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The nature and treatment of stuttering as revealed by fMRI
A within- and between-group comparison

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Abstract

This article reviews some of our recent functional magnetic resonance imaging (fMRI) studies of stuttering. Using event-related fMRI experiments, we investigated brain activation during speech production. Results of three studies comparing persons who stutter (PWS) and persons who do not stutter (PWNS) are outlined. Their findings point to a region in the right frontal operculum (RFO) that was consistently implicated in stuttering. During overt reading and before fluency shaping therapy, PWS showed higher and more distributed neuronal activation than PWNS. Immediately after therapy differential activations were even more distributed and left sided. They extended to frontal, temporal, and parietal regions, anterior cingulate, insula, and putamen. These over-activations were slightly reduced and again more right sided two years after therapy. Left frontal deactivations remained stable over two years of observation, and therefore possibly indicate a dysfunction. After therapy, we noted higher activations in persons who stutter moderately than in those who stutter

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severely. These activations might reflect patterns of compensation. We discuss why these findings suggest that fluency-inducing techniques might synchronize a disturbed signal transmission between auditory, speech motor planning, and motor areas.

Educational objectives: The reader will learn about and be able to: (1) identify regions of brain activations and deactivations specific for PWS; (2) describe brain activation changes induced by fluency shaping therapy; and (3) discuss the correlation between stuttering severity and brain activation.

Keywords: Persistent developmental stuttering; fMRI; Frontal operculum; Fluency shaping; Therapy effects

Hypotheses about proximate causes of persistent developmental stuttering (PDS) have focussed on dysfunction of speech motor control, atypical lateralization of speech and language processes (Caruso, 1991; Moore, 1984a; Travis, 1978; Webster, 1993; Zimmermann, 1980), deficiencies of the language production system (Perkins, Kent, & Curlee, 1991; Wingate, 1988), sensory impairments, in particular auditory (Salmelin et al., 1998; Stromsta, 1986), or a complex combination of motor and linguistic deficits (Peters, Hulstijn, & van Lieshout, 2000). According to Webster (1990) PDS results from instability of the left motor area and reduced lateralization normally observed in most right-handed fluent individuals.

Although behavioral and electrophysiological studies have revealed much information about motor and cognitive behavior in humans (e.g., Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983; Moore, 1984b), these methods did not provide precise localization of cerebral activations (De Nil & Kroll, 2001a). Neuroimaging techniques have largely contributed to current knowledge about the possible neural correlates of stuttering and have given a new impetus to hypothetical implications that may help to improve stuttering therapies. Most of these studies have employed positron emission tomography (PET), but functional magnetic resonance imaging (fMRI) is expected to provide new insights about timing processes of stuttering. In this article, we review recent neuroimaging findings and discuss their possible therapeutic implications with a focus on long-term effects.

1. Recent neuroimaging findings about stuttering

Previous neuroimaging studies have shown distributed neurofunctional correlates of stuttering in frontal and prefrontal, speech motor planning, and executive areas in language, auditory, limbic, and subcortical regions (Braun et al., 1997; De Nil, Kroll, Kapur, & Houle, 2000; Fox et al., 1996; Ingham, Fox, Ingham, & Zamarripa, 2000; Salmelin, Schnitzler, Schmitz, & Freund, 2000). Stuttered speech was mainly associated with widespread over-activation in right cortical and left cerebellar motor regions and often with deactivations in left hemisphere language and auditory areas (Braun et al., 1997; De Nil & Bosshardt, 2001; Fox et al., 1996,

2000; Kroll, De Nil, Kapur, & Houle, 1997; Pool, Devous, Freeman, Watson, & Finitzo, 1991; Sommer, Koch, Paulus, Weiller, & Büchel, 2002; Wu et al., 1995). Over-activations of the SMA, anterior insula, anterior cingulate cortex (ACC), and deactivations of temporal regions have also been reported occasionally during stuttered speech (Braun et al., 1997; De Nil, Kroll, & Houle, 2001; Fox et al., 1996; Ingham et al., 2000; Salmelin et al., 1998).

Induced fluency has largely diminished the cerebral activation differences between persons who stutter (PWS) and persons who do not stutter (PWNS), but right-sided over-activations of motor cortices (M1 and SMA) persisted (Braun et al., 1997; Fox et al., 1996). Over-activations in PWS during silent speech have been proposed to reflect less automatized speech processing (De Nil & Bosshardt, 2001) and compensation for disturbed neuronal communication between speech motor areas and temporal or frontal language areas (Sommer et al., 2002).

In PWS, processing of speech production might be affected by timing disturbances of neuronal signal transmissions between premotor, auditory, and speech motor (Broca) regions (Foundas, Bollich, Corey, Hurley, & Heilman, 2001; Ingham, 2001; Salmelin et al., 2000; Sommer et al., 2002). Recent neuroimaging findings support this notion by showing (1) a failure of temporal lobe activation, with deactivations during speech (Ingham, 2001), (2) a reversed processing sequence between the left inferior frontal cortex, which is implicated in articulatory programming, and the left premotor and motor cortices, which is implicated in motor preparation (Salmelin et al., 2000), and (3) an anomaly of white matter below the motor representation of tongue and larynx, possibly reflecting impaired connections between the left precentral cortex (premotor) with temporal and frontal language areas (Sommer et al., 2002). Accordingly, right-hemisphere over-activation in PWS could reflect compensation, although one cannot rule out the hypothesis that such over-activation could have produced a subsequent dysfunction in the left hemisphere (Sommer et al., 2002). Fluency-inducing procedures (e.g. chorus reading) restore activation in regions that are deactivated in the absence of external fluency inducements in auditory regions (Braun et al., 1997; Fox et al., 1996). This effect could reflect a normalization of synchronization among language regions.

2. Implication of the right frontal operculum in stuttering

Recently, we investigated the hypothesis that alterations of fiber tracts underlying the left sensorimotor cortex are causal for PDS, as suggested by recent data (Sommer et al., 2002), and therefore that right-hemisphere over-activation in PWS reflects compensatory mechanisms (Preibisch et al., 2003a). We performed two fMRI studies with 16 male adult PWS and 16 PWNS. Reading aloud was contrasted with a condition in which participants passively watched letter-like meaningless signs. Over-activation consistent across all 16 PWS was detected in the

right frontal operculum (RFO), reflecting an effect specific to stuttering. To judge the influence that stuttering severity might have on RFO activation, we divided the sample into subjects who stutter severely and those who stutter moderately. Stuttering severity was defined by subjects' percentage of disfluent syllables in four speaking situations (talking with the therapist; overt reading; making a telephone call to an unknown person; interviewing people on the street). Those having more than 10% stutters were categorized as severe, those with less as moderate stutterers. We hypothesized that the over-activation of the RFO reflects a compensatory process rather than a primary dysfunction, because (1) RFO activation was negatively correlated with stuttering severity, and (2) we observed a generally more distributed over-activation in persons who stutter (PWS) moderately than in those who stutter severely (Neumann et al., 2003). Because the RFO might be considered as the right homologue of Broca's area, it seems plausible that it compensates for deficient signal transmissions between Broca's area and left-sided articulatory motor representations, as suggested by Sommer et al. (2002), or for a dysfunctional Broca's area, by automatically taking over its disturbed functions, as occurs during recovery from aphasia after frontal injury (Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Rosen et al., 2000) or for a dysfunction in the left frontal cortex in dyslexia (Pugh et al., 2001).

To investigate whether over-activation of the RFO in PWS was related to motor output, participants were also asked to make silent semantic judgments of synonyms without producing an overt utterance. The RFO was the only region that was over activated in PWS across the reading and the semantic tasks. This activation is not a correlate of stuttering, because PWS spoke fluently while reading in the scanner and did not speak at all during the semantic task. A compensatory mechanism during early processing of speech production was therefore assumed to act independently of speech motor output demands. Initiation of articulatory routines may occur even when there is no need for speech and possibly before critical, early stages of speech production involving phonological processes. This view would be consistent with an inversion of speech production steps in PWS, with the initiation of articulatory routines preceding activation of phonological output codes (Salmelin et al., 2000).

