Mechanisms of disease

Disconnection of speech-relevant brain areas in persistent developmental stuttering

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Summary

Background The neuronal basis of persistent developmental stuttering is unknown. The disorder could be related to a reduced left hemisphere dominance, which functional neuroimaging data suggest might lead to right hemispheric motor and premotor overactivation. Alternatively, the core deficit underlying stuttering might be located in the speech-dominant left hemisphere. Furthermore, magnetoencephalography study results show profound timing disturbances between areas involved in language preparation and execution in the left hemisphere, suggesting that persistent developmental stuttering might be related to impaired neuronal communication, possibly caused by a disruption of white matter fibre tracts. We aimed to establish whether disconnection between speech-related cortical areas was the structural basis of persistent developmental stuttering.

Methods We analysed the speech of 15 people with persistent developmental stuttering and 15 closely matched controls for the percentage of syllables stuttered. We used diffusion tensor imaging to assess participants' brain tissue structure, and used voxel-based morphometry and two-sample *t* test to compare diffusion characteristics between groups.

Findings Diffusion characteristics of the group with persistent developmental stuttering and controls differed significantly immediately below the laryngeal and tongue representation in the left sensorimotor cortex (mean difference in fractional anisotropy 0·04 [95% CI 0·03–0·05]).

Interpretation Our findings show that persistent developmental stuttering results from disturbed timing of activation in speech-relevant brain areas, and suggest that right hemisphere overactivation merely reflects a compensatory mechanism, analogous to right hemisphere activation in aphasia.

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Introduction

Generation of fluent speech is dependent on the precise temporal synchronisation of phonatory and articulatory muscle groups.[1] Language content modulates this process in a top-down fashion,[2] indicating the close interaction between speech and language. This complex system is severely compromised in developmental stuttering, a disorder that presents with involuntary repetitions, lengthened sounds, or arrests of sounds and occurs in about 4–5% of all children[3] aged 3–5 years. Although stuttering can be characterised as a speech disorder, symptoms seem specifically related to use of language, and are especially prominent in emotionally and syntactically demanding speech.[2] Spontaneous remission is common, but speech impairment persists after puberty in about 1% of people, more often in men than in women,[3] and has a genetic basis.[4] Despite decades of research, the origin of persistent developmental stuttering and its structural basis are unclear.[2]

Various theories of the pathophysiology underlying persistent developmental stuttering have been proposed: incomplete or abnormal patterns of cerebral hemispheric dominance[5,6] with a shift of activation to the right hemisphere, supported by experimental data for motor, premotor,[7,8] and auditory cortices;[9] impaired oral motor control,[10] with patients with persistent developmental stuttering showing slower reaction times in tasks involving increasing complexity of bimanual decisions; [11] impaired auditory self-monitoring of speech, supported by temporal deactivation[7,8,12,13] and negative correlation between temporal activation and stuttering in positron emission tomography studies;[8,12] and synchronisation deficits in speech preparation and execution, shown in a magnetoencephalography study.[14] The magnetoencephalography study results[14] point towards disconnection of speech-related cortical areas in the left hemisphere, which affects the synchronisation of motor and premotor cortex.

We tested the hypothesis of a disconnection between speech-related cortical areas as the structural basis of persistent developmental stuttering by characterising brain tissue structure through DIFFUSION TENSOR IMAGING (DTI) in patients with persistent developmental stuttering. DTI can be used to measure the diffusion characteristics of water in vivo. The orientation of white matter fibre can be established with DTI because water diffuses faster if moving parallel rather than perpendicular to the longitudinal axis of axons.[15] FRACTIONAL ANISOTROPY (FA) OF DIFFUSION is a measure of the coherence of the orientation of fibres within each voxel (the smallest distinguishable box-shaped part of a three-dimensional space). In multiple sclerosis, lower FA values can indicate decreased fibre coherence or myelination defects.[16] DTI has also been shown to be sensitive to subtle white matter abnormalities in dyslexia, a developmental language disorder.[17]

GLOSSARY

DIFFUSION TENSOR IMAGING (DTI)
An MRI technique sensitive to diffusion properties (direction, coherence) of water protons. A set of six scans is obtained, each of which is sensitised for one of six non-colinear directions.

FRACTIONAL ANISOTROPY (FA) OF DIFFUSION
A measure of the coherence of diffusion within each voxel. In highly ordered fibre bundles such as the corpus callosum, diffusion is mainly in the direction of, rather than perpendicular to, the fibre, resulting in high FA values. Low FA values can indicate decreased fibre coherence or myelination defects as seen in multiple sclerosis.

