Evidence for compensation for stuttering by the right frontal operculum

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Abstract

There is recent evidence of focal alteration in fibre tracts underlying the left sensorimotor cortex in persistent developmental stuttering (PDS) [Lancet 360 (2002) 380]. If, as proposed, this anatomical abnormality is the cause of PDS, then overactivation in the right hemisphere seen with functional neuroimaging in stutterers may reflect a compensatory mechanism. To investigate this hypothesis, we performed two functional magnetic resonance imaging (fMRI) experiments. The first showed systematic activation of a single focus in the right frontal operculum (RFO) in PDS subjects during reading, which was not observed in controls. Responses in this region were negatively correlated with the severity of stuttering, suggesting compensation rather than primary dysfunction. Negative correlation was also observed during the baseline task that consisted in passive viewing of meaningless signs, indicating that RFO compensation acts independently of specific demands on motor speech output. The second experiment, that involved a covert semantic decision task, confirmed that RFO activation does not require overt utterances or motor output. In combination these findings suggest that the RFO serves a nonspecific compensatory role rather than one restricted to the final stages of speech production.
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Introduction

While early theories of stuttering proposed psychological and environmental causes, more recent ideas suggest central nervous system dysfunction of epigenetic origin (Rosenfield, 1984; Ambrose et al., 1993). Current pathophysiological hypotheses include dysfunction of motor control, altered hemispheric dominance (Travis, 1978; Zimmermann, 1980; Caruso, 1991; Webster, 1993; Bloodstein, 1995), defects in the language production system (Wingate, 1988; Perkins et al., 1991), sensory, in particular auditory impairment (Stromsta, 1986; Salmelin et al., 1998), or a complex combination of motor and linguistic deficits (Peters et al., 2000). Previous neuroimaging studies (PET, EEG, and MEG) showed distributed neural correlates of stuttering in motor, language, auditory, prefrontal, limbic, and subcortical regions (Fox et al., 1996, 2000; Braun et al., 1997; Kroll et al., 1997; De Nil et al., 2000, 2001; Ingham et al., 2000; Salmelin et al., 2000; Foundas et al., 2001; Conture, 2001). Nonfluent speech is generally associated with deactivations in left hemispheric language and auditory areas and overactivations in right cortical and left cerebellar motor regions (Fox et al., 1996, 2000; Braun et al., 1997; Kroll et al., 1997). During induced fluency, e.g., by chorus reading, these deactivations are largely diminished but some overactivations in right hemispheric motor areas (M1 and SMA) persist (Fox et al., 1996, 2000; Braun et al., 1997). Together, these studies suggest that stuttering involves multiple neural components.

It remains unclear whether these distributed anomalies are manifestation of stuttering or whether they include

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compensatory mechanisms recruited to produce as fluent a speech output as possible. A recent study showed a reduction of the white matter located just below the sensorimotor cortical representation of the tongue and larynx in the left hemisphere (Sommer et al., 2002). Such an alteration could account for previous findings, e.g., disturbed timing of neural activity in left language regions (Salmelin et al., 2000) that might contribute to the generation of stuttering. In that case, increased brain activity in the right hemisphere might reflect compensation for disturbed signal transmission between left-sided frontal language areas and motor regions. According to this view, the cause of stuttering would lie in a defect of motor output so that compensation would be at the level of the final stages of speech production. However, the possibility that the white matter abnormality is a consequence of dysfunction in the right hemisphere could not be ruled out completely.

Previous brain imaging studies (Fox et al., 1996, 2000; Braun et al., 1997; Kroll et al., 1997) repeatedly found excess right-sided activations in PDS subjects. However, the specificity of these findings in stuttering has never been clearly established. Several criteria must be met to conclude that right-sided overactivation is specifically associated with stuttering. First, to generalize to all stutterers, comparisons between affected and unaffected subjects should be established on the basis of random effects statistics. Second, the finding should be reproducible across affected subjects to demonstrate that the pathological features are present consistently. Third, the finding should be absent in controls at the statistical threshold at which all stutterers show the functional abnormality.

We sought to find cortical regions that act to compensate for nonfluency and to investigate the role of right-sided overactivation in stuttering. We performed two fMRI experiments in 32 male subjects (16 stutterers and 16 controls). The first experiment aimed at identifying regions overactivated in PDS subjects successfully compensating for a stutter. It contrasted tasks where subjects read aloud fluently or passively looked at letter-like meaningless signs. The interpretation of results was constrained by the criteria above.

