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Severity of dysfluency correlates with basal ganglia activity in persistent developmental stuttering

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Abstract

Previous studies suggest that anatomical anomalies [Foundas, A. L., Bollich, A. M., Corey, D. M., Hurley, M., & Heilman, K. M. (2001). Anomalous anatomy of speech-language areas in adults with persistent developmental stuttering. *Neurology*, 57, 207–215; Foundas, A. L., Corey, D. M., Angeles, V., Bollich, A. M., Crabtree-Hartman, E., & Heilman, K. M. (2003). Atypical cerebral laterality in adults with persistent developmental stuttering. *Neurology*, 61, 1378–1385; Foundas, A. L., Bollich, A. M., Feldman, J., Corey, D. M., Hurley, M., & Lemen, L. C. et al., (2004). Aberrant auditory processing and atypical planum temporale in developmental stuttering. *Neurology*, 63, 1640–1646; Jancke, L., Hanggi, J., & Steinmetz, H. (2004). Morphological brain differences between adult stutterers and non-stutterers. *BMC Neurology*, 4, 23], in particular a reduction of the white matter anisotropy underlying the left sensorimotor cortex [Sommer, M., Koch, M. A., Paulus, W., Weiller, C., & Buchel, C. (2002). Disconnection of speech-relevant brain areas in persistent developmental stuttering. *Lancet*, 360, 380–383] could be at the origin of persistent developmental stuttering (PDS). Because neural connections between the motor cortex and basal ganglia are implicated in speech motor functions, PDS could also be associated with a dysfunction in basal ganglia activity [Alm, P. (2004). Stuttering and the basal ganglia circuits: a critical review of possible relations. *Journal of Communication Disorders*, 37, 325–369]. This fMRI study reports a correlation between severity of stuttering and activity in the basal ganglia and shows that this activity is modified by fluency shaping therapy through long-term therapy effects that reflect speech production improvement. A model of dysfunction in stuttering and possible repair modes is proposed that accommodates the data presented here and observations previously made by us and by others.

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1. Introduction

A reduction in the white matter anisotropy situated just below the left sensorimotor cortex has been reported in

persistent developmental stuttering (PDS) (Buchel & Sommer, 2004; Sommer, Koch, Paulus, Weiller, & Buchel, 2002), which corroborates the more general observation that the perisylvian region is anatomically more heterogeneous in people who stutter than in controls (Foundas, Bollich, Corey, Hurley, & Heilman, 2001; Foundas et al., 2004). In contrast with developmental stuttering, acquired

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stuttering is more often associated with subcortical lesions, in particular in the basal ganglia, than with lesions in cortical speech and motor regions (Carlier et al., 2000; Fawcett, 2005; Ludlow & Loucks, 2003). As in these acquired forms of stuttering cerebral lesions are likely to be a direct cause of stuttering, it is plausible that subcortical regions are also implicated in developmental stuttering, even though in this case a basal ganglia disorder might be secondary to the dysfunction of another brain region. The numerous arguments in favor of an implication of the basal ganglia circuits in stuttering and possible mechanisms have recently been reviewed by Alm (2004). Like in Parkinson's patients, external cues help people who stutter to produce fluent motor output. Speech production is greatly facilitated by external cues such as the rhythm produced by a metronome, chorus speech, singing or even the simple presence of a background noise (e.g., Saltuklaroglu, Kalinowski, & Guntupalli, 2004). One hypothesis for such facilitation is that a defective basal ganglia-cortical route is by-passed and compensated by a cerebellar-cortical route (Alm, 2004). This hypothesis would fit with the observation that the cerebellum is overactivated in stutterers (Brown, Ingham, Laird, & Fox, 2005).

As the basal ganglia contribute to facilitate self-generated movements and to inhibit competing involuntary movements, a dysfunction within the striato-cortical circuits might impair voluntary movement or yields involuntary movements, or both (Mink, 2003). Accordingly, PDS subjects exhibit more tic-like involuntary movements when producing speech than non-stuttering control subjects (Mulligan, Anderson, Jones, Williams, & Donaldson, 2003). This association between dysfluency and tics fits within the profile of focal dystonia resulting from basal ganglia disorder, which further supports the idea that basal ganglia dysfunction might be involved in developmental stuttering. Furthermore, positive effects of dopamine antagonists (haloperidol, risperidone, olanzapine, Burns, Brady, & Kuruvilla, 1978) and deleterious effects of L-Dopa on the fluency of spoken language constitute indirect evidence for a dopaminergic dysfunction in PDS, and indicate that the latter might be due to a hyper-dopaminergic state (Anderson, Hughes, Rothi, Crucian, & Heilman, 1999; Brady, 1991, 1998; Louis, Winfield, Fahn, & Ford, 2001; Maguire, Riley, Franklin, & Gottschalk, 2000; Wu et al., 1997). However, the level of dopamine is not related in either direction (increase or decrease) to the severity of dysfluency induced by Parkinson's disease (Goberman & Blomgren, 2003). Thus, basal ganglia dysfunction in PDS remains to be established more directly, and the nature of a possible dysregulation in the cortico-striato-cortical loop is yet to be characterized.

