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Making the most of fMRI at 7 T by suppressing spontaneous signal fluctuations

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Abstract

The presence of spontaneous BOLD-fMRI signal fluctuations in human grey matter compromises the detection and interpretation of evoked responses and limits the sensitivity gains that are potentially available through coil arrays and high field systems. In order to overcome these limitations, we adapted and improved a recently described correlated-noise suppression method (de Zwart et al., 2008), demonstrating improved precision in estimating the response to ultra-short visual stimuli at 7 T. In this procedure, the temporal dynamics of spontaneous signal fluctuations are estimated from a reference brain region outside the area targeted with the stimulus. Rather than using the average signal in this region as regressor, as proposed in the original method, we used Principal Component Analysis to derive multiple regressors in order to optimally describe nuisance signals (e.g. spontaneous fluctuations) and separate these from evoked activity in the target region.

Experimental results obtained from application of the original method showed a 66% improvement in estimation precision. The novel, enhanced version of the method, using 18 PCA-derived noise regressors, led to a 160% increase in precision. These increases were relative to a control condition without noise suppression, which was simulated by randomizing the time-course of the nuisance-signal regressor(s) without altering their power spectrum. The increase of estimation precision was associated with decreased autocorrelation levels of the residual errors.

These results suggest that modeling of spontaneous fMRI signal fluctuations as multiple independent sources can dramatically improve detection of evoked activity, and fully exploit the potential sensitivity gains available with high field technology.

Keywords

Evoked responses; spontaneous signal fluctuations; noise modeling; correlated noise; estimation precision; temporal autocorrelation; BOLD fMRI; high field strength

Introduction

Recent developments in high field technology and detector arrays have dramatically increased the sensitivity of MRI. The resulting increases in image signal to noise ratio (SNR) have led to substantial improvements in both anatomical and functional resolution, revealing the laminar and columnar resolution of human brain in-vivo (Duyn et al., 2007, Yacoub et al., 2008).

On the other hand, attempts at converting increases in SNR into improved measurement of the response amplitude in BOLD fMRI experiments have had limited success. In part, this has

been due to the fact that fMRI estimation precision is not only dependent on image SNR, but also on temporal signal stability over repeated images as reflected in the temporal SNR (TSNR).

Undesired signal variability can originate from a number of sources, including thermal (electrical) noise, physiologic processes, subject motion, and spontaneous neural activity. Thermal noise is inherent to the MRI imaging process, has a “white” character (uniform power spectral density) and originates from both the brain tissue as well as from the detector electronics. It is the noise included when calculating image SNR, and can be reduced with state of the art technology such as high field MRI and multi-channel detector arrays. Non-thermal noise sources on the other hand are generally proportional to signal strength (Hyde et al., 2001). Their effective suppression is not as straightforward but nevertheless necessary to fully exploit the available SNR and achieve optimal fMRI sensitivity.

Several methods have been proposed to suppress non-thermal noise sources, including head motion correction, correction for changes in global signal level, instrumental drift correction, and correction of physiologic fluctuations. The latter is based on using additional information based on concurrently acquired physiological signals such as end-tidal CO₂ (Wise et al., 2004), cardiac and respiratory cycles (Josephs et al., 1997; Glover et al., 2000), respiratory flow rate (Birn et al., 2006), and cardiac and respiratory rate (Shmueli et al., 2007). Although these methods can be applied quite effectively, substantial signal variability generally remains, in part because some of the signal fluctuation does not correlate with physiologic parameters. An example is the so-called “resting state activity” (Biswal et al., 1995; De Luca et al., 2006), which generally presents as multiple independent spatio-temporal patterns of signal fluctuation that might relate to spontaneous neuronal activity.

Recently, a novel method was introduced that allows suppression of non-thermal noise sources without relying on physiological signals (de Zwart et al., 2008). This method exploits the fact that in many brain regions, temporal signal fluctuation are spatially correlated (Fox et al., 2006; de Zwart et al., 2008). Noise suppression is achieved by deriving a noise estimate from a brain reference region that has little or no involvement with the stimulus protocol. The reference region is derived from a short rest scan, making the acquisition of 1-2 minutes of additional data the only requirement of this strategy.