To determine whether the activations characteristic of PDS were specifically related to compensation for a deficit at the motor output level, we included a semantic decision task during which subjects performed a silent synonym judgment without producing an overt response. This second task was designed to minimize engagement of compensatory mechanisms and to exclude processing stages that might be targeted by compensation for a deficit at the motor level. We assumed that regions activated by a passive task would not be involved in compensation for a deficit in the final stages of speech production.

Materials and methods

Subjects

Two experiments were performed in 32 male subjects: 16 fluent speakers (mean age 32 ± 10 years, range 19 to 51 years) with no history of stuttering during childhood, and 16 subjects who stuttered (mean age 30 ± 8 years, range 18 to 48 years). The diagnosis of persistent developmental stuttering (PDS) was confirmed by an experienced speech-language pathologist. Twelve of these subjects stuttered since age 3 or 4, four subjects had begun to stutter before the onset of puberty. The severity of stuttering was assessed as stutter frequency (percentage of nonfluent syllables) averaged over four different speaking contexts (speaking to a therapist; reading; telephoning; speaking to a passerby) and was rated 11.2 ± 6.2% (range 4.1 to 24.8%) for the group. According to the Edinburgh Handedness Inventory (Oldfield, 1971), all but two of the stutterers and three controls were right-handed. In compliance with the requirements of the local ethics committee, all subjects gave written informed consent before participating in this study.

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 $3.6 \times 3.6 \times 6$ mm^3, an interslice gap of 0.6 mm, and 18 slices. The subjects watched a screen via a mirror mounted on the head coil. We used an experimental design that permits effective suppression of speech production artefacts. Stimulus-correlated signal fluctuations are potentially caused by direct head motion and by magnetic field variations induced by the changing pharyngeal space during speaking. Our approach temporally segregated the instantaneous motion-related signal fluctuations from the task-related brain activation (Preibisch et al., 2003). 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 (Montreal Neurological Institute template), and smoothed using an isotropic 10-mm Gaussian kernel. Low-frequency fluctuations were removed with a high-pass filter with a cutoff at 35 s (reading) and 80 s (semantic decision making), respectively.

Tasks

In the first task subjects read aloud 78 short sentences (6 words/sentence, SD = 2 words). Passive, silent viewing of letter-like meaningless signs (matched to the sentences) constituted the control condition. Both conditions were interleaved, and the visual stimuli were presented for 3 s with

an interstimulus interval of 15.5 s in each case. The duration of 3 s retained almost natural speaking conditions while most of the hemodynamic response remained unaffected by motion artifacts. The combination of a measurement repetition time of 3 s and an interstimulus interval of 15.5 s yielded an effective sampling of the hemodynamic response of 2 Hz (Preibisch et al., 2003). Speech production during the reading task was monitored via the scanner's built-in microphone.

The semantic decision task was a German adaptation of Wilde's intelligence test, subtest word meaning (Jaeger and Althoff, 1994). Subjects were asked to compare the meaning of a target word with four other words presented simultaneously and to decide which one was synonymous with the target. (e.g., subjects had to decide whether the word "sorrow" is semantically equivalent to "fear," "grief," "harm," or "anxiety"). A control task involved color judgment (one target color presented together with four other colors, one of which was similar to the target). The stimuli were presented in blocks of 8 periods of synonym decisions and 9 periods of colour decisions (20 s each, 68 measurements, TR 5 s beginning with the control condition).

Statistics

Statistical parametric maps of t values (SPM(t)) were created for each subject. In a second level analysis (random effects) common and differential activations were determined for each group and task by one- and two-sample t tests.

For a more sensitive and specific determination of group differences and to apply the necessary criteria (consistency across patients and studies, absence of effect in controls), data from both tasks were incorporated into a joint statistical analysis (fixed effects, high-pass filter cutoff = 80 s) in which differential activations were determined by appropriately specified contrasts. Corrections for multiple nonindependent comparisons were applied in accordance with Gaussian random field theory.

To enhance the specificity of the fixed-effects analysis and ensure consistent activations across all subjects, group differences were masked by contrasts obtained from each subject. The masking procedure thus constrained the results to effects that are present (inclusive mask) or absent (exclusive mask) in each single subject. Each contributing contrast was set at $P < 0.05$, uncorrected, which yields a probability of a chance activation occurring across 16 subjects of close to $P = 0.05$[16]. The contrast stutterers ($n = 16$) > fluent speakers ($n = 16$) during reading > viewing

meaningless signs was successively masked by all stuttering subjects and by all fluent speakers (reading > viewing meaningless signs) using the inclusive and exclusive masking procedures of SPM99, respectively. Inclusive and exclusive masking were reversed when probing the contrast fluent speakers > stuttering subjects.

