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Event-related fMRI for the suppression of speech-associated artifacts in stuttering

Christine Preibisch,[a,*] Peter Raab,[a] Katrin Neumann,[b] Harald A. Euler,[c] Alexander W. von Gudenberg,[d] Volker Gall,[b] Heinrich Lanfermann,[a] and Friedhelm Zanella[a]

[a] *Department of Neuroradiology, University Frankfurt, Frankfurt, Germany*
[b] *Clinic for Phoniatrics and Paedaudiology, University Frankfurt, Frankfurt, Germany*
[c] *Department of Psychology, University Kassel, Kassel, Germany*
[d] *Kasseler Stottertherapie, Kassel, Germany*

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Abstract

The purpose of this study was to establish functional magnetic resonance imaging (fMRI) for the investigation of brain function during overt speech production in stuttering. Up to now this technique has rarely been used for the investigation of speech production paradigms because artifacts related to overt speaking largely impair the sensitivity toward task-related activation. Recently, the temporal delay of the hemodynamic response has been exploited to achieve a suppression of speech-related artifacts. By the limitation to very short utterances (one word), a temporal segregation of the respective effects was accomplished by means of an event-related experimental design. However, the investigation of speech production in persons who stutter requires a more extensive speaking situation. Since longer and more complex utterances evoke more symptoms of stuttering than reading of single words, a useful task should at least include the reading of full sentences. In this study we performed simulations to investigate the correlation of speech-related artifacts with the respective hemodynamic response in dependency on speech duration and rate of data sampling. Furthermore, we show that prolonged stimulus durations and repetition times of 3 s still allow an effective suppression of speech-related artifacts in fluent as well as in nonfluent speakers. Not only were obvious false activations at high contrast cerebrospinal fluid tissue borders widely eliminated, subjects also displayed consistent activation in speech-related and motor areas. As these results widely resemble those obtained by earlier neuroimaging studies on language production, event-related fMRI seems to be capable of recording neurophysiological correlates of overt speech production.

Introduction

In the last decade, functional magnetic resonance imaging (fMRI) has evolved into a valuable tool for the imaging of human brain function. However, from the very beginning the detrimental effects of subject motion have been recognized (Hajnal et al., 1994; Birn et al., 1998; Bullmore et al., 1999; Field et al., 2000), and efforts were taken to develop methods for correcting the destructive effects of bulk head motion in image time series (Friston et al., 1995a; Hajnal et al., 1995; Woods et al., 1993). Even more severe problems arise from overt speech (Achten et al., 2000; Barch et al., 1999): Artifacts are not only caused by bulk head motion (Hajnal et al., 1994; Bullmore et al., 1999), which could potentially be corrected for (Friston et al., 1995a; Hajnal et al., 1995; Woods et al., 1993), but also by magnetic field variations caused by the changing pharyngeal space during speaking (Birn et al., 1998). This type of artifact is especially destructive because it leads to signal fluctuations and image distortions that depend on the individual anatomy and movement patterns during speaking. Theoretically, one could take simultaneous measurements of magnetic field changes and carry out an individual unwarping of all acquired images, but even with complete information this task would be hardly possible to perform (Birn et al., 1998). This

* Corresponding author. Institut für Neuroradiologie, Universität Frankfurt, Schleusenweg 2-16, D-60528 Frankfurt, Germany. Fax: +49-69-6301-5989.
E-mail address: preibisch@em.uni-frankfurt.de (C. Preibisch).

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is the reason that, up to now, paradigms depending on overt speech have seldom been investigated (Small et al., 1996), although overt verbal responses are usually thought to be very desirable for the monitoring of correct task performance. Therefore, at least three groups have recently tried to overcome these limitations (Birn et al., 1999; Barch et al., 2000; Palmer et al., 2001).

Signal intensity changes caused by motion result in false positive activation if they are completely synchronized with the expected task-related response. This is the case in conventional experimental setups where periods of task performance alternate with periods of rest (blocked experimental design). A potential solution for this problem is the temporal segregation of the motion-related signal fluctuations from the relevant task-related hemodynamic response. Ideally, speaking should be completely separated from the data acquisition. While this would require rather lengthy acquisition protocols, recent studies demonstrated that with very short utterances (one word) it is possible to overcome the limitations imposed by stimulus-correlated signal fluctuations (Birn et al., 1999; Barch et al., 2000; Palmer et al., 2001). Each of these studies relied on the temporal segregation of the delayed hemodynamic response (Aguirre et al., 1998; Janz et al., 2000, 2001) from the instantaneous signal fluctuations related to motion (Birn et al., 1999) by means of an event-related experimental design. Even very short stimuli like a single button press evoke a temporally extended hemodynamic response reaching its maximum after about 5 to 6 s (Aguirre et al., 1998). With prolonged stimulus durations the rising time to the maximum of the hemodynamic response increases to about 10 s in a blocked experimental design (Janz et al., 2001). Thus, motion-related signal fluctuations can be split off when the disturbance is limited to a time interval that is sufficiently short. This seems to be the case if the verbal output is restricted to a single word (Birn et al., 1999; Barch et al., 2000; Palmer et al., 2001). However, in persons who stutter it would be desirable to examine more extended speaking periods, because dysfluency symptoms occur more often in longer and grammatically complex utterances than in shorter and simpler ones (Wingate, 1988; Conture, 2000). This phenomenon seems to be related to speech motor processing, and to the planning of speech production (Peters et al., 2000). Therefore, it would be favorable if the experimental design at least permitted the reading of short sentences.