Here we propose an improvement of this method that is based on a more accurate characterization of spontaneous fluctuations by extracting multiple noise regressors from the reference region using principal component analysis (PCA) (Pearson K, 1901). PCA is a powerful tool for characterizing structured noise and has been applied to fMRI previously (Thomas et al., 2002). In the following, the use of multiple noise regressors, derived from a brain reference region, is evaluated in an fMRI experiment at 7 T in which the response to weak visual stimuli is measured.

Materials and Methods

Suppression Strategy

The novel noise suppression method aims at separating task-evoked activity from non-thermal, spatially correlated noise sources. The method is an extension of an earlier version (de Zwart et al., 2008) and is based on modeling the temporal characteristics of the noise with regressors that are derived from a brain reference region that exhibits noise behavior similar to the region targeted with the stimulus (ROI_{active}, e.g. see Figure 1). This reference region (ROI_{ref}, e.g. see Figure 1), is selected from the pixels that show the strongest correlation with the average signal in ROI_{active} during an additional fMRI resting scan that is acquired in the absence of stimuli. In brief, the original procedure consists of the following five steps (de Zwart et al., 2008):

1. An initial estimate of the activated region, ROI_{active} (e.g. see Figure 1), is made using conventional general linear model (GLM) analysis of the task scan.
2. From the rest data, the average time-course signal in ROI_{active} is calculated. This is an estimate of the structured noise in the activated area(s) during the rest scan, since the thermal noise is largely suppressed by the averaging over voxels in ROI_{active} .
3. ROI_{ref} (e.g. see Figure 1) is determined by correlation of each voxel time-course signal during the rest scan with the structured noise estimate determined in step 2. Voxels with significant correlation are included in ROI_{ref} with the exception for voxels that exceeded a liberal significance threshold in step 1 (see (de Zwart et al., 2008) for more details about this threshold).
4. An estimate of non-thermal signal fluctuations during the functional run is computed as the average signal in region ROI_{ref} using the data from the task scan.
5. An improved estimate of the extent and amplitude of activation is made using a modified GLM analysis, in which the structured noise estimate derived in step 4 is used as an additional regressor.

In the original implementation, a single noise regressor is derived from the average signal in the reference region (step 4). Although this method can substantially improve the measurement of evoked responses, it was not designed to deal with the potential presence of multiple non-thermal noise sources. Here, we propose to address this issue by modifying step 4 of the original procedure by using multiple regressors derived from PCA on the reference region. This allows the identification of multiple noise sources in ROI_{ref} to potentially allow better modeling of spontaneous fluctuations in ROI_{active} . In step 5, the principal components explaining the largest variance in the signals within ROI_{ref} are used as spontaneous-signal-fluctuation regressors (instead of a single regressor) in a GLM analysis. The number of PCA components used as spontaneous-signal-fluctuation regressors can be determined from the relative contribution of non-thermal noise to the overall noise in the experiment, as will be set out below.

fMRI stimulation protocol

The novel noise suppression strategy was evaluated in a visual stimulation experiment at 7 T with the aim of demonstrating improved estimation of the response to weak visual stimuli. For this purpose, two different retinotopic stimuli were used that occupied small regions of the visual field (Figure 2) and targeted correspondingly small areas in the occipital cortex. Each of these stimuli was briefly (100 ms) presented in separate event related (ER) paradigms, using 32 trials at fixed inter-trial intervals of 14.9 s.

Each ER stimulation run was immediately followed by 2 minutes of rest (eye-fixation on the central dot) that served to select ROI_{ref} (see (de Zwart et al., 2008)). To allow improved selection of ROI_{active} , functional localizer runs were also performed for each stimulus. These functional localizer runs employed a block-design, containing 6 cycles of 30 s OFF and 30 s ON for a total of 6 minutes for each stimulus type. During ON periods stimuli reversed contrast at 7.5 Hz, using the same stimuli as in the corresponding ER experiment (Figure 2). An example of the brain areas identified as ROI_{active} and ROI_{ref} with these stimulation protocols is shown in Figure 1. During all tasks, subjects were asked to fixate on a dot displayed in the center of the visual field. In order to guarantee fixation and passive viewing of visual stimuli, subjects were asked to press a button whenever the brightness of this central dot changed. The dot changed brightness (toggle between light and dark grey) on average every 15 s, within the range 10-20 s.

