

Right rolandic activation during speech perception in stutterers: a MEG study

Katja Biermann-Ruben,^{a,*} Riitta Salmelin,^b and Alfons Schnitzler^a

^aDepartment of Neurology, MEG Laboratory, University of Duesseldorf, Germany

^bBrain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, Finland

Received 17 May 2004; revised 9 August 2004; accepted 19 November 2004

Available online 10 February 2005

The focus of our magnetoencephalographic (MEG) study was to obtain further insight into the neuronal organization of language processing in stutterers. We recorded neuronal activity of 10 male developmental stutterers and 10 male controls, while they listened to pure tones, to words in order to repeat them, and to sentences in order to either repeat or transform them into passive form. Stimulation with pure tones resulted in similar activation patterns in the two groups, but differences emerged in the more complex auditory language tasks. In the stutterers, the left inferior frontal cortex was activated for a short while from 95 to 145 ms after sentence onset, which was not evident in the controls nor in either group during the word task. In both subject groups, the left rolandic area was activated when listening to the speech stimuli, but in the stutterers, there was an additional activation of the right rolandic area from 315 ms onwards, which was more pronounced in the sentence than word task. Activation of areas typically associated with language production was thus observed also during speech perception both in controls and in stutterers. Previous research on speech production in stutterers has found abnormalities in both the amount and timing of activation in these areas. The present data suggest that activation in the left inferior frontal and right rolandic areas in stutterers differs from that in controls also during speech perception.

© 2004 Elsevier Inc. All rights reserved.

Keywords: Stutterer; Speech; Rolandic activation

Introduction

Stuttering is primarily a motor speech disorder that affects about 1% of the population, with men being affected three to four times more often than women (Starkweather, 1987). Many techniques that may improve speech performance of stutterers have been known for decades—such as external timing of speech

flow (Brady, 1969), suppression or alteration of acoustic feedback of speech (Cherry et al., 1955; Natke, 2000; Neelley, 1961) or chorus reading (Johnson and Rosen, 1937) but the neural mechanisms underlying language processing in stutterers have only been investigated with modern imaging techniques (PET, MRI, MEG) during the past 10 years.

According to two PET studies, brain metabolism during rest does not differ between stutterers and controls (Braun et al., 1997; Ingham et al., 1996). During stuttering, neuronal activity is stronger in speech-motor-related brain areas than during fluent speech, particularly in the right hemisphere (Braun et al., 1997; Fox et al., 1996, 2000). Furthermore, in fronto-temporal and temporo-parietal areas of the left hemisphere there is less activation during stuttering than during induced fluency and, in general, less activation in stutterers than in fluent speakers (Braun et al., 1997; Fox et al., 1996, 2000; Wu et al., 1995). Finally, just prior to overt reading of single words, stutterers show an unusual time course of activation in the left inferior frontal speech planning area and left rolandic motor executive areas as compared with fluent speakers: fluent speakers first activate the inferior frontal area and thereafter rolandic areas, but in stutterers, the order is reversed (Salmelin et al., 2000). A recent MRI study using diffusion tensor imaging revealed that stutterers show structural differences in the left rolandic operculum in terms of less fiber coherence within this region, which may contribute to the observed differences in timing (Sommer et al., 2002).

The aim of the present study was to provide further information about the time course of activation during auditory language processing and speech preparation in stutterers and fluent speakers. On the basis of neuroimaging results described above we expected to detect differences between stutterers and controls in the timing or strength of activation of the left-hemisphere language-related areas and the rolandic areas. Such differences in activation were also assumed to be task dependent: we hypothesized that activation in stutterers increases when the task becomes more complex and requires more articulatory planning. Altered auditory feedback is known to enhance fluency in stutterers, suggesting that the auditory system has a modulating effect on stuttering (e. g. Cherry et al., 1955; Natke, 2000; Neelley, 1961). Therefore, it is likely that

* Corresponding author. Department of Neurology, MEG-Laboratory, Moorenstrasse 5, Heinrich-Heine-University, 40225 Duesseldorf, Germany. Fax: +49 211 81 19033.

E-mail address: K.Biermann-Ruben@uni-duesseldorf.de (K. Biermann-Ruben).

Available online on ScienceDirect (www.sciencedirect.com).

the expected differences in activation patterns between fluent speakers and stutterers could be evident already during the reception phase when subjects listen to speech, at least when they know that they have to speak subsequently. We are not aware of any neuroimaging data addressing this question. In the present study, we used whole-head MEG providing high spatial and temporal resolution to non-invasively monitor cortical dynamics during a simple word repetition task and a more complex sentence repetition/transformation task.

Materials and methods

Subjects

Ten male developmental stutterers (age 26–40 years, mean 30 years) and 10 fluently speaking male subjects (age 26–42 years, mean 31 years) participated in our study. The control subjects had no language or speech disorders, nor did they have a family history of such disorders for at least two generations. None of the control subjects showed signs of stuttering during the entire measurement procedure. All stuttering subjects had participated in at least one therapy, but no subject was in therapy during the year immediately preceding this MEG study. Therapies varied with respect to onset (early childhood to late thirties), duration (2 weeks to 4 years), and therapists (speech therapists, psychologists, physicians, other). Most subjects reported that they had difficulties transferring the therapeutical contents into their daily life and positive results therefore only persisted for a short while. Stuttering severity was classified as mild to moderate in three subjects, moderate to severe in three subjects and severe to very severe in four subjects according to Riley (1972). None of the subjects suffered from any other neurological or otological disease and the mother tongue was monolingually German for all. Handedness of all subjects was tested right dominant with no statistically significant difference between subject groups (Hand-Dominanz Test (Steingrüber, 1976) Mann-Whitney U test; $P = 0.597$, handedness questionnaire (Annett, 1970) U test; $P = 0.823$). Subjects were contacted via newspaper article and were paid for participation. They signed an informed consent.

Paradigms

Auditory cortical responses to simple nonspeech tones were determined using alternating stimulation of the left and right ear with 1 kHz pure tones of 50 ms duration and 15 ms rise and fall times. Loudness was individually adjusted for each ear to 70 dB above hearing threshold. The interstimulus interval (ISI) was randomized between 800 and 1200 ms. Auditory stimulation was performed twice, before each of the two language paradigms described below. Each ear was stimulated about 150 times per measurement. The simple nonspeech tones were used to evaluate basic auditory cortical processing in fluent speakers and stutterers.

