How the brain repairs stuttering

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Stuttering is a neurodevelopmental disorder associated with left inferior frontal structural anomalies. While children often recover, stuttering may also spontaneously disappear much later after years of dysfluency. These rare cases of unassisted recovery in adulthood provide a model of optimal brain repair outside the classical windows of developmental plasticity. Here we explore what distinguishes this type of recovery from less optimal repair modes, i.e. therapy-induced assisted recovery and attempted compensation in subjects who are still affected. We show that persistent stuttering is associated with mobilization of brain regions contralateral to the structural anomalies for compensation attempt. In contrast, the only neural landmark of optimal repair is activation of the left BA 47/12 in the orbitofrontal cortex, adjacent to a region where a white matter anomaly is observed in persistent stutterers, but normalized in recovered subjects. These findings show that late repair of neurodevelopmental stuttering follows the principles of contralateral and perianomalous reorganization.

Keywords: plasticity; recovery; functional MRI; speech production; orbitofrontal

Abbreviations: FA = fractional anisotropy; PWS = people who stutter; PS = persistent stutterers; RS = recovered stutterers

Introduction

Developmental stuttering is a heritable speech disorder (Dworzynski et al., 2007) affecting about five percent of children during the phase of speech acquisition (Bloodstein, 1995). Dysfluency typically manifests around the age of three, which suggests a single aetiology during development of the neural system underlying speech production. Yet, distinct groups of people who stutter (PWS) emerge, depending on the subsequent development of symptoms. Three in four stuttering children, more girls than boys, recover unassisted and the likelihood of such a recovery dwindles until adolescence (Yairi and Ambrose, 1999; Howell et al., 2008). Like the disorder itself, unassisted recovery in childhood is heritable (Ambrose et al., 1993; Dworzynski et al., 2007) and therefore most probably engages robust and reproducible neural mechanisms. The failure of recovery during childhood yields a stuttering prevalence of 1% in the adult population with a male/female gender ratio of about 4:1 (Andrews, 1964). Overall, the course of stuttering is variable across individuals and a common neurodevelopmental anomaly presumably triggers different compensatory processes yielding variable outcome.
Children who stutter tend to show developmental anomalies of Broca’s area, e.g. less grey matter in the left inferior frontal gyrus, and a disorganization of the white matter in the left Rolandic operculum below the motor representation of articulation (Chang et al., 2008). These anomalies of the left brain are still seen in adult persistent stutterers (PS) (Foundas et al., 2001; Sommer et al., 2002) usually with a weaker functional lateralization of speech-related processes (Brown et al., 2005). Relative to fluent controls, neural activity in adult PS during speech production is typically enhanced in right fronto-parietal brain regions, including the frontal operculum (Brodmann area (BA) 47/12), the anterior insula, and in the cerebellar vermis (Fig. 1). Abnormal activations are also detected in the basal ganglia (Giraud et al., 2008).

Behavioural ‘fluency shaping’ therapies (Webster, 1980), which modify speech tempo, prosody, rhythm, speech onsets and breathing techniques, successfully reduce stuttering severity to less than 1% of stuttered syllables (Euler and Wolff von Gudenberg, 2000). Fluency-shaping therapies reduce right-hemispheric over-activation, normalize basal ganglia activity and reactivate left-hemispheric cortex (De Nil et al., 2003; Neumann et al., 2005; Giraud et al., 2008). However, a stabilized therapeutic outcome requires repeated training and refresher sessions. Relateralization of the speech network is therefore typically only a transient and, overall, an insufficient repair process.

A subset of PWS manage to recover unassisted even in adulthood (Ingham et al., 2005). Recovery in adulthood is unpredictable, does not seem to be heritable and is not associated with a consistent recovery strategy (Finn, 1996; Finn et al., 2005; Ingham et al., 2005; Howell et al., 2008). By exploring the neural mechanisms in these recovered stutterers (RS) we expect to identify those mechanisms that underlie long-lasting repair of stuttering. In particular, a comparison of neural activity induced by behavioural therapy with the reorganization profile of unassisted RS should elucidate the limitations of current stuttering management and identify possible targets for future behavioural and/or pharmacological therapy.

We compared brain morphology (grey and white matter) and activations during fluent speech production in PS (before and after a fluency-shaping therapy), in RS, and in control subjects using magnetic resonance imaging (MRI). We dissociated pathogenesis-related anomalies from compensation effects by relating the magnitude of the neural anomaly to individual degree of symptom (off-line stuttering severity). We reasoned that when an anomaly appears most prominent in the least symptomatic stutterers, it signals a compensation effect resulting in an attenuation of stuttering. In contrast, when an anomaly is most pronounced in the most affected stutterers, it denotes a primary dysfunction related to the origin of stuttering. The involvement of a given region in original pathophysiology is further confirmed if a positive correlation of neural activity with stuttering severity is abolished by therapy. This paradigm allows us to identify brain mechanisms associated with optimal compensation to eventually mobilize such mechanisms in future therapies.