All stimuli were rear-projected on a translucent screen positioned on the scanner head coil, which was viewed by the subject through a mirror and a prism. A DLP projector, located outside

the magnet room, was employed to project the visual stimuli, and stimulus delivery was controlled by Presentation 11.0 software (Neurobehavioral Systems Inc., Albany, CA, USA). The stimulation computer monitored MR scanner triggers to synchronize stimulation timing with image acquisition. These pulses were recorded, as were the subject's button presses, using a data acquisition card (National Instruments Corp., Austin, TX, USA) at a sampling rate of 250 Hz.

Subject Preparation

Ten healthy subjects (age 33 ± 2 , 7 males) participated in the study after giving written informed consent. The protocol was approved by the Institutional Review Board (IRB) of the National Institutes of Health (NIH).

Image Acquisition

Data were acquired on a 7 T GE scanner using 16 coils out of a 32-channel Nova Medical array (de Zwart et al., 2004), predominantly covering the occipital lobe. Gradient-echo EPI scans were performed on each volunteer at 2.5 mm in plane isotropic resolution, with the following parameters: $240 \times 180 \text{ mm}^2$ FOV; 2 mm slice thickness; 0.4 mm slice-gap; 1 s TR; 32 ms TE; 60° flip-angle, SENSE rate 2, and a bandwidth of 250 kHz. Sixteen slices were acquired in interleaved order, stretching caudally starting from the vertex, and covering primary and extra-striate visual cortices in the occipital lobe. In the block design localizer run and in the event-related design run 360 and 480 scans were acquired, respectively. Coil sensitivity maps were derived from the first twelve image-volumes acquired in each run (de Zwart et al., 2002), which were not included in the functional analysis.

Compensation of B_0 fluctuations related to chest motion was achieved by modulation of B_0 shims in real time, with the procedure described in van Gelderen et al., 2007. A two-minute training scan for this correction procedure was performed at the beginning of each subject scan session.

Image Processing and Statistical Analysis

The aim of data analysis was to quantify the increase in efficiency in estimating stimulus-related fMRI responses to ultra-short stimuli when modeling the spontaneous fMRI fluctuations in the visual cortex using either a single regressor (SR) or a number of PCA-derived regressors. The same analyses were performed for the two stimulus types employed (foveal and wedge stimuli, see Figure 2).

The analysis involved pre-processing of the time-series data, GLM analysis with regressors representing the evoked response and correlated noise sources, GLM analysis with regressors representing the evoked response and randomized noise regressors representing a control condition, and calculation of relative estimation precision. These steps are briefly outlined below.

Pre-processing—Images were reconstructed off-line with custom code using IDL 7.0 (ITTVIS, Boulder, CO, USA). Image pre-processing included: a) slice-timing correction, b) realignment of head movements, and c) spatial co-registration between the four measured 4D-volumes per subject. Step a) and c) were performed with the FMRIB Software Library (FSL4.0, <http://www.fmrib.ox.ac.uk/fsl/>); step b) by the use of SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>).

GLM analysis—Univariate linear regression analysis was performed (in IDL) for both the functional localizer scans and the runs employing the ultra-short event-related paradigm. In all analyses, at least the stimulus regressor and 8 nuisance signals, modeling noise at very low

frequencies (offset, linear trend and 7 polynomials), were included in the design matrix (DM_0). The stimulus regressor was obtained by convolving the stimulation paradigm with a hemodynamic response function, modeled by a single gamma function (time between onset and response peak = 3.5 s, dispersion of the response = 3.5 s).

Data acquired during the block design stimulation were fitted to DM_0 in order to define a functional active area (ROI_{active}) responding to each stimulus type. For each subject, the slope of the fit with the stimulus regressor was tested for significance at $p < 0.05$, Bonferroni corrected for multiple comparisons.

In the short-stimulus scans, additional modeling of spontaneous spatially-correlated fluctuations was carried out by expanding the design matrix (DM) with a single regressor (SR) to explain spontaneous fluctuations ($DM = [DM_0 \text{ SR}]$, “SR-corrected” procedure). SR was estimated as described in de Zwart et al. (de Zwart et al., 2008), with the exception that ROI_{active} was determined from the block design data analysis using DM_0 .

