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Research article

A Typical Anatomy of the Hand Representation in Adults who Stutter

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Abstract

Atypical hand preference may be more common in Adults Who Stutter (AWS). One implication is that stuttering may be a manifestation of a more general dysfunction in motor organization and planning. This study was designed to determine whether AWS have atypical motor cortical anatomy compared to controls, and whether there are group differences in handedness that correlate with anatomical measures. Volumetric MRI was used to measure the anterior bank of the Central Sulcus (CS) and Motor Knob (MK), a structure that corresponds precisely to the motor hand representation, in Adults Who Stutter (AWS) and fluent, matched controls divided into three groups (right-handed and left-handed men, right-handed women). There was an interaction between fluency group and handedness-sex group (p=0.024) with reduced CS volume in right-handed men who stutter (p=0.001). For MK volume there was an interaction with the right MK larger in the left-handed male controls, and the left MK larger in the left-handed AWS (p=0.024). AWS and controls did not differ in hand preference score or finger tapping rate. There was a relationship between CS asymmetry and finger-tapping laterality (p=0.042) with a faster right-hand tapping speed associated with a larger left CS and vice-versa. When controls were examined independently, there were no correlations between finger-tapping laterality and anatomical asymmetry; there was a correlation in the AWS (r= 0.642; p= 0.007). Left hander AWS tapped faster with the right hand and had a larger left CS (atypical). One subgroup of right handed AWS (atypical) tapped faster with the left hand and had a larger right CS. Another subgroup of right handed AWS (typical) tapped faster with the right hand and had a larger left CS. These results show that handedness may systematically influence cortical motor representations in AWS. Further study is warranted in a larger sample of adults and in children who stutter.

Introduction

Developmental stuttering is characterized by dysfluent speech that includes repetitions, blocks, and prolongations of speech sounds, and associated involuntary and/or ancillary movements. Converging evidence has shown neuronal activity is reduced in the auditory temporal cortex and increased in right hemisphere speech-motor control areas in Adults Who Stutter (AWS) [1-6]. These atypical patterns of neural activation may result in dissociations between auditory speech perception and motor planning. It is unclear whether the consistently observed right hemisphere over-activity and the reduced pattern of lateralization of function is a cause, consequence, or correlate of stuttering. Whether hand preference moderates these atypical functional patterns has not been determined, as most imaging studies have excluded left-handers, and have not characterized the degree of hand preference in right-handers. Atypical handedness and reaction times have been reported in behavioral studies with AWS showing difficulty with bimanual tasks [7-8], slower reaction times for phonatory non-language but not for finger responses [9-11], finger tapping or sequential finger movements [12]. One implication is that the dysfluency of stuttering may be a manifestation of a more general dysfunction in motor organization and planning. There is evidence that left-handers or less consistent right-handers may be over-represented among individuals with a diagnosis of persistent developmental stuttering [13-16], although several studies have not found an association between handedness and stuttering [17-20].

The major goal of this study was to determine whether AWS have atypical anatomy of the cortical motor areas compared to controls. The second goal was to examine laterality patterns of hand preference and hand performance including the possibility that subgroups may emerge that dissociate on behavioral measures of handedness that may in turn correlate with anatomical asymmetries. Our sample included self-reported right- and left-handed adults with a diagnosis of persistent developmental stuttering and a group of matched controls. In vivo volumetric Magnetic Resonance Imaging (MRI) methods were used to measure the superior genu of the anterior bank of the central sulcus (Brodmann's area 4), and the motor knob, a sub-region that corresponds to the motor hand representation. Anatomical variables included cortical volume and asymmetry quotients. Handedness was evaluated using two measures: a hand preference inventory and a finger-tapping task. We hypothesized that the AWS would have structural abnormalities in motor brain areas compared to controls. We also predicted that these anatomical anomalies would be

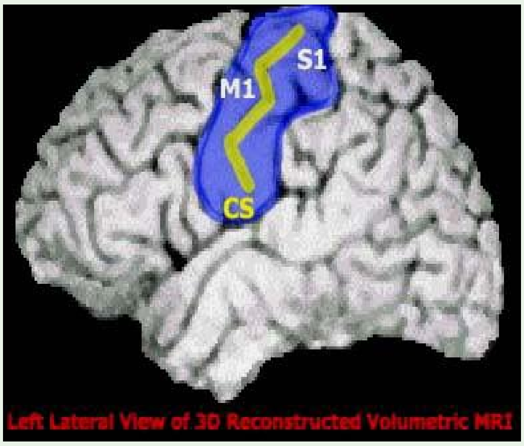

Figure 1(a): Anatomical Measure of the Anterior Bank of the Central Sulcus: The measure of the anterior bank of the Central Sulcus (CS) is depicted on a three-dimensional MRI reconstruction of the lateral surface of the left cerebral hemisphere, and the ROI is outlined.
M1: Primary Motor Cortex; S1: Primary Somatosensory Cortex