Materials and Methods

Subjects

We ran an MRI speech production experiment and acquired structural data in: (i) 13 male PS [mean age 27 years, range from 18 to 39, mean handedness score of 50 (SD = 54) as measured by the Edinburgh Handedness Inventory (Oldfield, 1971)]; (ii) the same 13 subjects after a three week intensive course of the Kassel Stuttering therapy (Euler and Wolff von Gudenberg, 2000), modified after Webster (1980); (iii) 13 males who had recovered from stuttering to 1% stuttered syllables or less, unassisted (RS), i.e. without guided therapy; seven RS were recruited among acquaintances or family members of PS, six by means of press advertisements (mean age 40 years, range from 16 to 65, mean handedness score of 86, SD = 30, with no significant differences between the differently recruited subjects); for more detailed biographical information see Supplementary Table 1; and (iv) 13 male control subjects [mean age 30 years, range from 23 to 44, mean handedness score of 83 (SD = 17)]. Educational levels were coded in ordinal categories (<10 years of schooling, junior high school, high...
school with university admission, college or university) and did not differ significantly between the groups (Kruskal–Wallis test). All subjects were native Germans. Twelve other subjects were excluded due to uncertain diagnosis, co-morbidity or recent stuttering therapy.

The history of stuttering in RS was based on detailed analysis of previous medical records (Finn, 1996). In 10 of 13 subjects the diagnosis was supported by reports of close relatives who stuttered (Supplementary Table 1). Stuttering duration was not significantly different between groups [mean age of stuttering onset 4 years in PS (SD = 2) and 5 years in RS (SD = 3), with a mean stuttering duration of 18 years (SD = 7 in PS and 10 in RS)]. There was an age difference between PS and RS groups (P < 0.05) because it was impossible to recruit RS immediately after recovery. Handessed scores and age were entered in the analysis of co-variance (ANCOVA) of MRI data as nuisance covariates.

PS underwent a variety of therapies, e.g. behavioural therapy and logopaedic intervention during childhood or puberty without satisfying long-term result. None of our participants had stuttering therapy during the year before the MRI study. Those RS who had stuttering therapy did not benefit and recovered 4–38 years after their interventions (Supplementary Table 1), thus recovery was judged as unassisted. Participants had no neurological or other relevant chronic disorder and structural brain scans confirmed the absence of focal brain lesions or global atrophy. All subjects gave informed consent to participate in the study, which was approved by the local ethics committee.

**Behavioural screening**

Together with the past medical history, an open-end interview confirmed the diagnosis of either persistent or recovered stuttering.

Stuttering severity, speech rate and speech naturalness were assessed before the MRI session by digital audio recordings of the subjects’ speech (at least 300 analysable syllables) in four speaking situations: (i) an open conversation with a therapist; (ii) reading a standard newspaper text; (iii) calling an unknown person by telephone; and (iv) interviewing a passer-by on the street. Quality criteria of these measures are reported elsewhere (Euler and von Gudenberg, 2000), with a place-to-place inter-rater agreement of 78.8% and a split-half reliability between \( r = 0.83 \) (telephone call) and \( r = 0.99 \) (interviewing a passer-by).

Stuttering severity was defined as the percentage of stuttered syllables according to the guidelines by Boberg and Kully (1994). This dysfluency measure contains only the number of unambiguous moments of stuttering (Jones et al., 2000) and incorporates syllable repetitions and audible and inaudible sound prolongations (Conture, 2001). The measure does not include normal dysfluencies such as interjections, whole-word repetitions, revisions and phrase-repetitions. The scores of the percent stuttered syllables were the non-weighted means of the percent stuttered syllables at the four measurement occasions and were used subsequently for parametric analysis of the MRI dataset. The mean speech rate was defined as number of syllables per minute over all the recorded speaking conditions. The speech naturalness was rated on a 9-point scale (1 = highly natural, 9 = highly unnatural) (Martin et al., 1984) by an independent observer and the mean speech naturalness was averaged over the four speaking situations.

Self-assessments were based on standard German inventories, adapted from Vanryckeghem and Brunten (2001): the inventory ‘Stotter-Iusizations’ gives the subjective occurrence of dysfluencies in several speaking situations on a 5-point rating scale, the inventory ‘Negative Emotions’ a measure of negative emotions in several speech situations (both min. 0 max. 255), and the inventory ‘Sprechfussigkeitshilfen’ the strategies which are used to improve speech fluency in several speech situations (min. 0 max. 475). The self-evaluated stuttering severity was rated on a 9-point scale (0 = no stuttering, 8 = severe stuttering).