Two paradigms using acoustically presented language stimuli were performed. The first was a “word-paradigm” while the second was a more complex “sentence-paradigm”.

In the word-paradigm, subjects heard a binaurally presented single German noun spoken by a female German speaker and digitized at 44.1 kHz (STIM Audio System, NEUROSCAN, INC). All of the 245 presented words derived from a stimulus list used in a previous MEG study investigating word reading (Salmelin et al.,

2000). The words had two (128 words), three (107), or four (10) syllables, and had a concrete (48%) or abstract (42%) meaning, or both (10%). Durations ranged from 613 to 1132 ms (mean 849 ms). Five hundred milliseconds after word offset, subjects heard a tone (1 kHz, 50 ms) indicating that they now should repeat the word. The next noun was presented at a constant ISI of 4.1 s after tone offset.

In the sentence-paradigm, subjects heard binaurally presented sentences that consisted of three words (subject–verb–object, e.g., “doctors heal wounds”). Sentences were spoken and digitized in the same way as words. All of the 400 presented sentences were different. Sentence duration ranged from 1221 to 2595 ms (mean 1854 ms). The set of sentences was divided into comparable halves taking into account the distribution of sentence lengths and regularity/irregularity of verbs. Five hundred milliseconds after sentence offset subjects heard either “[we:]” or “[pe:]”. Those stimuli prompted subjects to repeat the sentence (“[we:]” for “wiederholen”, i.e., repeat) or to transform the sentence into the German passive form (“[pe:]” for “passiv”, i.e., passive, for example “wounds are healed by doctors”, which is more common in German language than in English). “[we:]” and “[pe:]” had a duration of 450 ms each and differed in sound only by the onset consonant. Both subject groups were randomly divided into halves, one half performing sentence set 1 with “[we:]” and 2 with “[pe:]” and vice versa. Stimulus onset asynchrony (SOA) between sentence onsets was adjusted to individual speech performance during the measurement, that is, the next sentence was presented only when the subject had completely finished repeating or transforming the previous sentence. Mean SOA was $7.8 \text{ s} \pm 1.7 \text{ SD}$ for controls (range 4.5–30.2 s) and $9.0 \text{ s} \pm 4.0 \text{ SD}$ for stutterers (range 5.3–103.9 s).

Data acquisition and data processing

A 122-channel whole-head neuromagnetometer device was used for this study (Neuromag-122™; Ahonen et al., 1993). MEG signals are associated with synchronous postsynaptic activation in tens of thousands of parallel apical dendrites of pyramidal cells (Hämäläinen et al., 1993). MEG is most sensitive to electric currents flowing parallel to the skull, that is, fissural activation. Magnetic signals were digitized at 397 to 513 Hz depending on the paradigm, filtered between 0.03 and 130 Hz and continuously recorded for offline analysis. Eye movements and blinks were recorded with horizontal and vertical electrooculography (EOG) for offline artifact rejection (individually adjusted thresholds, range 50 to 250 μV). Mouth movement was measured with lip-electromyography (lip-EMG) for data analysis of the speech production phase (not reported here). Furthermore, two microphone signals were recorded, with one directly fed into the AD-converter and stored in the same file with the MEG signals and the other stored on a digital audio tape (TASCAM, TEAC CORPORATION). Continuous data was high-pass filtered at 0.2 Hz offline and averaged to stimulus onset (pure tones, words, sentences).

Anatomical MR images were obtained for 19 subjects. Coordinate systems of MRI and MEG space were aligned using a 3D-digitizer (Polhemus Isotrak®) to mark anatomical landmarks that can be easily detected in anatomical MR images (nasion, right and left preauricular points) and small Head Position Indicator (HPI) coils attached to the subject’s head. The HPI coil positions were measured by the MEG system prior to each stimulus set.

The averaged data was analyzed using the equivalent current dipole source modeling technique (Hämäläinen et al., 1993), as previously applied in several studies of language function (e.g., Helenius et al., 1998; Salmelin et al., 2000). Magnetic fields to pure tone stimulation were modeled by sources in each hemisphere about 100 ms after stimulus onset. For this purpose, 20 sensors covering each temporal cortex were selected and one equivalent current dipole (ECD) per hemisphere was selected that explained the field best. The source locations were kept fixed while their amplitudes were allowed to vary over time to best account for the field pattern recorded by all 122 sensors. Euclidean distances between the sources within each hemisphere (1st vs. 2nd measurement) were calculated to estimate replicability of localization. Differences between groups and hemispheres were tested using a two-way ANOVA with factors group (2) and hemisphere (2). One source was then selected per hemisphere to represent the auditory cortical activation, according to goodness of fit of the source modeling procedure ($>85\%$; mean \pm SEM $96 \pm 0.5\%$). The localization of the sources on the subject's anatomical MRI was used as an additional criterion to discard sources that were located unreasonably superficial or deep in the brain. Then, these selected source locations in the left and right auditory cortex were kept fixed, while source strengths [nAm, nanoampere-metre] were calculated over time, separately for both measurements. Peak amplitudes of the prominent N100m were taken and correlated between the two measurements to estimate replicability of activation strengths within subjects. Peak amplitudes furthermore were compared between groups for both measurements and hemispheres (ANOVA, between group factor "group" (2), within group factors "measurement" (2) and "hemisphere" (2)).

For the two language paradigms, magnetic fields were averaged from -100 to 1000 ms with respect to word onset and sentence onset. Because stuttering did not occur in a sufficient number of trials to obtain a good signal-to-noise ratio for evoked responses, only epochs with subsequent fluent speech were taken into account. The resulting fields were modeled with equivalent current dipoles individually for each subject and task. The process of source modeling consists of a continuous interplay between visual inspection of local signal variations in the measured magnetic response (122 sensors), search for dipolar field patterns and an evaluation of how well the model explains the measured field (goodness-of-fit). Neuromagnetic activity is modeled at the times when each dipolar pattern is clearest; for the estimation of a dipole, only those sensors are selected that cover the active area (usually 12 to 20 sensors). A dipole's location and orientation represent the center of gravity of the active cortical patch and the direction of current flow within this area, respectively. The amplitude of a dipole [nAm] represents the magnitude of cortical activity. The current dipoles were identified one by one in a time interval from 0 to 1000 ms. The goodness-of-fit value ranged between 73% and 99% across subjects and analysis intervals.