In the proposed modification of the method, principal component analysis (PCA) was used to extract the M strongest noise sources from the reference region ROI_{ref} (de Zwart et al., 2008) for use as spatially-correlated fluctuation regressors ($DM = [DM_0 \text{ } DM_{PCA}]$, “PCA-corrected” procedure). M was chosen on the basis of an estimate of the amount of signal variance in the reference region that represents non-thermal noise and of the explained cumulative variance by each component (Figure 3). The ratio of overall SNR relative to thermal image SNR was computed as $1 - (TSNR/SNR)^2$, with TSNR and SNR equal to respectively the average temporal SNR and the (thermal) image SNR across voxels of ROI_{ref} and subjects. The image SNR was computed by dividing the signal in each voxel at a fixed time point (the 14th volume acquired after the beginning of each scan) by the square root of the noise covariance in the same voxel. To compute the noise covariance we acquired a noise image (obtained with 0° flip angle but otherwise identical scan parameters) for each coil and applied SENSE coil combination following the method of Pruessmann et al. (Pruessmann et al., 1999). The temporal SNR in each voxel was calculated as the ratio of the signal at the same time point (14th volume) and the standard deviation of the signal over time.

Correlated noise regressors were orthogonalized with respect to the stimulus regressor (X_{stim}). For the single regressor (SR), orthogonality with respect to the stimulus regressor was achieved by subtracting from SR that part which relates to X_{stim} , i.e. $SR_{\perp} = SR - X_{stim} (X_{stim}^T X_{stim})^{-1} X_{stim}^T \cdot SR$ (“ T ” is the transpose operator) (see also (de Zwart et al., 2008)). For the PCA-based regressors, PCA analysis was run on time-series data in ROI_{ref} after removal of the component related to X_{stim} from these data, employing the same formula as above (for example, for each voxel time-series signal y in ROI_{ref} we computed $y_{\perp} = y - X_{stim} (X_{stim}^T X_{stim})^{-1} X_{stim}^T \cdot y$).

GLM analysis with randomized regressors—In order to validate the proposed strategy we repeated the GLM analysis with randomized versions of the correlated noise regressors. This control strategy allows assessing whether performance changes might relate to over-fitting, rather than to true removal of non-thermal (i.e. non-white) noise sources. The use of randomized regressors results in design matrices $[DM_0 \text{ } SR_c]$, and $[DM_0 \text{ } DM_{PCA_c}]$, for the “SR-control” and “PCA-control” procedures respectively. Randomization was performed on the phase of the complex Fourier components, a procedure that leaves power spectral density (and hence the autocorrelation) unaffected. GLM analysis was repeated using 100 different randomizations of each original regressor, after which results were averaged and compared with the analysis using the original regressors.

Calculation of estimation precision—In the SR-corrected, PCA-corrected, SR-control and PCA-control data the average time-course signal in the active region ROI_{active} was computed after reintroducing the fitted stimulus regressor; subsequently the average short-stimulus fMRI response over 31 stimulus-events (the first was discarded from analysis) was calculated (Figure 4).

The estimation precision (EP), as a measure of improved fitting performance, was computed as follows:

$$EP = \frac{1}{\sigma_E \sqrt{c^T (DM^T DM)^{-1} c}} \quad (1)$$

with $c = [1 \ 0 \ \dots \ 0]$, and σ_E equal to the standard error of the short stimulus fMRI response across trials averaged over the 15 time points (seconds) following each stimulus onset. σ_E was computed from the short stimulus fMRI response obtained both with and without signal averaging across ROI_{active} , leading to a measure of EP at the ROI level and the voxel level respectively. For the voxel level computation, as a final step, σ_E was averaged across ROI_{active} . The square root of the first element of the matrix $(DM^T DM)^{-1}$ accounts for the different efficiencies in detecting the evoked response for the distinct design matrices (Liu et al., 2000).