Previous functional neuroimaging reports (Neumann et al., 2003, 2005; Wu et al., 1995) showed an involvement of the putamen in speech motor control in PDS. However, this observation so far remained an accessory finding and basal ganglia function has never been specifically implicated in PDS. In the present report, we present an original analysis of functional magnetic resonance imaging (fMRI)

from a larger cohort than in our previous paper (Neumann et al., 2005) in which we investigate the potential implication of the basal ganglia in PDS. Basal ganglia function in PDS was probed by correlating cerebral activations during fluent speech produced in the scanner (Neumann et al., 2003, 2005) with individual stuttering severity as measured by testing several everyday speech situations. We additionally studied the impact of fluency shaping therapy on basal ganglia function by computing correlations between reading-related fMRI activations and initial stuttering severity, both before and after 3 weeks of intensive therapy.

2. Experimental procedures

2.1. Subjects

Data were obtained from 16 male PDS subjects (mean age 30 ± 8 years, range 18–48 years). The diagnosis of PDS was confirmed by an experienced speech-language therapist. Twelve of these subjects had stuttered since age 3 or 4, four subjects had begun to stutter later in childhood. Severity of stuttering was defined as the percentage of stuttered syllables over four different speaking contexts (speaking to a therapist, reading, phoning, speaking to a passer-by), and averaged 11.2% ($\pm 6.2\%$, range 4.1–24.8%) for the sample. In each speaking context, at least 300 syllables were collected, except during the telephone call before therapy, which appeared too stressful for several subjects. In the phone context, subjects were asked to talk with an unfamiliar person, i.e. calling a hotel and asking for availabilities and prices. Speaking to a passer-by consisted of standard interview questions about stuttering asked to passers-by on the street. Collected speech samples were processed by an unbiased independent person who measured speech rate (syllables/minute) and percentage of nonfluent syllables according to the guidelines by Boberg and Kully (1994). The therapist who assessed subjects' speech was the same before and after therapy. For more details of the procedure employed see Euler and Wolff von Gudenberg (2000).

According to the Edinburgh Handedness Inventory (Oldfield, 1971) all but two of the stuttering speakers were right-handed. The inclusion of left-handed subjects could be problematic given that there is evidence of lateralized anatomical differences between stuttering and fluent speakers (Foundas et al., 2001, 2003, 2004; Sommer et al., 2002). Since our study focuses on the basal ganglia, we considered it less problematic to leave left-handed subjects in the analysis. This matter remains however unclear since the dopaminergic system may interact with motor lateralization (de la Fuente-Fernandez, Kishore, Calne, Ruth, & Stoessl, 2000). Our results must therefore be interpreted with precaution as far as laterality is concerned.

In compliance with the requirements of the local ethics committee, all subjects gave written informed consent before participating in this study.

To assess the effects of therapy nine of the 16 subjects underwent fMRI again with the same task within 12 weeks

after a fluency shaping intensive course. The other 7 subjects could not be included because they were no longer available. The inclusion criterion was to display a reduction of the amount of stuttered syllables after therapy. Accordingly, in the nine PDS subjects who could be followed-up, the mean dysfluency was 9.9% before therapy and was reduced to 0.9% after therapy (see individual behavioural data in Table 1).

2.2. Stuttering therapy

All subjects underwent the same treatment, The Kassel Stuttering Therapy (KST), which is a modified version of the Precision Fluency Shaping Program (Webster, 1975). It consists in a 3-week in-patient intensive treatment and a structured 1- to 2-years maintenance program. The main modification is the use of a computer program which provides biofeedback for syllable prolongation, soft voice onset, a special kind of diaphragmatic breathing, and smooth sound transitions (speak:gentle[®], Bioservices Software, Munich, Germany). Details about the treatment and its short-term and long-term effects on objective and subjective fluency measures are described by Euler and Wolff von Gudenberg (2000, 2002).

2.3. Data acquisition

Imaging was performed on a 1.5 T Siemens Vision Scanner (Siemens, Erlangen, Germany) using gradient echo EPI with an echo time of 50 ms, repetition time 3 s, a voxel size of $3.6 \times 3.6 \times 6 \text{ mm}^3$, an inter-slice gap of 0.6 mm and 18 slices. The subjects read written sentences aloud from a screen via a mirror mounted on the head coil.

2.4. Reading task

The reading aloud task included 78 short sentences. Silent viewing of letter-like meaningless signs (matched to the sentences) constituted the control condition as described in Preibisch et al. (2003b). Both conditions were

interleaved, and the visual stimuli were presented for 3 s with an interstimulus interval of 15.5 s in each case (Preibisch et al., 2003b). This rate enabled close to natural speaking conditions and left most of the imaging signal from hemodynamic response unaffected by motion artifacts. The combination of the repetition time and the interstimulus interval yielded an effective sampling of the hemodynamic response of one datapoint every 0.5 s. The experimental design permits effective suppression of speech production artefacts and is described in detail elsewhere (Preibisch et al., 2003b). Speech production during the reading task was monitored via the scanner's built-in microphone.