The complete set of sources was brought into a multi-dipole model where the dipole locations and orientations were kept fixed while the amplitudes were allowed to vary to best explain the measured MEG signals. To be evaluated as active and to be included in the further analysis, a dipole's maximum amplitude had to exceed three standard deviations of its prestimulus base level activation (-100 to 0 ms with respect to word/sentence onset), which corresponds to a probability of approximately 99.8% .

The resulting sources for word reception and sentence reception were then combined to one multi-dipole "receptive model" for each

subject to make the tasks comparable with respect to source strengths and latencies. When a specific source area (dipole location and orientation) was found to be active in both tasks, we opted for the dipole that was appropriate for both conditions. Guiding criteria were again goodness of fit (%) and resulting interaction with other sources of the model. Interaction was measured as the angle between any pair of dipoles and was not smaller than 30° . In case a source was calculated only for one language task, we selected it for the combined model. This final receptive model was then applied to both the word and sentence data to determine the time courses of activation in the different source areas.

The sources of the receptive model were displayed on the individual subjects' brains. According to anatomical landmarks, that is, sylvian fissure, central sulcus, and bordering gyri, sources of all subjects were then transferred to one representative brain.

Regions of interest (ROIs)

Sources were clustered interindividually according to anatomical criteria as well as source orientation and time course of activation to represent comparable activation in different subjects. A cluster was only used for further analysis if it contained sources from at least five stutterers or five controls. If a subject did not have a source in a defined cluster, the activation was set equal to zero nAm, representing the assumption that the activation was too small to be detected. If one subject had two sources within one cluster, the time courses of these activations were added together. For each cluster, activations were averaged separately for fluent speakers and stutterers for word reception and sentence reception.

Time windows of interest (TOIs)

Because activations evolved rather slowly, we did not calculate peak amplitudes for statistical comparisons between conditions and groups, but defined time windows of interest (TOIs; Salmelin et al., 2000). Time-locked responses are typically quite sharp within the first few hundred ms after stimulus onset and become temporally more widespread or sustained at longer latencies. Therefore, in each ROI, we searched for time windows where the mean source strengths plus/minus the standard errors of mean (SEM) in stutterers and fluent speakers did not overlap for at least 50 ms up to latencies of 400 ms, or for at least 100 ms at latencies beyond 400 ms. This comparison was done separately for the word and sentence tasks. If one TOI was found for only one task, it was also applied for the other task. Within a defined TOI, mean amplitudes were calculated for each subject and task.

Statistical evaluation

Mean amplitudes within certain ROI/TOIs were compared between groups for each ROI/TOI using two-way ANOVA with group (controls, stutterers) as between group factor and task (word, sentence) as within group factor.

Results

Pure tone stimulation

Auditory responses to simple 1 kHz tones were obtained in nine controls and nine stutterers before both language experiments. The

sources of activation were located in the superior temporal cortex within Heschl's gyrus or Planum temporale. The source areas were very similar in the two recordings: in the control group, the Euclidean distance between the corresponding sources was 4.5 ± 0.8 mm (mean \pm SEM) in the right hemisphere and 6.2 ± 0.7 mm in the left hemisphere. For the stutterers, the distance was 7.8 ± 2.2 mm in the right hemisphere and 5.8 ± 1.8 mm in the left hemisphere. There were no significant differences by hemisphere or subject group.

Peak amplitudes of the activations to contralateral stimulation did not differ between the two recordings as indicated by a high correlation of 0.96 for the right hemisphere sources and 0.95 for the left hemisphere sources. Peak amplitudes of stutterers and controls (Table 1) did not differ by group or recording session. Auditory processing up to 100 ms as probed by tonal stimulation should thus be comparable in the two subject groups.

Auditory word and sentence presentation

Stutterers performed both tasks almost fluently. Only three subjects stuttered occasionally in the word task (1, 12, and 90 times). Six subjects stuttered in the sentence task (1 to 127 times depending on the condition); stuttering occurred more frequently in sentence transformation than repetition (cumulative sum of stuttered trials 266 versus 102). Because of insufficient number of stutter events, only fluent epochs were included in the further analysis.

Fig. 1 shows whole-head MEG recordings during word and sentence perception (overlaid) in one representative control subject. The signals are strongest over the temporal areas, with a sharp peak of activation at about 100 ms, followed by more sustained activity.

MEG data averaged with respect to the onset of word and sentence presentation was analyzed using source modeling procedure as described in Materials and methods. One "reception-model" was obtained for each subject (5–8 sources per subject, mean 6.6).

Regions of interest (ROIs)

The sources were transferred to one representative brain and they clustered in four main areas in each hemisphere (Fig. 2). According to location, direction of current flow, and time course of the sources, we defined a superior-temporal cluster (I, II), a temporo-parietal cluster (III, IV), an inferior-frontal cluster (V, VI), and a rolandic cluster (VII, VIII). The superior-temporal cluster mainly covers Heschl's gyrus and Planum temporale, with current flow in the superior-to-inferior direction. The temporo-parietal area

was defined as the area surrounding the posterior part of the Sylvian fissure containing gyrus supramarginalis, gyrus angularis, and gyrus temporalis superior pars posterior. Here, current flow was typically in the posterior-to-anterior direction. The inferior-frontal area was limited by the central sulcus, the inferior frontal sulcus and the anterior ascending part of the Sylvian fissure. The rolandic area mainly contains the precentral but also to some extent the postcentral gyrus, being laterally bordered by the inferior frontal gyrus. Sometimes dipolar sources exceeded the structural borders defining a cluster but had a typical direction of current flow of the sources within that cluster. Direction of current flow was therefore taken as a functional criterion supplementing anatomical criteria for the definition of a cluster. The number of controls and stutterers who had sources in the defined clusters is given in Fig. 2.