**Experimental procedure**

The functional MRI study involved reading sentences aloud in the scanner. Prior to scanning, participants were familiarized with the experimental setting. Data were collected using a 3T magnetic resonance scanner (Siemens Trio, Erlangen, Germany) by constant acquisition of 902 volumes of a gradient echo planar imaging (EPI) sequence with an echo time of 30 ms, repetition time of 2000 ms and voxel size of 3 × 3 × 3 mm³ (1 mm gap, 33 slices to cover the entire brain). Structural scans were obtained using a magnetization rapid-acquisition gradient echo sequence (144 slices, one slab, TR 2300 ms, voxel size 1 × 1 × 1 mm³) and five acquisitions of a high-resolution diffusion tensor imaging sequence (70 slices, TR 10 s, TE 83 ms, voxel size 1.9 × 1.9 × 1.9 mm³, six non-collinear directions with \( b = 700 \text{s/mm}^3 \)). Subjects lay comfortably supine with the head immobilized by a cushion and wore headphones for noise protection and delivery of acoustic cues. Visual stimuli were presented on a screen and viewed through a mirror. The task consisted of three seconds of overt sentence reading, which had no detrimental effects on continuously obtained images (Preibisch et al., 2003b) and three seconds of covert reading as baseline. The material involved written phonologically balanced, semantically neutral and syntactically identical German sentences (‘Grosse Frauen spielen selten Fussball’, translated as ‘Tall women rarely play soccer’). They were presented for three seconds, preceded 2–4 s earlier by an auditory cue (‘mute’ or ‘normal’) indicating whether sentences should be read covertly or overtly. The intertrial interval varied within a range of 2 and 10 s with a mean of 6 s. In total 90 sentences were presented in a pseudo-randomized order. Subjects were instructed to stop reading aloud when the screen turned black (after 3 s), but all completed adequately within time limits. PS after therapy were explicitly asked to talk normally inside the scanner, without intentionally applying any newly acquired techniques. Subject behaviour was recorded with an MRI-compatible microphone (mr con fon, Magdeburg, Germany); recordings were analysed after filtering out the scanner noise (Adobe Audition, San Jose, USA) for task performance, stuttered syllables and speech production rate.

**Data analysis**

**Behavioural data**

Between-group ANCOVAs were calculated with % stuttered syllables, speech rate, speech naturalness and the self-report items as dependant variables. Subsequent two-tailed \( t \)-tests revealed significant (\( P < 0.05 \)) group differences.

**Structural data**

**Grey matter**

A voxel-based morphometric (VBM) analysis of T1-weighted scans was performed using a modified version of the VBM utility tool (DARTEL toolbox) (Ashburner, 2007) for statistical parametric mapping (SPM5; http://www.fil.ion.ucl.ac.uk/spm/), which uses the unified segmentation approach (Ashburner and Friston, 2000). Spatial normalization and iterating grey matter segmentation with voxel size \( 1 \times 1 \times 1 \text{mm}^3 \), bias correction and warping were applied until no significant change of estimates occurred. Data were modulated using the
Jacobian determinant of the normalization process to correct for individual differences in brain shape. The processed grey matter images were smoothed using a 10-mm full width at half maximum isotropic Gaussian kernel and entered in a group comparison in which age, handedness score and the sum of grey and white matter (to control for different brain size) were defined as nuisance variables. First, we compared the obtained images of all PWS to those of controls to delineate common deviation from norm; secondly, the separate group images were contrasted against each other to identify differences between distinct PWS groups. On the basis of previous literature, we expected differences in the left inferior frontal gyrus and bilateral planum temporale (Foundas et al., 2001, 2004; Chang et al., 2008). We report data corrected for multiple comparisons on the voxel level within corresponding search volumes defined by the anatomy toolbox for SPM (Eickhoff et al., 2006, 2007). After registering the FA maps nonlinearly to a standard brain (Lancaster et al., 2004), the ROI volume was defined anatomically on an MNI standard brain using the Talairach daemon and applied to the normalized brains following standard protocols (Lancaster et al., 2000; Ernst et al., 2004).

White matter
For analysis of white matter differences between groups, diffusion tensor images were preprocessed (including correction for eddy current distortion and head motion) using Functional Magnetic Resonance imaging of the Brain’s (FMRI B) diffusion toolbox (FSL; http://www.fmrib.ox.ac.uk/fsl) to obtain values of fractional anisotropy (FA). This parameter measures the restriction of water diffusion by organic barriers like cell membranes, thus mirroring fibre tract orientation with the largest FA values for the highest coherence of axonal bundles (Beaulieu, 2002). The resulting FA maps were analysed voxel-wise using tract based spatial statistics (TBSS) for FSL (Smith et al., 2006, 2007). After registering the FA maps non-linearly to a standard FA-template, FA values were projected on a white matter skeleton that represents fibre tracts that are common across subjects. Monte Carlo permutation with 105 trials was performed and group contrasts for data in the skeleton were generated with age and handedness score and report them with their respective correlation coefficients and P-values.