2.5. Data analysis

Spatial preprocessing and statistical analyses were performed using SPM99 (Wellcome Department of Imaging Neuroscience, London, UK). The data were corrected for acquisition time (slice timing), realigned to the first volume (motion correction), normalized into a standardized neuro-anatomical space (template by courtesy of the Montreal Neurological Institute) and smoothed using an isotropic 10 mm Gaussian kernel. Low frequency fluctuations were removed with a high-pass filter with cut-off at 35 s.

2.6. Correlation with stuttering severity

We identified brain regions where activity during speech production correlated with the severity of stuttering measured under clinical conditions prior to scanning including all 16 subjects. Separate pre/post-therapy correlation analyses were performed in the nine subjects who could be followed-up post-therapy.

Stuttering severity prior to treatment is assumed to indicate the starting point for subsequent therapy-related plastic brain changes that enabled the treated PDS sample to then speak fluently. Stuttering was successfully corrected in all nine followed-up PDS subjects; hence, those subjects with the most severe initial symptoms are also those in

Table 1

Age of stuttering onset, handedness (laterality quotient, LQ), and stutter rate as well as speech naturalness before, immediately after and one year after a fluency shaping intensive therapy course of the nine male PDS subjects; speech naturalness in all four speaking contexts rated on a 9-step scale (1 = very natural, 9 = very unnatural); 1-year follow-up data only available for subjects 1–5

Subject	Age at stuttering onset	LQ	Stutter rate (% syllables)			Speech naturalness		
			Before therapy	After therapy	1 year after therapy	Before therapy	After therapy	1 year after therapy
1	4	−64	7.59	1.37	1.63	6.5	1.0	1.5
2	3	87	5.56	1.52	1.25	7.5	2.5	1.0
3	3	100	10.30	.47	.15	8.0	4.5	1.0
4	4	100	17.44	.23	.37	4.0	2.0	1.0
5	6	100	8.58	.48	5.09	3.0	2.0	1.0
6	3	100	9.59	3.05	n.a.	5.5	1.5	n.a.
7	4	100	20.24	.09	n.a.	9.0	3.0	n.a.
8	4	83	4.13	.57	n.a.	3.0	2.0	n.a.
9	6	100	6.09	.00	n.a.	2.0	3.0	n.a.

whom the largest brain plasticity can be assumed to occur during therapy. Some of these changes appear as changes in the strength of the correlation between the level of activity and stuttering severity.

Correlations with severity of stuttering were assessed here in a set of data that correspond in part to original data and in part include a re-analysis of data reported previously in a study on therapy-induced changes in brain activations (Neumann et al., 2003) in which we did not yet use stuttering severity as a variable of interest.

Statistical parametric maps of t -values (SPM(t)) were created for each individual subject from the contrast reading aloud—viewing meaningless signs. In a second level analysis (random effects), severity of stuttering, as determined before therapy in the speech clinic, was used as a regressor for brain activation both before and after a 3-week intensive fluency shaping therapy.

Correlations associated with $p < .001$, uncorrected, were considered significant. We also explored activations at a lower threshold ($p < .01$) in other regions of the dopaminergic system.

3. Results

Subjects stuttered less in the scanner during the pre-therapy assessment. Effect of noise in reducing stuttering has previously been described in persons who stutter (e.g., Stager & Ludlow, 1998). In our particular setting, it offers the advantage that we can compare the activations observed with fMRI before and after speech has been normalised through therapy. That people who normally stutter do not actually stutter during our experiment is a key point of all our studies (Preibisch et al., 2003a; Preibisch et al., 2003b; Neumann et al., 2003, 2005), as we did not seek to investigate the correlate of dysfluent speech production, but rather to identify potential neural hallmarks of the

“stuttering brain”. This implies that we must either compare functional activations in persons who stutter and in fluent speakers during tasks where both groups performed equally, or as here, in persons who stutter before and after behavioural therapy without the behavioural confound by the amount of stuttered speech. This precaution does not prevent us from correlating the resulting brain activity (unconfounded by explicit dysfluency) with stuttering severity clinically assessed in silence (see Table 1) as an index of the underlying dysfunction.

The results of the correlation analyses are presented in Table 2 and Figs. 1 and 2. Before therapy stuttering severity positively correlated with a very distinct pattern of activation that included bilateral caudate nuclei and the left medial superior posterior parietal/post central region (confluence of BA 4/5/7). This pattern had disappeared after therapy, and the initial severity of stuttering correlated only with a very small cluster of activation in the caudate nucleus. Fig. 1b shows the size of the effect in the left caudate nucleus as a function of stuttering severity in all nine stutterers who underwent treatment. When including all subjects ($n = 16$) before therapy, correlations between stuttering severity and the size of effect were significant in both caudate nuclei ($r = .65$ in the left and $r = .55$ in the right caudate, significant on a confidence level of $p < .001$). After therapy, i.e. in the same nine subjects as those shown on Fig. 1b, the slope was reduced and the correlation ($r = .21$ in the left and 0.17 in the right caudate) was no longer significant even at a reduced level of significance ($p < .05$). There was no significant correlation between the gain in fluency due to therapy and the increase in activity in the caudate nucleus, as we would expect it to be the case if the caudate was actively driving compensation (Fig. 1c).