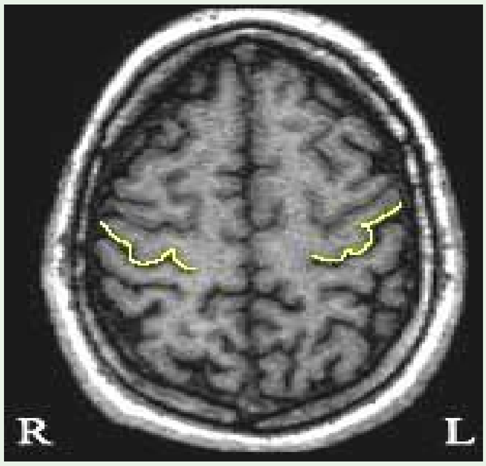

Figure 1(b): Anatomical Measure of the Motor Knob: The motor knob is outlined on the axial volumetric MRI image with the "omega" configuration shown in the left hemisphere, and the inverted "epsilon" configuration shown in the right hemisphere.

associated with atypical handedness. Secondary exploratory analyses were conducted to examine structure-function relationships in handedness subgroups.

Materials and Methods

Participants

Participants included adults with persistent developmental stuttering (n=16) and controls (n=16). Each group included: 9 right-handed men, 3 right-handed women, and 4 left-handed men. Because no left handed female participants who stutter could be recruited, left handed females were excluded. To be considered an adult with persistent developmental stuttering for purposes of this study, each individual fulfilled the following criteria: (1) current conversational speech that contained three or more stuttering (i.e., sound/syllable repetitions, sound prolongations, whole-word repetitions and broken words) per 100 words, (2) stuttering continually present with the onset before 8 years of age (i.e., exhibit development not acquired stuttering), and (3) have a negative history of other developmental, psychiatric conditions, epilepsy, stroke, or head injury. Stuttering severity was also determined according to the procedures described in the Stuttering Severity Index [21]. A family history of stuttering was present in 50 percent of the AWS.

Controls were fluent adults with no personal or family history of stuttering; no personal history of any other developmental disorder. All participants were native English speakers with no history of a major medical or neuropsychiatric condition. All participants gave informed consent. Groups were matched on age and education (Table 1).

Procedures

Image acquisition: Volumetric MRI scans were acquired on a General Electric 1.5 Tesla Signa Advantage scanner (St. Louis, MO) as a gapless series of T1-weighted sagittal images using fast spoil gradient recall sequence. Data sets were aligned in the sagittal, axial, and coronal planes; MRI scans were maintained in real space. The examiner performing the measurements was blinded to subject, group, handedness, sex, and hemisphere. Each MRI measure was performed twice with excellent inter- and intra-rater reliability (>0.95).

Anatomical measures: The full length of the central sulcus, which includes the motor representation of the hand, was measured in 6 to 8 contiguous axial MRI sections (medial to lateral) from the superior to the inferior extent of the superior genu of the central sulcus (Figure 1a) [22]. The functional representation of the motor hand area can be localized to a precise anatomical landmark described in the axial plane as a "knob" (motor knob) (Figure 1b) [23]; the surface area of this ROI was measured in 6 to 8 continuous axial MRI images (medial to lateral) using a cursor to trace the exposed gyral surface area in the left and right cerebral hemispheres (Figure 1b). Volume was computed in cm^3, and Asymmetry Quotients (AQs) were computed using the following formula: $\left(AQ = 100 * \frac{L-R}{(L+R)*.5}\right)$. A positive AQ would indicate a larger left hemisphere size or leftward asymmetry; a negative AQ would indicate a larger right hemisphere size or rightward asymmetry.

Behavioral measures: Hand Preference was measured using the Hand Preference Index (HPI) [24], which includes common items from both the Edinburgh (Oldfield, 1971) and modified Annett [26] inventories. HPI scores were defined as a continuous measure ranging from -100 (strong left-hand preference) to +100 (strong right-hand preference). Individuals were also categorized into discrete groups as follows: consistent left handers (≥ −76), mixed handers (HPI between −75 to +75), and consistent right handers (≥ +76) [27]. A finger-tapping measure was obtained from a mechanical counter switch affixed to a 23 cm x 30 cm board (Psychological Assessment Resources, Inc) with the average of three 10-second trials per hand used to evaluate hand performance. This score was multiplied by 100 for a laterality quotient (LQ): $\left(LQ = 100 * \frac{R-L}{R+L}\right)$. A positive LQ indicates a greater right-hand tapping speed; a negative LQ indicates a greater left-hand tapping speed.