Group comparisons (ANCOVA)
After calculating the contrast (overt > covert speech production) in each individual (first level analysis), the contrast images were used in a separate step for a second level random effects group analysis where age and handedness score were entered into the ANCOVA as nuisance variables. For analysis of pre- and post-therapeutic measurements, repeated measures were taken into account. To control for non-specific test/re-test effects, this analysis was restricted to PWS-specific regions by masking the results inclusively with the contrast of (PS>controls) (mask threshold P < 0.05, uncorrected). From the ANCOVA, we report group (PS before therapy, PS after therapy, RS, controls) by task (overt and covert speech) interactions with group differences thresholded at P < 0.001, uncorrected and present only in clusters exceeding the expected size (Friston et al., 1996).

Correlation with symptom severity
We used stuttering severity assessed off-line, before therapy outside the scanner, as a clinical parameter to relate symptomatology with neural activity during overt reading. We did not use post-therapeutic values as all subjects were fluent. Age and handedness scores were entered into the regression analysis as nuisance variables. We report clusters where activity co-varied with stuttering severity at a threshold of P < 0.001 in unpredicted regions, and of P < 0.05 in regions selected on the basis of previously published data on stuttering (Preibisch et al., 2003a; Brown et al., 2005). The effect of therapy on symptom severity was probed by entering the extracted beta values as dependant variable into a univariate general linear model with stuttering severity as covariate and group as random variable. Interactions were considered significant at P < 0.05.

Results

Behavioural data
Behavioural group differences are summarized in Supplementary Table 2. Intensive therapy in PS reduced the overall percentage of stuttered syllables (across the four tested speaking conditions) from 7.4% (range from 1.4% to 13.9%) stuttered syllables to 0.6% (range from 0% to 1.95%). PS differed only before therapy from controls (t = 6.33, df = 12.3, P < 0.001, d = 2.48) or RS (t = 6.40, df = 12.2, P < 0.001, d = 2.56). RS stuttered 0.6% (range from 0.1% to 1%) syllables and did not differ significantly from controls with respect to stuttering severity.
Consequently, there was no significant difference in self-estimated stuttering severity between RS and controls, while PS judged their stuttering more severe than controls (t = 8.88, df = 12.0, P < 0.001, d = 3.45) or RS (t = 5.12, df = 19, P < 0.001, d = 2.30). Yet, RS reported more speech situations that could evoke stuttering with associated negative emotions compared to controls, although less than PS (Supplementary Table 2).

PS spoke more slowly than controls (t = 7.43, df = 24, P < 0.001, d = 2.97) or RS (t = 8.75, df = 17.6, P < 0.001, d = 3.50). The difference between controls and RS was not significant. Speech rate in PS was not significantly modified by therapy.

Speech was less natural in PS before therapy than in controls (t = 11.59, df = 14.2, P < 0.001, d = 4.55) or RS (t = 11.13, df = 14.5, P < 0.001, d = 4.36). Due to acquired technique, speech after therapy was also significantly less natural in PS than in controls (t = 5.14, df = 13.9, P < 0.001, d = 2.01), or RS (t = 4.75, df = 14.2, P < 0.001, d = 1.86).

Behavioural results from the scanning sessions were independent from the measures acquired at interview. This is necessary for group comparisons of functional data (Preibisch et al., 2003a; Neumann et al., 2005; Giraud et al., 2008). The underlying assumption was that stutterers can occasionally produce fluent speech, e.g. when they are alone or in a noisy context, using the speech network that has been shaped by their clinical condition. Due to noise-induced fluency (continuous scanner noise) and short duration of verbal output, all subjects produced fluent speech during scanning (all subjects stuttered <1% syllables inside the scanner), yet involved a different brain network (see below). PS reported effortless speech during scanning and groups did not differ with respect to speech production rate. Speech production after therapy was indistinguishable from pre-therapy because subjects already produced fluent speech under scanning conditions. The instruction that they should refrain from intentionally applying any acquired anti-stuttering technique in the post-therapeutic session also contributed to this outcome, which means that intentional articulatory efforts were unlikely to affect our functional results.

Grey matter differences between PWS and controls

A focal decrease in grey matter volume was found in all PWS relative to controls in the left inferior frontal gyrus (BA 44; in PWS together and PS separately –41, 25, 28; P < 0.05, corrected; Fig. 2A; in RS –47, 24, 30, P < 0.05 corrected). Grey matter volume in this region correlated negatively with stuttering severity in PS (r = –0.8, P = 0.002; Fig. 2A), suggesting a possible role in the origin of stuttering. We found no further significant cortical or subcortical grey matter reduction or increase in persistent or RS compared to controls. However, when analysing uncorrected data (P < 0.001), two additional clusters of decreased grey matter volume were detected in PS, compared to fluent controls: in the left medial frontal gyrus (–46, 48, 6) and left supramarginal gyrus (–61, −43, 30), both consistent with findings in childhood stuttering (Chang et al., 2008).

