A sagittal and axial view of the white matter volume contrast in the CC ROI between the AWS and NFA.

($d = 0.7$) and anterior midbody ($d = 0.7$); a small effect for the splenium ($d = 0.16$) and a small negative effect for the posterior midbody ($d = -0.24$).

To evaluate group variation, the anterior half of the CC, which included the total absolute areas of the rostrum and anterior midbody was plotted against the posterior half, which included the total absolute areas of the posterior midbody and splenium (Fig. 3). A linear regression function was fit to the data of each group separately. The R^2 values for each group (AWS: $R^2 = 0.75$; NFA: $R^2 = 0.69$) indicate that the size of the anterior callosal and posterior callosal segments are generally inter-related with greater variability within NFA than AWS. In addition, AWS tended to exhibit a smaller posterior/anterior callosa value than NFA ($t(21) = -2.50$, $p = 0.021$). It is clear that the values of the anterior callosal segments of the AWS are shifted to the right of the NFA corroborating the findings in Fig. 2 and the statistical results of the planned comparisons.

3.2. VBM analysis

The comparison of white matter volume in the CC indicated that AWS show a cluster of increased white matter volume predominantly encompassing the rostrum of the anterior CC (1 cluster of 63 voxels, $p < 0.01$ uncorrected). In Fig. 4, these results are superimposed on a representative anatomical image, which indicates the extent of the cluster that is distributed in a symmetric manner across the midline portion of the rostrum.

Correlations between the area of the CC segments, overall CC area and stuttering severity were estimated for the stuttering participants to assess possible relationships. None of the correlations were significant or approached significance.

4. Discussion

The present study documented different lines of evidence for an atypical presentation of the corpus callosum in AWS. In comparison to NFA, AWS showed larger anterior midline area and larger volume of the rostrum. The larger overall callosa in AWS is accounted for by the larger rostrum and anterior midbody segments. These structural differences in the CC may be associated with the atypical functional brain organization in AWS and may be a factor in the performance of AWS on tasks, such as dichotic listening.

A relationship between callosal size and interhemispheric connectivity (Witelson, 1989; Yazgan et al., 1995) may be pivotal in the development of hemispheric lateralization. A larger callosa is thought to contain a larger number of fibers which potentially allows greater communication between cerebral hemispheres and consequently, reduced functional lateralization (Witelson, 1989). Past studies have reported an inverse correlation between right ear performance and total callosa size, and also the anterior callosa size in right-handed individuals in dichotic listening tests, possibly as a result of increased competition for resources from the left ear or inhibitory activity of the right hemisphere (Clarke, Lufkin, & Zaidel, 1993; Clarke & Zaidel, 1994; Westerhausen & Hugdahl, 2008). Interestingly, Clarke et al. (1993) reported a negative correlation between right ear performance and CC size in males but not females with the highest correlation found for the anterior callosa possibly as a consequence of functional interhemispheric inhibition where increased connectivity allows the right hemisphere to increase suppression of the left hemisphere processing of right ear stimuli. Surprisingly, no significant correlation was found between right ear performance and the posterior midbody of the CC. This observation suggests that auditory processing may also be mediated by the anterior callosa and at least some fibers connecting the auditory areas could be located more rostrally (Degos et al., 1987; Risse, Gates, Lund, Maxewell, & Rubens, 1989; Westerhausen, Grüner, Specht, & Hugdahl, 2009). These observations also support results of the present study as the larger overall callosa and larger anterior CC in AWS is consistent with diminished right ear advantage or no ear advantage in dichotic listening investigations (Blood & Blood, 1989; Newton et al., 1986; Sussman & MacNeilage, 1975). In bimanual coordination tasks requiring concurrent tapping of the index finger of both hands, AWS performed equivalently to controls (Hulstijn, Summers, van Lieshout, & Peters, 1992). However, when finger tapping was executed concurrently with overt speech, AWS demonstrated poorer coordination than controls perhaps as a result of increased competition for resources (Hulstijn et al., 1992). These atypical observations are potentially related to anomalies in interhemispheric communication as a consequence of aberrations in the CC structure.