Individual levels of activation in the RFO were additionally checked in both groups of subjects using single subjects fixed-effects analyses.

Finally, we performed a regression analysis between the severity of stuttering (assessed outside the scanner) and the level of activation in the RFO during reading and passive viewing of meaningless signs.

Results

Analysis of subjects' behaviour during scanning

During reading, speech output was fluent in all subjects. They managed to read entire sentences within the 3 s of presentation or stopped reading as soon as text presentation ended. Nine stuttering subjects were completely fluent, in seven we noted sporadic initial hesitations that did not amount to a significant difference in speech rate. This performance during scanning agrees with established knowledge that a loud masking noise (the sound of the scanner) improves fluency (Ingham, 1984). Thus, differences between PDS and control subjects in the fMRI data cannot be attributed to differences in behaviour. This consideration is further supported by the fact that we restricted our analyses to common effects across all PDS subjects including the nine perfectly fluent readers and seven with initial hesitation.

Motion due to overt speech in the reading task did not exceed 2 mm in either x, y, or z directions and angular deviations remained within $1°$ in most subjects. In some subjects incremental translations up to 5 mm and angular deviations of $5°$ were observed; the absence of motion artifacts at CSF tissue boundaries was visually checked in these.

No behavioural data were collected during the second task since it was designed to exclude speech production and any motor output. Psychophysical data suggest that stutterers perform silent verbal tasks with the same reaction times as control subjects (van Lieshout et al., 1996).

Together, potential confounds from motion artifacts and reaction times differences cannot account for our observed effects since our analysis retained only findings that were

Fig. 1. Higher activation in subjects with PDS compared to controls. (a) Reading sentences vs. viewing meaningless signs. Random effects analysis, $P <$ 0.001, uncorrected. (b) Reading sentences vs. viewing meaningless signs. Fixed effects analysis, $P < 0.05$, corrected, masked with the conjunction of all 16 stuttering subjects (each contrast $P < 0.05$, uncorrected). (c) Semantic decision task: Synonym decision vs. colour decision. Fixed effects analysis, $P < 0.001$, uncorrected, masked with main effect of 16 stuttering subjects. (d) The right frontal operculum (RFO) is the only common activation in the reading and semantic decision task.
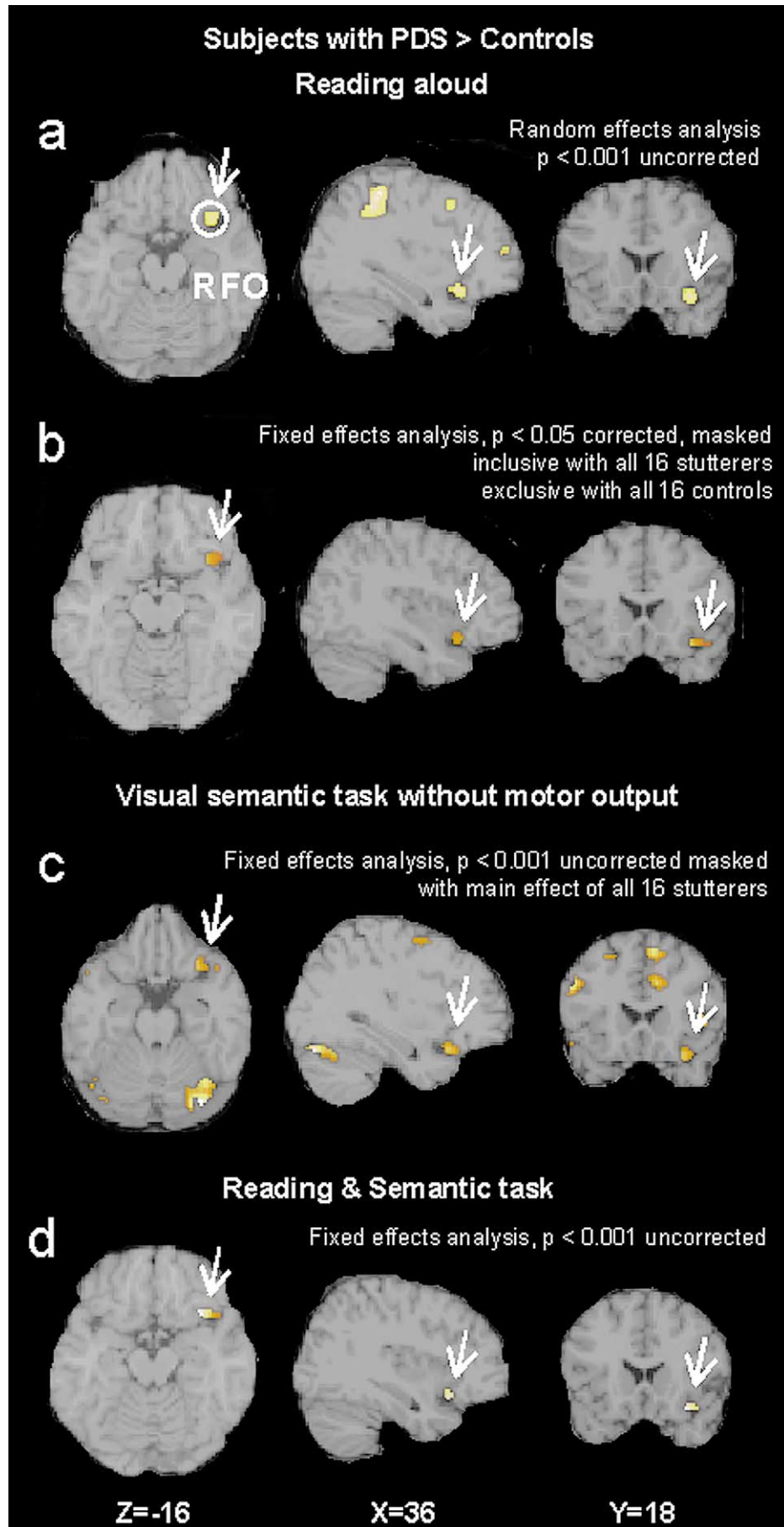
Subjects with PDS > Controls
Reading aloud

