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Journal of Fluency Disorders 30 (2005) 23–39

FLUENCY DISORDERS

Cortical plasticity associated with stuttering therapy

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Received 14 May 2004; received in revised form 9 December 2004; accepted 20 December 2004

Abstract

Neuroimaging studies have indicated that persistent developmental stuttering (PDS) may be associated both with an abnormality in white matter of left-hemispheric speech areas and a right-hemispheric hyperactivity. The latter may compensate for the deficient structural connectivity in the left hemisphere. To investigate the effects of stuttering therapy on brain activity nine male adults with PDS underwent functional magnetic resonance imaging (fMRI) before and within 12 weeks after fluency shaping therapy. Brain response differences during overt sentence reading before and after therapy were assessed by utilizing random effects analyses. After therapy, a more widespread activation was observed in frontal speech and language regions and temporal areas of both hemispheres, particularly and more pronounced on the left side. Interestingly, distinct posttreatment left-sided activation increases were located directly adjacent to a recently detected area of white matter anomaly [M. Sommer, M.A. Koch, W. Paulus, C. Weiller, C. Büchel (2002). Disconnection of speech-relevant brain areas in persistent developmental stuttering. *The Lancet*, 360, 380–383] suggesting that fluency shaping techniques reorganize neuronal communication between left-sided speech motor planning, motor

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doi:10.1016/j.jfludis.2004.12.002

execution, and temporal areas. Hence, a therapeutic mechanism can be assumed to remodel brain circuitry close to the source of the dysfunction instead of reinforcing compensation via homologous contralateral brain networks.

Educational objectives: The reader will learn about and be able to: (1) describe brain activation changes detected shortly after fluency-shaping therapy; (2) identify left-hemispheric regions where a (re)functionalization after fluency-shaping therapy seems to occur adjacent to a recently described abnormal white matter region in PDS subjects; and (3) discuss how an effective cerebral compensation mechanism for stuttering could work.
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Keywords: Stuttering; Fluency shaping; fMRI; Therapy effects

1. Introduction

A recent magnetoencephalography (MEG) study has indicated that during speech production in persistent developmental stuttering (PDS) neuronal communication between the left sensorimotor cortex, inferior frontal speech regions (Broca's area), and temporal regions appears to be disturbed (Salmelin, Schnitzler, Schmitz, & Freund, 2000). The sequence of cortical activation during speech production was altered in this MEG experiment with PDS subjects when compared to nonstuttering speakers. Whereas the left inferior frontal cortex (articulatory programming) activated before the left motor cortex (motor preparation) in control subjects, this sequence was inverted in PDS subjects (Salmelin et al., 2000). One possible reason for an abnormal timing pattern could be a functional disconnection between the left sensorimotor and frontal (Broca's area) cortex.

This hypothesis is supported by observations from diffusion tensor imaging (DTI). DTI exploits the effect that the random diffusion-driven displacement of molecules in tissues, in particular of water molecules, may be anisotropic. Because molecular diffusion is a truly three-dimensional process (Brownian motion), mobility of molecules in tissues may not be the same in all directions. This anisotropy may result from a peculiar physical arrangement of the medium or the presence of obstacles that limit molecular movement in some directions. Hence, DTI enables fiber tracking in the white matter of the brain by exploiting diffusion anisotropy effects, providing details on tissue microstructure beyond the usual imaging resolution (Le Bihan et al., 2001). With DTI a decreased fractional anisotropy of diffusion in white matter has been detected in PDS subjects compared with control subjects, indicating an area of decreased white matter tract coherence or decreased myelination below the left sensorimotor representation of tongue and larynx (Sommer, Koch, Paulus, Weiller, & Büchel, 2002). Although functional irregularities cannot be derived with certainty from anatomical differences, and although the findings in question need to be replicated, structural abnormalities may possibly parallel functional deviations in stuttering. This tentative conclusion is also suggested by another anatomical study using high-resolution MRI (Foundas, Bollich, Corey, Hurley, & Heilman, 2001). In addition to abnormalities of size and asymmetry in the planum temporale, the latter study showed abnormal gyrification patterns

in PDS subjects in frontal and perisylvian speech and language regions. Considering that gyrification is a complex developmental procedure, these findings indicate a developmental disorder (Büchel & Sommer, 2004).