Stuttering severity negatively correlated before therapy with bilateral activation in inferior temporal areas (BA20,

Table 2
Brain regions where activity (during a reading task) correlated with stuttering severity

	Before therapy		After therapy			
	Positive	Negative	Positive	Negative		
<i>p < .001, uncorrected</i>						
Caudate Nucleus left	-16184	4.21	—	—	—	—
	-161016	3.47	—	—	—	—
	-84-2	3.17	—	—	—	—
Caudate Nucleus right	12206	3.55	—	61612	3.18	—
	82610	3.34	—	—	—	—
	14366	3.28	—	—	—	—
Med. post. central (BA 4/5/7)	-4-3872	3.79	—	—	—	—
	-12-4872	3.53	—	—	—	—
	-32-4264	3.40	—	—	—	—
Inf. temporal left	—	58-10-32	3.79	—	36-26-24	3.19
Inf. temporal right	—	-58-8-30	3.37	—	—	—
Precuneus	—	—	—	—	8-6026	3.32
Thalamus	—	—	—	—	-6-1012	3.15
<i>p < .01, uncorrected (Region of interest)</i>						
Substantia Nigra left	—	-14-16-2	2.81	—	—	—
Substantia Nigra right	—	—	—	—	20-18-4	2.41

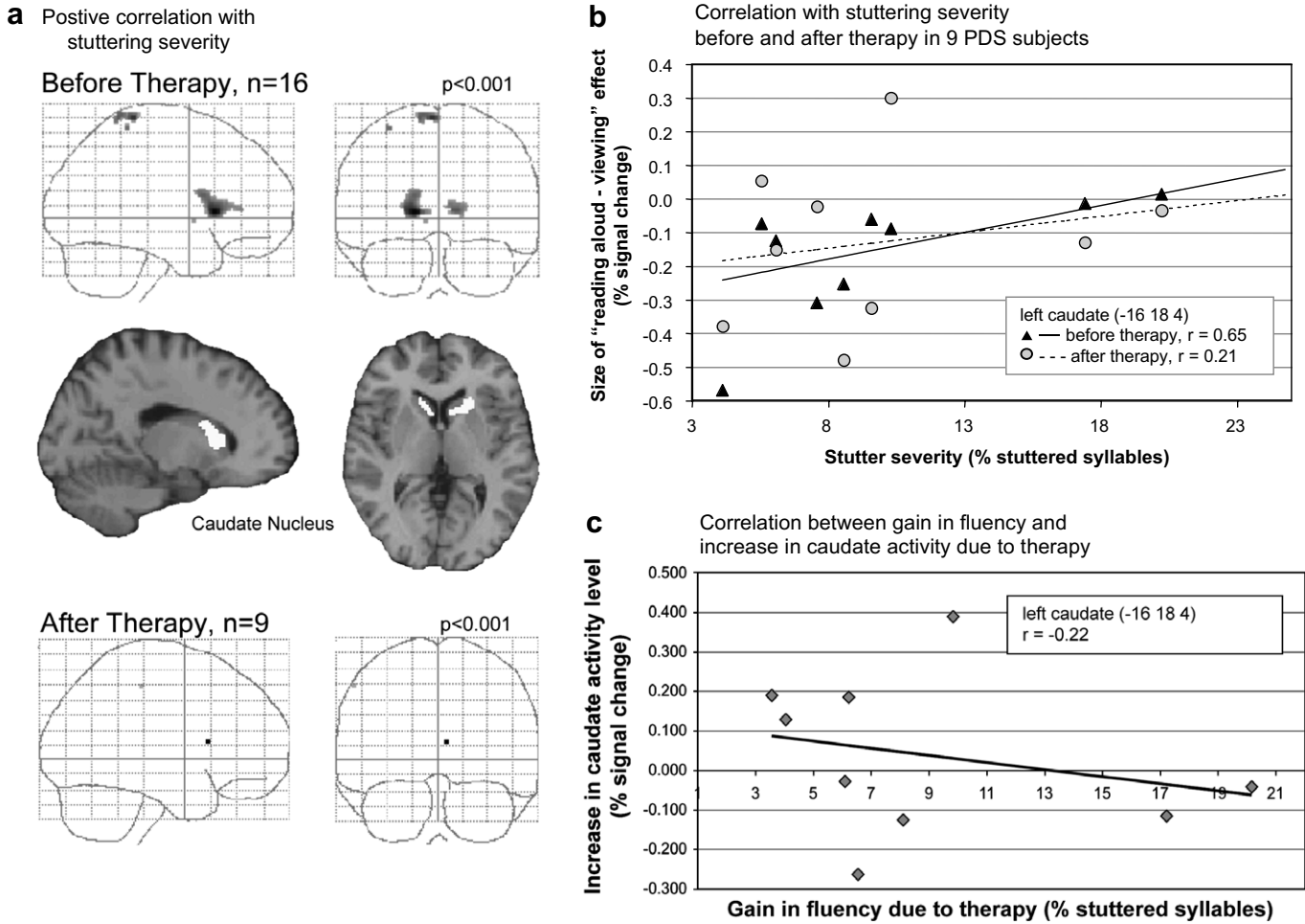


Fig. 1. (a) Brain activations during fluent reading that positively correlate with severity of stuttering, before and after fluency shaping therapy. (b) representing the size of the effect in the left caudate nucleus in each stutterer who subsequently underwent speech therapy ($n = 9$) as a function of stuttering severity before (▲) and after (●) therapy, together with respective regression lines (before — and after ---) therapy. Correlation coefficient drops from 0.65 before to 0.20 after therapy. (c) Gain in fluency (% stuttered syllables) is plotted against the increase in the activity level in the left caudate. No significant correlation is observed.

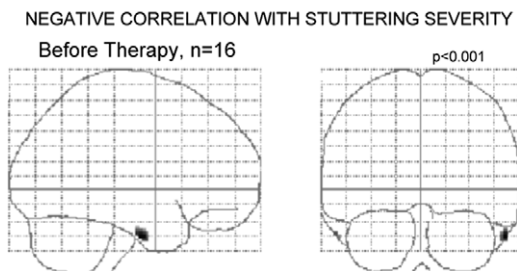


Fig. 2. Brain activations during fluent reading that negatively correlate with stuttering severity before fluency shaping therapy. After therapy no effect was detected.

Fig. 2, Table 2). This correlation was not observed any longer after therapy. Only one voxel remained negatively correlated with stuttering severity in the left inferior temporal region. Additionally, severity of stuttering correlated negatively after therapy with activation of the precuneus and the anterior nucleus of the thalamus. At a lower observation threshold ($p < .01$) negative correlations with stut-

tering severity were observed which we assigned to the SN (Table 2). These correlations were detected on the left side before therapy and on the right side after therapy.