3. Short-term effects of fluency shaping therapy

New insights into cerebral functioning in PDS may lead to new approaches that would improve the efficacy of therapy. The way that cerebral activation patterns are altered should guide modern therapy concepts. Fluency shaping therapies start with slowed speech, training of soft voice onsets and continuous phonation (Webster, 1974), and end, if successful, in more natural sounding, fluent speech, corresponding to an acquisition of new speech automatisms. According to the hypothesis of a disturbed neuronal synchronization during speech processing (Sommer et al., 2002), the new speech production pattern could induce a compensatory,

synchronization mechanism based on external pacing (i.e., clock generator). Consequently, the replacement of one type of automatized speech pattern (i.e., stuttering) with another one (i.e., fluent speech) can be expected to produce a shift in the cerebral activation patterns implicated in the timing of speech processing. Alternatively, if we conceptualize fluency shaping effects as solely due to decreasing demands on the speech–motor system through prosodic changes and the prolongation of speech, reduced neuronal activity would be expected after fluency therapy.

A number of EEG and PET experiments have investigated the changes in cerebral activation due to stuttering-reducing therapies during the past two decades (Boberg et al., 1983; De Nil & Kroll, 2001a, 2001b; Kroll et al., 1997; Moore, 1984a). One of the more intriguing findings reported by these experiments was a shift in brain activity to the left hemisphere after therapy. Kroll et al. (1997) observed higher activation of the ACC during silent and overt reading in untreated PWS compared to PWNS, which was not found in treated persons. The authors confirmed their findings in a more recent PET study (De Nil & Kroll, 2001a, 2001b), in which 13 PWS were scanned before, immediately after, and one year after fluency shaping therapy, and their brain activations were compared to PWNS. During silent reading before therapy, PWS showed higher activation of the ACC than the PWNS. This effect was reduced after therapy and continued to decrease during the following year. Additionally, PWS showed higher bilateral activation in the frontal cortex, including Broca's area and the insular cortex, than did PWNS. Immediately after therapy, frontal activation in PWS had become more left lateralized, a process that continued during the year after therapy. PWS also displayed increased left, sensorimotor activations during overt reading. During a verb generation task, in which participants had to produce aloud a verb associated with a noun, only minimal differences were found between PWS before therapy and PWNS, which was also true of the changes from before to after therapy and the subsequent follow-up. PWS generally showed higher levels of brain activation before therapy during silent reading, suggesting relatively high levels of cognitive demand when performing this task. Overall, PWS evidenced more activation before therapy than PWNS in cortical and subcortical areas known to be involved in the motor execution of articulatory movements, and in the ACC, which normally participates in articulatory planning, rehearsal, and response selection. The latter was interpreted by the authors as possibly reflecting subjects' covert anticipations of stuttering. The reduction in ACC recruitment following therapy and proportional increase in motor activation were more pronounced in the left hemisphere. These changes were interpreted as (1) an increased level of automaticity during speech production, (2) reduced anticipatory needs to scan words for potential stuttering, (3) increased emphasis of on-line self-monitoring, and (4) optimized sequencing and timing of articulatory, phonatory and respiratory movements gained through fluency shaping therapy. The absence of significant between-group differences during the verb generation task, together with the significant differences during speech production, were taken to indicate a deficiency

in motor planning and speech execution rather than at the cognitive–linguistic level.

Recently we performed an fMRI study of nine, adult male PWS before and immediately after a three-week Precision Fluency Treatment program. Findings were compared with those of 16 PWNS (Neumann et al., 2003). Reading aloud before therapy was associated with more widespread activation of the bilateral premotor and motor cortex in PWS than in PWNS. After therapy, PWS showed even more widespread and more left-sided frontal activation. We also observed increased activation of the ACC, the putamen, and bilateral temporal regions. Over-activation of the RFO, present before therapy, was no longer observed after therapy. Therapy also induced higher levels of activation in the left inferior frontal cortex during semantic decisions. Stable pre- versus post-therapy deactivations were noted in the left pre-central region during aloud reading and in the left inferior frontal and cingulate regions during silent, semantic decisions. These deactivations might indicate a dysfunction of these regions, as has been assumed in recent neuroanatomical studies (Sommer et al., 2002), whereas the task-specific higher activations after therapy could be interpreted as successful compensation in gaining speech motor control. These activation patterns suggest that fluency-inducing techniques might synchronize disturbed signal transmissions between auditory, speech motor planning, and motor areas.

Although stuttering therapy is relatively effective in improving the fluency of many PWS, approximately 50% of all subjects receiving therapy show varying degrees of relapse within one year following therapy (De Nil & Kroll, 1995). Kassel Stuttering Therapy (KST) program focuses on achieving long-lasting effects of the improvement through continued, computer-aided, self-managed practice after the intensive program, participation in refresher courses, and follow-up over one to two years. Three years after their intensive therapy, the majority of PWS had maintained their fluency (Euler & Wolff von Gudenberg, 2002a, 2002b). Some PWS showed a relapse during the first half year, which disappeared partially or completely in the following period. Subjective data, such as self-assessments of speech in several situations and of tendencies to avoid speaking and speaking situations, covaried with objectively assessed disfluencies (i.e., percentage of disfluencies in four different speaking situations) and showed the same course as objective measures of disfluencies (Euler & Wolff von Gudenberg, 2000).

The aim of this study was to identify changes in the cerebral activation patterns attributable to improved fluency two years after intensive fluency shaping therapy followed by regular practicing of maintenance techniques. Using fMRI, we compared cerebral activations in the same subjects as a function of the time elapsed since therapy, as well as between-group comparisons with controls. Based on our previous findings suggesting that some initial over-activations reflected compensation (Preibisch et al., 2003a) and the findings reported by De Nil and Kroll (2001b), we expected to observe a reduced participation of the regions, which were over activated in PWS immediately after therapy, and maintenance of the deactivations two years after intensive therapy.

4. Methods

4.1. Participants

Five male adults with developmental stuttering (mean age 34 years, range 26–41 years) underwent fMRI at three different assessment times: (1) before and (2) within 12 weeks of completing an intensive course of fluency shaping therapy, and (3) after finishing a two-year follow-up period. Sixteen fluent speakers who had no history of stuttering during childhood served as controls (mean age 32 years, range 19–51 years). The five PWS had a handedness Laterality Quotient (L.Q.) of 100, 100, 100, 87, and −64, respectively according to the Edinburgh Handedness Inventory (Oldfield, 1971). Eight of the PWNS had a L.Q. of 100, the other eight had L.Q.s of 90, 89, 88, 50, 50, 20, 0, −73, and −80. Thus, the two groups were of comparable handedness, with L.Q. medians of 100 (PWS) and 90 (PWNS), and means of 65 (PWS) and 69 (PWNS). All participants were native German speakers, gave written informed consents for participation, and were screened by a phoniatrician for relevant neurological or other medical problems and for the presence of any speech or language problem other than stuttering.

The PWS were selected from the therapy waiting list of the Institute of the Kasseler Stottertherapie, Baunatal, Germany. Their diagnoses of PDS were confirmed by an experienced speech–language pathologist. None of the PWS had ever undergone fluency therapy before.

Stuttering was measured as the percentage of stuttered syllables in four speaking situations (talking with therapist, aloud reading, calling an unknown person by telephone, and interviewing people on the street). The PWS had a mean stutter rate of 9.9% (range 5.6–17.4%) before therapy, of 0.9% (range 0.2–1.5%) immediately after their intensive therapy, and of 1.7% (range 0.2–5.1%) at the one-year follow-up period.

So that we could compare PWS who stutter severely with those who stutter moderately in a sufficiently large sample, 11 more PWS were added. They were of comparable age, handedness, and stuttering severity as the original sample of five PWS. Severe stuttering ($n = 7$) was defined as more than 10% stuttered syllables and moderate stuttering ($n = 9$) as less than 10%. The larger sample of PWS was available only before therapy.

4.2. The Kassel Stuttering Therapy

The KST is a modified version of the Precision Fluency Shaping Program (Webster, 1974) and consists of a three-week, in-patient intensive therapy and a structured maintenance program for one to two years. The main modification of Webster's program is the utilization of a computer program (speak:gentle®, Bioservices Software, Munich, Germany) that provides biofeedback for syllable prolongation, soft voice onset, and smooth sound transitions. Details about the

therapy and its short- and long-term effects on objective and subjective measures of fluency are described in Euler and Wolff von Gudenberg (2000).

4.3. Apparatus

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 (TR) of 3 s, a voxel size of 3.6 mm × 3.6 mm × 6 mm, an inter-slice gap of 0.6 mm, and 18 slices. Participants watched a screen via a mirror mounted onto the head coil.

4.4. Procedure

Images of the PWS were taken before therapy began, within 6–12 weeks after finishing it, and two years later. At their last assessment, all PWS were still engaged in the long-term maintenance program. The PWNS were scanned only once. All participants performed two language tasks while being scanned.