We also found other sources, located outside of these clear clusters, in total 10 sources in the left hemisphere and eight sources in the right hemisphere (nine sources from the control group, nine sources from the stutterers). These sources were scattered over various brain areas in a rather unsystematic manner and they were not included in the further analysis.

Group mean activation strengths of clustered sources are overlaid for both groups for word and sentence task and separately for all ROIs in Fig. 3. There was a transient bilateral activation of the superior-temporal area at about 100 ms that was followed by a sustained activation, predominantly in the left hemisphere, which reached the maximum between 400 and 600 ms. At 200–400 ms, bilateral temporo-parietal and inferior-frontal activity was detected in 8–14 subjects depending on cluster and hemisphere (details concerning the number of subjects are given in Fig. 2). In controls, rolandic activity peaked at about 200 ms bilaterally followed by a sustained signal in the left hemisphere up to 1000 ms and a rapid decrease in the right hemisphere. In stutterers, left rolandic activity was delayed (word task) with respect to that in controls by about 100 ms (see below for evaluation of time windows of interest, TOIs). Furthermore, the right rolandic area showed a persistent activation up to 800 ms in the word task and up to 1000 ms in the sentence task. The pattern of activation was comparable for word and sentence processing.

Time windows of interest (TOIs)

We identified five time ranges (in five ROIs) where activation patterns potentially differed between the stutterer and control groups (arrowheads in Fig. 3). Three of these time windows of interest (TOIs) stem from comparisons of activation in the sentence task, two result from comparisons within the word task. The TOIs, ROIs, group means, and *P* values revealed by analyses of variance are given in Table 2, and the results are illustrated in Fig. 4.

Significant group differences emerged in the left inferior frontal area at 95–145 ms and in the right rolandic area at 315–1000 ms. In these ROI/TOIs, stutterers had stronger activations than control subjects. Activation of the left inferior frontal ROI at 95–145 ms also showed a significant task effect, with clear activation in the sentence task but essentially no signal in the word task. This effect is predominantly caused by the stutterers, as confirmed by post hoc tests of simple effects (planned comparisons; controls: sentence > word, *P* > 0.50; stutterers: sentence > word, *P* < 0.01). Furthermore, analysis revealed significant group-by-task interactions in the right temporo-parietal ROI at 330–390 ms and the left rolandic ROI at 235–330 ms. Both interactions resulted from controls showing less activation in the sentence task compared

Table 1
N100m amplitudes to tone stimulation

Measurement		Left hemisphere mean (SD)	Right hemisphere mean (SD)
Controls	1st	43.9 (15.7)	51.3 (21.7)
	2nd	46.6 (13.3)	51.1 (23.9)
Stutterers	1st	43.2 (27.0)	61.5 (31.4)
	2nd	45.2 (26.2)	68.3 (29.2)

Mean peak amplitudes and SD [nAm] of the N100m in both hemispheres for controls and stutterers in the first and second measurements of tone stimulation.

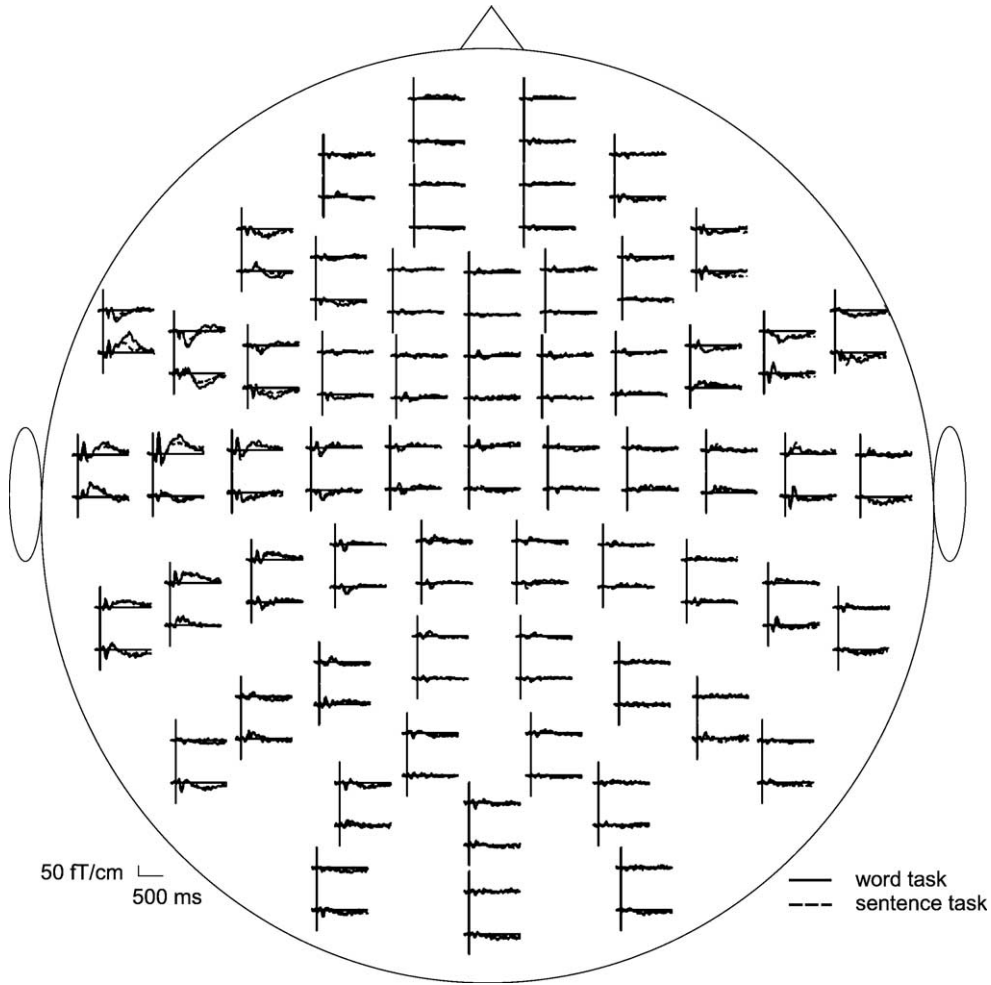


Fig. 1. MEG signals measured with 122 sensors for one representative control subject in the word and sentence tasks. The sensor array is viewed from above with the subject's right ear on the right and left ear on the left. Vertical lines indicate word/sentence onset.