Analysis

Handedness-sex was combined into a single grouping factor with three levels (right-handed men, left-handed men, right-handed

Table 1: Demographic information by group.

Group	Sex	Writing Hand	HPI	Age	Education
Stutter	Female	Right Handed	100.00	40	14
Stutter	Female	Right Handed	100.00	33	18
Stutter	Female	Right Handed	100.00	41	16
Stutter	Male	Right Handed	100.00	47	16
Stutter	Male	Right Handed	100.00	43	14
Stutter	Male	Right Handed	96.90	33	16
Stutter	Male	Right Handed	78.10	36	12
Stutter	Male	Right Handed	75.00	42	18
Stutter	Male	Right Handed	67.20	23	16
Stutter	Male	Right Handed	59.40	23	16
Stutter	Male	Right Handed	56.30	43	15
Stutter	Male	Right Handed	43.80	21	15
Stutter	Male	Left Handed	-46.90	21	15
Stutter	Male	Left Handed	-87.50	44	18
Stutter	Male	Left Handed	-90.60	32	20
Stutter	Male	Left Handed	-90.60	19	12
Control	Female	Right Handed	100.00	47	12
Control	Female	Right Handed	100.00	31	18
Control	Female	Right Handed	90.60	29	20
Control	Male	Right Handed	100.00	33	15
Control	Male	Right Handed	93.80	31	19
Control	Male	Right Handed	90.60	27	19
Control	Male	Right Handed	90.60	25	17
Control	Male	Right Handed	87.50	29	19
Control	Male	Right Handed	87.50	22	17
Control	Male	Right Handed	81.30	23	17
Control	Male	Right Handed	78.10	24	17
Control	Male	Right Handed	42.20	23	16
Control	Male	Left Handed	-40.60	29	18
Control	Male	Left Handed	-71.90	29	21
Control	Male	Left Handed	-75.00	35	16
Control	Male	Left Handed	-100.00	37	16

women). Group differences were tested with significance levels (*p*-values) for all pair wise comparison adjusted to reflect control of Type I error rate inflation via sequential Bonferroni methods [28-29].

Anatomical measures: Volume dependent variables were analyzed via three-way mixed analysis of variance (ANOVA) with Fluency group (Stutter and Control) and Handedness-Sex level (right-handed men, right-handed women, and left-handed men) entered as grouping variables and Hemisphere (right and left) entered as a repeated measure. AQs were analyzed via two-way between-groups ANOVA with Fluency and Handedness-Sex as independent variables.

Behavioral measures: Scores from the HPI were compared between the groups via a one-way between-group ANOVA. Individual degree of handedness by fluency group was summarized as a categorical variable (consistent right-handed, mixed, consistent left-handed) and the groups were compared. For Finger-tapping, the score dependent variables were analyzed via three-way mixed ANOVA with Fluency and Handedness-Sex entered as a grouping variable and Hand Used (right and left) entered as a repeated measures variable. LQs were analyzed via two-way between-group ANOVA.

Anatomical-Behavioral relationships: Inter-correlations were computed among: anatomical volume and AQs, and behavioral scores (HPI, LQ). Secondary exploratory analyses were conducted to assess anatomical-behavioral associations-dissociations.

Results

Anatomical measures (Table 2a-2c)

Central sulcus: Volume: There was a significant interaction between Fluency group and Handedness-Sex level, $F(2,25) = 4.361$, $p = 0.024$. The interaction was driven primarily by right handed men, for whom the CS, independent of side, was significantly smaller in the AWS compared to Controls ($p = 0.001$).

Asymmetry: No group differences were detected (all ps > 21).

Motor knob measures:

Volume: An interaction between Fluency group, Hemisphere, and Handedness-Sex level was found, $F(2,26) = 3.78$, $p = 0.037$. The right MK was larger in the left-handed male controls; the left MK was larger in the left-handed AWS ($p = 0.024$).

Asymmetry: An interaction between Fluency groups (AWS, Controls) and Handedness-Sex level was found, $F(2,26) = 3.477$, $p = 0.047$. There was a difference in MK asymmetry between Fluency groups only for left-handed men ($p < 0.010$). Specifically, the left-handed control males had a significant rightward MK asymmetry ($p < 0.05$); the left-handed males who stutter had a non-significant asymmetry ($p > 0.05$).

Behavioral measures

Hand preference inventory: For the entire sample, there were no differences between the AWS (Mean HPI = +41.32; Range = +100 to -90.60; SD=74.48) and Controls (Mean HPI = +47.17; Range = +100 to 100, SD=73.06) on HPI score. There were differences in HPI scores in the stutter subgroups, $F(2, 15) = 91.038$, $p < 0.0001$ (Mean HPI: Right-handed men = +75.19, SD = 20.51; Right-handed women = +100, SD = 0.0; Left-handed men = -78.90, SD = 21.38). There were

Table 2(a): Mean (Standard Error) central sulcus size. Means shown demonstrate the significant fluency group x Handedness-Sex Level interaction.