This prompted us to investigate whether prolonged stimulation periods still allow the effective suppression of speech-related artifacts in conjunction with a sensitive detection of task-related activation during sentence reading. To analyze the effects of stimulus-correlated motion, we performed simulations for various speech durations and data sampling rates. This procedure provides some information about protection against false positive activations, but increased time course fluctuations as induced by the speaking events will certainly also degrade sensitivity toward the underlying task-related activation. Moreover, artifactual signal changes severely depend on the actual motion, and the simple boxcar model only yields a very rough estimate. Thus, the effects of increased speech durations were also investigated experimentally. Since fluent speakers need about 3 s to complete a short sentence, this speech duration was used in a larger set of experiments to demonstrate the practical feasibility of this approach.

Materials and methods

Simulations

To estimate the confounding effects of speech-related motion on the detection of task-induced activation, we calculated the correlation of hypothetical artifactual signal changes with the expected hemodynamic responses. To this end, we used customized software written in MATLAB (Mathworks Inc., Sherborn, MA). The artifact regressor was modeled as a simple rectangular boxcar function whose length was given by the respective speech duration. The hemodynamic response was represented by the canonical hemodynamic response function (HRF) included in SPM99 (Wellcome Department of Cognitive Neurology, London, UK: www.fil.ion.ucl.ac.uk). In Fig. 1 both functions are illustrated for a speech duration of 3 s and various repetition times. From this figure it can also be seen that an interstimulus interval (ISI) of about 15 s appears to be quite optimal. For shorter ISIs the HRF would not return to baseline between subsequent events and the dynamic range would thus be restricted. For longer ISIs the number of events per unit time would be reduced, resulting in a less efficient design. For this reason, the ISI was considered to be fixed and the correlation coefficient was determined for just one 32-s period of both functions at various speech durations (0.5, 1, . . . , 10 s) and repetition times (0.1, 0.5, 1.0, . . . , 4.0 s).

Subjects

We investigated a total of 28 fluent speakers (16 male, 12 female; mean age, 32 years; range, 19 to 51 years) and 34 persons who stutter (32 male, 2 female; mean age, 30 years; range, 18 to 48 years). According to the Edinburgh Handedness Inventory (Oldfield, 1971) the majority of persons were right-handed with the exception of three persons who stuttered and four subjects with fluent speech. The subjects who stuttered were recruited from the participants of a 3-week intense fluency training course offered by the Kasseler Stottertherapie. All subjects gave written informed consent prior to the investigation in compliance with the regulations of the local ethics board. During the examinations subjects lay supine with their heads comfortably fixed inside the standard head coil using cushions of rubber foam.