4.4.1. Overt reading task

For the overt reading task an event-related design was developed which allowed investigation of participants' speech through the effective suppression of speech production artifacts (Preibisch et al., 2003b). Until now, fMRI has rarely been used for investigations of speech production paradigms, because speech-related artifacts largely impaired sensitivity of task-related activation. Stimulus-correlated artifacts are caused by direct head motion and magnetic field variations induced by the changing pharyngeal space during speech (Van Borsel, Achten, Santens, Lahorte, & Voet, 2003). Our approach temporally segregated these signal fluctuations from task-related brain activation. Recently a suppression of speech-related artifacts was achieved by exploiting the temporal delay of hemodynamic responses (duration of the rise ∼8 s), but the utterances used in these experiments were restricted to single words (Birn, Bandettini, Cox, & Shaker, 1999). However, in order to avoid the effects of unnatural speech tasks instead of stutter-specific fMRI activations, a more natural and extensive speaking task was needed. Such tasks should include, at a minimum, the reading of full sentences; therefore, we investigated the correlation between speech-related artifacts and the hemodynamic responses for various speech durations and repetition times. The use of prolonged stimulus durations and repetition times of 3 s, allowed us to achieve effective suppression of speech-related artifacts in both fluent and non-fluent speakers (Fig. 1). Because fluent speakers need about 3 s to complete a short sentence and our PWS generally read fluently during imaging procedures, this speech duration was used in our experiments. This design widely eliminated false activations at high contrast CSF-tissue borders, and PWS displayed consistent activation in speech-related and motor areas, which resembled those obtained by earlier neuroimaging studies of language production. Thus, this design seemed highly suitable for recording the neurophysiological correlates of overt speech production in PWS.

The participants read aloud 78 short, phonetically balanced sentences presented on a screen. Speech production was monitored via the scanner's built-in microphone. As a control condition, participants also viewed letter-like meaningless signs, which were alternated with the sentences that were read. The visual stimuli were presented for 3 s, with interstimulus intervals of 15.5 s in each condition. This presented a more natural speaking condition than would the reading of single words and left most of the hemodynamic responses unaffected by motion artifacts. The repetition time of the image acquisition combined with the interstimulus interval yielded an effective sampling rate of the hemodynamic responses of one data point every 0.5 s, because all subsequently gathered data points were shifted into one TR period for evaluation (see Fig. 1).

Motion due to overt speech did not exceed 2 mm in either *x*, *y*, or *z* directions, and angular deviations remained within 1° in most participants. In some participants, however, 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 participants.

Speech output was generally fluent for all participants. Before therapy the PWS managed to read entire sentences (i.e., 6 words per sentence, ±2 words) within

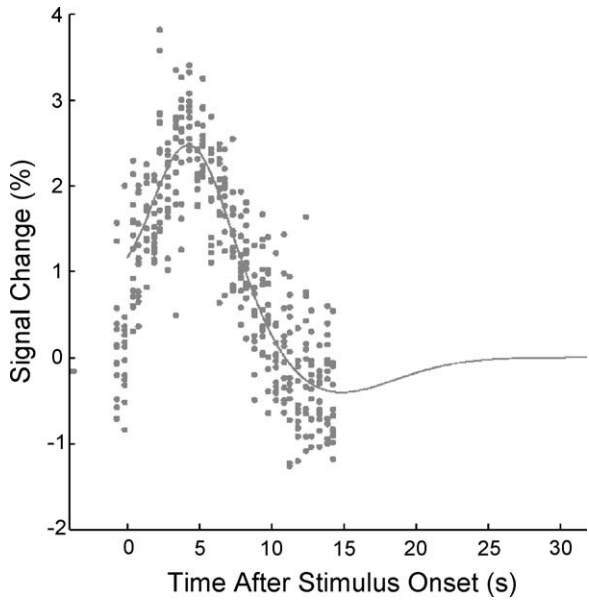

Fig. 1. Temporal separation of stimulus and hemodynamic response in the event-related design. After reading short sentences (stimulus duration 3 s, marked by the rectangle) the delayed rise of the hemodynamic response (duration of rise ~8 s) ensures that the remaining response is disturbed less by motion-related signal fluctuations. Thus relevant activation is more easily detected in the regression analysis.

the 3 s duration of their presentation and stopped reading as soon as text presentation ended. Four of five PWS spoke fluently during scanning sessions at any assessment time; however, one evidenced sporadic initial hesitations that did not result in a noticeable reduction in speech rate. Their fluent speech was possibly induced by the loud noise of the scanner and the segmentation of speech. Masking noise has fluency-inducing effects, and the segmentation of speech into short periods separated by pauses is also known to aid fluency (Ingham, 1984). PWS spoke more slowly (i.e., 2 words per reading period of 3 s, ±1 word) immediately after therapy than during recordings made prior to therapy. At their follow-up assessment time, none of the PWS spoke remarkably slower than before therapy.

4.4.2. Semantic decision task

A conventional blocked design was employed for this task, in which periods of task performance alternated with control condition periods. Participants had to compare silently the meaning of a target word with four other words presented simultaneously and decide which was the best synonym for the target word (e.g., target word *sorrow*, choice words *fear*, *grief*, *harm*, *anxiety*). This task was a German adaptation of Wilde's Intelligence Test, subtest Word Meaning (Jaeger & Althoff, 1994), except that no overt speech motor output was involved. The control task was a comparative color judgment task, in which a target color was presented together with four choice colors. The stimuli were presented in blocks of eight periods for semantic decisions and nine periods for color decisions, beginning with the color decisions, with each block having four stimuli, a stimulus duration of 20 s each, and a repetition time of 5 s. This semantic decision task is expected to engage neural processes activated during silent reading of the presented words and the cognitive processes involved in the selection of a synonym that is semantically related to the target word.

4.5. Data analysis

Spatial pre-processing and statistical analyses were performed using SPM99 (Wellcome Department of Imaging Neuroscience, London, UK). The event-related data were corrected for acquisition time (slice timing), all data were realigned to the first volume (motion correction), normalized into a standardized neuroanatomical space (Montreal Neurological Institute template), and smoothed using a 10 mm Gaussian kernel. Low-frequency fluctuations were removed with a high-pass filter cut-off at 35 s for reading aloud and 80 s for semantic decisions, respectively.

Statistical parametric maps of *t*-values (SPM(*t*)) were created for each participant using SPM99. In order to achieve a sensitive and specific determination of group differences as well as consistency across participants for each task, data for all 16 PWNS and for the five PWS that were obtained before, immediately after therapy, and after the follow-up period, underwent a joint statistical analysis

(fixed-effects analysis), in which common and differential activations of the group averages were determined by the specification of appropriate contrasts (high-pass filter cut-off: 80 s; Preibisch et al., 2003a).

To obtain statistical inferences about differences between groups, without the visual activations attributed to reading, overt reading was contrasted with passive viewing, and group comparisons of this difference were performed. To enhance the specificity of the results and ascertain consistent activations across all subjects, the fixed-effects group differences were jointly masked by contrasts obtained from each subject. This stringent approach (inclusive masking) assured that only those regions in which each of the five PWS subjects reached a significant activation threshold were counted as being activated in the group analysis. Each contributing contrast was set at $P < 0.05$, uncorrected, which yields a probability of an activation occurring by chance across the five PWS of close to $P = 0.05^5$.

The contrast where PWS before therapy ($n = 5$) were more activated than PWNS ($n = 16$) during reading and more when viewing meaningless signs was masked by all PWS before therapy using the inclusive masking procedures of SPM99. Inclusive masking was reversed when probing the contrast where PWS before therapy were less activated than PWNS. The respective masking procedures were applied to the between-group comparisons of PWNS versus PWS immediately after therapy and at two years follow-up, and to within-group comparisons of before therapy versus immediately after therapy versus two-year follow-ups, as well as to the between-group comparisons of persons who stutter more severely ($n = 7$) versus those who stutter less severely ($n = 9$). Corrections for multiple non-independent comparisons were applied in accordance with Gaussian random field theory.

5. Results

5.1. Overt reading

5.1.1. Between-group comparisons (PWS versus PWNS)

In agreement with previous observations (Neumann et al., 2003), we detected a variety of regions in which PWS showed significantly higher activation than PWNS at every assessment time (Fig. 2, Table 1). Before therapy these over-activations were located bilaterally, but more right-sided in frontal speech motor and speech planning regions, among them the RFO, as well as in temporal, parietal, and limbic regions, including the ACC, and in the insula. Immediately after therapy over-activations were more widespread and especially more left-sided than before and involved, additionally, left temporal regions and the putamen, bilaterally. At follow-up, such over-activations had partially shifted back to a right-sided predominance, but now included more regions than before therapy.