In a previous study, we reported negative correlation with stuttering severity in the right ventral prefrontal cortex (right frontal operculum, RFO). This observation could only be confirmed, in the present dataset before therapy that included a larger patient sample, at a lower statistical threshold ($p < .05$, uncorrected) than the one used previously ($p < .001$). We mention however activation in this region for the sake of coherence across our studies. Activation in the RFO is an important finding as it indicates potential compensation for left hemispheric functional alterations by right-sided homologue regions.

4. Discussion

Severity of stuttering was associated with a pattern of activation that included the head of the caudate nucleus bilaterally (positive correlation) and the left SN (negative

correlation). If PDS subjects indeed have a reliable anomaly in the white matter underlying the left sensorimotor cortex (Sommer et al., 2002), such a left sided pattern of activation in other components of the motor system could reflect further lateralized deviant motor functions, either genuinely defective or secondary to the structural abnormality and potentially of compensatory nature. One could argue that a small white matter anomaly is unlikely to produce important cerebral reorganization. It must be considered, however, that the finding by Sommer et al. (2002) denotes the region that is probably commonly impaired across all stuttering speakers but that the individual anomalies may be larger. Furthermore, we do not know how much of the grey matter is targeted by the altered fibers and might thus be de-afferented through a deficit in white matter. Therefore it remains possible that the deficit is actually important enough to drive significant cortical and subcortical reorganization.

It is also possible that stuttering results more directly from a dysfunction in the basal ganglia that would directly disturb the timing in speech production (Alm, 2004). The current findings speak to this hypothesis by showing that the activity in the caudate nucleus correlated with stuttering severity before therapy, but not after. Therapy appeared to have different effects in the caudate depending on whether subjects had a low or a high activity level beforehand. It decreased in those subjects who had high initial activity level and increased in those who had initial low activity levels. Motor learning is associated with differential impact on the basal ganglia depending on its degree of automaticity. Decreases in caudate activity are observed during the initial stages of a motor learning, while increases are observed when a sequence is already acquired but when maintenance of speed in the execution is required (Lehericy et al., 2005). It is possible that for those subjects who stuttered most, therapy required learning completely new motor sequences, while it acted more like an “advanced training” in the least affected of them.