The standard error σ_E was corrected for the degrees of freedom lost due to the use of additional regressors, as follows:

$$\sigma_E = \sqrt{\frac{n - p_1}{n - p_1 - p}} \langle s.d.(r_{[1 \dots 15]}(\text{trial}[1 \dots 31])) \rangle_{[1 \dots 15]} \quad (2)$$

with r equal to the short stimulus fMRI response for each trial (15 time points following stimulus onset for that trial); n equal to the number of scans used in GLM analysis, p_1 equal to the rank (number of independent regressors) of DM_0 (i.e. 10, considering nine regressors modeling ultra-low-frequency noise plus one stimulus regressor) and p equal to the number of structured noise regressors employed. Furthermore, s.d. stands for standard deviation and $\langle \rangle$ for the average across the 15 time points following stimulus onset.

In GLM, the normal distribution of error terms is an important assumption in order to have a controlled number of false positive errors. We hypothesized that expansion of the design matrix with proper noise regressors, as is done here, would be beneficial not only for improving the efficiency of detecting evoked responses, but also for more closely meeting this GLM assumption. To this end, we determined the temporal autocorrelation level (AL) of the residual errors after applying the SR- and PCA-correction procedures as well as the control correction strategies. AL was computed as the root mean square of the autocorrelation function (ACF_r) across lag 1 to 15 of the residual error terms (r) after running each analysis:

$$AL = \sqrt{\sum_{lag=1}^{15} ACF_r^2} \quad (3)$$

AL was evaluated on a voxel-by-voxel basis and results were averaged across $\text{ROI}_{\text{active}}$.

Results

On the basis of their behavioral performance (less than 15% errors in button presses), seven subjects out of ten were included in group analysis for the evaluation of the spontaneous fluctuations correction procedure. On average across these subjects, correlated noise sources could be adequately described by 18 PCA components, as determined from the cumulative variance explained by each component and the fraction of variance explained by non-thermal noise sources (see Figure 3). This was based on a comparison of SNR with TSNR in the reference region (see Materials and Methods) which averaged 110.2 ± 6.4 and 36.8 ± 2.4 (mean $\pm$ standard error (s.e.) across subjects) respectively.

An example of the effectiveness of the SR- and PCA-based correction methods and their controls is shown in Figure 4. Despite the brevity of the total stimulation time ($31 \times 100 \text{ ms} = 3.1 \text{ s}$), the response can be readily detected. It can be seen that inter-trial reproducibility (as observed from reductions in standard error) increases substantially relative to the control data. Note also that the standard error across trials remains approximately constant over time, suggesting that this error is not related to variability in the stimulus-induced response but rather originates from response-independent sources.

Averaged over all subjects, estimation precision (EP, see Figure 5 upper row) improved significantly ($p < 0.01$, paired t-test) for the SR-procedure, and further gains are seen with multiple PCA-derived regressors (with respect to SR- and PCA-control procedures, respectively). On average across stimulation types and volunteers, 66% and 160% increased estimation precision was achieved for ROI averaged signals with SR- and PCA18-correction respectively. Using standard error (σ_E in eq. (1)) values derived from voxel-by-voxel analysis, the increase of EP averaged 9% and 48% for SR- and PCA18-based correction respectively. In addition, the autocorrelation level (AL) of residual errors (Figure 5, lower row) significantly decreased ($p < 0.01$, paired t-test) when including the extra regressors (-10.3% and -42.4% for SR- and PCA18-procedures, respectively), approaching the autocorrelation level of simulated white residuals for the PCA18-based correction strategy.

Discussion

General Remarks

The presented work shows that modeling spatially-correlated spontaneous fMRI fluctuations can substantially increase fMRI sensitivity to stimulus-induced responses when fMRI performance is limited by non-thermal (correlated) noise sources. This is an issue of mounting importance, as the ever-increasing performance of MRI hardware leads to reduced thermal noise in fMRI experiments. Estimation of the correlated spontaneous fluctuations from the fMRI data acquired during the performance of the task paradigm is straightforward. Only a limited number of additional scans during a rest control condition are required (~ 1 -2 minutes).

For quantification purposes, the demonstration described above used an additional block paradigm to allow for improved ROI selection. This additional measurement might not be needed for all applications. In specific cases, the extent of the activated region can be derived from the stimulus run itself, as was described for the original method, or from alternative measures, such as anatomical data.