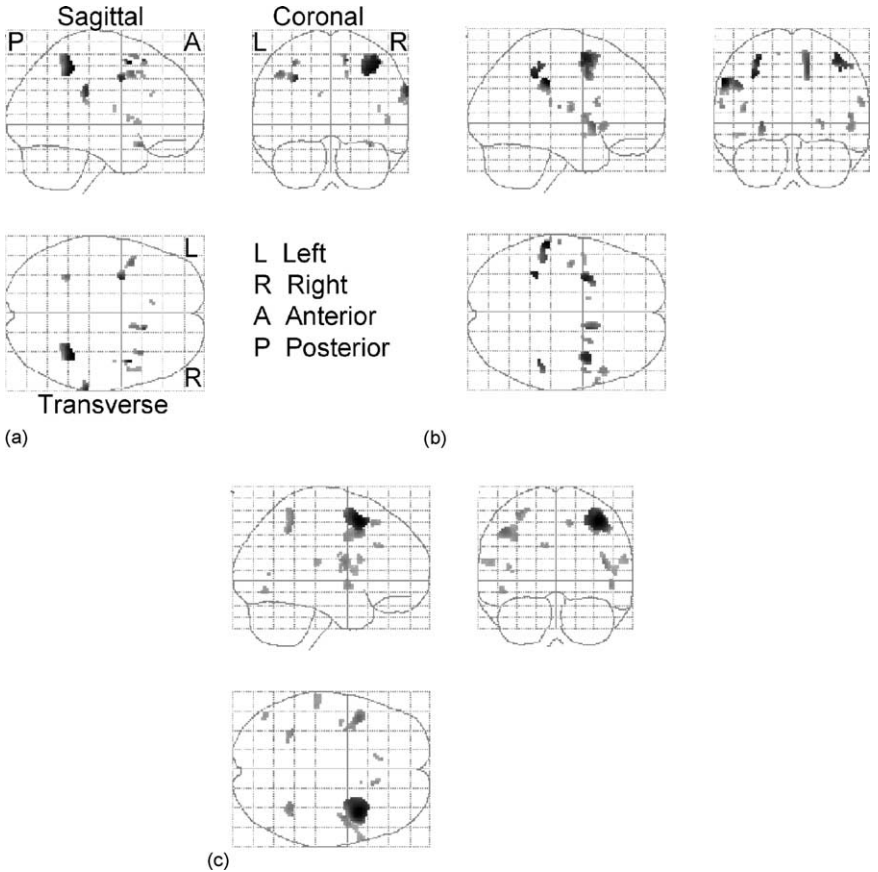

Fig. 2. Overt reading: statistical parametrical maps of between-group comparisons (PWS vs. PWNS) for *higher* cerebral activation in PWS (a) before therapy, (b) after therapy, and (c) after two years of follow-up.

Table 1
Localizations of peak activations during overt reading for the between-group comparisons

Side	Lobus	Gyrus	Brodman area	MNI			*t*
				x	*y*	*z*	
Higher activations in PWS before therapy than in PWNS							
R	Frontal	Superior	BA 6	14	20	56	7.98
L	Frontal	Pre-central	BA 6	−30	0	40	8.69
R	Frontal	Middle	BA 6	42	8	54	10.70
L	Frontal	Middle	BA 8	−44	10	46	6.52
R	Frontal	Inferior	BA 47	34	16	−18	6.46
R	Frontal	Inferior	–[a]	48	14	4	4.95
R	Sub-lobar	Insula	BA 13	42	−6	16	4.60
R	Temporal	Superior	BA 22	50	6	4	4.96
R	Limbic	Cingulate	BA 32	14	14	46	5.38
L	Limbic	Anterior cingulate	BA 32	−10	26	26	4.94
R	Parietal	Post-central	BA 40	66	−30	20	4.90
R	Parietal	Inferior	BA 40	36	−42	48	10.43
L	Parietal	Inferior	BA 40	−32	−46	54	6.64
Higher activations in PWS after therapy than in PWNS							
R	Frontal	Pre-central	BA 44	50	2	6	6.41
R	Frontal	Middle	BA 6	40	4	56	10.90
L	Frontal	Middle	BA 6	−28	2	56	11.50
L	Frontal	Medial	BA 6	−12	4	60	5.02
R	Frontal	Inferior	BA 44	62	12	18	6.34
R	Frontal	Inferior	BA 47	52	18	−2	6.40
L	Sub-lobar	Insula	BA 13	−42	−10	12	6.34
R	Limbic	Cingulate	BA 24	14	4	48	9.05
L	Temporal	Transverse	BA 42	−60	−20	14	6.14
L	Temporal	Superior	BA 38	−46	2	−10	5.06
L	Parietal	Post-central	BA 2	−48	−32	36	8.67
L	Parietal	Post-central	BA 40	−62	−28	18	5.50
R	Parietal	Inferior	BA 40	42	−38	48	10.00
L	Parietal	Inferior	BA 40	−60	−32	38	13.00
R	Sub-lobar	Lentiform nucleus	Putamen	24	6	0	6.23
L	Sub-lobar	Lentiform nucleus	Putamen	−26	10	−2	8.17
Higher activations in PWS at follow-up than in PWNS							
R	Frontal	Superior	BA 6	12	12	52	4.78
R	Frontal	Middle	BA 6	36	10	52	18.50
L	Frontal	Middle	BA 8	−44	10	44	9.43
R	Frontal	Medial	BA 8	14	22	50	6.99
L	Frontal	Pre-central	BA 6	−34	−2	36	6.55
R	Frontal	Pre-central	BA 44	50	6	8	5.29
R	Frontal	Inferior	BA 44	62	12	18	5.76
R	Sub-lobar	Insula	BA 13	42	−2	16	8.45
L	Sub-lobar	Insula	BA 13	−40	−6	12	5.63
L	Limbic	Cingulate	BA 32	−8	30	30	6.02
R	Temporal	Superior	BA 22	48	2	−4	6.97
R	Temporal	Middle	BA 37	52	−68	6	5.68
R	Parietal	Post-central	BA 5	40	−48	60	7.93

Table 1 (*Continued*)

Side	Lobus	Gyrus	Brodman area	MNI			*t*
				x	*y*	*z*	
L	Parietal	Post-central	BA 5	−34	−48	58	7.48
L	Parietal	Post-central	BA 40	−56	−26	16	5.68
R	Parietal	Precuneus	BA 7	32	−48	50	7.82
L	Parietal	Superior	BA 7	−24	−52	62	6.11
L	Occipital	Inferior	BA 19	−46	−72	−10	5.92
Lower activations in PWS before therapy than in PWNS							
L	Frontal	Pre-central	BA 6	−48	−4	32	27.54
R	Occipital	Lingual	BA 18	10	−78	2	15.29
L	Occipital	Lingual	BA 18	−6	−74	2	15.25
Lower activations in PWS after therapy than in PWNS							
L	Frontal	Pre-central	BA 6	−52	−2	42	26.10
L	Occipital	Lingual	BA 18	−6	−74	2	17.48
R	Occipital	Lingual	BA 18	8	−78	2	17.36
Lower activations in PWS at follow-up than in PWNS							
L	Frontal	Pre-central	BA 6	−52	−2	42	27.29
L	Occipital	Lingual	BA 18	−6	−76	4	17.90
R	Occipital	Lingual	BA 18	8	−78	2	17.06

Note. MNI: Montreal Neurological Institute template; *x*, *y*, and *z* are the coordinates of the region. "after therapy" means assessment within 12 weeks after intensive therapy course; follow-up assessment was two years after intensive therapy course. Where multiple foci were identified in a given region, only the one with the highest *t* value is shown.

[a] No BA given by the anatomical software.

Lower activations in PWS than in PWNS were located in the left frontal, pre-central cortex, and in bilateral, occipital lingual regions (Fig. 3, Table 1). These deactivations remained remarkably stable from before to after therapy and throughout the two-year follow-up period.

5.1.2. Within-group comparisons (PWS before therapy versus after therapy versus follow-up)

Immediately after therapy more extended over-activations were detected than before therapy in right frontal and parietal, bilateral temporal, and limbic regions, and in the putamen (Fig. 4, Table 2). After two years the majority of these over-activations persisted, except for the putamen, but included additionally the red nucleus. Several regions of lower activation were observed after therapy and at follow-up than were seen before therapy (see Table 2). However, these deactivations appear unstable and thus possibly unsystematic, because they totally disappear if the activation patterns after therapy and at follow-up are collapsed. There were some regions with decreased and some with increased activations from after therapy to follow-up, but with a clear tendency towards reduced activation at follow-up.