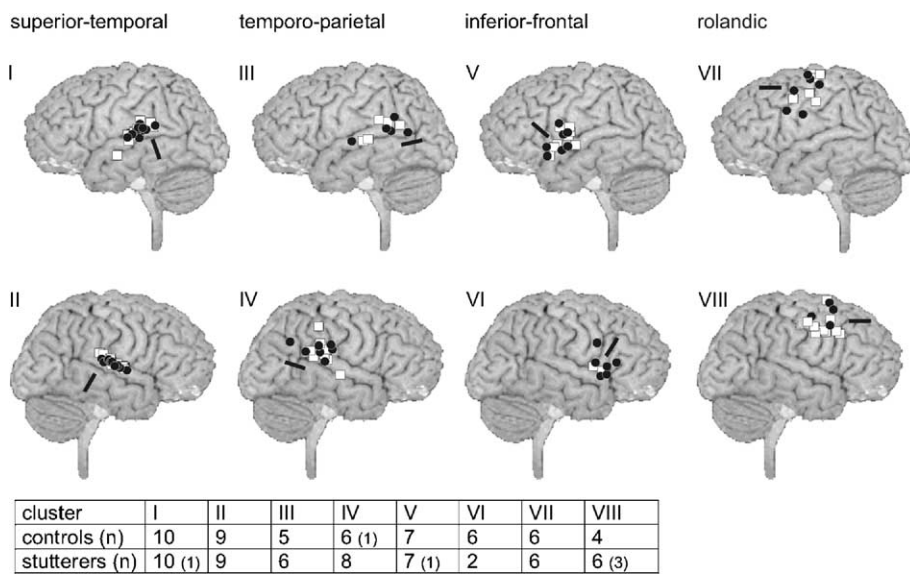


Fig. 2. Individual sources for word and sentence reception transferred to one representative brain. Sources of stutterers (white squares) and controls (black circles) clustered within four areas in each hemisphere. The black bars indicate typical directions of current flow in each cluster. The amount of subjects who had at least one source in the respective cluster is given in the table below. The number of subjects with more than one source in the cluster is given in parentheses.

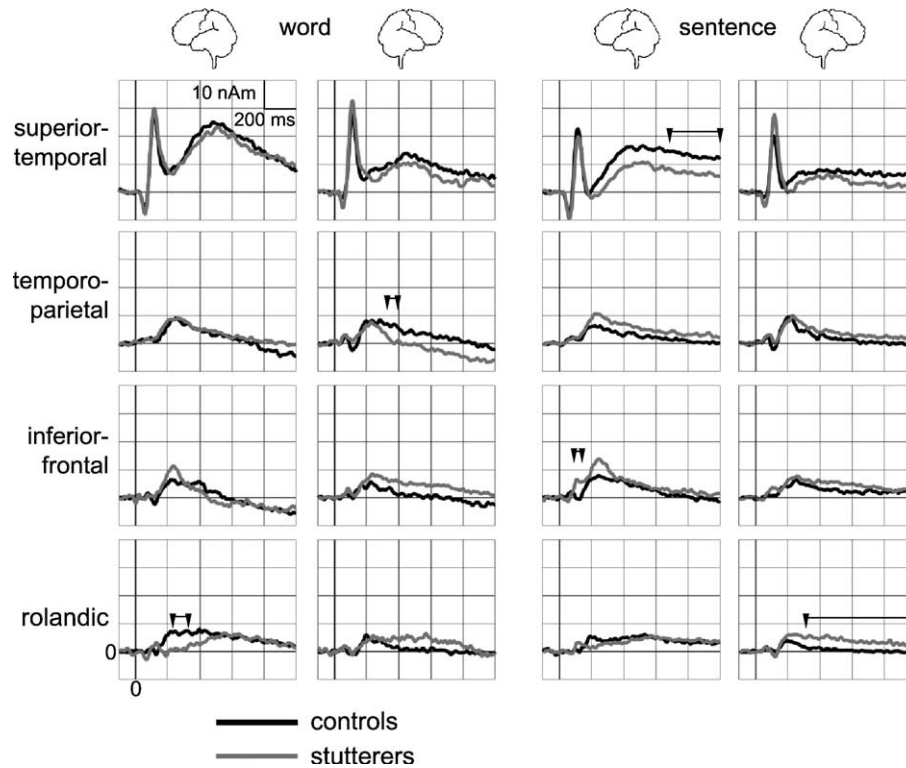


Fig. 3. Mean activation strengths [nAm] of clustered sources of stutterers (grey) and controls (black) overlaid for word (left columns) and sentence task (right columns). Left hemisphere activation is plotted in the first and third columns, right hemisphere activation in the second and fourth columns. Time scales refer to word and sentence onsets. Black arrowheads indicate time windows of interest (TOIs, see text).

with the word task, while in stutterers, the activations increased from word to sentence task. Post hoc planned comparisons revealed no significant differences between groups when each task was tested separately, either in the right temporo-parietal or in the left rolandic area. These results therefore will not be discussed in detail.

Discussion

Auditory processing up to 100 ms was probed by tonal stimulation, which was performed before both the word and the sentence task. The locations of activated areas and activation

strengths were indistinguishable between the two recordings. No group differences were found between the fluent speakers and stutterers. Differences in the language tasks therefore cannot be directly attributed to basic auditory processing per se.

For the language tasks sources of both subject groups mainly clustered in four areas typically referred to as areas of auditory processing (superior-temporal area), language reception (temporo-parietal area), speech preparation (inferior-frontal area), and sensorimotor processing (rolandic area) (for a review of the neuroimaging literature, see Cabeza and Nyberg, 2000).