a — Random effects analysis p < 0.001 uncorrected

RFO

b — Fixed effects analysis, p < 0.05 corrected, masked inclusive with all 16 stutterers exclusive with all 16 controls

Visual semantic task without motor output

c — Fixed effects analysis, p < 0.001 uncorrected masked with main effect of all 16 stutterers

Reading & Semantic task

d — Fixed effects analysis, p < 0.001 uncorrected

Z=-16   X=36   Y=18

Table 1
Greater activation in subjects with PDS than in controls during reading

Anatomical region		Random effects, $P < 0.001$, uncorrected				Fixed effects, $P < 0.05$, corrected masked inclusive by conjunction of 16 subjects with PDS at $P < 0.05$, uncorrected				further masked exclusive by conjunction of 16 controls at $P < 0.05$, uncorrected.				further masked inclusive by fixed effects difference in the silent semantic decision task			
		x	y	z	t	x	y	z	t	x	y	z	t	x	y	z	t
R precentral frontal	BA 6	60	2	30	3.79	58	−2	32	17.60				n.s.				n.s.
		28	−12	64	3.67												
R superior frontal	BA 8	18	24	52	3.56												
R middle frontal	BA 6	28	8	42	3.97												
		36	12	48	3.79												
R middle frontal	BA 10	36	54	14	3.62												
R inferior frontal	BA 47	36	18	−16	4.45	34	20	−16	12.53	32	22	−22	8.26	36	18	−16	13.2[a]
						54	10	−12	10.01								
R insula	BA 13	44	−8	16	3.74												
L inferior frontal	BA 47					−42	18	−16	5.32				n.s.				n.s.
L cingulate gyrus	BA 24	−4	−6	30	3.53												
L superior temporal	BA 22 (Wernicke)					−54	−40	14	7.96				n.s.				n.s.
R superior temporal	BA 22	54	4	2	3.54	60	2	−10	9.02				n.s.				n.s.
R anterior temporal	BA 22					54	−6	−12	5.94				n.s.				n.s.
R intraparietal sulcus	BA 40	36	−42	54	4.78												
		24	−42	58	4.11												
L intraparietal sulcus	BA 40	−30	−42	60	3.89												

[a] Corrected threshold $P = 0.04$ ($t = 4.57$) in silent speech paradigm for stutterers > controls (words > colours).

common to both tasks, one without overt speech, the other without timing differences.