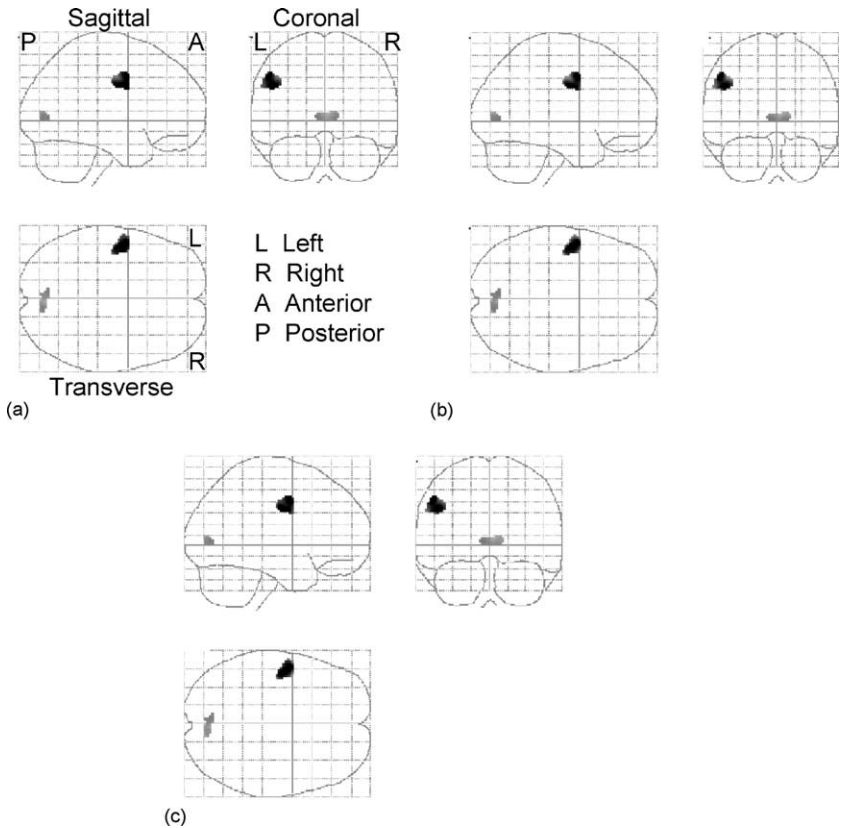

Fig. 3. Overt reading: statistical parametrical maps of between-group comparisons (PWS vs. PWNS) for *lower* cerebral activation (a) before therapy, (b) after therapy, and (c) after two years of follow-up.

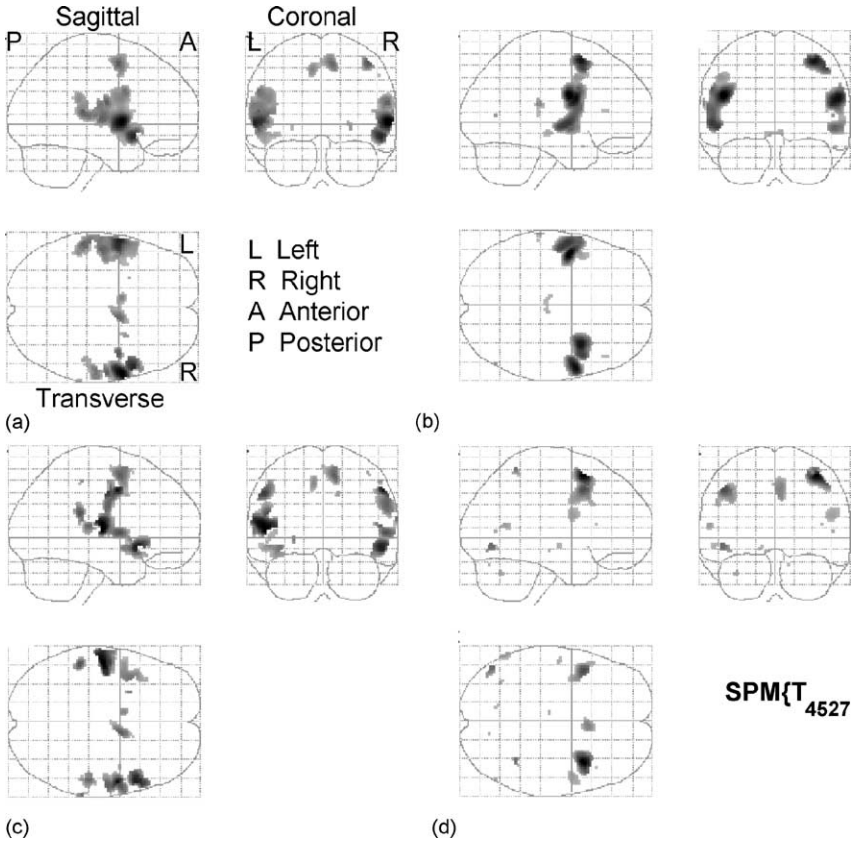

Fig. 4. Overt reading: statistical parametrical maps of within-group comparisons for *higher* cerebral activation at PWS (a) after vs. before therapy, (b) after two years of follow-up vs. before therapy, (c) after therapy vs. after two years of follow-up, and (d) after two years of follow-up vs. after therapy.

5.2. Semantic decision

5.2.1. Between-group comparisons of PWS versus PWNS

We did not observe any over-activations in PWS compared to PWNS (i.e., PWS before therapy versus PWNS, PWS immediately after therapy versus PWNS, and PWS at follow-up versus PWNS). However, after collapsing the data acquired from PWS over all three assessment times, we detected over-activations in the left middle and inferior frontal and the left temporal cortices (Table 3). We also observed deactivations in PWS, compared to PWNS, that were stable across all three assessment times in the left insula, cingulate, and frontal inferior region (Fig. 5, Table 3). After averaging the activations over all three assessment times, however, PWS activated less than PWNS only in the left insula and the left frontal inferior region (Table 3).

Table 2
Localizations of peak activations in PWS during overt reading for the within-group comparisons

Side	Lobus	Gyrus	Brodman area	MNI			*t*
				x	*y*	*z*	
Higher activations after therapy than before therapy							
R	Frontal	Medial	BA 6	10	0	54	7.12
R	Frontal	Middle	BA 6	42	0	56	7.63
L	Limbic	Cingulate	BA 24	−8	2	50	6.24
R	Temporal	Superior	BA 22	60	4	2	10.77
R	Temporal	Superior	BA 38	54	14	−12	9.25
R	Temporal	Superior	BA 41	58	−20	8	6.68
R	Temporal	Superior	BA 42	66	−34	18	4.88
L	Temporal	Superior	BA 22	−60	2	0	9.37
L	Temporal	Superior	BA 42	−56	−32	12	7.35
R	Temporal	Transverse	BA 41	48	−30	12	5.28
R	Parietal	Post-central	BA 43	60	−10	20	7.36
R	Sub-lobar	Lentiform nucleus	Putamen	26	8	−2	5.56
L	Sub-lobar	Lentiform nucleus	Putamen	−26	10	−2	4.73
Higher activations at follow-up than before therapy							
R	Frontal	Middle	BA 6	36	8	56	8.64
L	Frontal	Inferior	BA 9	−46	−2	24	9.34
R	Frontal	Inferior	BA 44	56	4	22	8.87
R	Frontal	Inferior	BA 46	46	30	10	4.63
R	Temporal	Superior	BA 22	54	−2	−4	6.70
L	Temporal	Superior	BA 22	−56	−2	0	7.71
L	Temporal	Superior	BA 42	−58	−30	8	4.53
R	Temporal	Middle	BA 37	52	−68	6	5.31
R	Temporal	Middle	BA 21	54	10	−22	4.61
L	Parietal	Post-central	BA 40	−64	−28	18	5.69
R	Brainstem	Midbrain	Red Nucleus	6	−22	−10	4.87
L	Brainstem	Midbrain	Red Nucleus	−6	−20	−10	4.71
Higher activations at follow-up than after therapy							
R	Frontal	Middle	BA 6	36	10	56	14.31
R	Frontal	Middle	BA 8	46	14	48	9.19
L	Frontal	Middle	BA 8	−46	12	44	10.03
L	Frontal	Middle	BA 9	−52	18	32	5.49
R	Frontal	Inferior	BA 44	50	0	20	5.74
R	Limbic	Cingulate	BA 32	4	14	44	7.32
L	Temporal	Middle	BA 22	−54	−12	−8	5.14
L	Temporal	Superior	BA 22	−58	−60	12	5.91
L	Temporal	Inferior	BA 37	−48	−72	−6	8.52
R	Parietal	Superior		34	−50	62	8.33
Lower activations after therapy than before therapy							
L	Frontal	Middle	BA 8	−44	10	46	6.39
L	Temporal	Superior	BA 22	−60	−58	10	4.76
R	Parietal	Superior	BA 7	32	−54	60	7.10
R	Occipital	Cuneus	BA 23	2	−74	8	5.31
L	Occipital	Cuneus	BA 18	0	−80	2	4.83
R	Limbic	Cingulate	BA 24	4	12	34	8.64