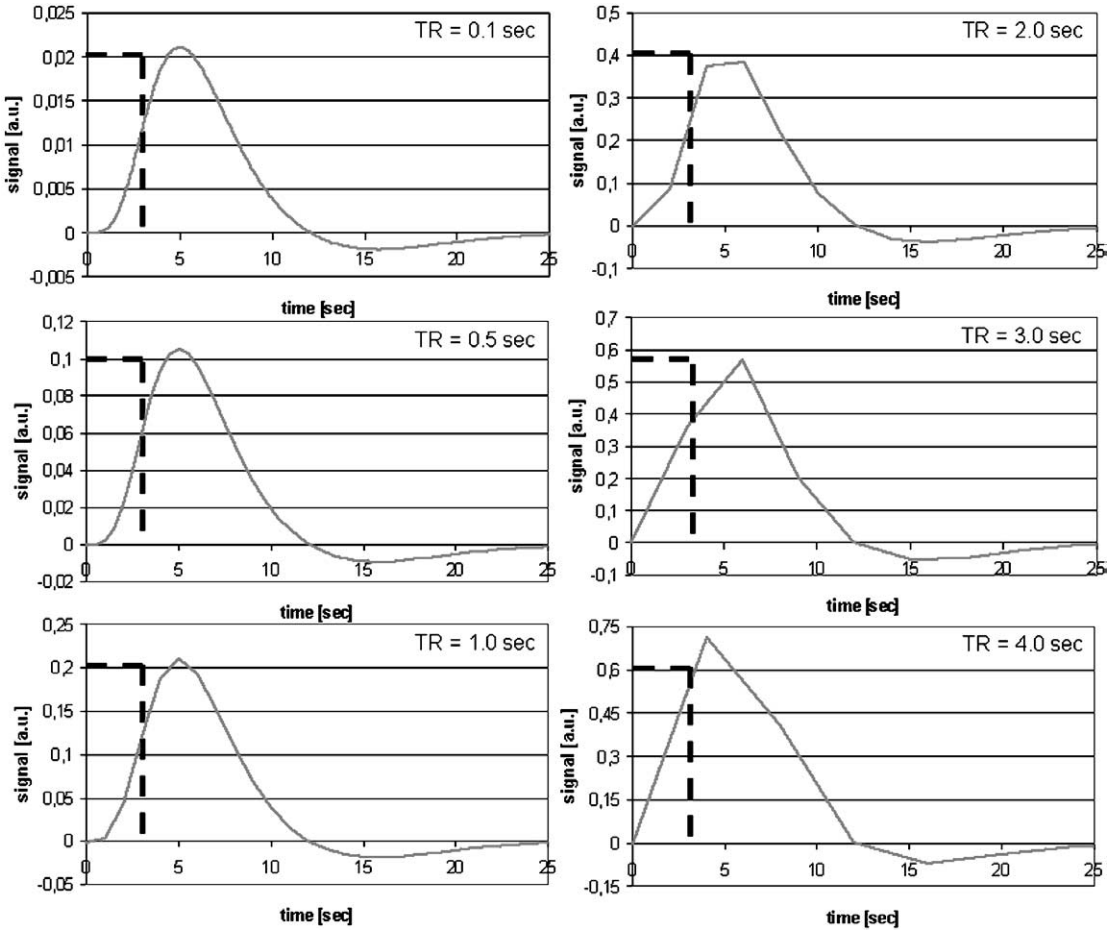

Fig. 1. Representation of the canonical hemodynamic response function compared to a rectangular boxcar function of 3-s duration (dashed lines). The different subplots illustrate the undersampling with increasing repetition time (TR).

Imaging

Imaging was performed on a clinical 1.5-T Siemens Magnetom Vision Scanner using gradient echo EPI with an echo time of 50 ms, a voxel size of $3.6 \times 3.6 \times 6$ mm^3, an interslice gap of 0.6 mm, and 18 slices.

Tasks

The tasks consisted of reading aloud words or phonetically balanced sentences, which were projected onto a screen in front of the scanner and could be watched by the subjects via a mirror mounted on the head coil. The subjects were advised to stop talking as soon as the respective text presentations ended. Three subjects performed an event-related reading task with five different speech durations (0.5, 1, 2, 3, and 4 s) comprising 42 reading events. Fifty-five subjects performed the event-related reading task with a stimulus duration of 3 s and 78 reading events. In both cases a fixed ISI of 15.5 s was used. Together with the measurement repetition time (TR) of 3 s, this led to an effective time resolution of 0.5 s for the sampling of the hemodynamic response. The exact timing and order of events is depicted schematically in Fig. 2. To directly assess the potential benefits of the proposed event-related experimental design, the reading task was also performed in a conventional blocked design consisting of 12 alternating periods of rest and reading (each period with a duration of 24 s, a total of 121 measurements, and TR 4 s). Twelve subjects (2 with, 10 without dysfluencies) performed the

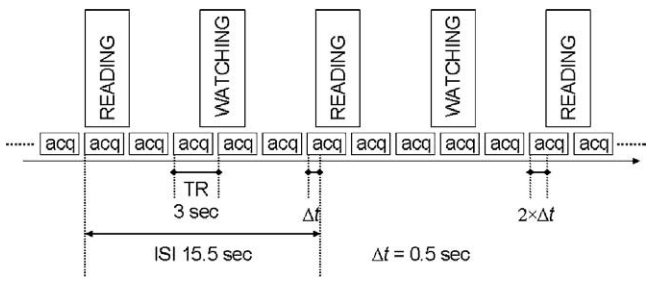

Fig. 2. Acquisition scheme for the event-related design. The interstimulus interval is 15.5 s for reading as well as control events (watching of meaningless signs). Together with the repetition time (TR) of 3 s this leads to an effective time resolution of the hemodynamic response of 0.5 s.

reading paradigm under blocked as well as event-related conditions. Four subjects only performed the blocked, 46 only the event-related reading tasks.