	Fluency Group			
	Control		Stutter	
Handedness-Sex Group	M	(SE)	M	(SE)
Right Handed Females	347.59	(32.27)	327.68	(32.27)
Right Handed Males*	422.16	(19.76)	320.17	(18.63)
Left Handed Males	362.94	(27.95)	397.93	(27.95)

*p = 0.001

Table 2(b): Mean (Standard Error) Motor Knob size. Means shown demonstrate the significant Fluency Group x Hemisphere x Handedness-Sex Level interaction.

		Fluency Group			
		Control		Stutter	
Handedness-Sex Group	Hemisphere	M	(SE)	M	(SE)
Right Handed Females	Left	167.05	(25.54)	175.42	(25.54)
	Right	184.61	(16.16)	203.35	(16.16)
Right Handed Males	Left	192.36	(15.64)	179.52	(14.74)
	Right	184.28	(9.90)	179.66	(9.33)
Left Handed Males*	Left**	155.37	(22.12)	242.90	(22.12)
	Right	213.37	(13.99)	201.04	(13.99)

*p = 0.010 (Stutter > Control)
**p = 0.024 (Left Hemisphere > Right Hemisphere, Control group only)

Table 2(c): Mean (Standard Error) Motor Knob asymmetry quotients. Means shown demonstrate the significant Fluency Group x Handedness-Sex Level interaction.

	Fluency Group			
	Control		Stutter	
Handedness-Sex Group	M	(SE)	M	(SE)
Right Handed Females	-0.129	(0.158)	-0.154	(0.158)
Right Handed Males	0.044	(0.097)	-0.018	(0.091)
Left Handed Males**	-0.366*	(0.137)	0.174	(0.137)

also differences, when degree of handedness subgroups (consistent right-handed; mixed; consistent left-handed) were compared in the two fluency groups (AWS, Controls). Among the AWS, 7 of 16 (44%) were consistent right-handers, and 6 of 16 (37%) were mixed, and 3 of 16 (19%) were consistent left-handers. In the Control group, 11 of 16 (69%) were consistent right-handers, 4 of 16 (25%) were mixed, and one (6%) was a consistent left-hander.

Finger tapping measure: No significant differences between AWS and Controls were found (all ps > 0.22). Overall, participants tapped significantly more times with their right (M = 48.34, SE = 1.34) than left hand (M = 45.07, SE = 1.39), F (1,26) = 11.30, p = 0.002. There was an effect of the Handedness-Sex variable, F (2,26) = 10.79, p < 0.0005. Right-handed women (M = 37.44, SE = 2.65) tapped significantly fewer times than right (M = 50.24, SE = 1.53) and left-handed men (M = 52.42, SE = 2.30), via Student-Newman-Keuls test (p < 0.05). Number of taps produced by right and left-handed men did not differ (p > 0.05). There was a significant Hand Used x Handedness-Sex interaction, F (2,26) = 4.68, p < 0.018. In other words, the difference between right and left hand Finger Tapping rates varied across the Handedness-Sex groups. Means are shown in (Table 3). This interaction was driven primarily by the strong right hand advantage in the right-handed men (p < 0.0005). Right-handed women and left-handed men showed no significant difference (ps > 0.21) in the number of Taps.

Table 3: Mean (Standard Error) Number of Finger Taps. Means shown demonstrate the significant Hand Used x Handedness-Sex Level interaction.

	Hand Used			
	Left		Right	
Handedness-Sex Group	M	(SE)	M	(SE)
Right Handed Females	36.17	(2.88)	38.72	(2.79)
Right Handed Males*	46.91	(1.67)	53.57	(1.61)
Left Handed Males	52.13	(2.50)	52.71	(2.42)

*p < 0.0005

Laterality quotients: No group differences were found (all ps > 0.07). There was a main effect of Handedness-Sex, F (2,26) = 4.133, p = 0.028. Consistent with the results of the raw tapping scores, the mean LQ of right handed men (M = 6.79, SE = 1.26) was positive (indicating a right hand advantage) and significantly greater than zero (p <0.05), whereas the right-handed women (M = 3.74, SE = 2.18) and left-handed men (M = 0.348, SD = 1.89) were not significantly different from zero.

