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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.

Keywords: Stuttering; fMRI; Plasticity; Dopamine; Striatum; Subtantia nigra; Speech motor control; Basal ganglia

Article Outline

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 and Sommer, 2004] and [Sommer et al., 2002]), which **corroborates** the **more general observation** that the **perisylvian region** is **anatomically more heterogeneous** in **people who stutter** than in controls ([Foundas et al., 2001] and [Foundas et al., 2004]). In contrast with developmental stuttering, acquired stuttering is more often associated with subcortical lesions, in particular in the basal ganglia, than with lesions in cortical speech and motor regions ([Carluer et al., 2000], [Fawcett, 2005] and [Ludlow and 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, 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 et al., 1999], [Brady, 1991], [Brady, 1998], [Louis et al., 2001], [Maguire et al., 2000] and [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% (±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], [Foundas et al., 2003] and [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).

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.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia, 9*, 97–113.

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) and (Euler and Wolff von Gudenberg, 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 × 3.6 × 6 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 neuroanatomical 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 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] and [Neumann et al., 2003]), 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 Fig. 1 and Fig. 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).

Table 2.

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

	Before therapy				**After therapy**			
	Positive		**Negative**		**Positive**		**Negative**	
p < .001, uncorrected								
Caudate Nucleus left	−16 18 4	4.21	—		—		—	
	−16 10 16	*3.47*	—		—		—	
	−8 4 −2	3.17	—		—		—	
Caudate Nucleus right	12 20 6	3.55	—		6 16 12	3.18	—	
	8 26 10	*3.34*	—		—		—	
	14 36 6	*3.28*	—		—		—	
Med. post. central	−4 −38 72	3.79	—		—		—	
(BA 4/5/7)	*−12 −48 72*	*3.53*	—		—		—	
	−32 −42 64	3.40	—		—		—	
Inf. temporal left	—		58 −10 −32	3.79	—		36 −26 −24	3.19

	Before therapy				After therapy			
	Positive		**Negative**		**Positive**		**Negative**	
Inf. temporal right	—		−58 −8 −30	3.37	—	—	—	
Precuneus	—		—		—		8 −60 26	3.32
Thalamus	—		—		—		−6 −10 12	3.15
p < .01, uncorrected (Region of interest)								
Substantia Nigra left	—		−14 −16 −2	2.81			—	
Substantia Nigra right	—		—		—		20 −18 −4	2.41