Data analysis

Evaluation was performed by using SPM99 (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk) running under the MATLAB environment (Mathworks Inc.). The event-related data were corrected for acquisition time (slice timing). All functional datasets were then realigned to the first imaging volume by using a six-parameter motion correction algorithm, and coregistered with the anatomical data of the individual subjects. Finally, the data were spatially normalized into a standardized neuroanatomical space (Friston et al., 1995a; template by courtesy of the Montreal Neurological Institute), and smoothed by using a Gaussian kernel (10 mm full-width-at-half-maximum). Low frequency fluctuations were removed by a high-pass filter with a cutoff at 35 s (event-related design) or 80 s (blocked design). Within the framework of the general linear model the expected hemodynamic responses were modeled by appropriate hemodynamic response functions included in SPM99 (Josephs et al., 1997; Josephs and Henson, 1999). Temporal shifts of the hemodynamic responses in the event-related design were accounted for by incorporation of the corresponding temporal derivatives. To decrease the residual variance and possibly increase the detectability of task-related activation, the artifactual signal fluctuations due to motion were modeled either by a boxcar function whose length was given by the respective speech duration, or by the six realignment parameters obtained from the motion correction. These regressors were also used to visualize areas of artifactual signal changes. Statistical parametric maps of t values [SPM(t)] were then created for each individual subject and condition by the specification of appropriate contrasts. The applied thresholds were corrected for multiple nonindependent comparisons by using the Gaussian random field theory (Friston et al., 1995b).

To assess the quality of the activation maps resulting from the blocked and event-related designs, the statistical parametric maps of the individual subjects were thresholded at $P < 0.05$ (corrected for multiple comparisons), and inspected with regard to obvious artifactual activation. To quantify the severity of obvious artifacts near cerebrospinal fluid (CSF) tissue borders, the maximum t values of artifactual activations were determined in the following six regions of interest: ROI 1 = fourth ventricle; ROI 2 = posterior part of lateral ventricle (left); ROI 3 = posterior part of lateral ventricle (right); ROI 4 = anterior part of lateral ventricle (left); ROI 5 = anterior part of lateral ventricle (right); ROI 6 = third ventricle.

On the basis of the single-subject statistics, we conducted a second-level random effects analysis that accounts for the variability between subjects (McGonigle et al., 2000). This means that the resulting activation maps should suffer from degraded sensitivity when the underlying data exhibit increased variability, as could be expected from data deteriorated by motion artifacts.

Results and discussion

Simulations

Fig. 3 shows the correlation coefficient of a boxcar-type artifact regressor with the canonical HRF as a function of speech duration. The influence of increasing TR is illustrated in different subplots. As could be expected, the correlation increases with speech duration. At short TRs, the calculated curves are rather smooth and cover the entire range of simulated speech durations from 0.5 to 10 s. The negative lobe is due to the small initial dip of the hemodynamic response function. Since the correlation coefficient was calculated for integer multiples of the speech durations and TRs, the increase in TR led to a reduced number of simulated points. Nevertheless, one can clearly see that the inadequate modeling of the hemodynamic response at longer TRs leads to a general increase in the correlation coefficient. This feature is emphasized in the lower right panel of Fig. 3 where the correlation coefficient for a speech duration of 3 s is displayed as a function of the TR. The reason for this behavior can be understood from Fig. 1, where the HRF is depicted for different TRs. Obviously, the increasing undersampling of the hemodynamic response advances its similarity with the simple boxcar function.

These simulations are rather simplified because of the boxcar model and the neglect of any changes in the hemodynamic response with increasing speech duration (Janz et al., 2001). Nevertheless, it is clear that TRs should be as short as possible to achieve the best separation of motion effects and hemodynamic response. Even if the upward shift of the maximum of the hemodynamic response with increasing speech duration would result in a somewhat slower rise of the correlation coefficient, the general dependency especially with respect to TR would remain unchanged. This means the correlation coefficient would still rapidly increase with TR. At the current simulation the correlation coefficient for a speech duration of 3 s more than triplicates (from 0.12 to 0.44) when TR increases from 1 to 3 s (see lower right panel of Fig. 3).

However, short TRs prohibit high image resolution and brain coverage. Therefore, temporal resolution must be carefully balanced against spatial resolution and brain coverage. Since language studies cannot be reasonably restricted to small brain areas, the minimal TR is prescribed by the shortest period allowing the acquisition of a whole brain volume. Probably, this time will decrease in the future due to the availability of faster gradient hardware and the application of novel acquisition strategies, e.g., parallel imaging. However, in the current study the shortest possible