Critically, the activity level in the caudate nucleus normalized after therapy, without expressing the hallmarks of a compensatory behaviour. Compensation would imply that the gain in fluency due to therapy correlates with a gain in neural activity. In sum, if a region primarily dysfunctions in stuttering it is unlikely to be actively mobilizable by therapy, but more likely to adjust its level of response to the consequences of compensation, as a passive element of the network. In accord with the hypothesis that the caudate is involved in the dysfunction in stuttering but not in compensation, we observed no positive correlation between the gain in fluency and the increase in caudate activity level due to therapy. A recent case report supports this view reporting acquired stuttering following an ischemic infarct near the left basal ganglia region (Fawcett, 2005). Our results, showing a positive correlation with stuttering severity in the caudate and a trend toward negative correlation in the SN ($p > .01$), further illustrate a general basal ganglia dysfunction. This pattern fits with physiolog-

ical models of basal ganglia function where the caudate and the SN operate in antagonism, i.e., when activity in the caudate is high, activity in the SN is low and vice versa (Gerfen et al., 1990). In the most severely affected PDS subjects, a high activation level in the caudate (striatum) concurred with a low activation level in the SN, a feature that usually characterizes L-Dopa-induced dyskinesia (Rajput, Fenton, Birdi, & Macaulay, 1997). An increased inhibitory feedback from the striatum to the SN and to the internal segment of the globus pallidus leads to an excessive thalamic disinhibition and a subsequent hyperactivation in the speech motor cortex. In PDS subjects, such an unbalanced state might be transient and subject to immediate regulatory control of the motor output by the inferior prefrontal cortex.

This hypothesis is consistent with previous findings that the right frontal operculum, which is recruited for self-monitoring and language repair, is systematically overactive in PDS subjects compared to matched controls when they perform language or verbal tasks (Preibisch et al., 2003a, 2003b; Blomgren, Nagarajan, Lee, Li, & Alvord, 2003). We further showed (and currently confirm) that the right frontal operculum is involved in compensation against stuttering (Preibisch et al., 2003a, 2003b). The most affected PDS subjects were those with the lowest activity level in the right frontal operculum, whereas the least affected of them strongly recruited this region. Activation of the right frontal operculum during speech was abnormal in the sense that it was not observed in controls, yet it was associated with the minimal symptomatology in stutterers. Abnormal activity levels and negative correlation with stuttering severity constitute the hallmarks of a successful compensatory effect. Compensation by the right frontal operculum, a region opposite to the side of a potential motor dysfunction, could result from the fact that a control by Broca's area is not available due to a functional disconnection between left prefrontal and motor regions, reflected both by the structural anomaly (Sommer et al., 2002) and the abnormal temporal sequence of speech processing steps in PDS subjects (Salmelin, Schnitzler, Schmitz, & Freund, 2000).

Stuttering severity positively correlated with activation in the left medial posterior superior parietal/postcentral region (BA 4/5/7). Several studies in macaque and cebus monkeys indicate that this region projects onto the caudate nucleus (Saint-Cyr, Ungerleider, & Desimone, 1990; Leichnetz, 2001). Furthermore, in Huntington's disease, neuronal loss in the caudate is associated with a reduction of volume in the vicinity of the medial posterior parietal cortex (Kassubek et al., 2004). Connections between this parietal region and the caudate nucleus seem to be bidirectional because this part of the cortex can regain activity with fetal striatal allografts (Gaura et al., 2004). We can therefore hypothesize that higher activity in the caudate in severely stuttering subjects could conceivably be associated with higher activity in the superior postcentral region. The interactions between the left post-central region and the basal

ganglia in stuttering seem however rather complex since stuttering can also appear after a left parietal infarction (Sahin, Krespi, Yilmaz, & Coban, 2005).

The major negative correlation between stuttering severity and activation observed before therapy was found in bilateral anterior inferior temporal cortices, with a strong right-hemispheric predominance. This result implies that the least affected PDS subjects activated the right inferior temporal cortex significantly more than the most dysfluent subjects. Because right anterior ventral temporal regions are known to be involved in processing of semantic information of auditory origin (Marinkovic et al., 2003; Noppey & Price, 2002), such an effect could suggest that less affected stuttering speakers succeed better than more dysfluent people in processing the meaning conveyed by their own auditory feedback. This view is in line with the recent hypothesis put forward by Brown et al. (2005) according to which a defect in speech motor planning should directly alter auditory feedback processing. In stutters, the efference copy that accompanies speech motor output could abnormally suppress auditory processing of subsequent utterances. It would therefore be logical that later processing stages, e.g. processing of sound meaning, be also affected. It is surprising, however, that we did not observe a correlation with severity of stuttering in regions underlying earlier auditory processing, as it usually is observed using conventional contrasts.

A more direct interaction between semantic processing and the basal ganglia function can come as an alternative hypothesis (Copland, 2003). Dysfunction of the basal ganglia has been shown to directly influence late language-related evoked potential responses (Frisch, Kotz, von Cramon, & Friederici, 2003; Kotz, Frisch, von Cramon, & Friederici, 2003). It is possible that an alteration of basal ganglia function is associated with an alteration of the semantic processing of spoken speech in the most affected stuttering speakers. This effect would then appear as an enhanced activation in cortical semantic regions in the least affected stuttering speakers.