For the auditory word task, we used the same words that were used previously in an overt word reading task comparing stutterers and controls (Salmelin et al., 2000). Interestingly, many of the

Table 2
Activations in the language tasks: comparisons between groups

TOI [ms]	ROI	Task	Mean (SD) controls [nAm]	Mean (SD) stutterers [nAm]	Effects (ANOVA)		
					Group	Task	Interaction
690–1000	left	word	12.9 (7.3)	12.6 (9.7)	n.s.	n.s.	n.s.
		sentence	13.0 (8.2)	6.7 (7.6)			
330–390	right	word	6.4 (9.8)	0.8 (5.5)	n.s.	n.s.	$P < 0.021$
		sentence	2.7 (6.6)	5.1 (8.9)			
95–145	left	word	−0.9 (3.8)	1.1 (4.6)	$P < 0.020$	$P < 0.021$	n.s.
		sentence	0.2 (3.0)	5.8 (5.0)			
235–330	left	word	6.9 (9.0)	1.0 (7.0)	n.s.	n.s.	$P < 0.032$
		sentence	4.0 (5.0)	2.7 (7.2)			
315–1000	right	word	0.3 (5.2)	3.0 (4.5)	$P < 0.024$	n.s.	n.s.
		sentence	0.3 (1.1)	3.8 (3.8)			

Time windows of interest (TOIs) for regions of interest (ROIs) and mean activations within these ROI/TOIs for controls and stutterers during word and sentence reception. P values of main effects and interactions revealed by analyses of variance (group (2) × task (2)) for each ROI/TOI are given in columns on the right.

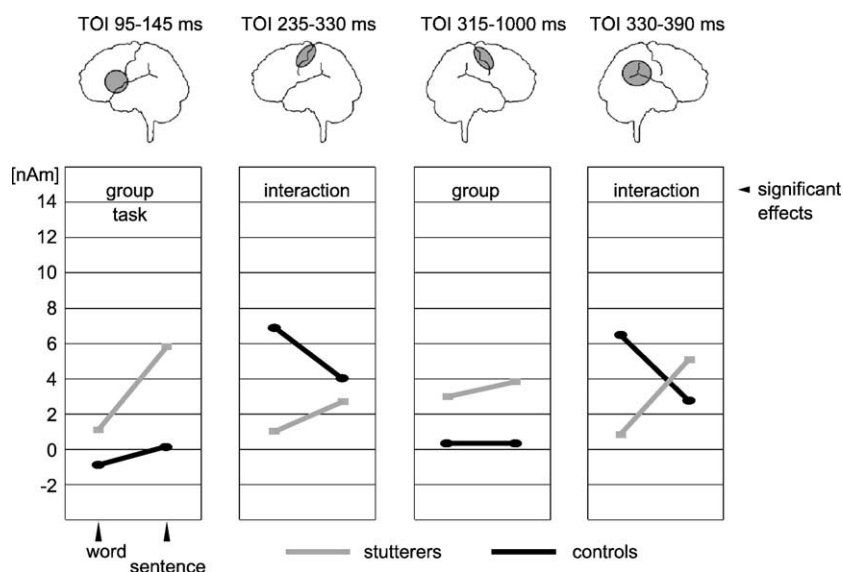


Fig. 4. Mean activation strengths [nAm] for ROI/TOIs (separate columns), tasks (word: left, sentence: right) and subjects (controls: black; stutterers: grey); only significant results of comparisons are shown. Effects (group, task, group-by-task interaction) are listed at the top of each box (for *P* values please see Table 2).

relevant source clusters in Salmelin et al. were rather similar to those found in the present study using auditory stimuli. The superior-temporal response around 400 to 600 ms was found bilaterally in the auditory task reported here but predominantly in the left hemisphere in the visual task reported by Salmelin et al. (2000). These observations are in agreement with previous MEG reports of bilateral temporal activation in speech comprehension (Helenius et al., 2002) but left-lateralized activation in reading comprehension (Helenius et al., 1998). Furthermore, the visual task resulted in activation of occipital areas, which was not present in the auditory task. The early modality-specific and later supramodal activation patterns are in line with recent reports on direct comparison of visual and auditory word processing (Booth et al., 2002; Marinkovic et al., 2003).

Of previous time-sensitive neuroimaging studies, the one that comes closest to the present experimental design is that on auditory word and sentence comprehension by Helenius et al. (2002). The authors compared responses to semantically appropriate and inappropriate sentence-ending words. Activation concentrated to the superior temporal cortex bilaterally, with a typical relatively non-specific auditory activation at 100 ms and a subsequent sustained activation at 200–600 ms, reflecting semantic processing (usually referred to as the N400 response; Kutas and Hillyard, 1984). In that study, the subjects only listened to the stimuli.

In the present study, the subjects were additionally required to prepare for articulation after the stimulus presentation. Indeed, we found a comparable type of bilateral superior-temporal activation, peaking at 100 ms and 400 to 600 ms, as Helenius et al. (2002) but there was clear-cut activation also in other brain regions, namely in the temporo-parietal and inferior-frontal areas at 200–400 ms and in the rolandic areas peaking at 200 ms and persisting in the left and right (stutterers) rolandic area at least up to 800 ms. In both subject groups and all regions of interest, activity could be determined in both hemispheres, pointing to a role of the right hemisphere in word and sentence processing and speech preparation.

As in word reading (Salmelin et al., 2000), group differences in this reception and preparation task emerged in the inferior frontal

and rolandic areas. In the left inferior frontal area, at 95 to 145 ms, stutterers showed enlarged activation as compared with controls when processing sentences. Some imaging studies have reported activation of left inferior-frontal area in subvocal or overt word repetition (Hinke et al., 1993; Price et al., 1996) or in auditory sentence comprehension (Schlosser et al., 1998). This area comprising inferior parts of the primary motor cortex (probably face/mouth area) and ventral premotor regions (Broca's area, Brodmann's area (BA) 44) as well as frontal opercular regions is necessary for articulatory planning of speech as well as for executive motor functions (Dronkers, 1996; Penfield and Roberts, 1959). Moreover, the inferior-frontal region also appears to be involved in functions of speech reception and phonetic analysis (Fiez et al., 1995; Price et al., 1996; Zatorre et al., 1992).