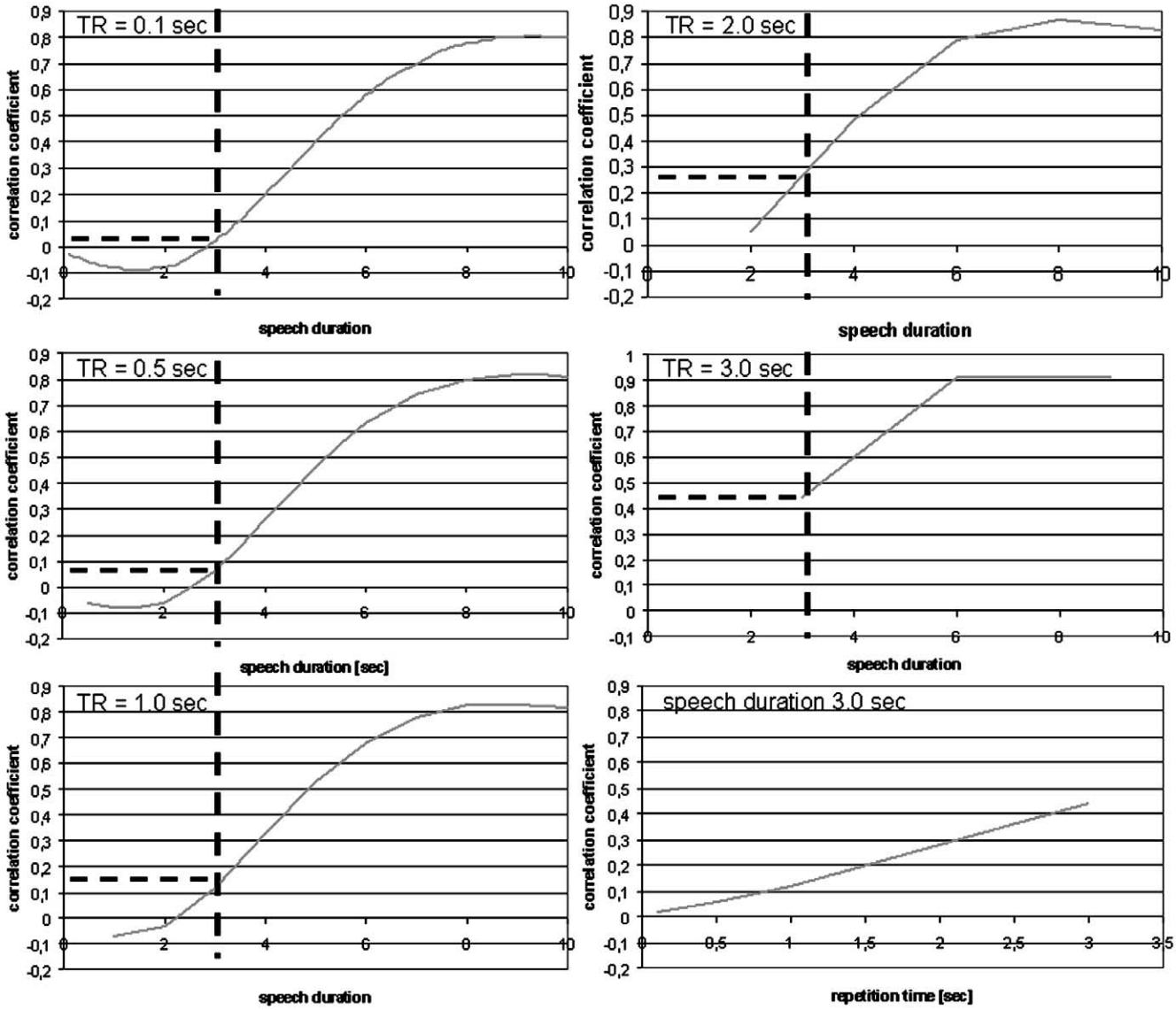

Fig. 3. Correlation of the hemodynamic response with a rectangular boxcar function of variable length corresponding to speech duration. To elucidate the effect of an increased undersampling of the hemodynamic response (see Fig. 1), the dependency of the correlation coefficient on speech duration is shown for five different repetition times (TRs). The lower right panel emphasizes the effect for a speech duration of 3 s.

acquisition time was 3 s, which allowed to cover the whole brain with 18 slices.

Stimulus-correlated motion

The automated motion correction algorithm detected significant motion in all subjects and conditions involving overt speech. Fig. 4 shows the accumulated translations in *x*-, *y*-, and *z*-direction detected in one single subject. For most subjects, incremental translations in either *x*-, *y*-, or *z*-direction did not exceed 2 mm and angular deviations usually remained within 1°. However, in singular subjects incremental translations up to 5 mm and angular deviations of 5° were observed. While the detected scan-to-scan motion during speaking events usually was rather large, the accumulated drift over the entire experiment remained comparatively small (see Fig. 4). This agrees with the observation of Barch and coworkers (1999, 2000) who found that during speaking subjects exhibited small movements to and from their current head positions rather than progressively shifting away from their initial head positions.