In terms of functional neuroanatomy PDS is characterized by an abnormal recruitment of right-sided cortical regions during speech preparation and production (Blomgren, Nagarajan, Lee, Li, & Alvord, 2003; Braun et al., 1997; De Nil, Kroll, Kapur, & Houle, 2000; Fox et al., 1996, 2000; Ingham et al., 2004). We recently observed with functional magnetic resonance imaging (fMRI) a systematic overactivation of the right frontal operculum (RFO) in PDS subjects compared to control subjects during fluent reading and silent semantic decision making (Preibisch, Neumann, et al., 2003). Because the level of activation in this region correlated negatively with the severity of stuttering, we concluded that the right frontal cortex participates in a spontaneous compensation mechanism. Our observation corroborates other neuroimaging studies in male right-handed PDS subjects showing that overactivations in motor planning and execution areas, which are located predominantly in the right hemisphere, accompany left-hemispheric or bilateral deactivations, for instance in auditory and motor planning and execution areas (Braun et al., 1997; De Nil & Kroll, 2001; Fox et al., 1996; Ingham, Ingham, Finn, & Fox, 2003; Fox et al., 2000; Ingham et al., 2004), and that fluency-inducing maneuvers reduce the predominantly right-hemispheric motor-system overactivations and left temporal deactivations (Fox et al., 1996, 2000; Ingham et al., 2003, 2004).

Stuttering can be treated by fluency-shaping therapies which effectively and durably replace the chronic stuttered speech pattern with a newly learned prolonged and rhythmic fluent speech (Webster, 1974). Although the effectiveness of these therapies has been proven at a behavioral level (J.C. Ingham, 1993), their effects on altering brain circuitry are still unclear. Theoretically, they may either (1) increase the efficiency of the right-sided compensatory mechanisms that are spontaneously recruited by untreated PDS people, or (2) induce new neural mechanisms that are not normally involved in speech production, or (3) restore mechanisms similar to those in normal functioning.

Previous EEG studies have indicated a shift in brain activity to left hemispheric brain regions after stuttering-reducing therapies (Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983; Moore, 1984). With positron emission tomography (PET), a left-sided increase of motor and superior temporal activation during overt reading was found after fluency-shaping therapy, which has been interpreted as an increased emphasis placed on the continuous self-monitoring of articulatory speech movements while the sequencing of articulatory, phonatory, and respiratory movements is optimized and speech is controlled actively for an effective use of the acquired speech patterns (De Nil & Kroll, 2001; De Nil, Kroll, Lafaille, & Houle, 2003). These authors also reported a higher activation in the anterior cingulate cortex in untreated PDS subjects compared to nonstuttering subjects during silent reading, which was reduced after therapy, and interpreted their findings as possible anticipation of stuttering which might be reduced after therapy. A higher cerebellar activation in subjects with PDS during oral reading, in particular after therapy, was related to an increased speech motor control (De Nil et al., 2003).

Recently, our group published preliminary results of a within- and between-group fMRI study about short-term and long-term effects of a fluency-shaping therapy on brain activation. The results were obtained with a fixed effects analysis of five subjects included

also in the study presented here (Neumann et al., 2003). During overt reading and before fluency-shaping therapy, PDS subjects showed larger and more distributed neuronal activation than nonstuttering subjects, located bilaterally in the premotor and motor cortex but predominantly in the right hemisphere. Immediately after therapy, activations were even more distributed, namely in frontal, temporal, and parietal regions, in the anterior cingulate, the insula, and the putamen, and were more left-sided. These overactivations were slightly reduced and again more right-sided two years after therapy when the mean stuttering rate had again slightly increased. Left precentral deactivations remained stable over two years of observation and therefore possibly indicate an intractable dysfunction. Larger right- and left-sided activations were detected in persons who stutter moderately than in persons who stutter severely (Neumann et al., 2003).

Together, these findings suggest that for people with PDS abnormal left-hemispheric neuronal communication yields spontaneous recruitment of the right hemisphere, in particular of the right homologue of Broca's area, but also that this process compensates only imperfectly for the impaired function. It seems that a more efficient compensation permitting greater accuracy of timing processes in speech production, as it could be gained by a more precise signal transmission between the left sensorimotor cortex, frontal speech regions, and temporal regions, requires a (re)functionalized left-sided network.

For the study reported here the data of short-term therapy effects (Neumann et al., 2003) were re-analyzed with a larger sample of PDS subjects and a more conservative and thus less sensitive random effects analysis, in order to provide evidence for the hypothesis that fluency-shaping therapy enhances compensation by shifting brain activity from circuits in the right to circuits in the left hemisphere and thus closer to the PDS-specific anatomical alterations.