White matter differences between PWS and controls

Compared to fluent controls, PWS showed elevated FA values in the white matter underneath the left inferior insula/inferior frontal region (–22, 24, –10) and the left orbitofrontal cortex (–12, 24, –12). This effect was mainly driven by PS, as in the separate comparison, only PS differed significantly from controls while RS showed intermediate FA values [mean FA values for PS: 0.54 (SD = 0.05), RS: 0.47 (SD = 0.05), controls 0.44 (SD = 0.04)]. PS additionally had elevated FA values underneath the left intra-parietal sulcus (–23, −59, 34). Overall, these group differences localized to fibres in the forceps minor of the corpus callosum, inferior occipito-frontal fasciculus and the posterior part of the anterior segment of the arcuate (superior longitudinal) fasciculus, respectively (Catani et al., 2002) (Fig. 2B). No covariation between FA and stuttering severity was detected for these clusters. There was no significant FA difference between persistent and RS. No reductions in FA values were observed in persistent and RS, relative to controls. Previously reported regions with reduced FA in stutterers could only be found when examining the uncorrected data. There was an effect in a more anterior portion of the left arcuate fasciculus (–38, –19, 29, P < 0.001) (Chang et al., 2008) than the cluster with enhanced FA values and in the left Rolandic operculum (–51, –7, 19, P < 0.001) (Sommer et al., 2002; Chang et al., 2008; Watkins et al., 2008).

Group comparisons during overt speech production

All PWS showed stronger activation of bilateral primary auditory cortices (Table 1) and decreased activation of bilateral medial orbitofrontal cortices (orbitofrontal region 13) and cerebellar hemispheres (Table 1). Relative to controls, untreated PS over-activated a large right-hemispheric network including Broca’s homologue, the right frontopolar operculum, right premotor, mesial prefrontal, cingulate, auditory cortices (primary auditory cortex extending to the planum polare, i.e. the portion of the superior temporal gyrus anterior to Heschl’s gyrus) and the parieto-temporal junction (Fig. 2C, Table 1). Therapy corrected this excess of neural activity in right dorsal frontal and parietal regions (Table 1), while over-activation persisted in right orbitofrontal (BA 47/12) and medial cortices, and in the right planum polare (Fig. 2C, Table 1). Compared to fluent controls, treated PS additionally over-activated the left auditory, frontomesial and cingulate cortices, and the cerebellar vermis III (Fig. 2C, Table 1); yet, these effects did not reach statistical thresholds in the direct comparison between post- and pre-therapeutic PS.

RS over-activated left middle frontal and primary motor cortices, and the right auditory cortex (Fig. 2C, Table 1). While all PWS over-activated the right orbitofrontal cortex (BA 47/12), RS further recruited its left homologue (Figs 2C and 3). Activity in this region selectively distinguished (P < 0.001) RS from treated or untreated PS.
Correlation with severity of stuttering

We distinguished brain regions that closely relate to the origin of stuttering from those involved in compensation by computing correlation analyses of neural activity with stuttering severity, a clinical measure of stuttering rate assessed outside the scanner before therapy (Fig. 4).

Stuttering severity of PS positively co-varied with activity of the left anterior insula ($r = 0.755$, $P = 0.003$), left rolandic operculum ($r = 0.76$, $P = 0.003$), bilateral planum polare (right $r = 0.603$, $P = 0.029$, left $r = 0.845$, $P < 0.001$), and bilateral striatum (right $r = 0.805$, $P < 0.001$, left $r = 0.685$, $P < 0.01$). A negative relationship with stuttering severity was found in the right orbitofrontal BA 47/12 ($r = -0.37$, $P = 0.048$), bilateral medial frontal gyrus ($-44$, $28$, $32$ and $44$, $24$, $36$) and bilateral angular gyrus ($-50$, $-40$, $48$ and $40$, $-54$, $50$), all at $P < 0.001$.

After therapy stuttering rate still co-varied with activity of the left articulatory motor region in the rolandic operculum (positive covariance, $r = 0.579$, $P = 0.038$) and of the right BA 47/12 (negative covariance, $r = -0.511$, $P < 0.05$), but no longer with that of the left anterior insula ($r = 0.357$, $P = 0.231$), bilateral planum polare (right $r = -0.288$, $P = 0.496$, left $r = 0.324$, $P = 0.281$), striatum ($r = 0.202$, $P = 0.508$) and bilateral medial frontal and angular cortices.

In left BA 47/12, no correlation with stuttering severity was found in PS before or after therapy.