Reading task

Reading aloud was contrasted with passive viewing, and group comparisons of this difference were performed with a random-effects analysis. As depicted in Fig. 1 and listed in Table 1, stuttering subjects activated the right superior and middle frontal regions including the precentral gyrus, the right superior temporal region, both intraparietal sulci, and the RFO region. Apart from the parietal region, which did not appear in previous imaging studies, these results confirm earlier findings (Fox et al., 1996, 2000; Braun et al., 1997; Kroll et al., 1997; De Nil et al., 2000, 2001; Ingham et al., 2000; Foundas et al., 2001; Conture, 2001).

We performed a series of individual analyses and a fixed-effects group analysis on only those regions that activated significantly in every one of the 16 PDS subjects. This analysis emphasised small and consistent activations and excluded those not reproducible across all subjects. With this approach we no longer observed intraparietal activations and superior/middle frontal activations were limited to the right precentral gyrus, but temporal activations were more extensive and bilateral. Recruitment of the RFO was confirmed at the same location as found in

the random-effects analysis (Table 1). It is to be noted that the fixed-effects approach with individual masking yielded more conservative results than the state-of-the-art random-effects analysis. The random-effects results, however, served to ensure the generalisability of the RFO over-activation in our sample of stutterers, at the population level.

We thus revealed cortical regions that, compared to controls, were significantly and systematically overactive when each of the stutterers read aloud even though no lack of fluency was manifest during scanning. However, these regions were not all specific to language processing in stutterers, e.g., Wernicke's area is a classical speech perception region that is also recruited in controls. To assess the specificity of regional activation in stuttering we excluded from our findings those regions that were also activated by fluent speakers. Hence, we further constrained our fixed-effects analysis to brain regions that were not activated in fluent speakers, even at low threshold ($P < 0.05$, uncorrected). We found that the only activation that was specific to stutterers occurred in the RFO. Separate single subjects analyses indicated that 14 controls had no detectable activation in the RFO, 2 controls and 2 stutterers had subthreshold activations at $P < 0.05$, while 14 stutterers significantly activated with a $P < 0.001$ (uncorrected) (Fig. 2).

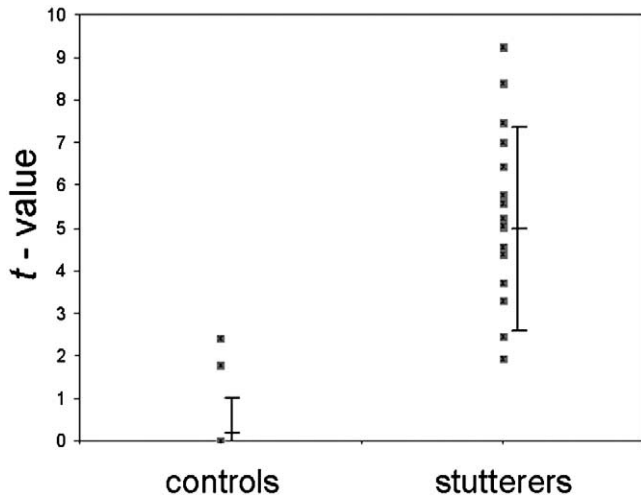The level of RFO activation during reading and passive

Fig. 2. *t* values in each single subject in the RFO during reading vs. viewing meaningless signs, as assessed in single subjects analyses. Error bars indicate mean values and standard deviations across controls and stuttering subjects.

viewing of meaningless signs was negatively correlated with the severity of stuttering assessed prior to scanning (*r* = −0.52, *P* = 0.04; *r* = −0.56, *P* = 0.03, for reading and passive viewing, respectively) (Fig. 3).

Semantic decision task

The reading task results and previous observations (Ingham et al., 2000) suggest that RFO activation may be characteristic of stutterers even in the absence of disfluency or overt speech production. We therefore tested for activation in this region during our passive visual semantic decision task. A difference between groups was observed in the RFO (fixed-effects, *t* = 4.57, *P* = 0.04, corrected; Fig. 1). This analysis revealed additional brain regions but the RFO was the only region that was consistently overactivated in stuttering subjects across reading aloud and passive semantic tasks (Table 1).

Regression analyses

Regression analyses (Fig. 3) indicate that activation in the RFO during both the reading and the passive viewing (control) tasks was negatively correlated with stuttering severity. The two tasks only differed with respect to the overall level of activation in the RFO but not with respect to the regression coefficient.