GAUSSIAN KERNEL
A three-dimensional, Gauss curve, used to filter images spatially (ie, blur). The wider the Gaussian curve, the more blurring will result.

VOXEL-BASED MORPHOMETRY
An objective method to compare brain parenchyma between groups of patients in each voxel of structural magnetic resonance images.

Methods

We studied 15 adults (five women) with persistent developmental stuttering (study group), no signs of cluttering, mean age 30·6 years (SD 7·5, range 18–44), and mean years of education 15·7 years (3·0, 10–20). The study group came from all parts of Germany: 13 were registered with an experienced speech and language pathologist in Hamburg, who confirmed the diagnosis of persistent developmental stuttering; and two people had stuttering diagnosed by a neurologist with experience in speech-language disorders (MS).

We matched 15 controls for age (mean 30·0 years, SD 7·2, range 23–43), sex (four women), and years of education (mean 17·2 years, SD 2·7, range 15–23). Controls had no personal or family history of stuttering or cluttering, were from the Hamburg region, and most were employees of the University of Hamburg hospital. Data for one control could not be used (technical equipment failure), which left 14 controls included in the study.

No participants had a neurological or unstable medical disorder or took any drugs that acted on the central nervous system. All participants apart from one stuttering patient were right-handed with a score of at least 15 of 22 points on the Edinburgh inventory.[18] We obtained the agreement of the Ethics Committee of the Medical Faculty of the Georg-August-University of Göttingen, and written informed consent from all participants.

Immediately before doing DTI, we assessed the severity of stuttering (ie, repetitions, lengthened sounds, overt speech blocks). Stuttering patients were asked to read aloud a newspaper article of 141 words and to talk spontaneously about their perception of an international event. In the fluent control group, the text passage was longer (1273 words) to accurately score subtle speech abnormalities. Participants' speech was recorded on audiotape and the percentage of syllables stuttered assessed by two independent analysts.[19] Individual percentages of syllables stuttered were averaged across both analysts.

DTI was done with a Magnetom Vision 1·5 T MR system (Siemens; Erlangen, Germany) with a circularly polarised head coil. Cushions were used to restrict participants' head movements. Participants wore earplugs for noise protection. We acquired DTI images with a stimulated echo acquisition mode sequence (STEAM:[20] flip angle 15°, TR [repetition time] 8872 ms, TE [echo time] 65 ms, 56×64 matrix, field of view 168×192 mm, and voxel size 3×3×5 mm^3) of 20 slices covering the whole brain apart from the cerebellum.

The full protocol consisted of a T_2-weighted image and six diffusion-weighted images sensitised for diffusion along six different directions. These measurements were repeated 40 times to improve the signal-to-noise ratio in the tensor maps. A T_1-weighted image was acquired by use of a three-dimensional fast-low-angle-shot sequence (flip angle 30°, TR 15 ms, TE 5 ms, 256×256×196 matrix, voxel size 1×1×1 mm^3). The first DTI image was discarded to exclude the transition to steady state. Image processing was done with SPM 99. DTI images were realigned with the second image without diffusion weighting, and co-registered with the high resolution T_1 image, which we spatially normalised to a standard template,[21] reorienting the diffusion gradient directions accordingly.

The DTI images were sinc interpolated to 3×3×3 mm^3 resolution. The diffusion tensor and FA were established for every voxel.[15] We compared FA between the fluent and stuttering groups using VOXEL BASED MORPHOMETRY. Corrections for eddy current distortions were not necessary for this STEAM DTI acquisition. The FA maps were smoothed with a GAUSSIAN KERNEL of 6 mm full width at half maximum.

Because of the densely packed fibres, FA is higher in white matter than in grey matter. Hence, FA could be artificially higher in controls if the voxel of interest lay predominantly in grey matter in the study group and in white matter in controls. To keep this source of error to a minimum, we did a post-hoc analysis in which we investigated the unsmoothed FA maps and compared the region of interest (10×10×10 mm^3 centred on the maximum [–48, –15, 18 mm]), between groups. Within this region of interest we established all voxels that contained white matter by use of the segmented high resolution T_1-weighted scan. Co-registration between diffusion weighted and T_1-weighted images ensured a perfect match of structures between modalities. By contrast with echo planar diffusion weighted imaging, STEAM imaging does not introduce geometrical distortions due to susceptibility gradients or eddy currents.