Discussion

Equal behaviour during scanning and correlation with offline stuttering severity allowed for classification of the results as...
Table 1 Regions with significant ($P < 0.001$, uncorrected) group differences in the contrast overt > covert reading

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<th>T-value</th>
<th>Pre versus Post</th>
<th>Post-therapy &gt; controls</th>
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<th>Post versus RS</th>
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<tr>
<td>R primary auditory/planum temporale</td>
<td>41</td>
<td>34, -30, 12</td>
<td>4.16</td>
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<tr>
<td>L primary auditory/planum temporale</td>
<td>41</td>
<td>-44, -32, 16</td>
<td>3.91</td>
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<tr>
<td><strong>Parietal</strong></td>
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<tr>
<td>R parietal operculum</td>
<td>OP1</td>
<td>50, -22, 20</td>
<td>3.75</td>
<td>4.14</td>
<td></td>
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<td>Posterior cingulate</td>
<td>31</td>
<td>0, -32, 38</td>
<td>5.54</td>
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<tr>
<td>R posterior cingulate</td>
<td>31</td>
<td>2, -58, 22</td>
<td>4.70</td>
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<tr>
<td>L posterior cingulate</td>
<td>31</td>
<td>-4, -48, 24</td>
<td>4.71</td>
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<tr>
<td>R supramarginal</td>
<td>40</td>
<td>56, -42, 30</td>
<td>3.80</td>
<td>4.37</td>
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<td>R angular</td>
<td>39</td>
<td>46, -54, 50</td>
<td>5.51</td>
<td>6.14</td>
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<td><strong>Cerebellum</strong></td>
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<tr>
<td>Vermis</td>
<td>III</td>
<td>2, -40, -10</td>
<td>4.23</td>
<td></td>
<td></td>
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<tr>
<td>Vermis</td>
<td>IV/V</td>
<td>-2, -60, -16</td>
<td>4.98</td>
<td></td>
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<tr>
<td>R hemisphere</td>
<td>I</td>
<td>46, -52, -36</td>
<td>-4.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22, -70, -18</td>
<td>-4.17</td>
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<tr>
<td>R hemisphere</td>
<td>VI</td>
<td>34, -62, -28</td>
<td>-4.57</td>
<td></td>
<td>38, -62, -22</td>
<td>-4.38</td>
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<td>28, -64, -28</td>
<td>-4.61</td>
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<tr>
<td>L hemisphere</td>
<td>VI</td>
<td>-24, -74, -22</td>
<td>-3.97</td>
<td></td>
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Coordinates (x, y, z) are given in MNI space.
a Also Pre vs. Rec. (BA 47/12: T = -4.11).
b As defined by Eickhoff (2006).
pathology-related anomalies (left-sided), contralateral compensation attempt, therapy-induced relateralization, and optimal brain repair by the left inferior frontal region itself (summarized in Fig. 5).

Left-sided anomalies and the origin of the disorder

The reduction of cortical grey matter observed in the left inferior frontal gyrus in all PWS co-varied positively with stuttering severity and was independent from recovery, i.e. effective compensation, suggesting the region is closely related to the origin of the disorder. This gyrus develops abnormally in children who stutter (Chang et al., 2008). In controls, it updates action plans as a function of immediate sensory context (Koechlin et al., 2003), a function highly relevant to integration of sensory feedback into the speech motor program, which is thought to be impaired in stuttering (Max et al., 2004). Auditory feedback from one’s own utterance controls the rhythmic flow of articulation, and dysfluency can be induced or corrected by temporal auditory feedback manipulation (Lee, 1951; Lotzmann, 1961; Van Borsel et al., 2003b).

Increased FA values relative to controls in inferior frontal segments of fibre tracts connecting the left temporal, parietal, and insular with the frontal lobe, have previously been reported (Watkins et al., 2008). As in Williams Syndrome (HoefT et al., 2007), they might reflect a focal pathological fibre branching appearing as a ‘hyperconnectivity’, originating in a failure to eliminate rudimentary synapses during development (Neil et al., 1998; Huang et al., 2008), and ultimately resulting in superfluous and irrelevant information transmission (Catani and ffytche, 2005; Catani, 2007). These findings thus confirm that the connectivity between left inferior frontal cortex and its contralateral homologue and posterior areas, such as the left articulatory motor cortex, is altered in PS (Salmelin et al., 2000).