2. Methods

2.1. Participants

Nine male adults with PDS (mean age 32 years, range 24–41) underwent fMRI before and no later than 12 weeks after an intensive course of a fluency-shaping therapy. Six of the nine PDS subjects had a handedness Laterality Quotient (LQ) of 100 according to the Edinburgh Handedness Inventory (Oldfield, 1971). The remaining three persons had LQs of 87, 83, and −64. All volunteers were native German speakers and gave written informed consent for participation. The medical examination of the participants and the diagnosis of stuttering were performed by a phoniatrician and a certified logopedist. None of the participants had relevant neurological, audiological, or other medical problems, drug abuse or any developmental or acquired speech or language difficulties other than stuttering. None of the PDS subjects had ever received fluency treatment before. None spoke with less than 3% stuttered syllables before therapy. The percentage of stuttered syllables had been assessed in four different speaking situations (talking with a therapist, overt reading, calling an unknown person on the telephone, and interviewing a passer-by), as reported in Euler and Wolff von Gudenberg (2000).

2.2. The Kassel stuttering therapy

The Kassel stuttering therapy (KST) is a modified version of the Precision Fluency Shaping Program (Webster, 1974). It consists of an intensive three-week in-patient treatment and a structured one- to two-year maintenance program. The main modification is the use of a computer program which provides biofeedback for syllable prolongation, soft voice onset, and smooth sound transitions (speak:gentle®, Bioservices Software, Munich, Germany). Details of the treatment and its short- and long-term effects on objective and subjective fluency measures, as well as quality criteria of the objective fluency measures, are described elsewhere (Euler & Wolff von Gudenberg, 2000). The overall (as opposed to point-to-point) interrater agreement was very high; the signed place-to-place agreement was 79%. The corrected split-half reliability ranged between $r = .83$ (telephone) and $r = .99$ (interviewing a passer-by). Cronbach alphas for the four measures were .84 before therapy and .79 after therapy (Euler & Wolff von Gudenberg, 2000).

Stuttering severity is defined in the KST as the percentage of stuttered syllables in the four different speaking situations named above. The mean stuttering rate of our nine study participants was 9.9% before therapy (range 4.1–20.2%) and 0.9 after therapy (range 0.7–3.1%). All subjects had reduced stuttering severity to 20% or less of their pretreatment level (median reduction to 6.5% of pretreatment stutter level). From pretherapy to post-therapy the mean speech naturalness, rated on a 9-point scale (1 = highly natural, 9 = highly unnatural) (Martin, Haroldson, & Triden, 1984) by an independent observer in the speech clinic, decreased from 5.4 (range 2–9) to 2.4 (range 1–4.5). Mean speech production rate, respectively, increased from 167 syllables per minute (range 13–242) to 181 syllables per minute (range 140–226).

2.3. Procedure

2.3.1. Data acquisition

Imaging was performed on a 1.5 T Siemens Vision Scanner (Siemens, Erlangen, Germany) using gradient echo EPI sequences (echo time 50 ms, repetition time 3 s, voxel size 3.6 mm × 3.6 mm × 6 mm, 18 slices, inter-slice gap 0.6 mm, field of view 230 mm, slice thickness 5 mm). The participants watched a screen via a mirror mounted onto the head coil and performed an overt sentence reading task.

2.3.2. Reading task

For this task an event-related design was used that permits an effective suppression of artifacts due to overt speech production by temporally separating motion-related signal fluctuations from the task-related brain activation (Preibisch, Raab, et al., 2003). The participants read aloud 78 short sentences which were phonetically balanced, that is representative for the German language. Their speech was mostly fluent during this task. Passive viewing of letter-like meaningless signs of comparable structure and length served as a control condition. Both conditions were interleaved serially, and the visual stimuli were presented for 3 s each with a fixed interstimulus interval of 15.5 s. The 3 s duration of overt sentence reading allowed for natural speaking conditions and left most of the hemodynamically delayed response unaffected by motion artifacts. The combination of repetition

time and interstimulus interval yielded an effective sampling of the fMRI response of one datapoint per half second.

Before therapy, the PDS subjects managed to read the entire sentence within the 3 s or stopped reading as soon as the text presentation ended (6 ± 2 words per 3-s reading interval). The speech within the MRI scanner was monitored by the microphone built in the scanner. Eight PDS subjects were largely fluent during reading, both before and after therapy, that is they spoke with less than 1% stuttered syllables. One subject showed initial blocks which, however, did not markedly influence the speech rate. Speech performance during scanning benefited from two conditions which aid fluency—the loud masking scanner noise and the segmentation of speech into short utterances with pauses in between (R.J. Ingham, 1984). After therapy the PDS subjects were requested to read using the newly acquired speaking technique. In order to hold the emotional and behavioral conditions as constant as possible the participants were instructed to speak in a comfortable manner, such that speech effort and concentration were comparable during the fMRI sessions before and after therapy. Seven of the nine participants spoke more slowly (2 ± 1 words per 3-s reading interval) than before therapy. This slowed-down speech only occurred under scanning conditions, but not under natural speaking conditions outside of the laboratory.