Deactivations in stutterers

Using the same statistical approaches, we determined activations that were greater in controls than stutterers (Table 2). A fixed effects analysis indicated that the left precentral region was more activated in controls than PDS

subjects in both tasks; but this finding could not be generalized beyond our study groups (random-effects).

Discussion

We based our analysis on the rationale that neural activations should characterize PDS only if consistent across stutterers and nondetectable in controls when performing the same tasks. By these criteria, we identified a unique region in the RFO that was activated in 14 of 16 PDS subjects during fluent reading and not activated in any controls. As stuttering was not manifest during this task, overactivation in the RFO may reflect a compensatory mechanism aimed at achieving speech fluency. This hypothesis is supported by a significant negative relationship between activation in the RFO, when there was no stuttering, and stuttering severity as assessed outside the scanner. In effect, if activation of the RFO was related to stuttering in a causal way, we would expect it to be positively correlated with the severity of the dysfluency manifestation. To the contrary, if implicated in the mechanism aimed at compensating for stuttering, a negative correlation was to be expected. Therefore, our finding suggests that overactivation of the RFO correlates with successful compensation rather than impaired fluency.

The RFO corresponds to the right homologue of Broca's area and is a good candidate to compensate for deficient signal transmission between Broca's area and left-sided articulatory motor representations as suggested by recent structural data (Sommer et al., 2002). Our results may also
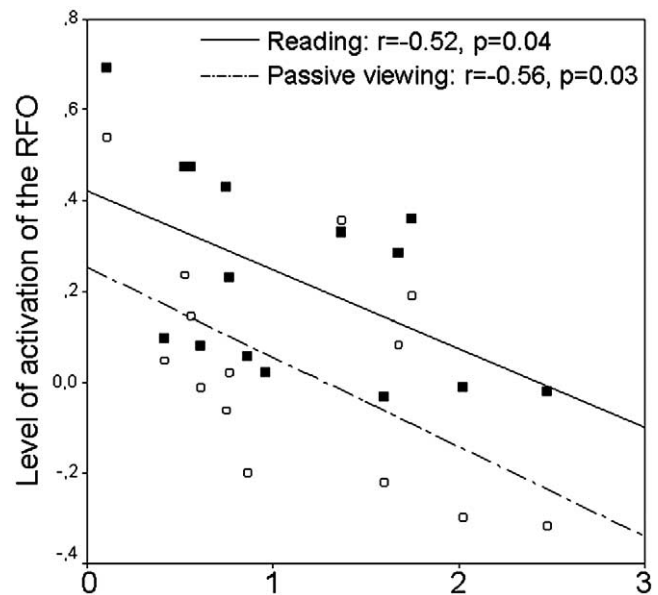

Fig. 3. Regressions of the level of activation of the RFO during the reading task and the passive viewing task with respect to severity of stuttering. Filled squares: reading; open symbols: passive viewing of meaningless signs.

Table 2
Greater activation in controls than in subjects with PDS during reading

Anatomical region		Random effects, $P < 0.001$, uncorrected				Fixed effects, $P < 0.05$ corrected masked inclusive by conjunction of 16 controls at $P < 0.05$, uncorrected				further masked exclusive by conjunction of 16 subjects with PDS at $P < 0.05$, uncorrected				further masked inclusive by fixed effects difference in the silent semantic decision task			
		x	y	z	t	x	y	z	t	x	y	z	t	x	y	z	t
L precentral frontal	BA 6					−46	−2	32	7.18				n.s.	−46	−2	32	5.02
L posterior cingulate	BA 30	0	−60	4	3.18												
L lingual occipital	BA 19	−10	−48	−6	3.41												

reflect compensation for a dysfunctional Broca's area. Observations of recovery from aphasia after frontal injury suggest that the right inferior prefrontal cortex can be automatically and immediately recruited to compensate for damage to its left homologue (Broca's area) (Rosen et al., 2000; Heiss et al., 1999). The RFO has also been implicated in compensation for dysfunction of the left frontal cortex in dyslexia (Pugh et al., 2001). However, the fact that we observed reduced activation in the left precentral regions, but not in Broca's area in stutterers suggests dysfunction downstream from Broca's area, which concurs with the anatomical findings of Sommer et al. (2002).