In summary, structural changes in PS that are prominent in the left inferior frontal region and below the left motor representation of articulation (Fig. 5) (Sommer et al., 2002; Chang et al., 2008; Watkins et al., 2008) most likely relate to stuttering pathology. The posterior orbitofrontal site appeared key in the recovery process.
Figure 4  Schematic representation of the results of the correlation analyses. The upper panel depicts subcortical regions correlating with stuttering severity assessed before therapy, the middle panel left-hemispheric, and the lower panel right-hemispheric cortical regions that correlate with stuttering severity. Pre-therapeutic contrast estimates (y-axis) are plotted against stuttering severity assessed before therapy (x-axis) in yellow, post-therapeutic estimates in blue, respectively. The same colour-coding is used for the schematic presentation, where circles indicate positive correlation with stuttering severity, squares indicate negative correlation. Significant therapy-induced changes in correlation of brain activation with stuttering severity are marked with an asterisk. Activity in the bilateral striatum, planum polare and left anterior insula positively co-varied with stuttering severity only before therapy, while the activity of the left rolandic operculum showed positive correlation both before and after therapy. Negative correlation was found only before therapy in the bilateral dorsolateral prefrontal cortex and angular gyri. Right BA 47/12 co-varied negatively with stuttering severity both before and after therapy.
The bilateral striatum, planum polare, left anterior insula and left rolandic operculum were most active in those subjects with the most pronounced symptoms in the functional (f)MRI part of the study, and are thus also presumably involved in the pathophysiology of stuttering (Fig. 5). The left rolandic operculum, just above the area of reduced white matter integrity, represents speech motor commands. We assume that the underlying defective white matter resulted in hyperactivity of corresponding cortex, a dysfunction that was not locally compensated by therapy. Hyperactivity of left articulatory motor cortex could thus be interpreted as a direct consequence of its functional disconnection and point to a trait characteristic of developmental stuttering.

The basal ganglia are often proposed to be involved in stuttering pathogenesis because stuttering shares clinical features with classical basal ganglia disorders (e.g. involuntary movements, improvement of symptoms with external temporal cueing or with antidopaminergic medication) (Bloodstein, 1995; Alm, 2004; Maguire et al., 2004). As no structural anomalies are found in the basal ganglia, abnormal functioning of the basal ganglia (Wu et al., 1997; Giraud et al., 2008) is likely to denote a response to a remote structural defect (i.e. left inferior frontal region). Altered articulatory motor programs (Salmelin et al., 2000; Max et al., 2004) could readily translate into hyperactivity in the basal ganglia via cortico-striatal loops (Alexander and Crutcher, 1990; Grillner et al., 2005).

A primary response to dysfunction was also found in the bilateral planum polare and left anterior insula. These regions are critical for metric processing (Liegeois-Chauvel et al., 1998; Vuust et al., 2006) and thus participate in the integration of auditory feedback into speech motor programs (Hashimoto and Sakai,
2003; Christoffels et al., 2007). Their activity profile in PS could thus directly point to impaired sensorimotor integration (Max et al., 2004) calling for compensational adaptive changes.

**Spontaneous compensation attempt by the right brain**

Before therapy, adaptive compensatory changes were localized to brain regions contralateral to the structural anomalies (Fig. 5). These over-activations of the right hemisphere during speech inversely correlated with stuttering severity, and thus are not maladaptive. We classify this neural profile as ‘attempted’ compensation, as their mobilization does not lead to recovery. The de-localization is not restricted to the speech network, because also various non-motor aspects of language are more strongly represented on the right (Ingham et al., 2000; Preibisch et al., 2003a; Biermann-Ruben et al., 2005). This de-localization is independent of handedness as we studied both right- and left-handed subjects.

Therapy abolished over-activations in right lateral prefrontal and parietal regions, which suggests that attempted compensation (but not therapy outcome) involves attentional and executive control (Fox et al., 2006).

Inverse correlation with stuttering severity was also observed in the right posterior orbitofrontal cortex (BA 47/12), which is critical in behavioural control (O’Doherty et al., 2003) and reliably participates in compensation for stuttering (Preibisch et al., 2003a). All groups of PWS under-activated more medial regions of bilateral orbitofrontal cortex (region 13). While BA 47/12 integrates auditory information in the orbitofrontal circuitry, somatosensory information reaches the orbitofrontal cortex more medially in region 13 (Kringelbach, 2005). We thus propose that orbitofrontal cortex exerts a differential control of somatosensory (suppressed) and auditory (enhanced) feedback integration when generating speech. We observed a similar dissociation in the cerebellum, where auditory-motor integration in the vermis was enhanced while the cerebellar hemispheres were relatively suppressed (Penhune et al., 1998; Schulz et al., 2005).

The compensatory effect of auditory feedback integration in the motor program also manifests in auditory cortex activation. When they speak fluently, PS seem able to incorporate elements of auditory feedback, which we see as enhanced auditory cortex activity during scanning. In previous studies, deactivation of auditory cortex was proportional to the severity of dysfluency (Fox et al., 1996; Braun et al., 1997; Fox et al., 2000; Stager et al., 2003 Van Borsel et al., 2003a), which presumably implies that the auditory cortex deactivates in anticipation of stuttered speech to reduce mismatch between programmed and actual speech in PS (Elides and Wang, 2008). Because right orbitofrontal, auditory and cerebellar activation are not modulated by recovery, assisted or not, this ventral set of brain regions constitutes the core system of stuttering repair which is mobilized to improve fluency (Fig. 5).