Motion due to overt speech in the reading task did not exceed 3 mm in either *x*, *y*, or *z* direction, and angular deviations remained within 3°. The absence of artifactual activation due to motion was visually checked in all participants.

2.3.3. Statistics

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. The general linear model was employed to create statistical parametric maps of *t*-values (SPM(*t*)) for all single subjects before and after therapy. In these single subject subtraction analyses signal intensity during reading was compared to that during passive viewing of letter-like meaningless signs to determine brain regions for each subject that were significantly activated above that baseline. In order to obtain generalizable results, the single subject activation maps were then fed into a second level random effects analysis (paired *t*-tests) to determine differences in activation before and after therapy. The data reported here have not been corrected for multiple comparisons. However, uncorrected thresholds are accepted in case of a hypothesis driven data screening, which we considered to be the case here. Therefore, the standard reasoning in case of region of interest analyses were applied (Nieto-Castanon, Ghosh, Tourville, & Guenther, 2003).

3. Results

Higher activation before therapy than after therapy in the within-group comparison was only observed in the right middle frontal cortex. After therapy, increases in activation were detected in the left inferior frontal cortex, the left insula and anterior cingulate, the left

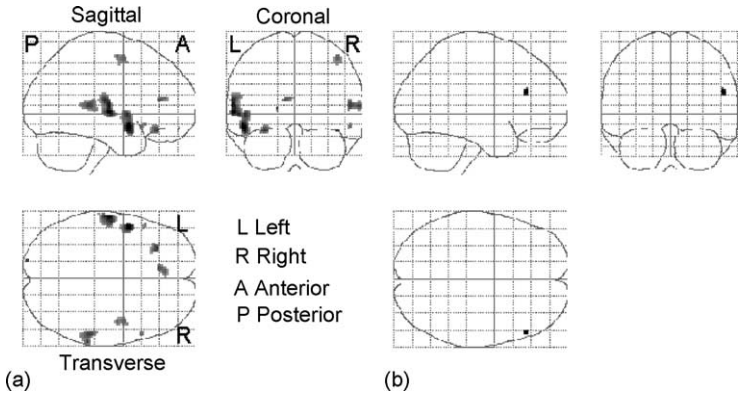

Fig. 1. Differential activation in PDS subjects before and after therapy during overt reading: (a) higher activation after therapy; (b) higher activation before therapy. Random effects analysis, paired *t*-test, $p < 0.001$ uncorrected.

superior and transverse temporal gyrus, as well as in the right middle frontal and superior temporal gyrus (see Fig. 1 and Table 1). Thus, after therapy more extended activations were observed than before, predominantly left-sided and bilateral temporal. Most interestingly, areas with increased activation after therapy were seen in the left insula (−46 2 2) and the

Table 1
Differential activation before and after therapy in PDS subjects during overt reading

Anatomical region, Brodmann area	MNI			*T*	Cluster size
	x	*y*	*z*		
Higher activation after therapy					
R middle frontal, BA 6	42	0	56	5.57	44
L anterior cingulate, BA 32	−10	36	14	5.90	31
L inferior frontal, BA 11	−30	34	−16	6.35	33
L inferior frontal, BA 47	−54	22	−10	5.25	4
L insula[a]	**−46**	**2**	**2**	**4.92**	**170**
L rolandic operculum[a]	**−62**	**−18**	**14**	**6.69**	**178**
R superior temporal, BA 22	64	−36	8	6.25	107
	56	−34	8	6.27	107
L superior temporal, BA 22	−50	4	−2	6.54	170
	−62	−14	2	7.67	178
L middle temporal, BA 21	−52	4	−12	9.82	170
R superior temporal, BA 38	56	18	−12	5.32	5
R superior temporal, BA 41	54	−30	12	5.33	107
Lower activation after therapy					
R middle frontal, BA 46	54	30	22	6.21	12

Localization of suprathreshold peak activation (anatomical region and *x*, *y*, and *z* coordinates), with associated *t*-values: random effects analysis (paired *t*-test), $p < 0.001$, uncorrected. MNI: Montreal Neurological Institute template.

[a] Bold type: Activation in the vicinity of the recently detected area of decreased white matter anisotropy (Sommer et al., 2002).