For a statistical power of 0·8 and α of 0·05, the sample size was sufficient to detect differences between stuttering patients and controls greater than 1 SD. To approximate a normal distribution, behavioural data were log transformed: f(x)=ln(x+0·1), x=percentage syllables stuttered. Adding a constant was necessary to avoid a logarithm of 0 in one control. FA values were compared between groups by use

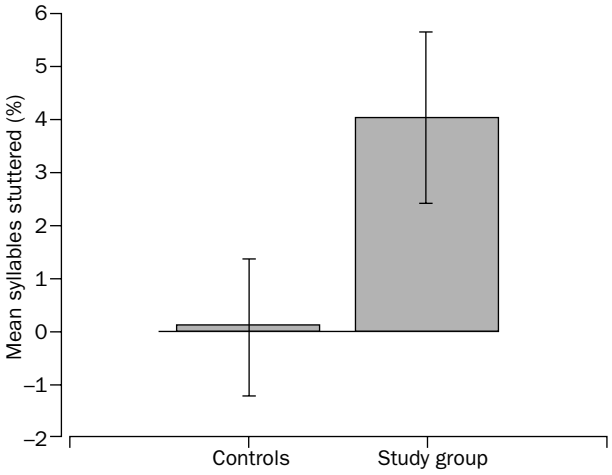

Figure 1: **Percentage of syllables stuttered by the study group and controls**
Bars=95% CIs.

of SPM 99 (two-sample *t* test) with the threshold set to p<0·05, corrected for multiple comparisons.

Role of the funding source
The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the paper for publication.

Results

Patients in the study group stuttered significantly more syllables (mean % stuttered syllables 4·04% [95% CI 2·42–5·66], range 1·0–20·4), than controls (0·12% [–1·17 to 1·41], range 0–0·9, one-tailed unpaired *t* test $p=1·48\times10^{-10}$; figure 1). The interanalyst reliability of scores was 0·85.

FA was significantly lower in the study group than controls (mean difference 0·04 [95% CI 0·03–0·05]; mean of relative FA reduction 32·8% [22·3–43·3], p=0·014, corrected for multiple comparisons in the whole brain volume), in the rolandic operculum of only the left hemisphere, immediately above the Sylvian fissure (figure 2). This region of reduced FA encompasses the white matter immediately below the sensorimotor representation of the oropharynx at the level of the central sulcus (Brodmann's area 43),[8,12] close to variations in gyral anatomy reported in persistent developmental stuttering.[22]

Post-hoc analysis of the region of interest showed a significant difference between groups (mean difference in FA 0·03 [95% CI 0·01–0·05]; mean of relative FA reduction in study group 15·1% [4·6–25·6], uncorrected p=0·0036), indicating FA differences within white matter (figure 2). The lower significance level in the post-hoc analysis was expected because the analysis was based on unsmoothed FA data to avoid further grey-white matter smearing.