Hypoactivation of the left precentral region may have a direct influence on articulation (Fox et al., 2001; Tanji et al., 2001). However, this relative deactivation did not meet our criterion for consistency across PDS subjects. It may therefore be less directly related to the stuttering syndrome than is the overactivation in RFO. As there is no evidence for consistency of the white matter changes in the vicinity of the left sensorimotor cortex, the possibility remains that it is one, but not the only cause of PDS. It is possible that in addition to "symptomatic" PDS with structural abnormality, there are also cases of PDS without detectable white matter abnormality that are indistinguishable in terms of clinical phenomenology.

That overactivation in the RFO reflects conscious strategies to prevent stuttering is unlikely. Speaking is indeed more effortful in stutterers than in normal subjects. An increase in cognitive resources dedicated to the prevention of stuttering should result in overactivation, as shown in previous studies where subjects compensated for other dysfunctions (Giraud et al., 2000, 2001). However, effortful individual compensatory strategies are unlikely to involve exactly the same brain region in every stuttering subject. Intraparietal activations that were found to be inconsistent may be due to nonspecific attentional efforts to prevent stuttering in some subjects but not others (Giraud et al., 2000). The fact that overactivation in the RFO was consistent in all stutterers suggests an involuntary and automatic takeover of disturbed functions by a homologue contralat-

eral region in a manner that is similar to mechanisms active following the onset of aphasia (Rosen et al., 2000; Heiss et al., 1999).

Although our data support a compensatory functional role of the RFO in PDS, we observed that this effect is not specifically related to speech production. Overactivation in PDS subjects compared to controls and a negative correlation between activation and stuttering severity were found in two tasks in neither of which did stuttering occur; in one case because they successfully compensated (reading) and in the other because they did not speak (passive viewing task). This result suggests that the RFO is implicated in a mechanism aimed at more than just achieving fluent utterances. The mechanism operates in the absence of speech and must therefore involve processing steps upstream from the execution of articulatory movements. This conclusion agrees with the view that stuttering may be associated with an inversion of the stages of speech production with initiation of articulatory routines preceding activation of phonological output codes (Salmelin et al., 2000). In this context, our observations suggest that initiation of articulatory routines takes place even when there is no explicit need for speech and so possibly before critical early stages of speech production, e.g., at the level of phonology. Our findings imply that the RFO is in repair "mode" rather than specifically influencing the final stages before speech production.

One recent theory about stuttering, the "covert repair hypothesis," assumes that difficulties in selecting correct phonemes are responsible for delays in internal monitoring and require covert repair. This repair attempt results in the repetition of wrongly selected phonemes while adjusting the choice of correct phonemes (Postma and Kolk; 1993). A possible involvement of the RFO in an abnormal repair process during phoneme selection is compatible with some aspects of the functional role of this region. A role of the RFO in speech production is supported by numbers of data: 1, lesions of the RFO result in severe dysarthria (Ropper, 1987; Broussolle et al., 1996); 2, stimulation during open brain surgery induces blurred speech or speech arrest (Lampl et al., 1997); 3, the RFO plays a role in deep

dyslexic symptoms (Price et al., 1998). Its functional role also extends to cognitive tasks, e.g., working memory (Jonides et al., 1998; Tsukiura et al., 2001) and inhibition of response during dual task performance (Garavan et al., 1999; Meyer et al., 2000; Bunge et al., 2001; Herath et al., 2001). Yet, the most specific relationship to language repair in stuttering probably lies in the involvement of the right frontal opercular region in a "repair mode" for anomalies of speech and language, operating when subjects have to notice and repair grammatical errors in auditorily presented sentences (Meyer et al., 2000).

Despite the absence of overt responses in the semantic decision task, our findings could be interpreted in terms of covert speech. Inner speech may occur during the passive visual semantic task and during reading as a dual process, as described by some subjects' introspective reports. However, two arguments suggest that RFO activity is not related to "normal" inner speech. First, the right inferior frontal region does not normally participate in inner speech (McGuire et al., 1996; Shergill et al., 2000, 2001). Second, during the semantic decision task RFO activation was not embedded in a pattern of speech production-related activations that would be expected for covert speech production attempts.

Together our findings point to a type of neural activity in the RFO that does not occur during inner or overt speech in fluent speakers, that characterizes PDS instead of being merely a phenomenon associated with speech and lack of fluency and thirdly, that negatively correlates with stuttering severity and hence probably reflects successful compensation.

Acknowledgments

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