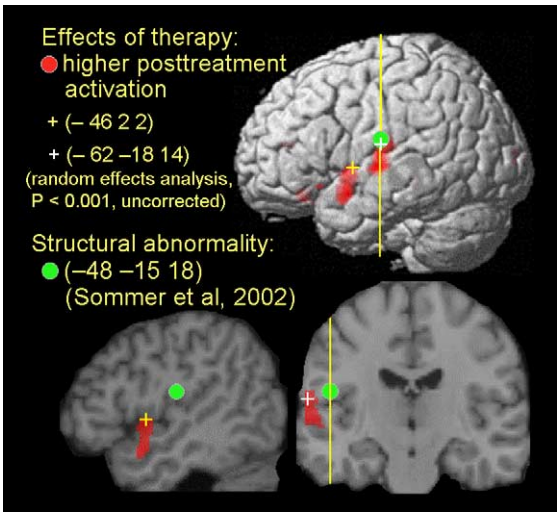

Fig. 2. Left hemispheric increase of activation (random effects analysis at $p < 0.001$, uncorrected) after therapy (dark blotches). Some of them are located in the direct vicinity of the recently detected structural abnormality (light point). Vertical lines indicate the respective positions of the depicted coronal and sagittal slice.

left Rolandic operculum (−62 −18 14), in the direct vicinity of the area where a decreased white matter anisotropy (−48 −15 18) was recently detected (see Fig. 2) (Sommer et al., 2002). Another conspicuous finding was the posttreatment higher activation in bilateral temporal regions.

4. Discussion

In this study we sought to find evidence that the right-hemispheric overactivations observed in male right-handed PDS subjects are expressions for a compensation mechanism which acts already spontaneously, albeit less effectively than with therapy, and that an enhanced compensation after a successful fluency-shaping therapy shifts brain activity from right-hemispheric circuits to left hemispheric ones and thus closer to the PDS-specific anatomical alterations. Indeed, our results showed that such a shift occurred within twelve weeks after an intensive fluency-shaping therapy course. Most of the posttreatment activation increases have been found in left-sided speech related regions like frontal and temporal areas, the insula, and the anterior cingulate cortex. Additionally, the more widespread posttreatment activation supports the hypothesis of a higher degree of compensation after a successful therapy.

One of the most interesting points is, however, that posttreatment activation increased in the insula and the Rolandic operculum in close vicinity to regions in which white matter alterations in PDS subjects have been detected by other researchers (Sommer et al., 2002). It is a long-standing question in clinical neuroscience whether plasticity after a cortical lesion relies on neighbouring areas or on regions distant from the lesion (Nudo, 2003). Because

PDS may be associated both with a left-sided white matter abnormality and a right-sided hyperactivity, the structural abnormality might play a causal role in the syndrome (initial lesion) and the functional abnormality a compensatory role. PDS would hence be a case of neuronal reorganization, with compensation of a functional deficit from disturbed prefronto-motor connectivity by remote contralateral networks. Our recent demonstration that the right frontal operculum is overactivated in persons with PDS, with the largest magnitude in PDS subjects who compensated best, supports such a compensatory role of right frontal activity in PDS (Preibisch, Neumann, et al., 2003). However, as all the participants of that study were dysfluent adults, we may also assume that large-scale spontaneous compensation only imperfectly takes over the impaired function.

To understand why functional success from spontaneous large-scale compensation in untreated PDS subjects remains limited, it would be of interest to analyse the cortical activations in spontaneously recovered PDS subjects (Ingham et al., 2003). This would enable one to determine whether the therapy works by enhancing the effectiveness of the existing compensation mechanisms, or whether it shifts compensation to pathways in other brain regions. Theoretically, such a shift of "rescue" activity to other brain regions could either involve new regions that do not normally participate in speech production, or (re)implicate regions that are close to those initially impaired.

By showing increased activity in left fronto-temporal speech and auditory regions, our study confirmed previous PET studies (De Nil & Kroll, 2001; Fox et al., 1996, 2000; Ingham et al., 2003, 2004). More interestingly, we observed that after therapy two activation foci appeared, one in the Rolandic operculum, that is, the upper bank of the left Sylvian fissure hosting the sensorimotor region of the mouth and pharynx, and the other in the insula. These foci were located within a centimeter from the regions indicated by Sommer et al. as the site of decreased white matter tract coherence in PDS (Fig. 2) (Sommer et al., 2002). This effect of posttreatment higher activation adjacent to this disturbed left precentral region was observed also two years after therapy (Neumann et al., 2003). Although both studies need replication, the results of the present study are compatible with those of Sommer et al. (2002). They are also compatible with the findings of Foundas et al. (2001) about aberrant gyral pattern along the upper bank of the Sylvian fissure in PDS subjects.