Since word and sentence tasks both started with auditory presentation of a noun which obviously lasted longer than the time window under consideration (95–145 ms), it is unlikely that the differences could be due to the stimulus material. Furthermore, those differences should then have affected both groups. Stuttering is more likely to occur with production of sentences than single words and, interestingly, it then occurs at the beginning of the sentence (Quarrington, 1965). In our sentence task subjects had to transform the sentences with a probability of 50% to the passive form, which they did not know before presentation of the auditory cue (“[we:]” or “[pe:]”). Enlarged load of linguistic and phonological planning typically results in higher amount of stuttering (Brown and Moren, 1942; Lanyon and Duprez, 1970; Soderberg, 1966). Interestingly, anticipation has a crucial influence on speech performance: a short sentence is stuttered more often if it is the first part of a long sentence than if it is the last part or if it stands alone (Jayaram, 1984; Tornick and Bloodstein, 1976). We interpret the obtained group difference in the left inferior frontal region in terms of anticipation of enlarged load of articulatory planning in stutterers dealing with sentences. Whether the exceptionally strong activation in stutterers is characteristic to their general linguistic-motor organization (also during fluent speech) or whether this increased activation might in fact prevent them from stuttering cannot be concluded from the present data set. No increased load

for articulatory planning was anticipated in the word task and, indeed, even stutterers had activity close to zero within this early time window in the left inferior-frontal area.

The observed interactions in the left rolandic area at 235 to 330 ms and in the right temporo-parietal area at 330 to 390 ms may also be interpreted as task effects specific to stutterers: they show enlarged activation in the sentence task with respect to the word task, whereas this pattern is reversed in controls. It seems that many areas become more active in stutterers when task complexity and, therefore, the tendency toward stuttering increases. That for controls activation in these areas is smaller than in the word task may be caused by the sequence of measurements: the word task always preceded the sentence task and control subjects may have become used to the experimental procedure.

Another difference between groups was detected at 315–1000 ms in the right rolandic area, again in the more complex sentence task. Whereas stutterers activated the right rolandic cortex at that time, controls showed essentially no activity there in this time window. In contrast, during actual word production, Salmelin et al. (2000) reported a pronounced activation of the right rolandic area in control subjects but an abnormally weak activation in the stutterers, as measured by the evoked responses.

Exceptionally strong activation of the right hemisphere in stutterers has been indicated in several PET studies (Braun et al., 1997; Fox et al., 1996, 2000; Wu et al., 1995). Because of the low temporal resolution of PET and the paradigms used (reading alone, chorus reading, narrative, paced, or overlearned speech) no information could be derived about the time frame of the increased activity. The present data suggest that right hemisphere rolandic activation of stutterers is abnormally enhanced when they listen to speech, before articulation. We interpret the left rolandic activation in controls and the additional involvement of the right rolandic area in stutterers as one piece of evidence for an altered cerebral dominance in stutterers, which becomes obvious in speech perception, well before overt speech production, and which may correlate with task complexity. The cerebral dominance theory of stuttering is very old, claiming that unusually weak left hemisphere lateralization of the “speech” function results in hemispheric rivalry during speech production, which causes stuttering (Travis, 1927). This explanation is obviously far too simple; the right hemisphere is strongly involved in speech perception and production also in fluent speakers. Present knowledge suggests that several interconnected bihemispheric cortical (and of course subcortical) areas are recruited in successful language performance. Nevertheless, as the general concept of lateralization accounts for handedness, it may also be applicable in characterizing the final stage of speech production, articulatory output. In this framework, the group differences in activation of the sensorimotor (rolandic) area may be interpreted in terms of weaker left hemisphere lateralization of speech sensorimotor functions in stutterers. The strength of rolandic activation in stutterers did not correlate with stuttering severity and, unfortunately, there were too few stuttered trials to allow direct evaluation of activation preceding stuttered versus fluent production. Therefore, interpretation of the unusually strong right rolandic activation in stutterers remains speculative at this point.

In conclusion, we showed that there are differences in the time course of neurophysiological signals between stutterers and fluent speakers during auditory reception, well before the overt spoken response. These differences are detected even when the stutterers speak fluently. The exceptionally strong early activation of the left

inferior-frontal cortex and later sustained activation of the right rolandic cortex did not correlate with the severity of stuttering. Direct comparison of the cortical dynamics of stuttered and fluent speech production in the same individuals could be best achieved in natural, continuous language tasks. Such experiments are now becoming feasible with the advent of analysis tools for time-sensitive cortico-cortical coherence (Gross et al., 2001).

Acknowledgments

This study was supported by the Human Frontier Science Program and the Academy of Finland. We thank Dr. Joachim Gross for helpful discussions especially during data analysis, Dr. Ulrich Natke for expert advice during the early phase of this project, and Frank Schmitz and Erika Raedisch for technical help.