PCA versus SR-procedure

The use of PCA to identify and separate multiple correlated noise sources leads to substantial improvements in terms of estimation precision and residual autocorrelation level over the

original method using a single regressor. This suggests that, in the visual cortex, spontaneous fMRI signal fluctuations do not originate from a single source but rather from a number of physical sources. These could represent spontaneous brain activity, but might also include other sources related to physiological fluctuations and instrumental instabilities (Hyde et al., 2001; Kruger and Glover, 2001). These noise sources are particularly important when $\text{SNR} \gg \text{TSNR}$, a condition that can be readily met at high field (7 T) and with detector arrays.

In general, the choice of the optimal number of PCA components (M) should be related to the experimental conditions (TSNR, SNR). Although the amount of explained variance by non-thermal noise sources was met using 18 PCA components, the performance of the PCA-based method is not expected to strongly depend on the precise number of components, within a reasonable range around M : for instance, for these data the cumulative variance explained by 10 and 26 components is respectively equal to 82.8% and 90.0% (see also Figure 3).

Residual autocorrelation and whitening

Increased detection efficiency can be associated with inflated false positive errors if the residual error terms after model fitting are not independent observations and do not follow a Gaussian distribution.

Both parametric and non-parametric temporal auto-correlation correction procedures (Bullmore et al., 1996, Purdon and Weisskoff, 1998; Worsley et al., 2002, Woolrich et al., 2001) have been tested and applied to fMRI data, and are often called pre-whitening strategies: the majority (Bullmore et al., 1996, Purdon and Weisskoff, 1998; Worsley et al., 2002) accounts for first order autocorrelations, assuming auto-regressive processes described by one parameter (AR_1 models). Only in a few studies the auto-correlation estimation has been extended to higher lags (Woolrich et al., 2001). In general, residual autocorrelation in fMRI is not a completely resolved issue, and there is no straightforward solution or strategy to deal with it.

Since the additional “noise” regressors, which describe spatially-correlated spontaneous fluctuations, also exhibit temporal autocorrelation, we hypothesized that their inclusion in the regression model (or design matrix) could decrease the residual error auto-correlation, associating higher estimation precision with controlled false positives rates. Indeed this was the case, with a significant decrease in the level of the autocorrelation between lag 1 and 15 ($\text{TR} = 1\text{s}$) after SR- and PCA18-correction with respect to the control procedures, showing good whitening properties of the procedure. Without claiming a complete removal of residual autocorrelations (as visible from Figure 5, lower row, with respect to simulated Gaussian noise), our findings predict a more controlled expected false positive error by the use of the additional covariates of spontaneous fluctuations.

Stimulation design and stimulus size

The increase in detection efficiency obtained with the “noise” correction procedure for the employed ultra-short event-related paradigm extends the previous findings for a block design (de Zwart et al., 2008); moreover, the use of a stimulus covering a small portion of the visual field enabled us to better appreciate the spatial extent of spatially correlated noise sources in primary and extra-striate visual areas. Those regions were mainly covered by the activation elicited by the full visual field stimulus employed in the previous work and hence excluded from the reference region (de Zwart et al., 2008). The spatial distribution of synchronous fluctuations in the visual cortex identified here during visual stimulation extends previous reports (De Luca et al., 2006; Fukunaga et al., 2006) of the presence of a resting-state pattern in occipital areas during resting conditions.

Generalization to other sensory modalities

In addition to the presence of spontaneous fMRI fluctuations in the visual cortex (De Luca et al., 2006), the existence of sensory-motor and auditory resting state networks is well established (Biswal et al., 1995; De Luca et al., 2006). If such networks persist during activation, the strategy proposed here could hence be applied to improve the detection of evoked responses in other brain areas.

In this procedure, the reference region (ROI_{ref}) is determined during resting state. One possible source of critique is that the correlation patterns (“networks”) found during rest possibly disappear or change during activation, which would negatively affect the filtering performance. Most of the studies of resting state networks are performed with eyes closed and little is known about the persistence of those patterns under other conditions, especially during task performance. However, previous fMRI studies in the motor cortex (Fox et al., 2006; Fox et al., 2007) and in occipital areas (Bianciardi et al., 2008), demonstrated the persistence of the sensory-motor and visual networks during motor tasks and passive visual stimulation, respectively. The persistence of spontaneous fluctuations during the generation of evoked responses agrees with intra-cortical and scalp electroencephalographic (EEG) recordings, as well as with optical imaging studies (Berger, 1929; Arieli et al., 1996; Steriade, 2001; Kenet et al., 2003; Buzsaki and Draguhn, 2004). Furthermore, if the networks identified during rest would substantially alter during evoked activity the proposed method would in all likelihood perform poorly. Nonetheless, further work aimed at identifying spontaneous fMRI fluctuations in other sensory cortices (for example the persistence of the auditory network during auditory stimulation) will help in generalizing our findings.