The comparison of single-subject activation maps without and with modeling of speech-related artifactual signal changes often revealed a decrease especially in the extent of activation. In the majority of cases this effect was more pronounced when the motion parameters were used instead of the simple boxcar function. This decrease in activation can be interpreted as some kind of subtraction of artifactual signal components from the task-related hemodynamic response. Since the effect generally increased when the mo-

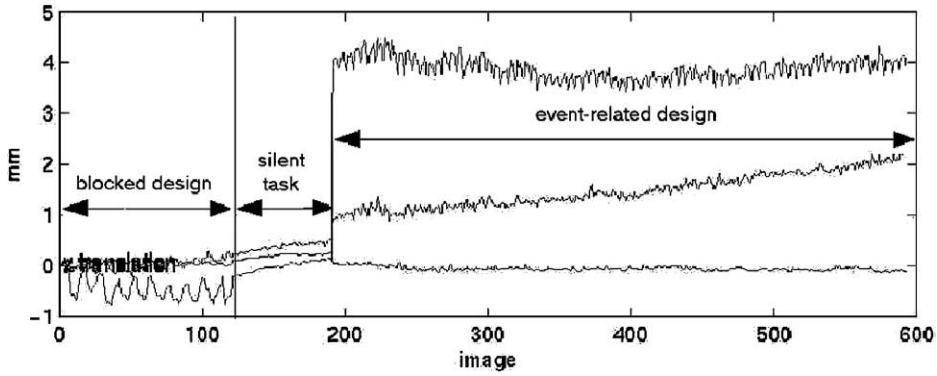

Fig. 4. Detected stimulus-correlated motion (*x*-, *y*-, and *z*-translation) for the blocked and event-related experimental design, and for a silent language task, displayed for one subject.

tion parameters were used instead of the simple boxcar regressor, one may conclude that the residual variance was more closely modeled by these parameters. This could also be expected since the motion parameters can be considered as a direct measure for the individual subject motion, which gives rise to additional signal fluctuations because of spin history effects and magnetic field variations, while the boxcar model is completely rigid. This view is also supported by a direct correlation of the motion parameters with the boxcar regressor. Even though the motion parameters often exhibited a rather high periodicity that looked similar to the boxcar at a first glance, the actual correlation coefficient usually remained rather low (<0.3) with some exceptionally high correlations up to about 0.6.

A direct estimation of the statistical effects of both types of artifact regressors revealed in some cases clustered artifactual activation in frontobasal brain regions or along slices at the height of the lateral ventricles. Most often, however, the artifactual activation did not survive corrected activation thresholds and was rather distributed and diffuse. It appears to be rather strange that artifacts seemed to spare high contrast CSF tissue borders, but these effects were most likely removed by the motion correction procedure. The remaining signal fluctuations most likely were mainly due to spin history effects and changing magnetic fields, which are not necessarily expected to concentrate at high contrast borders. In accordance with our observations in some subjects, spin history effects should be most severe in areas with long T_1-relaxation times (e.g., ventricles), while frontobasal brain regions are expected to be most susceptible to magnetic field fluctuations caused by the changing pharyngeal space.

Influence of speech duration

For the experiments performed at various speech durations, the maximum *t* values of artifactual activation were determined in the above defined six ROIs. One of three subjects never showed any obvious artifact. Two subjects showed slight artifacts in the fourth ventricle (ROI 1). In these subjects either the shortest or the three shortest speech durations were free of artifacts. With prolonged speech durations the maximum *t* value and extent of the artifactual activation increased. However, it is not quite clear whether the artifactual activation observed in the fourth ventricle can be solely attributed to motion. Since this area is also traversed by a large venous vessel, artifactual activation in this area could also be due to an unspecific large-vessel BOLD effect, which might also increase with increasing overall activation at increasing speech duration. Thus, it could not be discerned whether the increase in artifactual activation in two subjects is due to the rising influence of stimulus-correlated motion. In any case, the observed artifact level seemed to remain at moderate levels up to the longest investigated speech duration of 4 s.

In all three volunteers, the inclusion of an appropriate boxcar function or the realignment parameters as artifact regressors led to a clear reduction in the extent of activation as already discussed above. A qualitative comparison of the activation related to speech production revealed that the extent of activation clearly increased with speech duration. While short utterances did not evoke much activation beyond motor regions, prolonged speech periods of 3 or 4 s revealed a more extended activation in well-known language areas.

Artifacts and task-related activation at a speech duration of 3 s

A more reliable estimation of the relative artifact levels was possible when the larger group of subjects, who performed the event-related design with a speech duration of 3 s, was compared to the group of subjects who performed the reading task in a blocked design. The favorable effects of the event-related experimental design became apparent by determining the artifact levels (maximum *t* values) in the above-defined six ROIs. Table 1 summarizes the results for all subjects who performed the task in one or both experimental conditions. Obviously, the blocked design exhibited a clearly elevated artifact level. Thirteen of 16 subjects

Table 1
Severity of artifactual activation at cerebrospinal fluid tissue boundaries[a]

Experimental design	No. of subjects	Maximum t value in ROI (No. of subjects averaged)					
		1	2	3	4	5	6
Blocked	16	7.05 (13)	6.98 (7)	6.93 (10)	6.63 (7)	7.86 (5)	7.02 (10)
Event-related							
Dysfluent	33	6.86 (13)	—	—	—	—	4.33 (1)
Fluent	25	8.41 (6)	5.26 (1)	—	—	—	—

[a] Maximum t values in six regions of interest (ROIs) prone to artifactual activation: ROI 1 = fourth ventricle; ROI 2 = posterior part of lateral ventricle (left); ROI 3 = posterior part of lateral ventricle (right); ROI 4 = anterior part of lateral ventricle (left); ROI 5 = anterior part of lateral ventricle (right); ROI 6 = third ventricle.