Anatomical-Behavioral Relationships

There was no significant relationship between HPI score and CS asymmetry (r = -0.122, p = 0.506) nor between HPI and MK asymmetry (r = 0.083, p = 0.651) in the analysis of the entire sample. For the Stutter group alone, neither CS asymmetry (r = -0.238, p = 0.288) nor MK asymmetry (r = -0.349, p = 185) were significantly related to HPI score. When the entire sample was examined, no significant correlations between tapping scores and anatomical volume were found (all ps > 0.05). When anatomical AQs and finger-tapping LQs were examined, a significant relationship was found between CS AQ and Finger Tapping LQ, r = 0.367, p = 0.042. That is, tapping faster with the right than left hand was associated with a larger left than right CS, and vice versa. When Controls were examined independently, there were no other correlations between finger-tapping LQs and anatomical AQs (all ps > 0.10). When AWS were examined independently there was a significant relationship between Finger Tapping LQ and CS AQ, r = 0.642, p = 0.007.

All four left-handed AWS were atypical, as each one had a larger left CS and tapped faster with the nondominant right hand. Among right handers who stutter there were two behavioral-anatomic subgroups. One subgroup was atypical, as four of twelve right-handers (33%) had a larger right CS and either showed no tapping laterality or tapped faster with the nondominant left hand. The other subgroup was more typical and included eight of twelve right-handers (66%) with a larger left CS and right (dominant) hand tapping speed. Among the typical right-handed AWS only two of eight (25%) had a family history of sinistrality, whereas two of four (50%) atypical right-handers had a family history of sinistrality.

Discussion

The results of this study demonstrate that the motor hand area may be atypical in some AWS, offering partial support for the hypothesis that the organization of motor control systems is disrupted in developmental stuttering [30-31]. Precise relationships among speech, language, hand-preference and hand-performance/skill have not been established [32-38] limiting our ability to postulate whether atypical laterality may be found in other related cognitive systems in people who stutter [5,39,40].

The motor bank of the CS, measured from the superior to the inferior extent of the superior genu, was smaller in size in AWS compared to controls with this effect most pronounced in the right-handed men. Although the total CS length was smaller in the AWS, the motor knob, which corresponds to the functional hand representation, was larger in many of the AWS with this effect most pronounced in left-handed men. Furthermore, the anatomy of the MK showed dissociation in the left-handed men who stutter compared to the left-handed controls. Specifically, a larger right MK (rightward asymmetry) was found in the fluent left-handed men, which would be predicted based on our a priori hypothesis. In contrast, the left-handed men who stutter had an "atypical" larger left MK with a reduced asymmetry. Because our subjects who stutter had a smaller CS but a larger hand area, it is possible that the portion of the motor cortex that controls bulbar musculature is smaller in some AWS.

Another goal of this study was to determine whether AWS differed from controls when performing complex distal hand movements. Right handers generally have an asymmetry of tapping speed, with the faster response by the preferred right hand, and with the preferred hand capable of more precise movements than the non-preferred hand [34, 40]. Left-handers are more variable in manual performance tasks, and the sex of the individual is another factor that may be related to individual differences in the pattern of manual asymmetry [24,41]. Consistent with this expected pattern of asymmetry, we found that right-handed men tapped faster with the right hand than the left. Left-handed men and right-handed women did not have a significant handedness difference in tapping speed. When the AWS were compared to controls, there were no average performance differences on the finger tapping task. These findings are consistent with one study that found men who stutter and fluent speakers did not differ when compared on index finger tapping and sequential finger tapping tasks [12], although in another study fast finger extensions were slower in AWS [42]. In bimanual coordination tasks, however, some investigators have found that overall bimanual tapping rates were significantly slower in AWS [8], and right-handed AWS were found to have a higher proportion of participants who showed atypical performance when executing two tasks that require synchronous manipulation of the two hands, such as removing a nut from a bolt [43]. Studies of bimanual handwriting have shown that adults with persistent developmental stuttering were slower, produced more mirror reversed letters, and formed letters more poorly than matched controls [44].

When the sample was examined as a whole, there was a significant relationship between finger tapping asymmetry and CS asymmetry (i.e., tapping faster with the right hand was associated with a larger left CS, and vice versa). These results are consistent with converging evidence from tract-tracer, physiologic, and functional neuroimaging studies that show that independent finger movements are mediated by the contra lateral primary motor cortex [45-50]. Furthermore, the anatomical representation of the hand has been found to be asymmetric in postmortem [51], and in volumetric MRI studies [22,52], although a consistent relationship to hand preference has not been found. Several studies have investigated functional activation-deactivation of motor cortex in right and left handers with mixed results [53-55]. One study using whole brain Magneto encephalography (MEG) found functional asymmetries in primary motor cortical areas that were correlated with the asymmetry of hand performance in five right and five left-handed adults [56]. A voxel-based morphometry study that used a probabilistic ROI approach to measure the gray matter in the CS at the level of the hand area in 56 right and 55 left-handed adults found no anatomical differences between the handedness groups [57]. However, a multiple regression analysis showed that the maximum tapping rate of the dominant hand correlated with the contra lateral ROI gray matter volume in right but not left-handers. The study of skill acquisition, [58,59] and functional recovery [60,61] in motor control regions has shown that extensive training can modify motor maps. Despite this evidence of neural plasticity in motor control regions, it is not clear whether motor learning and high levels of skill modify gross anatomical representations within these neural circuits.