While PDS seems to be associated with a compensation by the right hemisphere, (Preibisch et al., 2003b; Biermann-Ruben, Salmelin, & Schnitzler, 2005) and increase in white matter volume (Jancke, Hanggi, & Steinmetz, 2004), fluency-shaping therapy induced a re-lateralization of the network involved in speech production in our sample of treated subjects, with increased activation not only in left auditory and motor cortices, but also in the putamen, as detected using a conventional subtraction design (Neumann et al., 2005). This suggests that therapy acted directly and noticeably on basal ganglia function. In the analysis correlating activation and stuttering severity, we observed only a remaining small positive correlation in the right caudate, and a negative correlation in the right substantia nigra (subthreshold, $p < .01$) after therapy. Thus, therapy corrected the abnormal activation of the caudate, which characterized the most severely affected PDS subjects. However, PDS subjects still showed altered activation in

the right hemisphere, which was in part residual (caudate) and in part new (right SN). The SN activation could be a side effect of a global shift of activations to the left motor cortex that might transiently alter the input to the basal ganglia. The new input appears normalized, i.e., in the range of that in controls, and yet could be transiently “abnormal” in stuttering speakers given that their “normal” state is a compensated one with increased right-sided motor activations.

Correction of anomalous neural function after remediation of the symptoms could be seen as trivial, if one assumes that abnormal activation patterns in stuttering speakers purely result from stuttering as a phenomenon without also reflecting the aetiology. However, since speech was non-stuttered during scanning both before and after therapy, we argue that the observed effect reflects a genuine normalization of speech production circuits.

In order to summarize our findings, we propose a simple functional model centered on cortico-striato-cortical loops inspired from classical models of dysfunctions of these loops as in Parkinson and Huntington disease, or in dystonia (Alm, 2004; Fig. 3a–d). Fig. 3a depicts the loop in non-stuttering persons with a positive feedback between Broca’s area and speech motor regions. In stutters, the model assumes a structural disconnection between Broca’s area and speech motor cortex regions as indicated by Sommer et al., 2002 (reconstructed focus of white matter anomaly is indicated by a dotted arrow in Fig. 3b, after personal communication from the authors). Although we conceived the model with this anomaly as a possible starting point of stuttering, the model does not require this assumption to be valid. As these circuits are organized in loops, the model we propose still holds even if the white matter anomaly was the consequence of a dysfunction situated elsewhere in the loop. The disconnection would in any case result in a temporal de-correlation, i.e., an altered sequencing between prefrontal and motor activations as described by Salmelin et al. (2000). The striatum would then receive inappropriate input from the motor cortex, inaccurate with respect to both timing and its phonological nature (lower dotted arrow in Fig. 3b). This lack of input accuracy could result in a diffuse activation of the striatum possibly associated with a lack of suppression of competitive phonological motor patterns due to the initial deficit of precision in the motor command (Mink, 2003). This aspect of the model accommodates the current observation that severity of stuttering is associated with increased caudate activity in the most affected stuttering speakers compared with mildly affected subjects.

Excessive and diffuse striatal activation could then engender an imbalance in striato-cortical feedback, which would result in an inappropriate excitation of the motor cortex that would further maintain or amplify the imbalance (fat arrows in Fig. 3b). The notion of an input to the striatum that lacks precision fits with the observation that stuttering corresponds neither to a hyper- nor to hypo-dopaminergic state but to a sort of dysregulation in