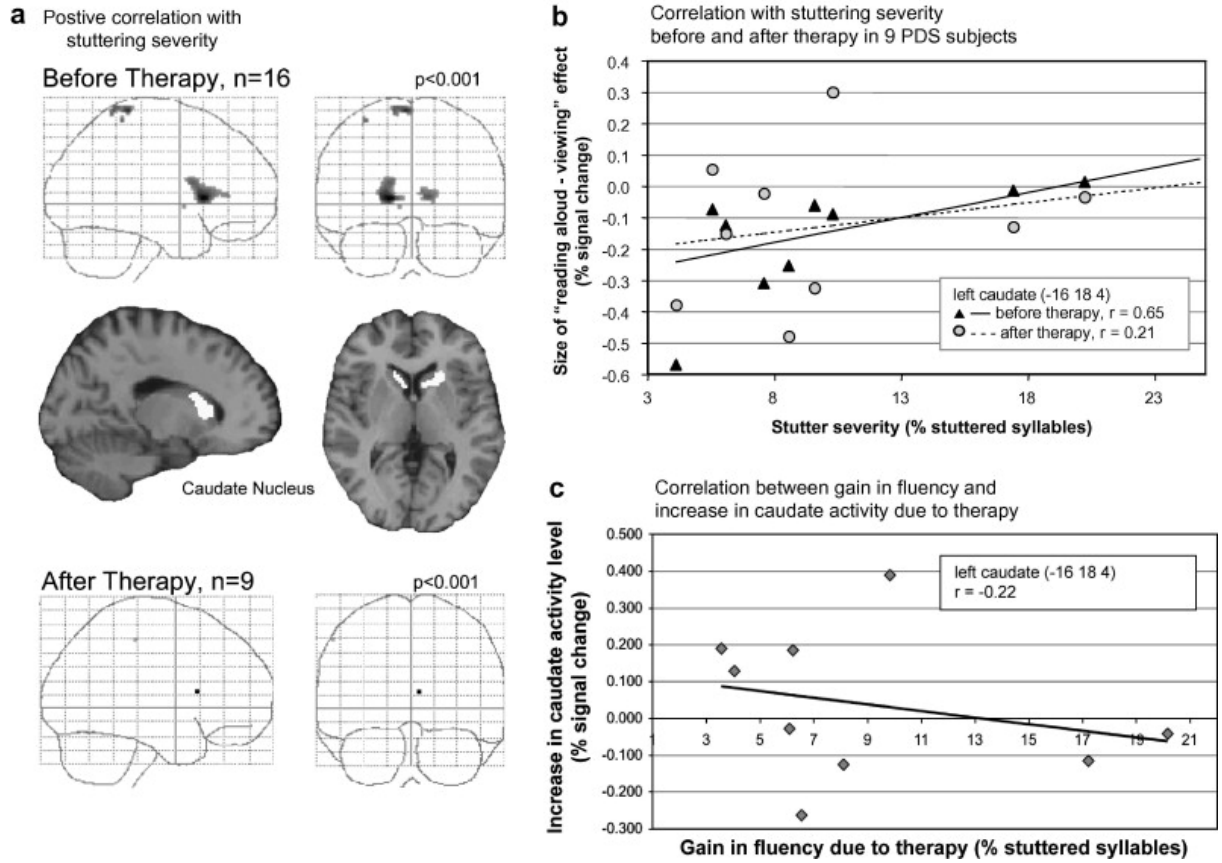

Fig. 1. (a) Brain activations during fluent reading that positively correlate with severity of stuttering, before and after fluency shaping therapy. (b) representing the size of the effect in the left caudate nucleus in each stutterer who subsequently underwent speech therapy (n = 9) as a function of 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.

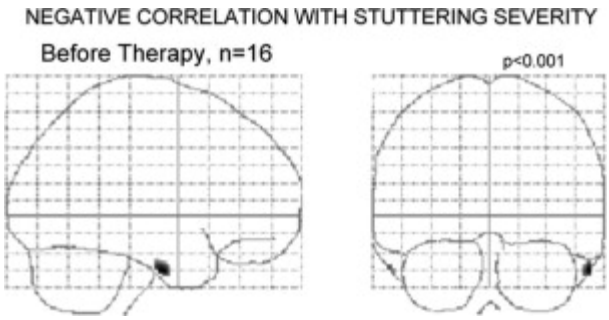

Fig. 2. Brain activations during fluent reading that negatively correlate with stuttering severity before fluency shaping therapy. After therapy no effect was detected.

Stuttering severity negatively correlated before therapy with bilateral **activation** in **inferior temporal areas** (BA20, 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 stuttering 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 **physiological 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 f**indings 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], [Preibisch et al., 2003b] and [Blomgren et al., 2003]). We further showed (and currently confirm) that the right frontal operculum is **involved** in **compensation** against stuttering ([Preibisch et al., 2003a] and [Preibisch et al., 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 et al., 1990] and [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] and [Noppeney and 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 stutterers, 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 et al., 2003] and [Kotz et al., 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] and [Biermann-Ruben et al., 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 **stutterers**, 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.