References

- Ahonen, A., Hämäläinen, M.S., Kajola, M.S., Knuutila, J.E.T., Laine, P.P., Lounasmaa, O.V., Parkkonen, L.T., Simola, J.T., Tesche, C.D., 1993. 122-channel SQUID instrument for investigating the magnetic signals from the human brain. *Phys. Scr.*, T 49, 198–205.
- Annett, M., 1970. A classification of hand preference by association analysis. *Br. J. Psychol.* 61, 303–332.
- Booth, J.R., Burman, D.D., Meyer, J.R., Gitelman, D.R., Parrish, T.B., Mesulam, M.M., 2002. Modality independence of word comprehension. *Hum. Brain Mapp.* 16, 251–261.
- Brady, J.P., 1969. Studies on the metronome effect on stuttering. *Behav. Res. Ther.* 7, 197–204.
- Braun, A.R., Varga, M., Stager, S., Schulz, G., Selbie, S., Maisog, J.M., Carson, R.E., Ludlow, C.L., 1997. Altered patterns of cerebral activity during speech and language production in developmental stuttering. An H2(15)O positron emission tomography study. *Brain* 120, 761–784.
- Brown, S.F., Moren, A., 1942. The frequency of stuttering in relation to word length during oral reading. *J. Speech Disord.* 7, 153–159.
- Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci.* 12, 1–47.
- Cherry, C., Sayers, B., Marland, P.M., 1955. Experiments on the complete suppression of stammering. *Nature* 176, 874–875.
- Dronkers, N.F., 1996. A new brain region for coordinating speech articulation. *Nature* 384, 159–161.
- Fiez, J.A., Raichle, M.E., Miezin, F.M., Petersen, S.E., Tallal, P., Katz, W.F., 1995. PET studies of auditory and phonological processing: effects of stimulus characteristics and task demands. *J. Cogn. Neurosci.* 7, 357–375.
- Fox, P.T., Ingham, R.J., Ingham, J.C., Hirsch, T.B., Downs, J.H., Martin, C., Jerabek, P., Glass, T., Lancaster, J.L., 1996. A PET study of the neural systems of stuttering. *Nature* 382, 158–162.
- Fox, P.T., Ingham, R.J., Ingham, J.C., Zamarripa, F., Xiong, J.H., Lancaster, J.L., 2000. Brain correlates of stuttering and syllable production: a PET performance-correlation analysis. *Brain* 123, 1985–2004.
- Gross, J., Kujala, J., Hämäläinen, M., Timmermann, L., Schnitzler, A., Salmelin, R., 2001. Dynamic imaging of coherent sources: studying neural interactions in the human brain. *Proc. Natl. Acad. Sci. U. S. A.* 98, 694–699.
- Hämäläinen, M., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography: theory, instrumentation, and applications to noninvasive studies of the working brain. *Rev. Mod. Phys.* 65, 413–497.
- Helenius, P., Salmelin, R., Service, E., Connolly, J.F., 1998. Distinct time courses of word and context comprehension in the left temporal cortex. *Brain* 121, 1133–1142.

- Helenius, P., Salmelin, R., Service, E., Connolly, J.F., Leinonen, S., Lyytinen, H., 2002. Cortical activation during spoken-word segmentation in nonreading-impaired and dyslexic adults. *J. Neurosci.* 22, 2936–2944.
- Hinke, R.M., Hu, X., Stillman, A.E., Kim, S.G., Merkle, H., Salmi, R., Ugurbil, K., 1993. Functional magnetic resonance imaging of Broca's area during internal speech. *NeuroReport* 4, 675–678.
- Ingham, R.J., Fox, P.T., Ingham, J.C., Zamarripa, F., Martin, C., Jerabek, P., Cotton, J., 1996. Functional-lesion investigation of developmental stuttering with positron emission tomography. *J. Speech Hear. Res.* 39, 1208–1227.
- Jayaram, M., 1984. Distribution of stuttering in sentences: relationship to sentence length and clause position. *J. Speech Hear. Res.* 27, 338–341.
- Johnson, W., Rosen, L., 1937. Studies in the psychology of stuttering: VII. Effect of certain changes in speech pattern upon frequency of stuttering. *J. Speech Disord.* 2, 105–109.
- Kutas, M., Hillyard, S.A., 1984. Brain potentials during reading reflect word expectancy and semantic association. *Nature* 307, 161–163.
- Lanyon, R.I., Duprez, D.A., 1970. Nonfluency, information, and word length. *J. Abnorm. Psychol.* 76, 93–97.
- Marinkovic, K., Dhond, R.P., Dale, A.M., Glessner, M., Carr, V., Halgren, E., 2003. Spatiotemporal dynamics of modality-specific and supramodal word processing. *Neuron* 38, 487–497.
- Natke, U., 2000. Stotterreduktion bei frequenzverschobener und verzögerter Rückmeldung. *Folia Phoniatri. Logop.* 52, 151–159.
- Neelley, J.N., 1961. A study of the speech behavior of stutterers and nonstutterers under normal and delayed auditory feedback. *J. Speech Hear. Disord.* 7, 63–82.
- Penfield, W., Roberts, L., 1959. *Speech and brain-mechanisms*. Princeton University Press, New York.
- Price, C.J., Wise, R.J., Warburton, E.A., Moore, C.J., Howard, D., Patterson, K., Frackowiak, R.S., Friston, K.J., 1996. Hearing and saying. The functional neuro-anatomy of auditory word processing. *Brain* 119, 919–931.
- Quarrington, B., 1965. Stuttering as a function of the information value and sentence position of words. *J. Abnorm. Psychol.* 70, 221–224.
- Riley, G.D., 1972. A stuttering severity instrument for children and adults. *J. Speech Hear. Disord.* 37, 314–322.
- Salmelin, R., Schnitzler, A., Schmitz, F., Freund, H., 2000. Single word reading in developmental stutterers and fluent speakers. *Brain* 123, 1184–1202.
- Schlösser, M.J., Aoyagi, N., Fulbright, R.K., Gore, J.C., McCarthy, G., 1998. Functional MRI studies of auditory comprehension. *Hum. Brain Mapp.* 6, 1–13.
- Soderberg, G.A., 1966. The relations of stuttering to word length and word frequency. *J. Speech Hear. Res.* 9, 584–589.
- Sommer, M., Koch, M.A., Paulus, W., Weiller, C., Büchel, C., 2002. Disconnection of speech-relevant brain areas in persistent developmental stuttering. *Lancet* 360, 380–383.
- Starkweather, C.W., 1987. *Fluency and Stuttering*. Prentice-Hall, New Jersey.
- Steingrüber, H.-J., 1976. *Hand-Dominanz-Test*. Verlag für Psychologie, Hogrefe, Göttingen.
- Tomick, G.B., Bloodstein, O., 1976. Stuttering and sentence length. *J. Speech Hear. Res.* 19, 651–654.
- Travis, L.E., 1927. *Studies in Stuttering*. Arch. Neurol. Psychiatry 18, 673–690.
- Wu, J.C., Maguire, G., Riley, G., Fallon, J., LaCasse, L., Chin, S., Klein, E., Tang, C., Cadwell, S., Lottenberg, S., 1995. A positron emission tomography [18F]deoxyglucose study of developmental stuttering. *NeuroReport* 6, 501–505.
- Zatorre, R.J., Evans, A.C., Meyer, E., Gjedde, A., 1992. Lateralization of phonetic and pitch discrimination in speech processing. *Science* 256, 846–849.