Subgroups emerged when the data were plotted to compare direction and degree of anatomical and behavioral asymmetry. All of the left-handed AWS had a larger left CS and tapped faster with the non-dominant right hand. Among the right-handed AWS, two anatomical-functional subgroups emerged. One subgroup (typical) had the expected relationship of a larger left CS associated with a faster tapping rate in the preferred right hand. The other subgroup was more atypical with a larger right CS associated with less lateralization of finger tapping rate. These two right-handed subgroups also differed on degree of handedness and the presence of family sinistrality. In the typical right handed subgroup, six of eight were consistent right handers. In contrast, the atypical subgroup included more individuals with a reduced degree of handedness and a family history of sinistrality.

Our findings suggest that handedness may influence how motor representations develop in people who stutter. Many investigators have postulated that atypical or anomalous handedness may be marker of atypical hemispheric specialization that in turn may be associated with factors that increase the risk of developmental disorders [14,62-65]. Further study is needed to determine how these variables relate to the lateralization of speech and language functions [66,67], and to anatomical asymmetries in perisylvian speech-language zones [35,68,69]. Future longitudinal studies in children with developmental stuttering may show how structural and functional anomalies in speech, language, and motor control areas relate to the development, maintenance, and exacerbation of stuttering.

There are several limitations to this study. First, the sample size was small and did not include left-handed women. Second, our MRI-based measure was limited to a carefully defined anatomical region without any converging functional or physiological measure. It is important to acknowledge that there are controversies about automated versus manually-based semi-automated methods. The method that was adopted is time-consuming but adheres to a morphological measurement in native-space using rigid anatomical boundaries that allow for quantification of individual differences in brain architecture with excellent inter- and intra-rater reliability. Finally, because of neural plasticity, it is unclear whether these morphological differences may be associated with age-related changes that may differ depending on overall motor skill and experience. Additional research would be helpful to examine these relationships in larger samples of adults, adolescents, and children who stutter.

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References

1. Blomgren M, Goberman AM. Revisiting speech rate and utterance length manipulations in stuttering speakers. J Commun Disord. 2008; 41: 159-178.

2. Braun AR, Varga M, Stager S, Schulz G, Selbie S, Maisog JM, et al. Altered patterns of cerebral activity during speech and language production in

developmental stuttering. An H_2 (15)O positron emission tomography study. Brain. 1997; 120: 761-784.

3. Fox PT, Ingham RJ, Ingham JC, Hirsch TB, Downs JH, Martin C, et al. A PET study of the neural systems of stuttering. Nature. 1996; 382: 158-161.

4. Preibisch C, Neumann K, Raab P, Euler HA, von Gudenberg AW, Lanfermann H, et al. Evidence for compensation for stuttering by the right frontal operculum. Neuroimage. 2003; 20: 1356-1364.

5. Watkins KE, Smith SM, Davis S, Howell P. Structural and functional abnormalities of the motor system in developmental stuttering. Brain. 2008; 131: 50-59.

6. Xuan Y, Meng C, Yang Y, Zhu C, Wang L, Yan Q, et al. Resting-state brain activity in adult males who stutter. PLoS One. 2012; 7: e30570.

7. Webster WG. Neural mechanisms underlying stuttering: evidence from bimanual handwriting performance. Brain Lang. 1988; 33: 226-244.

8. Webster WG. Evidence in bimanual finger-tapping of an attentional component to stuttering. Behav Brain Res. 1990; 37: 93-100.

9. Borden GJ. Initiation versus execution time during manual and oral counting by stutterers. J Speech Hear Res. 1983; 26: 389-396.

10. Reich A, Till J, Goldsmith H. Laryngeal and manual reaction times of stuttering and nonstuttering adults. J Speech Hear Res. 1981; 24: 192-196.

11. Till JA, Reich A, Dickey S, Seiber J. Phonatory and manual reaction times of stuttering and nonstuttering children. J Speech Hear Res. 1983; 26: 171-180.

12. Webster WG. Neuropsychological models of stuttering--I. Representation of sequential response mechanisms. Neuropsychologia. 1985; 23: 263-267.

13. Geschwind N, Behan P. Left-handedness: association with immune disease, migraine, and developmental learning disorder. Proc Natl Acad Sci USA. 1982; 79: 5097-5100.

14. Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology: III. A hypothesis and a program for research. Arch Neurol. 1985; 42: 634-654.

15. Orton ST. Studies in stuttering. Neurol Psychiatr. 1927; 18: 671-672.

16. Götestam KO. Left handedness among students of architecture and music. Percept Mot Skills. 1990; 70: 1323-1327.

17. Ardila A, Bateman JR, Niño CR, Pulido E, Rivera DB, Vanegas CJ. An epidemiologic study of stuttering. J Commun Disord. 1994; 27: 37-48.

18. Dellatolas G, Annesi I, Jallon P, Chavance M, Lellouch J. An epidemiological reconsideration of the Geschwind-Galaburda theory of cerebral lateralization. Arch Neurol. 1990; 47: 778-782.

19. Records MA, Heimbuch RC, Kidd KK. Handedness and stuttering: A dead horse? Journal of Fluency Disorders. 1977; 2: 271-282.

20. Webster WG, Poulos M. Handedness distributions among adults who stutter. Cortex. 1987; 23: 705-708.

21. Riley G. Stuttering severity instruments for children and adults. Tigerd, OR: CC Publications. 2009.

22. Foundas AL, Hong K, Leonard CM, Heilman KM. Hand preference and magnetic resonance imaging asymmetries of the central sulcus. Neuropsychiatry Neuropsychol Behav Neurol. 1998; 11: 65-71.

23. Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain. 1997; 120: 141-157.

24. Corey DM, Hurley MM, Foundas AL. Right and left handedness defined: a multivariate approach using hand preference and hand performance measures. Neuropsychiatry Neuropsychol Behav Neurol. 2001; 14: 144-152.

25. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971; 9: 97-113.

26. Briggs GG, Nebes RD. Patterns of hand preference in a student population. Cortex. 1975; 11: 230-238.

27. Schachter SC, Ransil BJ, Geschwind N. Associations of handedness with hair color and learning disabilities. Neuropsychologia. 1987; 25: 269-276.

28. Holm S. A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics. 1979; 6: 65–70.

29. Mulaik SA. Single-sample tests for many correlations. Psychological Bulletin. 1977; 84: 557-569.

30. Caruso AJ. Neuromotor processes underlying stuttering. In: Hulstijn HF, Starkweather CW, editors. Speech motor control and stuttering. Amsterdam: Elsevier Science Publishers. 1991; 1101-1116.

31. Zimmermann G. Stuttering: a disorder of movement. J Speech Hear Res. 1980; 23: 122-136.

32. Annett M. Predicting combinations of left and right asymmetries. Cortex. 2000; 36: 485-505.

33. Bryden MP, Roy EA, McManus IC, Bulman-Fleming MB. On the genetics and measurement of human handedness. Laterality. 1997; 2: 317-336.

34. Curt F, Maccario J, Dellatolas G. Distributions of hand preference and hand skill asymmetry in preschool children: theoretical implications. Neuropsychologia. 1992; 30: 27-34.

35. Guadalupe T, Willems RM, Zwiers MP, Arias-Vasquez A, Hoogman M, Hagoort P, et al. Differences in cerebral cortical anatomy of left- and right-handers. Front Psychol. 2014; 5: 261-269.

36. Main JC, Carey DP. One hand or the other? Effector selection biases in right and left handers. Neuropsychologia. 2014; 64C: 300-309.

37. Sainburg RL. Convergent models of handedness and brain lateralization. Front Psychol. 2014; 5: 1092.

38. Foundas AL, Bollich AM, Core DM, Hurley M, Heilman KM. Anomalous anatomy of speech-language areas in adults with persistent developmental stuttering. Neurology. 2001; 57: 207-215.

39. Sommer M, Koch MA, Paulus W, Weiller C, Buchel C. Disconnection of speech-relevant brain areas in persistent developmental stuttering. Lancet, 2002; 360: 380-383.

40. Chan T. An investigation of finger and manual dexterity. Percept Mot Skills. 2000; 90: 537-542.

41. Witelson SF, Nowakowski RS. Left out axons make men right: a hypothesis for the origin of handedness and functional asymmetry. Neuropsychologia. 1991; 29: 327-333.

42. Jäncke L, Hefter H, Kalveram KT. Fast finger extensions are slower in stutterers than in nonstutterers. Percept Mot Skills. 1995; 80: 1103-1107.

43. Vaughn CL, Webster WG. Bimanual handedness in adults who stutter. Percept Mot Skills. 1989; 68: 375-382.

44. Greiner JR, Fitzgerald HE, Cooke PA. Bimanual hand writing in right-handed and left-handed stutterers and nonstutterers. Neuropsychologia. 1986; 24: 441-447.