Table 2 (*Continued*)

Side	Lobus	Gyrus	Brodman area	MNI			*t*
				x	*y*	*z*	
R	Cerebellum	Posterior	Declive	6	−78	−22	4.79
L	Cerebellum	Posterior	Declive	−44	−60	−26	4.43
Lower activations at follow-up than before therapy							
R	Frontal	Pre-central	BA 6	58	−2	36	5.38
L	Frontal	Inferior	BA 47	−38	24	−12	5.50
L	Occipital	Cuneus	BA 18	0	−76	10	6.42
Lower activations at follow-up than after therapy							
R	Frontal	Medial Frontal	BA 6	10	0	56	6.61
L	Frontal	Medial Frontal	BA 6	0	−8	64	4.59
R	Frontal	Pre-central	BA 4	58	−10	30	6.49
R	Frontal	Pre-central	BA 6	54	−2	42	8.29
L	Frontal	Pre-central	BA 6	−52	−10	40	7.42
L	Sub-lobar	Insula	BA 13	−44	−12	10	7.68
L	Sub-lobar	Extra-nuclear	BA 13	−38	10	−10	6.05
L	Limbic	Cingulate	BA 24	−8	4	48	5.60
R	Limbic	Cingulate	BA 24	14	6	38	4.99
R	Temporal	Superior	BA 22	56	0	4	6.91
L	Temporal	Superior	BA 22	−48	4	0	4.78
R	Temporal	Superior	BA 38	52	14	−10	8.08
R	Temporal	Superior	BA 42	66	−34	18	6.05
L	Temporal	Transverse	BA 41	−54	−16	10	8.93
R	Temporal	Transverse	BA 41	52	−28	10	6.49
L	Sub-lobar	Lentiform nucleus	Putamen	−26	10	−2	5.73

Note. Where multiple foci were identified in a given region, only the one with the highest *t* value is shown.

5.2.2. Within-group comparisons of PWS before therapy versus after therapy versus follow-up

After collapsing the data acquired immediately after therapy and at follow-up, higher activations were observed in left frontal middle and inferior, as well as in cerebellar regions, than were found before therapy. Reduced activations from before therapy to the two-year follow-up assessment were detected in the left middle frontal gyrus and the left cerebellum. Compared to immediately after intensive therapy, follow-up assessments of PWS showed reduced activations in the left middle and inferior frontal cortices and in the left anterior cerebellum (Table 3).

5.3. Comparison of severe versus moderate stuttering participants

5.3.1. Overt reading

The seven persons who stuttered more severely did not activate any region more than the nine persons who stuttered moderately. On the contrary, persons

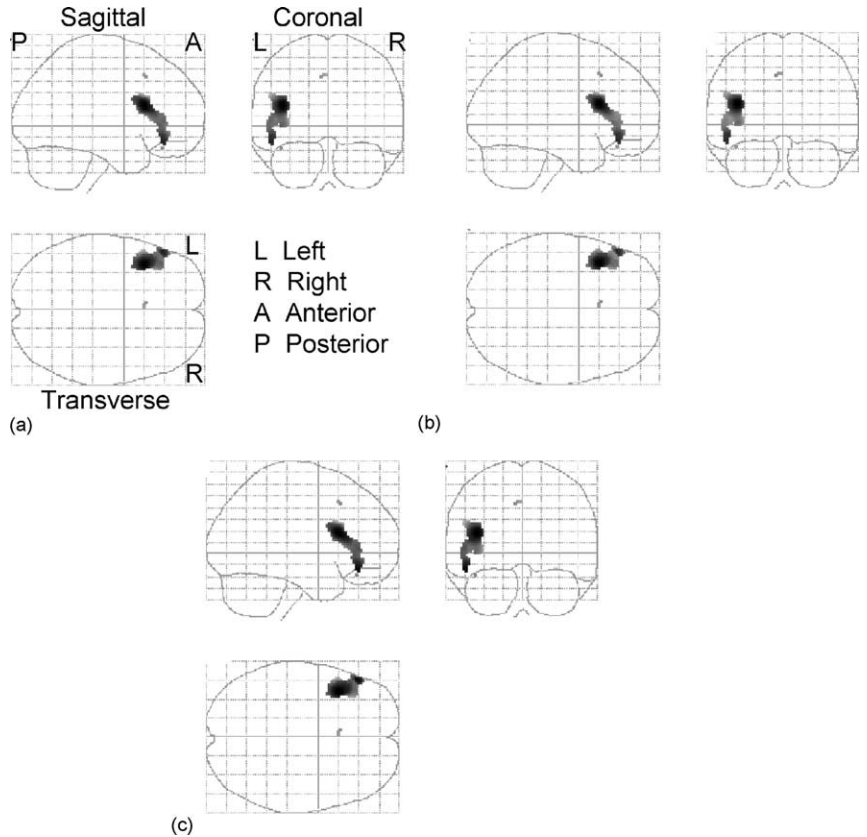

Fig. 5. Semantic decision: statistical parametrical maps of between-group comparisons (PWS vs. PWNS) for *lower* cerebral activation (a) before therapy, (b) after therapy, and (c) after two years of follow-up.

Table 3
Localizations of peak activations during semantic decision task for various comparisons

Side	Lobus	Gyrus	Brodman area	MNI			*t*
				x	*y*	*z*	
Between-group: PWS before therapy < PWNS							
L	Frontal	Inferior	BA 47	−52	34	−14	17.43
L	Sub-lobar	Insula	BA 13	−40	18	18	20.18
L	Limbic	Cingulate	BA 32	−6	20	44	10.67
Between-group: PWS after therapy < PWNS							
L	Frontal	Inferior	BA 47	−52	34	−14	16.81
L	Sub-lobar	Insula	BA 13	−40	18	18	19.95
L	Limbic	Cingulate	BA 32	−6	20	44	11.20
Between-group: PWS at follow-up < PWNS							
L	Frontal	Inferior	BA 45	−52	36	4	14.97
L	Frontal	Inferior	BA 47	−52	34	−14	19.37
L	Sub-lobar	Insula	BA 13	−40	18	18	20.63
L	Limbic	Cingulate	BA 32	−6	20	44	11.48
Between-group: PWS over all assessment times < PWNS							
L	Frontal	Inferior	BA 47	−52	34	−14	9.46
L	Sub-lobar	Insula	BA 13	−36	18	18	10.92
Between-group: PWS over all assessment times > PWNS							
L	Frontal	Middle	BA 8	−46	12	44	7.31
L	Frontal	Middle	BA 9	−52	14	36	5.57
L	Frontal	Inferior	BA 45	−48	22	6	5.82
L	Temporal	Fusiform	BA 37	−48	−64	−20	5.67
Within-group: PWS before therapy > follow-up							
L	Frontal	Middle	BA 6	−44	4	48	5.53
L	Cerebellum	Posterior	Declive	28	−76	−28	4.92
Within-group: PWS before < after therapy + follow-up							
L	Frontal	Middle	BA 8	−48	14	40	9.82
L	Frontal	Inferior	BA 47	−46	30	2	8.95
L	Cerebellum	Posterior	Declive	−46	−68	−18	6.75
Within-group: PWS at follow-up < after therapy							
L	Frontal	Middle	BA 6	−46	4	46	5.09
L	Frontal	Inferior	BA 45	−52	34	6	5.31
L	Cerebellum	Anterior	Culmen	28	−74	−28	4.66

Note. Where multiple foci were identified in a given region, only the one with the highest *t* value is shown.

who stuttered to a *lesser* extent exhibited *higher* activations, than did those who stuttered more severely, in bilateral superior frontal, pre-central, superior temporal, occipital, and brainstem regions, and in right inferior frontal, post-central, cingulate cortices, the right cerebellum, and the left medial frontal region (Fig. 6a, Table 4). The observation of right inferior frontal over-activations in moderately stuttering participants confirmed the negative correlation found between activation in the