**Normalization of perisylvian activity after assisted recovery from stuttering**

Fluency-inducing therapies are classically associated with a shift of over-activations to the left hemisphere (De Nil et al., 2003; Neumann et al., 2005), which in fact might only reflect a change in behaviour. Here, matched behaviour during scanning before and after therapy allowed us to relate therapy effects to adaptive changes rather than to mere changes in the manner of speaking. We observed that therapy reduced compensation attempt by dorsal brain regions and relateralized the speech production system, except for the ventral core compensation system (Fig. 5).

We thus expected a normalization of pathology-related functional anomalies. This was the case for the bilateral basal ganglia, planum polare, and left anterior insula, but not the left rolandic operculum above the area of reduced fibre coherence (Fig. 5). This indicates that therapy largely normalizes the function of these perisylvian regions involved in merging auditory feedback and motor programs (Hashimoto and Sakai, 2003; Christoffels et al., 2007). Therapy is likely to tap into this integration process by imposing meter onto speech production and by automating this strategy.

Right BA 47/12 was the only region showing an inverse correlation with stuttering severity before and after therapy, which confirms its compensatory function, but also raises the question as to why its recruitment does not yield long-lasting recovery. According to anatomical and functional data in macaques and humans (Petrides and Pandya, 2002), BA 47/12 exerts top-down control on the abovementioned regions involved in auditory feedback/motor program integration. Like the rest of the right-hemispheric over-activated network, control of feedback integration by right BA 47/12 is imperfect. This is presumably due to its contralateral location relative to the rest of the language network and its weaker specialization for language (Wildgruber et al., 2006). The cost of interhemispheric cross-talk (Ringo et al., 1994), given that white matter pathology is detected in the commissural fibres, could prevent full engagement of right BA 47/12 in speech control.

**Long-lasting unassisted recovery by left posterior orbitofrontal control**

While adult RS retain a permanent grey matter anomaly in the inferior frontal gyrus, they do not show significant white matter anomaly. In fact, RS had intermediate FA values between fluent controls and PS, like recovered children, indicating a normalization of stuttering-associated white matter changes in the process of recovery (Fig. 5) (Chang et al., 2008). White matter anomalies in children, however, are not found in the same location as in adult PS. Because a limitation of this study is the dependency on self-reports and medical records for diagnosis of former stuttering in RS, these differences could be influenced by a potential recruitment bias. More likely, additional white matter changes could occur during development. Ideally, longitudinal prospective studies on a large sample of PWS will allow for documentation of changes in the course of recovery. Such normalization of anatomical connectivity is documented and presumably results from plastic changes in the cortex neighbouring the white matter anomaly (Johansen-Berg, 2007). Accordingly, the only significant increase in brain activation during overt reading in RS relative to PS was...
found in the left orbitofrontal cortex adjacent to PS’ white matter pathology (Fig. 5). Mobilization of left BA 47/12 is beneficial because it is located in the specialized hemisphere and can thus more efficiently control sensorimotor feedback integration to induce speech fluency than its right-hemispheric homologue. Interestingly, left BA 47/12 specialization for executive control of sensorimotor feedback integration is not limited to speech rhythm: bilateral orbitofrontal BA 47/12 was specifically engaged by a sensorimotor integration task that required maintenance of a musical rhythm in the presence of a counter-meter. When the counter-meter was effectively integrated with the main meter this activation lateralized to the left BA 47/12 (Vuust et al., 2006). Within this framework, additional rhythmic motor disturbances in PS (but not in RS!) during nonverbal complex motor tasks (Forster and Webster, 2001) could be seen as a consequence of a general sensorimotor integration defect lying in a failure to recruit left BA 47/12, that could either be structural (a too serious white matter anomaly) or incidental (limitation by previous deleterious plasticity). This issue could be solved in the future by studying whether training not only speech but also non-speech rhythm can effectively produce longer-lasting therapeutic effects in PS than conventional therapies and whether therapy efficiency is inversely proportional to the extent of structural anomalies.

Conclusion

Developmental stuttering is associated with structural anomalies of the left inferior frontal region and with a secondary basal ganglia dysfunction. Attempted compensation involves the contralateral (right) hemisphere, yet does not grant sufficient symptom relief, probably due to the insufficient specialization of the right brain for linguistic tasks and/or to the timing issues of long-range connectivity. Restoring a left dominant network for speech production and reducing the involvement of dorsal brain regions is an effective result of fluency-inducing therapies, but an insufficient one as it does not yield long-lasting effects. In contrast, full unassisted recovery is underpinned by the engagement of the left posterior orbitofrontal cortex in the vicinity of a white matter anomaly. That this anomaly is manifest when stuttering persists, but no longer after recovery, suggests that anatomical connectivity can normalize in the course of recovery. Like recovery from acute brain lesions, where similar though less efficient compensation profiles are reported, brain repair for stuttering shows that optimal compensation follows very focal perianomalous plasticity.

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Supplementary material

Supplementary material is available at Brain online.

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