45. Brinkman J, Kuypers HG. Cerebral control of contralateral and ipsilateral arm, hand and finger movements in the split-brain rhesus monkey. Brain. 1973; 96: 653-674.

46. Colebatch JG, Deiber MP, Passingham RE, Friston KJ, Frackowiak RS. Regional cerebral blood flow during voluntary arm and hand movements in human subjects. J Neurophysiol. 1991; 65: 1392-1401.

47. Grafton ST, Woods RP, Mazziotta JC, Phelps ME. Somatotopic mapping of the primary motor cortex in humans: activation studies with cerebral blood flow and positron emission tomography. J Neurophysiol. 1991; 66: 735-743.

48. Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, UĂŸurbil K, et al. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science. 1993; 261: 615-617.

49. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 1937; 60: 389-443.

50. Rumeau C, Tzourio N, Murayama N, Peretti-Viton P, Levrier O, Joliot M, et al. Location of hand function in the sensorimotor cortex: MR and functional correlation. AJNR Am J Neuroradiol. 1994; 15: 567-572.

51. White LE, Lucas G, Richards A, Purves D. Cerebral asymmetry and handedness. Nature. 1994; 368: 197-198.

52. Amunts K, Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, et al. Asymmetry in the human motor cortex and handedness. Neuroimage. 1996; 4: 216-222.

53. Dassonville P, Zhu XH, Uurbil K, Kim SG, Ashe J. Functional activation in motor cortex reflects the direction and the degree of handedness. Proc Natl Acad Sci USA. 1997; 94: 14015-14018.

54. Gut M, Urbanik A, Forsberg L, Binder M, Rymarczyk K, Sobiecka B, et al. Brain correlates of right-handedness. Acta Neurobiol Exp (Wars). 2007; 67: 43-51.

55. Singh LN, Higano S, Takahashi S, Kurihara N, Furuta S, Tamura H, et al. Comparison of ipsilateral activation between right and left handers: a functional MR imaging study. Neuroreport. 1998; 9: 1861-1866.

56. Volkmann J, Schnitzler A, Witte OW, Freund H. Handedness and asymmetry of hand representation in human motor cortex. J Neurophysiol. 1998; 79: 2149-2154.

57. Hervé PY, Mazoyer B, Crivello F, Perchey G, Tzourio-Mazoyer N. Finger tapping, handedness and grey matter amount in the Rolando's genu area. Neuroimage. 2005; 25: 1133-1145.

58. Li S, Han Y, Wang D, Yang H, Fan Y, Lv Y, Tang H. Mapping surface variability of the central sulcus in musicians. Cereb Cortex. 2010; 20: 25-33.

59. Schlaug G. The brain of musicians. A model for functional and structural adaptation. Ann N Y Acad Sci. 2001; 930: 281-299.

60. Delvaux V, Alagona G, Gérard P, De Pasqua V, Pennisi G, de Noordhout AM. Post-stroke reorganization of hand motor area: a 1-year prospective follow-up with focal transcranial magnetic stimulation. Clin Neurophysiol. 2003; 114: 1217-1225.

61. Tecchio F, Zappasodi F, Tombini M, Caulo M, Vernieri F, Rossini PM. Interhemispheric asymmetry of primary hand representation and recovery after stroke: a MEG study. Neuroimage. 2007; 36: 1057-1064.

62. Annett M. Laterality and types of dyslexia. Neurosci Biobehav Rev. 1996; 20: 631-636.

63. Annett M. The theory of an agnosic right shift gene in schizophrenia and autism. Schizophr Res. 1999; 39: 177-182.

64. Crow TJ. A theory of the origin of cerebral asymmetry: epigenetic variation superimposed on a fixed right-shift. Laterality. 2010; 15: 289-303.

65. Leonard CM, Eckert MA. Asymmetry and dyslexia. Dev Neuropsychol. 2008; 33: 663-681.

66. Knecht S, Dräger B, Deppe M, Bobe L, Lohmann H, Flöel A, et al. Handedness and hemispheric language dominance in healthy humans. Brain. 2000; 12: 2512-2518.

67. Tzourio N, Crivello F, Mellet E, Nkanga-Ngila B, Mazoyer B. Functional anatomy of dominance for speech comprehension in left handers vs right handers. Neuroimage. 1998; 8: 1-16.

68. Foundas AL, Leonard CM, Heilman KM. Morphologic cerebral asymmetries and handedness. The pars triangularis and planum temporale. Arch Neurol. 1995; 52: 501-508.

69. Foundas AL, Leonard CM, Hanna-Pladdy B. Variability in the anatomy of the planum temporale and posterior ascending ramus: do right- and left handers differ? Brain Lang. 2002; 83: 403-424.