Table 4
Localizations where persons who stutter less severely activate more than persons who stutter more severely

Side	Lobus	Gyrus	Brodman area	MNI			*t*
				x	*y*	*z*	
Overt reading							
L	Frontal	Medial	BA 6	−4	6	60	5.44
R	Frontal	Pre-central	BA 4	60	−6	30	5.89
R	Frontal	Pre-central	BA 6	50	0	30	23.72
L	Frontal	Pre-central	BA 6	−52	−2	28	20.53
R	Frontal	Superior	BA 6	10	6	58	7.07
L	Frontal	Superior	BA 6	−2	6	60	5.99
L	Frontal	Inferior	BA 45	−58	12	20	14.05
R	**Frontal**	**Inferior**	**BA 47**	**34**	**16**	**−16**	**7.53**
L	Sub-lobar	Insula	BA 13	−42	14	16	10.77
L	Sub-lobar	Insula	BA 22	−44	−30	0	11.67
R	Limbic	Cingulate	BA 24	8	4	46	5.20
R	Limbic	Cingulate	BA 32	10	18	44	5.00
R	Temporal	Superior	BA 22	50	−22	2	13.05
L	Temporal	Superior	BA 22	−62	−42	10	20.47
R	Temporal	Superior	BA 38	48	16	−18	6.56
L	Temporal	Superior	BA 38	−54	14	−8	11.46
L	Temporal	Superior	BA 41	−38	−30	6	16.56
R	Temporal	Superior	BA 42	64	−30	8	5.56
L	Temporal	Transverse	BA 42	−60	−12	6	5.29
L	Temporal	Middle	BA 21	−62	−46	10	19.21
R	Parietal	Post-central	BA 43	48	−8		4.58
R	Occipital	Cuneus	BA 17	12	−80	8	7.33
L	Occipital	Cuneus	BA 17	−2	−82	8	7.20
R	Brainstem	Midbrain	SN	8	−18	−8	8.78
L	Brainstem	Midbrain	SN	−10	−18	−10	8.94
R	Cerebellum	Posterior	Uvula	14	−72	−26	5.33
Semantic decision							
L	Frontal	Middle	BA 6	−42	10	48	10.81
L	Frontal	Inferior	BA 9	−54	22	22	5.98
L	Frontal	Inferior	BA 45	−50	38	4	4.55
L	Frontal	Inferior	BA 46	−48	38	8	5.85
L	Frontal	Inferior	BA 47	−54	20	−8	8.55
L	Sub-lobar	Insula	BA 13	−38	22	14	9.47
R	Occipital	Cuneus	BA 17	12	−84	4	5.27
R	Occipital	Lingual	BA 18	14	−82	−12	7.04
L	Occipital	Lingual	BA 18	−12	−90	−18	8.91
L	Cerebellum	Posterior	Tuber	−40	−72	−24	8.64
L	Cerebellum	Posterior	Uvula	−34	−82	−26	6.28

Note. Where multiple foci were identified in a given region, only the one with the highest *t* value is shown. Fat: right frontal operculum.

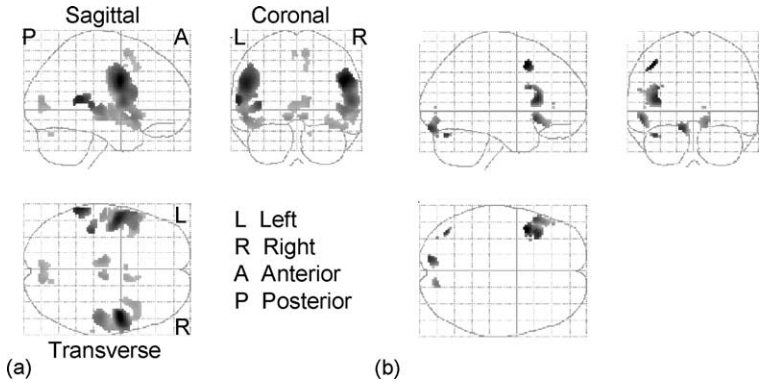

Fig. 6. Statistical parametrical maps of between-group comparisons of persons who stutter severely vs. persons who stutter moderately, both before therapy, for *lower* cerebral activation during (a) overt reading and (b) semantic decision making.

RFO and severity of stuttering that we reported in a previous study (Preibisch et al., 2003a).

5.3.2. Semantic decision

As was true during overt reading, there was no region in persons who stuttered severely that was activated more than that of persons who stuttered moderately. Once again, the participants who stuttered moderately had higher activations in the left middle and inferior frontal regions, the left insula, and in the bilateral visual cortex and cerebellum compared to those participants having more severe symptoms (see Fig. 6b and Table 4).

Overall, persons with moderate stuttering showed larger brain activations during both overt reading and semantic decisions compared to persons with more severe symptoms. Their over-activations were more widespread and more bilateral in the overt reading task than in the semantic decision task, and more left-sided in the latter, than in the speech production task.

6. Discussion

During overt reading, which requires motor planning and execution, widespread neuronal over-activations were detected in PWS when compared to PWNS. Before therapy, over-activations were located mainly in the right hemisphere and included pre-central sensorimotor, frontal motor, parietal, right temporal, and limbic regions as well as the right insula. Immediately after therapy, however, the over-activations were more widespread and distributed more bilaterally than before. Left-hemisphere over-activations especially involved frontal, temporal, and parietal regions. At follow-up assessment, the majority of over-activations had

shifted back to the right hemisphere, but still remained more widespread than before therapy.

The semantic task did not produce higher neuronal activation in PWS than in PWNS. Only after collapsing activation patterns over both post-treatment measures did within-group comparisons of PWS display higher activations than before therapy in left middle and inferior frontal and cerebellar regions.

These results confirm our previous observations on short-term therapy effects in a larger sample of nine PWS, which included five of the current subjects (Neumann et al., 2003). In that study, the untreated PWS showed more widespread activations in frontal and prefrontal cortices during overt reading than did PWNS. This overall effect was enhanced after therapy and shifted to more left-sided activation in frontal and temporal regions, the basal ganglia, and the ACC. In the semantic task of this study, higher neuronal activation in PWS than in PWNS was also not detected, but PWS showed higher activation after therapy in the inferior frontal cortex than before therapy. Our results are also consistent with those of others (Braun et al., 1997; De Nil & Kroll, 2001a, 2001b; Fox et al., 1996) who reported higher activations in PWS than in PWNS and left-sided increases in activation when speech became more fluent.

Furthermore, our findings during overt reading confirm our previous observations of higher RFO activation in untreated PWS compared to PWNS (Preibisch et al., 2003a). After therapy and at follow-up, such RFO activation was no longer detected, indicating that its hypothesized compensatory functions may have been assumed by other regions or have become unnecessary, presumably because of more efficient timing of speech production.

We detected regions of deactivations in PWS for both tasks, which remained remarkably stable from before to after therapy to two years later. These results support those of our previous study (Neumann et al., 2003), in which we detected stable deactivations immediately after therapy in the left pre-central and bilateral occipital regions during overt reading, and in the left inferior frontal and left cingulate regions during silent decision making. The stability of these deactivations has two implications. First, it indicates that our measurements were reliable, even over a period of two years and across different tasks. Moreover, because the PWS spoke slower and with different speech patterns immediately after therapy than before therapy and at follow-up, the results indicate that these behavioral changes had only a minor influence on their brain activations. This leads us to the second implication that the uniform deactivations observed might reflect these regions' dysfunction, whereas the task-specific and time-varying over-activations after therapy might reflect successful compensations in gaining speech motor control.

Our data differ from the findings of De Nil and Kroll (2001a, 2001b), who did not report any deactivations. However, several studies have reported deactivations of or deficient fiber connections in speech and language and auditory regions of PWS (Braun et al., 1997; De Nil & Bosshardt, 2001; De Nil et al., 2001; Fox et al., 1996; Fox et al., 2000; Ingham et al., 2000; Pool et al., 1991; Salmelin et al.,

1998; Sommer et al., 2002; Wu et al., 1995), which would be consistent with our findings.

What could deactivations of particular regions indicate? Deactivation in the right visual cortex can be attributed to visual processes not specifically related to stuttering. Deactivations of the insula in PWS have not been described before, to our knowledge. The anterior insula is involved in phonological planning (Dronkers, 1996), and one might speculate, therefore, that the occurrence of such deactivations depends on specific task demands of semantic decision, which may require some phonological planning that is deficient in PWS. In this case, deactivation of the insula during the present study's semantic decisions, together with the over-activations that were previously observed in the same region during reading immediately after therapy (Neumann et al., 2003), would suggest a functional rather than an anatomical dysfunction.