(81%) showed artifacts in the fourth ventricle (ROI 1), 10 of these subjects (63%) had further artifacts in one or more additional ROIs. Only 1 subject did not show any artifactual activation in these ROIs. With the event-related design only 20 of 58 (34%) subjects showed odd activation. In 19 subjects the suspected artifact was located solely in the fourth ventricle (ROI 1). Only 1 subject showed an additional artifact in ROI 2. Fig. 5 shows selected axial slices at

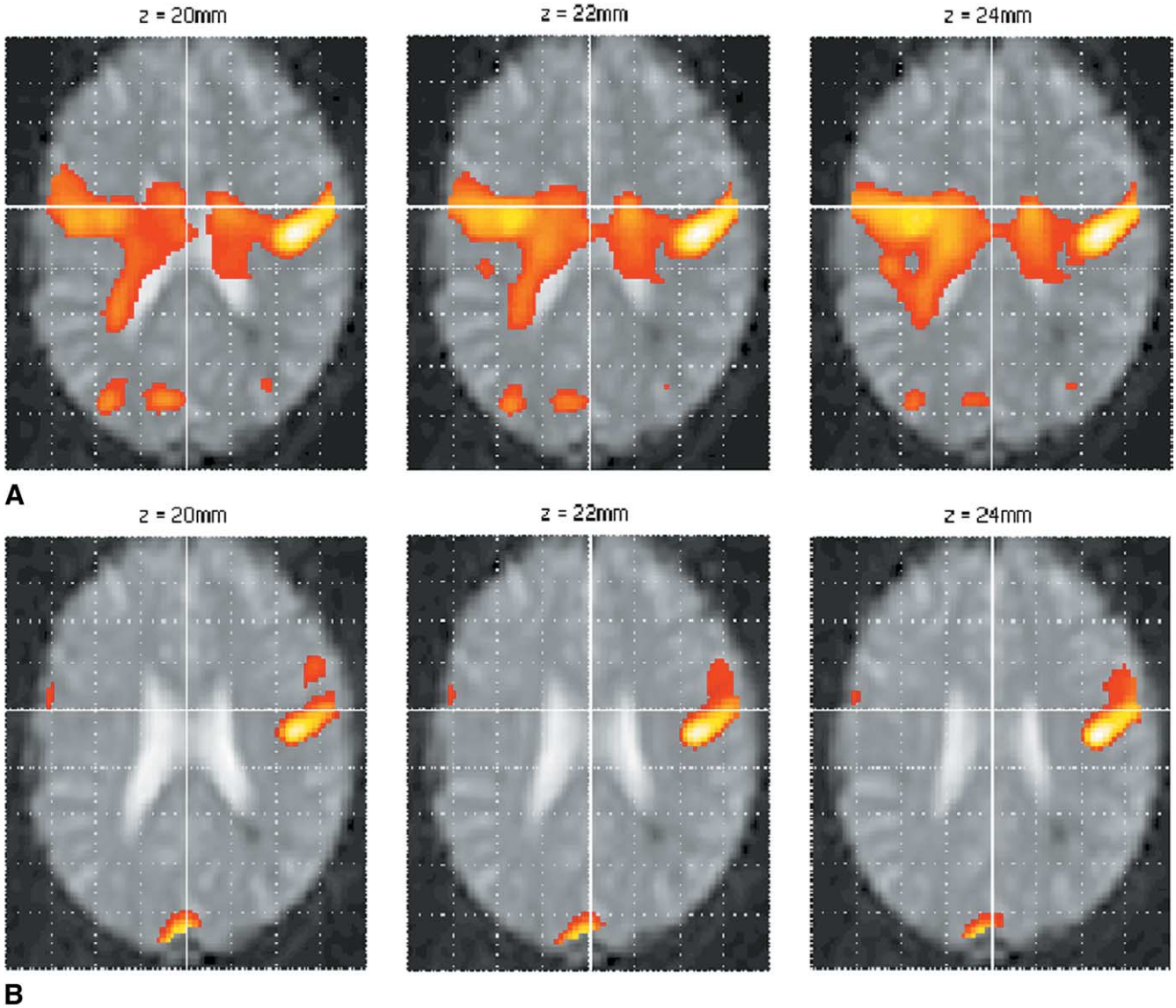

Fig. 5. Activation pattern found in one subject ($P < 0.05$, corrected). Blocked design (A); event-related design (B).