Several authors reported deactivations in the auditory processing system during stuttering (Braun et al., 1997; Fox et al., 1996; Ingham, Fox, Ingham, & Zamarripa, 2000). One of the most conspicuous patterns after therapy in the study reported here was a bilateral increase in temporal activation, suggesting a (re)functionalization of those regions. This observation concurs with the report that fluency-inducing maneuvers increase temporal activations (Fox et al., 1996), and it strengthens the assumptions that temporal regions are part of a cortical and subcortical fluency-generating system (Pool, Devous, Freeman, Watson, & Finitzo, 1991) and are implicated in an auditory-articulatory loop of the working memory (Jancke, Shah, Posse, Grosse-Ryuken, & Muller-Gartner, 1998). The importance of alterations in the temporal system in PDS is underlined by the structural findings of Foundas et al. (2001) of a larger planum temporale and a reduced planar asymmetry in PDS subjects, and those of Sommer et al. (2002) who indicated that the immediate surrounding region of that with reduced anisotropy included the inferior arcuate fascicle linking temporal and frontal language areas.

It is important to note how the activations and deactivations of PDS subjects following treatment compare to those of nonstuttering subjects performing the same task. Only this comparison enables to judge whether the posttreatment brain activation changes of PDS subjects compared to nonstuttering people represent 'normalization', or whether a functionalization is derived from the acquisition of new connectivities. Therefore, in a previous study a control group of 16 nonstuttering male subjects with comparable age and handedness was compared to the current group of 9 PDS subjects by means of a fixed effects analysis (Neumann, Euler, Preibisch, & Wolff von Gudenberg, in press).[1] Because fixed effects analyses might be biased by extraordinary strong activations in single subjects, results cannot be generalized to the population of stutterers. Therefore, a random effects analysis (Friston, Holmes, & Worsley, 1999; Holmes & Friston, 1998) was used to analyse the influence of therapy in the sample of PDS subjects. Because the overactivations of PDS subjects as compared to control subjects before and after therapy largely resembled the results of the fixed effects analysis (Neumann et al., in press), for the sake of clarity we concentrated on the results of the within group comparison before and after therapy in this study.

However, to deal with the issue of normalization of deficient networks versus functionalization of new neural networks, some of the results of the between group comparisons ought to be considered. Before therapy the PDS subjects showed in the fixed as well as in the random effects analysis a more distributed neuronal activation than nonstuttering control subjects in the right frontal cortex (precentral, superior, and inferior). On the other hand, the left hemispheric activation is inconsistent and thus less reliable, with overactivation in the left middle and inferior frontal cortex in the fixed effects analysis, and in the left superior frontal cortex in the random effects analysis. After therapy the overactivation in PDS subjects was in both analyses even more widespread and especially more left-sided than before therapy. In the fixed effects analysis this higher activation was located in additional left frontal (middle and precentral) and bilateral temporal regions (bilateral superior and left transverse temporal gyrus) as well as in the left anterior cingulate cortex and putamen. Overactivation as revealed by the random effects analysis also comprised left frontal (precental and inferior) as well as bilateral temporal (middle and superior) cortical regions. In the fixed effects analysis, areas with lower activations in PDS subjects than in nonstuttering control subjects (left precentral and bilateral occipital regions) remained totally unaffected by therapy. However, the random effects analysis did not reproduce the persistent left precentral deactivation which in the fixed effects analysis was most likely due to strong effects in single subjects. Thus, this effect cannot necessarily be regarded as a typical feature of stuttering.

In the fixed effects within-group comparison the PDS subjects activated after therapy more than before therapy in the left frontal (precentral and medial frontal gyrus), the right (superior temporal gyrus) as well as left temporal lobe (superior and transverse temporal gyrus), and in the left anterior cingulate cortex and putamen. The following comparison between the results of the fixed effects analysis and those of the

[1] Because among PDS people there is a larger part of left-handed or at least not clear right-handed people compared with nonstuttering people we left the one left-handed subject in the analysis but included two left-handed nonstuttering control subjects (out of 16) in the fixed effects analysis.

random effects analysis has to be interpreted with caution because both analyses are only partly comparable. The fixed effects analysis may be dominated by particularly strong activations in single subjects while the random effects analysis might miss activations which show high variability across subjects. Because a bilateral temporal overactivation has been detected after therapy in both the within-group and between-group comparison and both types of statistical analysis, these might be considered as particularly reliable and possibly indicate that new neuronal connections in PDS subjects in these regions may be recruited after therapy. This process may be paralleled by the improvement of a disturbed auditory self-monitoring which is frequently assumed in PDS subjects. Additionally, however, a kind of normalization may have taken place in the light of temporal deactivations in PDS subjects (Braun et al., 1997; Fox et al., 1996; Ingham et al., 2000).