Left frontal inferior deactivation during semantic decisions might be related to the inappropriate involvement of this region in semantic processes. Lesion, neuroimaging, and neuropsychological studies indicate that this region (BA 47) is critically implicated in supramodal semantic and phonological processing (Poldrack et al., 1999). The left frontal pre-central deactivation detected during aloud reading in the present study and also in our study of short-term therapy effects (Neumann et al., 2003) implies that this region may have a direct influence on articulation (Preibisch et al., 2003a). Our data are consistent with the reports of an alteration in the white matter of the left pre-central cortex (Sommer et al., 2002) and support the theory that disturbed signal transmissions between Broca's area and left-sided articulatory motor representations may cause disturbed timing in speech-relevant areas of the brain in PWS. De Nil and Bosshardt (2001), who observed deactivation in the pre-central cortex of PWS during overt sentence production in a PET study, interpreted their findings as a sign of reduced automaticity. In this context, post-treatment increases in activity of the left pre-central cortex during overt reading that are adjacent to the regions of deactivation observed by Neumann et al. (2003) could be interpreted as compensatory efforts to gain motor control. Hypoactivation of the left pre-central region was also observed by Preibisch et al. (2003a), but this finding did not meet our criterion for consistency across all PWS.

Our current and recent data (Neumann et al., 2003) showed higher activations after than before therapy and predominantly during aloud reading. These over-activations were detected in frontal, temporal, limbic, and basal ganglia (putamen) regions. If over-activation patterns in PWS reflect compensation, as we assume, they should increase immediately after therapy and become more left sided. Indeed, we observed such an effect in auditory and frontal speech motor planning and execution areas, as well as in regions that are normally involved in more complex articulatory tasks, such as the ACC (Neumann et al., 2003), and higher timing demands (putamen) among PWNS. We assume that fluency-inducing techniques might reduce stuttering by providing an external "clock generator" and that such external pacing could use projections from peri-auditory areas to synchronize disturbed signal transmissions between auditory, speech motor planning, and motor

areas. A compensation for deficient synchronization is supported by data from previous studies (Fox et al., 1996; Salmelin et al., 1998; Sommer et al., 2002). In particular, the reversed sequence between premotor and motor preparation and articulatory planning, as was suggested by Salmelin et al. (2000), could be compensated for by paced speech serving as an external "clock generator." Indeed, our data suggest that deficiencies are not erased by therapy but are compensated for, or rendered partially nonfunctional, by artificial pacing.

Our within-group comparisons in this and a previous study (Neumann et al., 2003) observed higher cerebral activation directly after therapy during aloud reading. A similar but weaker tendency was also observed during semantic decision. In addition, moderate reductions in brain activation from immediately after therapy to follow-up assessment was observed, mainly in temporal, frontal, and limbic regions, the insula, and the putamen during aloud reading, and in left frontal and cerebellar regions during semantic decision making. Differences between reading and semantic decision making were related to the tasks, but we observed stable deactivations in each task over the whole span of observation and an overall tendency toward progressive decreases in activation from after therapy to follow-up. Such reductions during the maintenance program concur with the findings of De Nil and Kroll (2001a, 2001b), in which reduced brain activations were observed in several regions during the follow-up period. The shift of renewed activation of the right-hemisphere observed at follow-up, while maintaining the therapy-induced increased regional spread of activation, parallels objective measures of fluency of these subjects. This could be interpreted as indications of an incipient partial relapse or partial loss of left-hemisphere compensation mechanisms that were still higher than before therapy.

One of the more intriguing findings of this study was the larger activation in persons who stutter moderately than in those who stutter severely. This suggests that successful compensation mechanisms already exist in untreated PWS and supports previous findings (Preibisch et al., 2003a). We noted that the higher activations observed in the whole group of participants after therapy, irrespective of stuttering severity, mainly involved the same regions (frontal, temporal, parietal, limbic, and basal ganglia) that were over-activated in the persons who stuttered moderately. This seems to suggest that a unique neural network is recruited for compensation. This possibility is supported by a joint PET and behavioral study by De Nil and Bosshardt (2001) which indicated that speech planning and speaking of PWS involve similar neural systems but that different networks are recruited in controls.

It is critical to discuss the cognitive processes that were targeted by our subtraction design and whether there were additional behavioral biases not specific to PDS and therapy. The following points indicate that such influences were largely excluded from our study. (1) No relevant motion artifacts occurred during aloud readings. (2) Artificial speaking situations were avoided by the use of everyday sentences. (3) Disturbing emotional influences can largely be excluded because the PWS were alone in the scanning room and spoke without communicative demands.

(4) All PWS read fluently during scanning, which was facilitated by the masking effects of scanner noise. (5) Reaction time, which might account for brain activation differences between PWS and PWNS, is not expected to differ between these groups in silent verbal tasks (van Lieshout et al., 1996). (6) The fluency-aiding conditions inherent in the assessment process, such as auditory masking and segmentation of speech, were present during all assessment times, including prior to therapy. Activation changes, however, were shown to occur from before to after therapy and to follow-up. Therefore, the brain activation differences observed between and within groups can hardly be attributed to behavioral differences arising from motion artifacts, reaction time differences, emotional influences, or unnatural, demanding, fluency-aiding speaking situations during scanning. This argument is supported by the fact that analyses were restricted to common effects across all PWS, including completely fluent readers and the one having initial hesitations.

Although we believe that our findings were sufficiently specific and minimally biased by behavioral confounds, one remaining problem arises from the fact that the PWS spoke slower during their first recordings after therapy. Therefore differences observed immediately after therapy could reflect their slower speech. This effect, however, was transient, and their speech rates were higher at two-year follow-up assessments than before therapy. Comparison of before therapy to two-year follow-up assessments shows similar task-specific activation patterns as the comparison of before to immediately after therapy assessments. Thus, this indicates that behavioral effects cannot account for the observed activation differences. Moreover, because the patterns of deactivation are the same in all three groups, slowing speech did not have a significant influence on activation patterns.

7. Implications and further directions

Together, our findings suggest dysfunctions in left inferior frontal and pre-central regions, and task-related compensation mechanisms that work with a greater efficiency in persons who stutter moderately than in those who stutter severely. The compensation patterns we observed immediately after therapy were similar to those spontaneously at work in moderately stuttering participants. These patterns decreased slightly during the follow-up period, in parallel with increasing automatization of learned speech production patterns and a reduced emphasis on self-monitoring. The effects of therapy may be achieved by an optimized sequencing of speech processing steps. It seems to target speech motor planning and execution processes rather than cognitive–linguistic processes and recruits mostly the left hemisphere. Further studies should involve more PWS for testing long-term therapy effects to distinguish between participants who are able to maintain their fluency and those who are not. Future experiments should also exploit the high time resolution of fMRI for investigating the critical sequencing of single steps during speech processing.

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CONTINUING EDUCATION

The nature and treatment of stuttering as revealed by fMRI. A within- and between-group comparison

QUESTIONS

1. Higher severity of stuttering, compared to less severe stuttering:
   a. is associated with a more widespread brain activation
   b. is associated with a less widespread brain activation
   c. is a sign of a more disturbed hemisphere interaction
   d. does not affect brain activation
2. Fluency shaping therapies:
   a. are thought to synchronize a disturbed sequencing between several speech processing steps
   b. repair malfunctioning fiber tracts in the left sensorimotor cortex
   c. reduce over-activations in temporal regions
   d. achieve initial fluency mainly by chorus reading and masking noises
3. Long-term effects of fluency shaping therapies:
   a. are thought to reset a reversed processing sequence between initiation of motor programs and preparation of articulatory code
   b. indicate an increased emphasis on self-monitoring of articulation
   c. reduce tendentially higher brain activations observed immediately after therapy
   d. are attributed to a higher activation in the right frontal operculum
4. Immediately after a fluency shaping therapy:
   a. lower brain activations in tasks using overt speech are detected
   b. a compensation of deficiency takes place mainly by an ACC activation
   c. more left-hemispheric activations than before are observed
   d. more right-sided activations than before are observed, mainly in the right frontal operculum

5. Deactivations in neuroimaging in subjects who stutter:
   a. are thought to indicate a real dysfunction during speech processing
   b. are reversed into over-activations after a successful fluency shaping therapy
   c. are less widespread after a fluency shaping therapy
   d. are mainly observed in the right frontal and cerebellar regions