Finally, the described procedure is a general strategy that can be a valuable tool in discriminating evoked from spontaneous fMRI fluctuations. This is an issue of increasing importance, considering the recent interest in the interpretation of fMRI resting state-networks and to investigate their presence, either unaltered or subject to changes in amplitude and extent, during task conditions. The suggested procedure can distinguish these two types of activity for any type of employed stimulus design, requiring only few additional scans.

Conclusion

Modeling of nuisance signals in the visual cortex substantially improves the measurement of fMRI evoked responses to ultra-short stimuli at 7 T. The strategy employed with multiple noise regressors also significantly whitens the residual error terms, which is crucial for valid statistical inference. The procedure can be generally employed to discriminate between spontaneous and evoked signal fluctuations, allowing the assessment of “resting-state” patterns during task fMRI paradigms.

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Figure 1. Map of the active (ROI_{active}, green) and the reference region (ROI_{ref}, red) for two example slices of a foveal-stimulus data-set for one of the volunteers. Activations were significant at $p < 0.05$, Bonferroni corrected for multiple comparisons.

Figure 2.

The two visual stimuli employed in the experiments, each consisting of a black-and-white checkerboard: A) a very small ring-shaped checkerboard with 0.5-1.2° eccentricity range (“foveal stimulation”), and B) a narrow wedge-shaped checkerboard (“wedge stimulation”) in the lower-left quadrant (eccentricity range = 0-11°, width = $\pm 10^\circ$ around polar angle 225°). In both cases, the visual angle of the entire image was 42°×32°.

Figure 3.

Plot of the percentage of (cumulative) explained variance as a function of the number of PCA components, employed to determine the number of PCA components to use during analysis. The procedure employed to define the number of principal components describing non-thermal noise sources in ROI_{ref} was as follows: The explained variance in ROI_{ref} (see Figure 1) for each rank-ordered PCA component (blue) is shown. The variance is computed after eigenvalue decomposition of the data covariance matrix, by dividing each eigenvalue with the sum of all eigenvalues. The cumulative variance (magenta), equal to the sum of the variances across all the components from 1 to each rank-ordered component number, is also shown. To establish the number (M) of principal components describing non-thermal noise sources in ROI_{ref} , first the fraction of variance explained by non-thermal noise sources was determined. This fraction is equal to $1 - (\text{TSNR}/\text{SNR})^2$, which was 87.3% on average for the data in ROI_{ref} in these experiments (solid horizontal line, black). The number (M) of components needed to describe that amount of variance was identified from the cumulative variance, resulting in M equal to about 18 for these data (dashed vertical line, black).

Figure 4.

Sample time-courses for the ultra-short stimulus runs for one volunteer, with A) foveal stimulation, and B) wedge stimulation. After applying the SR-, and PCA-based noise correction procedures and the control procedures, the average time-course signal in ROI_{active} was computed. Eighteen principal components were included in the PCA-correction procedure. Subsequently the average short-stimulus response over 31 stimulus-events was calculated and displayed (error bars indicate the s.e. across trials). The average standard error σ_E in the estimation precision formula (EP, Eq. 1) was computed as the mean of the standard-errors for the 15 time points following stimulus onset.

Figure 5.

Estimation precision (EP, upper panel) for stimulus-related responses, and the temporal autocorrelation level (AL, lower panel) of residual errors, after general linear model fitting with additional SR- (red) and 18 PCA (green)-regressors. Control conditions with randomized regressor(s) are indicated in cyan and blue. AL for simulated residuals with Gaussian properties is also displayed (yellow). The groups of bars on the left (A) and right (B) show results for foveal stimulation and wedge stimulation (ultra-short stimulus runs), respectively. The error bars indicate the average $\pm$ s.e. across subjects ($n = 7$).