While a posttreatment increase of activation in left inferior frontal regions was only detected with the random effects analysis, and might thus be considered as being less reliable, the increase in the left insula and the left Rolandic Operculum was detected with both the random and the fixed effects analysis. These activation increases seem to reflect again both a kind of normalization, because the activation is located in left-hemispheric regions normally involved in speech production, and a new acquisition of left-hemispheric networks. These new networks exceed a plain 'normalization' of speech functions in PDS subjects because the activations are more widespread than in nonstuttering people, do not involve exactly the same regions, and are positioned adjacent to left-hemispheric structural abnormalities (Foundas et al., 2001; Sommer et al., 2002). Additionally, the remaining right frontal overactivations after therapy indicate that the posttreatment state recruits more than the normal speech and language brain regions. In sum, there are indications for a kind of normalization of speech and language regions, and in addition the recruitment of new neuronal networks in the vicinity of the regions with structural deficits.

The statistical power of a random effects analysis is low with a sample as small as the one used here. It is therefore possible that some activations were missed. This might explain the difference between the results reported here and those obtained with a previous fixed effects analysis (Neumann et al., in press). However, we accept this loss in sensitivity to ensure that the results of the analysis are not biased by strong atypical activations of single subjects.

The interpretation of the pretreatment to posttreatment fMRI activation changes as genuine therapy effects has to be done under consideration of the following arguments. (1) Because PDS subjects were generally fluent during reading under fMRI conditions, even before therapy (fluency induced by noise and speech segmentation), posttreatment performance and thus treatment effects cannot be explained by the mere disappearance of dysfluency. (2) Although stuttering therapy resulted in overall increased speech rate, we observed a comparatively slower speech rate under scanning conditions, possibly due to the fact that the volunteers tried to speak well after therapy. However, a pretreatment/posttreatment comparison in the same subjects should reflect the impact of therapy even if the speech within the scanner may not be a valid sample of speech under natural conditions. (3) Posttreatment neuroimaging effects may result from the transient slowdown of speech because by the induction of a more rhythmic and prolonged output, therapy could reduce the

demands imposed on the speech-motor system (Packman, Onslow, Richard, & van Doorn, 1996). Two arguments, however, contradict the possibility that speech slowdown solely accounts for the effects: (a) Motor cortex regions usually show more activity when speech rate increases (Wildgruber, Ackermann, & Grodd, 2001). To the contrary, decreasing speech rate is unlikely to produce more activation in the sensory-motor region, which would counteract the observed effects of higher posttreatment speech motor activation. (b) The activations immediately after therapy reported here were largely maintained two years after treatment when speech rate was on average higher than before therapy (Neumann et al., 2003).

The results reported earlier (Neumann et al., 2003) are based on a fixed effects statistical analysis which only included a subgroup of five of the total of nine subjects involved in the complete study. Moreover, the results presented here were obtained by means of a random effects analysis which takes into account the intersubject variability, and therefore allows inferences about the general population. Thus, the overactivations after therapy are more circumscribed because of the more restrictive statistical analysis, but are also more reliable. It is possible that fluent paced speech per se restores some functionality in circuits that were disturbed by or during dysfluencies. Therefore, restoring fluency should normalize the activations in these regions and in the long run produce stabilized reorganization, as demonstrated in the treated PDS subjects we re-examined after two years (Neumann et al., 2003). Restoring left motor activation should be associated with an improved communication between Broca's area, the speech motor cortex, and auditory regions, and should thus correct the chronological order in the steps leading to speech production. Although this interpretation needs to be confirmed with more data, it is supported by the findings of Neumann et al. (2003) with a fixed effects analysis, where posttreatment overactivations immediately after therapy and two years later included bilateral frontal speech motor, parietal, and auditory regions, as well as by those of the present study with the random effects analysis, where the posttreatment overactivations covered also bilateral frontal speech motor and auditory regions.