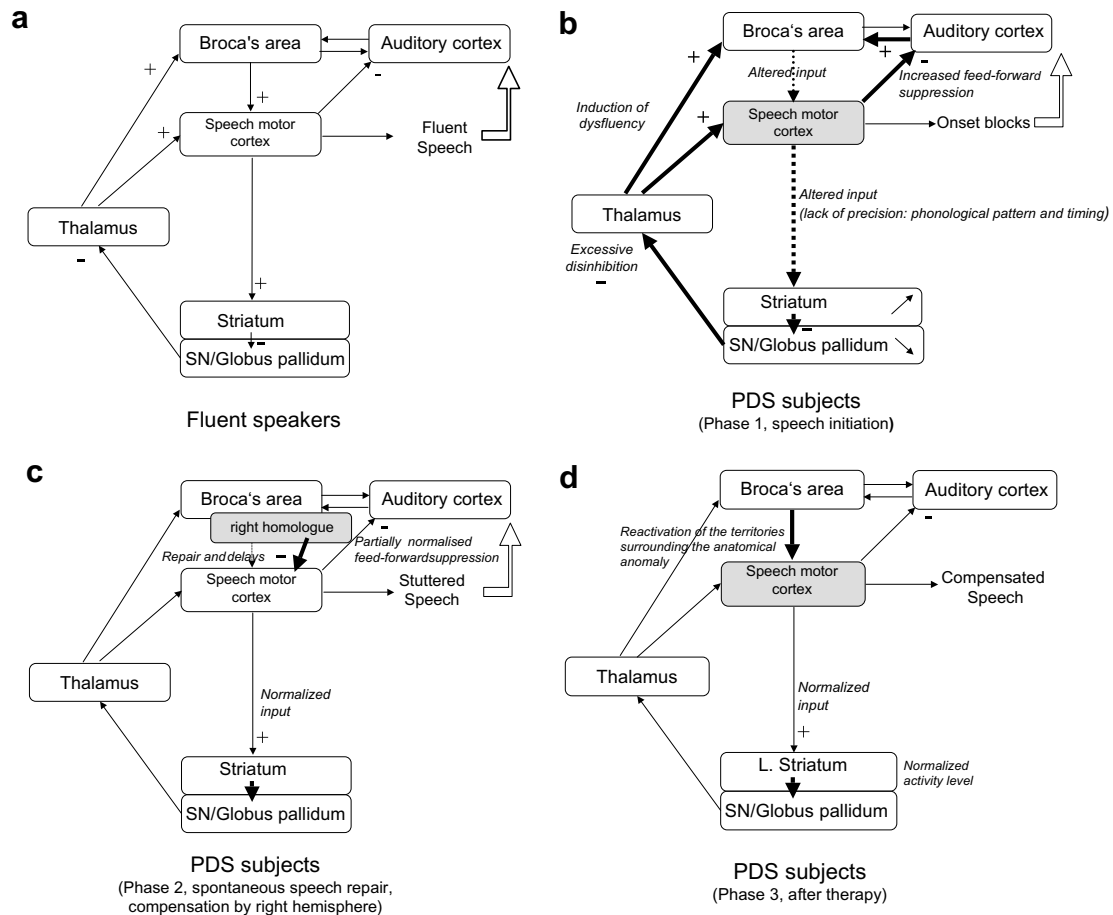


Fig. 3. (a–d) Proposed models of stuttering, compensation and repair. Simplified physiological model of speech production in (a) fluent speakers, (b) stuttering speakers during speech initiation, (c) stuttering speakers during spontaneous speech compensation, (d) stuttering speakers after relateralization by fluency-shaping therapy.

the dopaminergic system (Goberman & Blomgren, 2003). Stuttering symptoms like syllable repetition and blocks could reflect a lock into repetitive abnormal cortico-striatal loops. We may mention here that one side effect of an inappropriate excitation of the motor cortex could be an abnormally high feed-forward message sent to the auditory cortex, subsequently suppressing its activity. Our model thus agrees with and complements the efference copy hypothesis described by Brown et al. (2005), incorporated in our model in the form of a feed-forward suppression from motor cortex to the auditory cortex (Fig. 3). This suppression gets enhanced during initial blocks at onset of utterances. Mismatch between predicted and actual auditory inputs is reflected in a signal driving activity in Broca's area. As communication between Broca's area and the left speech motor cortex is supposedly impaired, this would result in eliciting alternative compensation involving the right homologue of Broca's area.

In a second step, therefore, PDS subjects would aim at restoring an appropriate input to the motor cortex (upper fat arrow in Fig. 3c). This spontaneous compensation strategy could initially involve the right prefrontal and motor regions that are typically found over-activated in func-

tional neuroimaging studies in PDS subjects (Braun et al., 1997; De Nil & Bosshardt, 2001; De Nil & Kroll, 2001a, 2001b; De Nil, Kroll, Kapur, & Houle, 2000; Fox et al., 1996; Ingham et al., 2004; Kroll, De Nil, Kapur, & Houle, 1997; Pool, Devous, Freeman, Watson, & Finitzo, 1991; Preibisch et al., 2003a). This aspect accommodates in particular our previous observation that the right frontal operculum was systematically over-activated in every of our 16 male stutterers (Preibisch et al., 2003a). We recently confirmed this observation on a new and independent cohort of subjects who stutter (unpublished data). Compensatory effect by the right prefrontal cortex could succeed in restoring an appropriate input and would subsequently result in more fluent speech. However, as contralateral compensation relies on inter-hemispheric cross-talk, it could therefore engender delays noticeable both in speech production and EEG responses.

Our previous observations suggest that speech fluency therapy contributes to re-lateralize speech pattern to the left motor cortex and to reactivate the region surrounding the white matter anomaly (Neumann et al., 2005). This might normalize the input to the motor cortex and the striatum. The third part of our model depicts these effects of

therapy (Fig. 3d). We observed minor activations that persisted in the right caudate and developed in the right SN after therapy. We assume the latter to reflect a transiently imbalanced state due to the fact that the right prefrontal and motor cortex used to be chronically over-activated for compensation in the very recent past of the subjects, and that the new speech pattern is not completely automated yet. This would agree with findings by Wu et al. (1995) indicating deactivations in the left hemisphere (Broca's and Wernicke's areas) during stuttering, and globally normal patterns with only deactivations in the left caudate and increased activity in the SN during fluent speech under chorus reading. Though compatible with the model, these minor post-therapy effects in the caudate and SN are not specifically depicted in Fig. 3d.

5. Conclusion

Our experimental results demonstrate an involvement of the basal ganglia in PDS, both by showing a correlation of the activity in this region with severity of stuttering and by showing an impact of stuttering therapy on this activity. Based on these observations and a number of other findings available in the literature, we proposed a functional model of stuttering, in which a dysfunction of the basal ganglia would result from a structural anomaly affecting the information flow between Broca's area (speech motor plans programming) and the motor cortex (execution of the motor plans).

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