Forster and Webster (2001) proposed that stuttering is a corollary of interhemispheric anomalies involving the supplementary motor area (SMA) which affect the left hemisphere speech motor control leading to atypical (over)activation of the right hemisphere. In addition to connecting the SMA, the anterior half of the CC which includes the rostrum and anterior midbody also connects the prefrontal cortices, primary and secondary motor cortices (including the premotor cortex) (Witelson, 1989) which are crucial to bilateral sensorimotor integration (Bonzano et al., 2008; Preilowski, 1972). In other words, a greater anterior callosa may signal increased connectivity and perhaps, interference between the areas involved in speech motor control and conceivably, account for aberrant activation of the right hemisphere in AWS during tasks that are typically left hemisphere lateralized in right-handed NFA.

The larger callosa size in AWS bears an interesting relationship to investigations documenting larger callosa in more symmetrical brains and smaller CC in more asymmetrical brains (Liederman, 1988). Investigations utilizing MRI and CT scans revealed larger right or equal left and right volumes of the PT, HG and cerebral lobes resulting in more symmetrical brains in AWS (Foundas et al., 2001, 2003; Jäncke et al., 2004; Strub et al., 1987). In contrast, the brains of NFA were more asymmetrical as a consequence of larger left hemisphere volumes. These observations may potentially explicate observations of reduced left hemisphere functional lateralization or greater bilateral symmetry in AWS. Our results also point to variation between AWS in the dimensions of the corpus callosum. Further work is needed to evaluate the significance of this variation.

The larger callosa observed in AWS may also be a corollary of left hemisphere dysfunction. Left hemisphere deficit or dysfunction may result in reorganization of interhemispheric connections to permit greater shift to and increased participation of the right hemisphere (Geschwind & Galaburda, 1985). Individuals with increased right hemisphere participation and/or dominance for speech have been observed to display a larger callosa (O'Kusky et al., 1988). Left-handed or ambidextrous individuals also possess a larger callosa compared to right-handed individuals (Witelson, 1985). Children with developmental language disorder which is typically associated with left hemisphere damage or deficit also feature a larger anterior and middle callosa compared to typically developing children (Preis, Steinmetz, Knorr, & Jäncke, 2000; Shields, Varley, Broks, & Simpson, 1996). Similarly, a left hemisphere deficit or dysfunction albeit mild may also be present in developmental stuttering and potentially result in greater right hemisphere participation and consequently, a larger CC in AWS.

Within the present paradigm, AWS presented larger callosa than NFA. This trend suggests CC size may be mediated by the presence of stuttering. It remains possible that the development of this structure may also be influenced by stuttering severity and degree of handedness. Thus, the inclusion of these factors will benefit future research.

5. Summary

Structural anomalies in the CC that connect speech and language areas may reflect an anatomical pathway for reorganization of hemispheric control of language that has been observed in AWS. The full implications of reorganization mediated by the corpus callosum across the span of development and persistence of the disorder need to be investigated but causal links between reorganization and callosal size could not be evaluated in this study. A larger callosa could be part of a positive adaptive response or maladaptive response as a consequence of reduced left hemisphere dominance. The most appropriate way to answer these questions is to assess callosal development in children who stutter and in children who recover from stuttering. The results of the present study suggest that neuroanatomical differences may be part of the biological basis for persistent developmental stuttering.

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Appendix A. Continuing education

1. Past research have identified a number of functional differences between AWS and NFA during language processing including:
   a. right lateralized cerebral activity in AWS
   b. left lateralized cerebral activity in AWS
   c. reduced right cerebral activity in AWS
   d. no differences exist between the two groups
2. In normally fluent adults, a larger corpus callosum could potentially signify
   a. reduced interhemispheric connectivity
   b. increased interhemispheric communication
   c. aberrant interhemispheric communication
   d. slower interhemipsheric communication
3. Fluent speech production by AWS was shown to be correlated with increased activity in the right frontal operculum (RFO). This suggests that
   a. the right RFO may have greater white matter density compared to the left RFO
   b. the left RFO may have greater white matter density compared to the right RFO
   c. the right RFO may serve a compensatory function
   d. the left RFO may serve a compensatory function
4. Which of the following is one of the major findings in the present study?
   a. the overall area of the corpus callosum is smaller in AWS compared to NFA
   b. NFA displayed atypical gyrification in the perisylvian region
   c. The anterior portion of the corpus callosum is larger in AWS than NFA
   d. No differences were found between AWS and NFA
5. Results of the present study suggests that
   a. the pattern of lateralization observed in AWS is not affected by the size of the CC
   b. the pattern of lateralization observed in AWS is affected by the size of the CC
   c. the CC is not an important factor in functional anomalies observed in AWS
   d. the size of the CC affects lateralization in NFA but not AWS

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