Our data suggest that therapy mobilized neural substrate in close vicinity of the regions for which indications have been reported to be initially functionally impaired by an alteration of their connectivity (Sommer et al., 2002). Because we additionally observed decreased activity in the right frontal cortex, a possible conclusion is that fluency-shaping therapy shifted the neural mechanisms recruited for compensation from the right to the left frontal cortex, that is, to regions that are physiologically recruited in non-stuttering subjects. However, the possibility that decreases in right hemisphere 'overactivation' may allow for 'normalized', that is increased left hemisphere activations due to decreased right hemisphere 'interference', cannot be ruled out. Nevertheless, in post-stroke recovery, 'normal-like' brain activations indicate good functional recovery whereas more activations outside the networks involved in control subjects signal poor outcome (Ward, Brown, Thompson, & Frackowiak, 2003). This observation implies that the functional takeover by cortical regions that do not normally participate in the impaired process is limited and bound to be insufficient. The same principle seems to apply to stuttering. Because in stroke the outcome and hence the scale of reorganization is in general predicted by the size of the cortical damage (Ward et al., 2003), a critical question for PDS is why reorganization in the case of focal cerebral alteration does not

occur spontaneously, that is without explicit therapy, in the vicinity but outside of the affected areas where neural tissue seems to remain recruitable for compensation. This question will be addressed in further studies by investigating untreated former stutterers.

Because we sought to demonstrate changes in brain activation due to therapy as a function of time, we had to assure comparable baseline conditions across both recordings. We assume that our results are reliable and therapy specific because the subjects were mostly fluent during reading. Disturbing emotions which could have caused secondary stuttering symptoms were unlikely because the sentences to be read were everyday utterances, and the participants were alone in the scanning room and spoke with only little communicative demands. Furthermore, the previous fixed effects results obtained from a subgroup demonstrated that regions of deactivations with respect to control remained stable at all three assessment times over a span of more than two years (Neumann et al., 2003). Therefore, disturbing behavioral influences are not very probable.

As noted already above, functional irregularities cannot be derived with certainty from anatomical differences. For instance, children with neurofibromatosis may exhibit possible widespread myelinization differences in MRI without any substantial behavioral consequences. Apart from an unlikely observation of a complete absence of a connection between typically functionally related areas, a nonfunctional assessment of brain anatomy, such as DTI, cannot differentiate whether particular cortical or subcortical connections are actually functionally disturbed or adequate (M. Blomgren, personal communication, June, 2004). Therefore, to find out whether structural abnormalities really parallel functional deviations in stuttering, our future research will focus on simultaneously recorded functional and anatomical data in PDS subjects.

5. Implications and further directions

In sum, the success of fluency shaping stuttering therapy may be related to the effectiveness in mobilizing well-functioning cortical substrate located in the vicinity of functionally impaired neural tissue. The posttreatment fMRI activation changes are assumed to reflect specific therapy effects, possibly cortical reorganization, rather than a mere consequence of a change in performance. This assumption does not exclude the possibility that with a relapse, the cerebral activations might return to their pretreatment pattern. Further research ought to address this point.

Acknowledgements

The authors are grateful to the subjects who participated in this study, to Klaus-Peter Ulbrich for providing phonetically balanced sentences, and to Andreas Kleinschmidt for his helpful comments on earlier versions of our manuscript. Anne-Lise Giraud is supported by the German Ministry of Education and Research (BMBF).

CONTINUING EDUCATION

Cortical plasticity associated with stuttering therapy

QUESTIONS

1. Spontaneous compensation mechanisms for stuttering in terms of brain activation can be indicated by:
   a. an involvement of widespread bilateral temporal activation
   b. reduced left hemispheric brain activation when the speech becomes more fluent
   c. increased activation of left-sided speech motor regions compared with nonstuttering subjects
   d. an association of less severe stuttering with a more widespread brain activation
2. Successful cortical reorganization is generally:
   a. indicated by recovered brain functions adjacent to the damaged areas
   b. indicated by the involvement of regions outside the networks used normally
   c. independent of the size of a damage
   d. paralleled by the repair of the damaged region
3. A successful fluency-inducing stuttering therapy may:
   a. increase the efficiency of the right-sided compensatory mechanisms that are spontaneously recruited by untreated PDS subjects
   b. induce new neural mechanisms that are not normally involved in speech production
   c. restore mechanisms similar to those in normal functioning
   d. decrease the activity of temporal speech and language regions
4. Immediately after a fluency-shaping therapy:
   a. a higher activation than before therapy has been detected in the right frontal operculum
   b. a decreased activity of left-sided speech regions like inferior frontal cortex and insula occurred
   c. left-hemispheric activations occurred adjacent to a region where abnormalities in white matter of PDS subjects have been detected
   d. a decrease in general cerebral activation during a speech motor task has been detected
5. Neuroanatomical and neuroimaging findings in PDS subjects showed:
   a. an abnormal gyrification
   b. a reversed sequence of the motor programming of different articulators like tongue and larynx
   c. an increased fractional anisotropy of diffusion below the left sensorimotor representation of tongue and larynx
   d. higher activations in left-hemispheric speech and language regions than in nonstuttering subjects

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