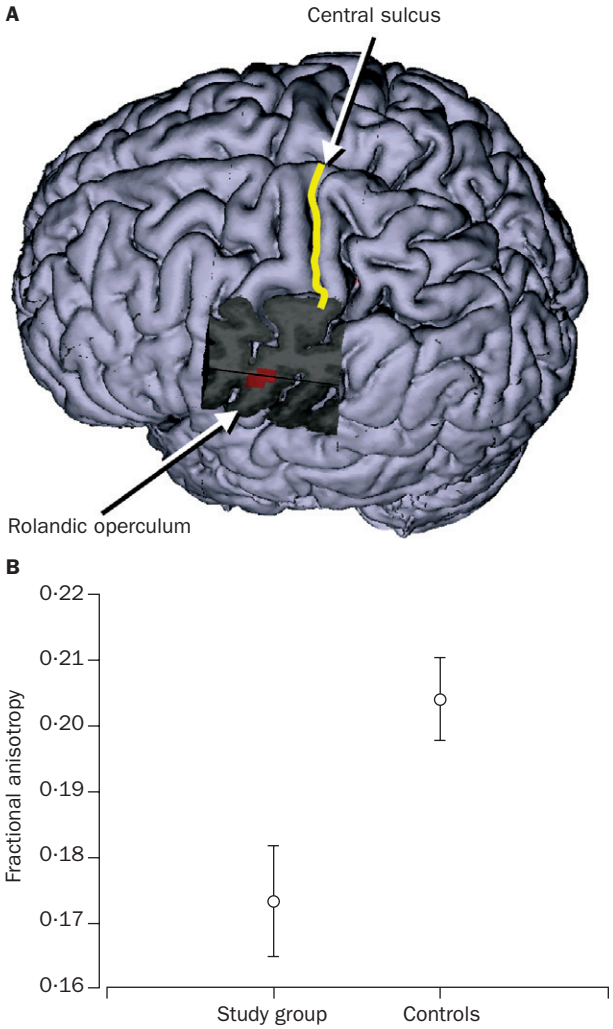

Figure 2: **Voxels with significantly lower FA in the study group than in controls (top panel), and comparison of post-hoc FA analysis results (bottom panel)**
Voxels are superimposed in red on a normalised T1-weighted anatomical image of a control at a threshold of p<0·001 (size of cluster=81 mm^3). The insert is cut at x<–48 mm, y between –40 and 5 mm, and z>18 mm; coordinates refer to the space defined by the Montreal Neurological Institute. Bars in the lower panel=SEs.

Discussion

Our results show signs of a cortical disconnection in people with persistent developmental stuttering immediately below the laryngeal and tongue representation in left sensorimotor cortex. The immediate surrounding region is composed of the sensorimotor representation of tongue, larynx, and pharynx in the subcentral sulcus; the ventral extension of the central sulcus; [23] and the inferior arcuate fascicle linking temporal and frontal language areas.[24,25]

In particular, fibre tracts in this area connect the sensorimotor representation of the oropharynx with the frontal operculum involved in articulation[26] and the ventral premotor cortex related to the planning of motor aspects of speech.[25] Thus, disturbed signal transmission through the left rolandic operculum could impair sensorimotor integration necessary for fluent speech production.[1,27] Our findings show that the normal temporal pattern of activation in premotor and motor cortex is disturbed[14] and, as a consequence, that right hemisphere language areas compensate for this deficit,[7,8] similar to recovery in aphasia.[28]

The alternative interpretation, that right hemisphere overactivation is the cause of persistent developmental stuttering and leads to subsequent atrophy of white matter in the left rolandic operculum as a secondary effect, cannot be discounted by our data. However, this mechanism is extremely unlikely: it is unclear how widespread right hemisphere overactivation could lead to a focal abnormality in the left hemisphere; and right hemisphere abnormality does not provide a plausible explanation for the synchronisation abnormality in the left hemisphere noted with magnetoencephalography.[14] Furthermore, a possible disconnection, as shown by our data, is consistent with decreased activation of the adjacent posterior inferior frontal cortex during stuttering.[7,29]

Fluency inducing techniques such as chorus reading or shadowing have a powerful effect in stuttering.[2] Chorus reading and shadowing might induce fluency by providing an external clock. Through projections from periauditory areas, this external clock might be able to functionally compensate the disconnection between frontal speech planning areas and motor areas by synchronising their activity via a common input. In accord with this theory, fluency-inducing procedures such as chorus reading increase activity in temporal areas.[7]

We can only speculate about the histological alterations underlying the difference in FA. Although brain myelination is essentially complete at age 5 years,[30] results from DTI studies in children aged 5–17 years[31] showed an increase of FA with age, indicating that DTI is a sensitive marker for white matter development beyond myelination. Similarly, results of a morphometric study

using T_1-weighted imaging[21] showed a correlation of white matter density in T_1-weighted images with age. In both studies, the correlation was most prominent in the motor system (internal capsule) and the speech-language system (left frontoparietal white matter). This finding parallels the development of these functional systems during childhood and adolescence. Since the density of white matter obtained with T_1 and FA show a similar correlation with age, the increase in FA after the completion of myelination probably arises from an increase in density and coherence of neuronal packing.[31]

A limitation of our study follows from the large voxel size that we chose because of little a-priori knowledge. Therefore, we do not know whether the FA difference is only in white matter or whether the grey-white border is also involved. A further limitation is that we did not control for any past or present therapy in the study group, which could have improved fluency scores and modified correlation between FA scores and fluency. The small sample size restricts our study only with regard to detection of strong differences of the mean between groups.

Overall, our findings provide evidence for a structural abnormality in speech-relevant areas in the left rolandic operculum in persistent developmental stuttering. This abnormality probably develops during the period of early language and speech acquisition in which many children experience a transient phase of stuttering.[2] Our methods could be used to ascertain why certain children develop persistent stuttering whereas others become fluent speakers.

Contributors

M Sommer was involved in planning, study coordination, manuscript writing, and data analysis. M Koch was involved in implementing MR pulse sequences and data analysis. W Paulus and C Weiller were involved in acquisition of funding and in planning the study. C Büchel was involved in study design, data analysis, review of data, manuscript writing, and overall study coordination.

Conflict of interest statement

None declared.

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