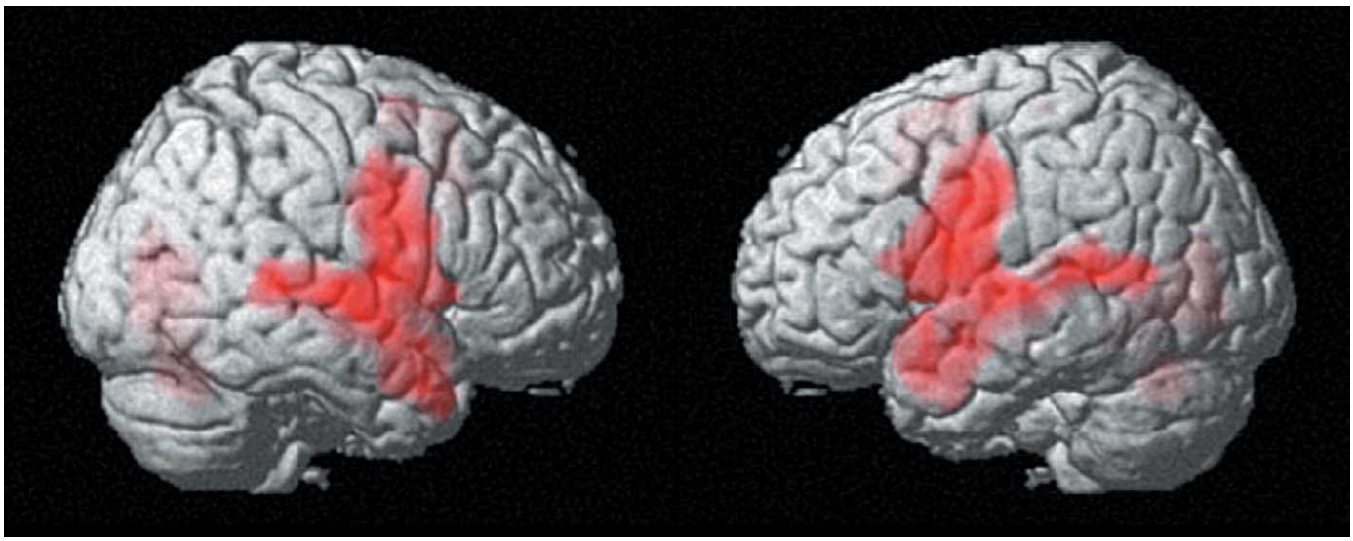

Fig. 6. Activation patterns found in the analysis of 16 fluent male subjects acquired with the event-related design (random effects analysis; $P < 0.01$, uncorrected).

the level of the lateral ventricles from a single subject as an example for artifact reduction. Statistical maps resulting from the blocked (Fig. 5A) and the event-related (Fig. 5B) designs were overlayed on EPI images taken from the respective time series. The activation map resulting from the blocked experiment (Fig. 5A) exhibits typical motion artifacts at high contrast CSF tissue borders, while such obvious artifacts are clearly missed in the map generated from the event-related data (Fig. 5B). Considering the frequency distribution of artifact severity for fluent and nonfluent speakers separately, there were 19 of 33 nonfluent and 18 of 25 fluent subjects, respectively, who did not show any artifacts in the investigated ROIs. The remaining subjects showed predominantly slight artifacts in the fourth ventricle (13 dysfluent, 6 fluent speakers). Only 1 fluent speaker showed additional artifacts in the posterior part of the left lateral ventricle (ROI 2).

As discussed above, it is not quite clear whether the artifactual activation observed in the fourth ventricle might be due to an unspecific large-vessel BOLD effect instead of motion. This effect could also be generally enhanced in stuttering subjects because of the higher overall brain activation. If the artifactual activation in ROI 1 is disregarded because of its unclear origin, the suppression of motion artifacts achieved by the event-related compared to the blocked design is excellent. Even with inclusion of ROI 1 the difference is convincing.

Fig. 6 displays an activation map obtained by a second-level random effects analysis of 16 fluent male speakers. Activated brain regions include auditory (primary and association cortices) and speech-related areas (Broca and Wernicke's area) as well as motor areas (primary and supplementary motor cortex, and cerebellum). The ability to detect these well-known areas, which are typically seen in speech production paradigms (Price, 2000; Fiez and Petersen, 1998), indicates that the proposed event-related experimental design is actually able to reliably detect task-related activation.

Conclusion

The results of our simulations indicate that a sufficiently short TR facilitates a proper separation of stimulus-correlated artifacts, while the actual length of the speaking interval is not so important, at least up to a duration of about 3 s. Nevertheless, an event-related experimental setup with a prolonged stimulus duration and TR of, in each case, 3 s already significantly reduced the influence of stimulus-correlated motion caused by overt speech. Not only were the resulting statistical maps in the majority of cases virtually free of typical artifacts near CSF tissue boundaries, they also revealed well-known task-related activation. This suggests that event-related fMRI provides the sensitivity to reliably investigate paradigms that depend on overt speech.

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