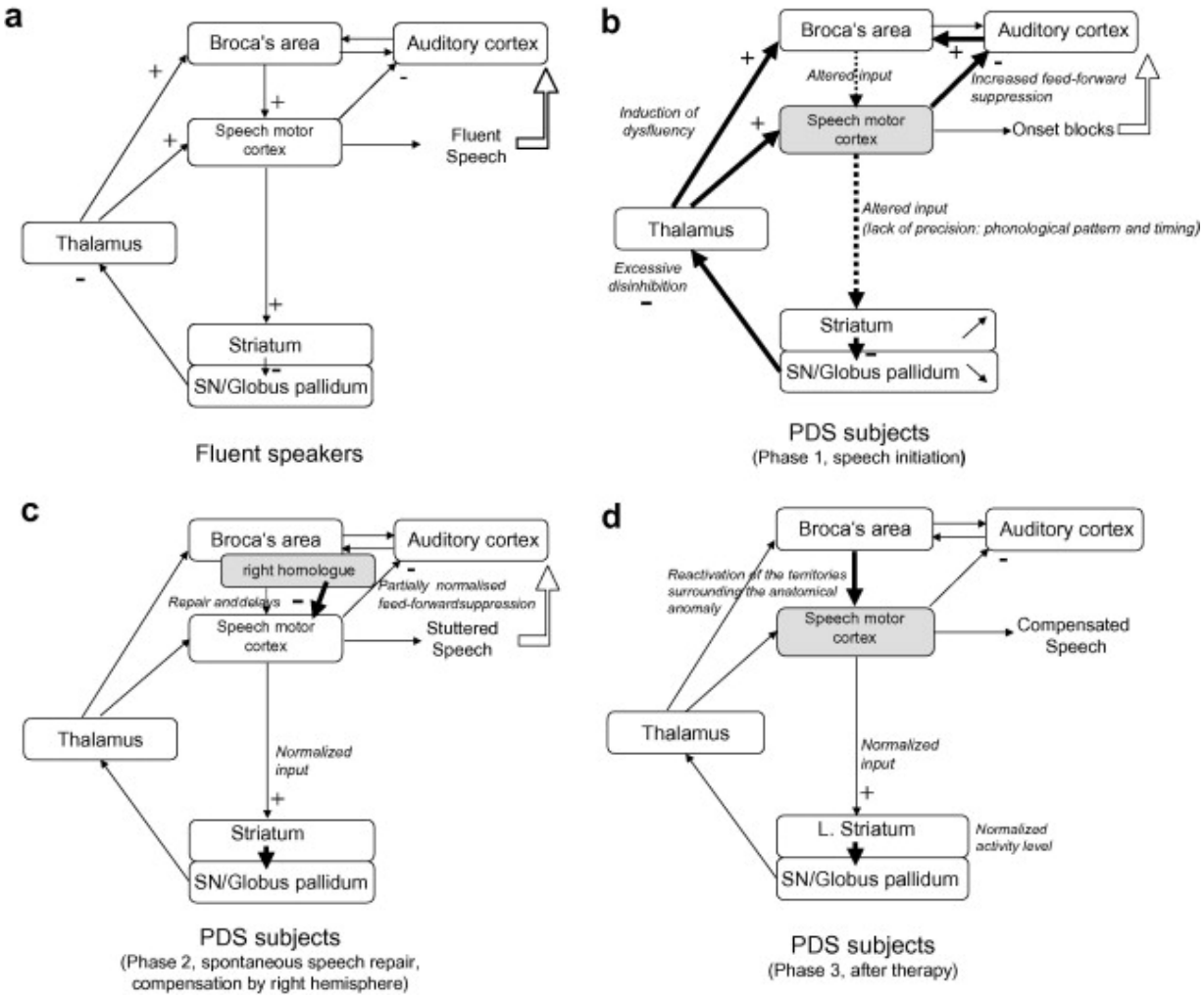

Fig. 3. (a–d) Proposed models of stuttering, compensation and repair. Simplified physiological model of speech production in (a) fluent speakers, (b) stuttering speakers during speech initiation, (c) stuttering speakers during spontaneous speech compensation, (d) stuttering speakers after relateralization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

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 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 functional neuroimaging studies in PDS subjects ([Braun et al., 1997], [De Nil and Bosshardt, 2001], [De Nil and Kroll, 2001a], [De Nil and Kroll, 2001b], [De Nil et al., 2000], [Fox et al., 1996], [Ingham et al., 2004], [Kroll et al., 1997], [Pool et al., 1991] and [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 crosstalk, 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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