Impact of Signal-to-Noise on Functional MRI

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Functional magnetic resonance imaging (fMRI) has recently been adopted as an investigational tool in the field of neuroscience. The signal changes induced by brain activations are small (~1–2%) at 1.5T. Therefore, the signal-to-noise ratio (SNR) of the time series used to calculate the functional maps is critical. In this study, the minimum SNR required to detect an expected MR signal change is determined using computer simulations for typical fMRI experimental designs. These SNR results are independent of manufacturer, site environment, field strength, coil type, or type of cognitive task used. Sensitivity maps depicting the minimum detectable signal change can be constructed. These sensitivity maps can be used as a mask of the activation map to help remove false positive activations as well as identify regions of the brain where it is not possible to confidently reject the null hypothesis due to a low SNR. Magn Reson Med 44:925–932, 2000. © 2000 Wiley-Liss, Inc.

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The advent of functional magnetic resonance imaging (fMRI) has produced a surge of activity in neuroscience research. Significant advancements in fMRI data acquisition, data processing, and paradigm design have improved the quality of the functional images. These new advances have led to a greater understanding of cognitive function. It is known that a time series of images with a high SNR is required to detect activation-related signal changes, which are on the order of 1–5%. However, a thorough investigation of the minimum SNR required to confidently reject the null hypothesis has not been explored. In this study, the development of an SNR model for two different statistical methods is described. The SNR model facilitates the calculation of the minimum required SNR for a set of experimental parameters. Furthermore, the minimum SNR value can be used to form a map depicting the sensitivity to activation-induced signal changes. The sensitivity map is applied to clinical fMRI data.

BACKGROUND

Three-dimensional, spatially resolved functional neuroimaging was introduced with positron emission tomography (PET) and the concept of "cognitive subtraction" (1–3). By imaging the brain in two different states and subtracting them, one is able to infer function relative to a baseline task. Many neuroscience investigators have utilized this subtraction method to study sensorimotor and cognitive functions in the human brain.

fMRI is a relatively new technique which measures signal changes due to alterations in local tissue oxygenation. Activation maps are thereby generated, exploiting hemodynamic variations which are thought to be related to neuronal activity. This technique is called blood oxygenation level dependent (BOLD) imaging (4,5). The advantages of fMRI over PET are the improved temporal and spatial resolution, and its noninvasive nature. These advantages can be exploited in paradigm designs, allowing more complex and rapid alternations of brain states. Similarly, the simple method of subtraction can also be improved by employing statistical tests based on significance, such as the *t*-statistic, cross correlation, or the general linear model (6–8). The combination of the improved paradigm design and statistical techniques allows the investigator to pose more complex and detailed questions related to cognitive function.

SNR

The SNR is typically used to compare imaging hardware or acquisition methods. The concept of generating the SNR is simple: the mean signal divided by the standard deviation of the noise. However, it is the choice and treatment of the noise measurement that is critical to the SNR value. Often in the literature the type of noise or the region of interest (ROI) of the noise measurement is not discussed. Furthermore, the origin of the SNR measurement, whether from a static image or time series data is usually not disclosed. This lack of information makes it difficult to compare SNR values across research groups or to replicate studies. It is important to note that it is the SNR of the time series data and the stability of the signal which are central to fMRI. A brief description of the noise components in the MRI image is given below.

The types of noise that can be measured within a brain image are the background noise outside the brain (region free of phase-encode ghosts, S_{back}), the background noise within the brain (sinus region or signal void within the brain, S_{obj}), and the noise in the brain itself (S_{brain}). Each region contains different components of the noise signal. The S_{back} noise is related solely to the acquisition/receiver system, whereas the S_{obj} noise contains patient motion-related noise as well as S_{back} noise. Finally, the S_{brain} noise contains all of the noise in S_{obj} plus physiologic noise, partial volume effects, flow artifacts, and MR spin history errors.

The typical application of SNR is in the comparison of static images, such as images from two different coils or pulse sequences. However, in fMRI the goal is to detect

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small fluctuations in the signal over a period of time. Each one of the noise types described above will have distinct temporal characteristics that affect the SNR differently. In this study, the SNR was determined independently for each voxel over the time course of the data and was not based on the SNR from a single "static" image. All references to SNR within this work pertain to a time series measurement of SNR.

The *t* Statistic

Many fMRI experiments utilize the *t*-test to determine the significance of signal changes related to brain activation. In this study, the two-sample *t*-test was investigated to understand the dependence of the functional activation map on the SNR (9). It was assumed that the variance in each population was equal. In fMRI, ΔS, the percent signal change expected from neuronal activation, can be substituted for the difference in means if the data are mean corrected and normalized. It was further assumed for this analysis that the standard deviation of the noise and the number of images in the active and rest state were identical. The definition of the *t* statistic can be simplified to

$$t = \frac{\Delta S \sqrt{N}}{2 S_p}, \qquad [1]$$

where N is the total number of images acquired in the time series ($N/2 = N_{active} = N_{rest}$), excluding any dummy scans required to drive the MR signal to steady state. Solving Eq. [1] for the standard deviation of the noise (pooled estimate, $S_{p,}$) and then substituting it into the definition of the SNR (normalized signal/σ) describes the dependence of SNR on the experimental parameters,

$$SNR = \frac{2t}{\Delta S \sqrt{N}}. \qquad [2]$$

From this equation, it can be seen that a higher SNR is required for small signal changes, experiments with a small number of images, or a high t-value threshold. In this derivation the Type I error, α, has been specified by the t-value chosen, but the power has not been defined. The power, β, of the statistic determines the ability to properly reject the null hypothesis (true positive). The SNR value calculated from Eq. [2] is for an unknown power level and is not useable for the purposes of this study. Equation [2] does give the dependence of SNR on the other parameters, so it is possible to predict how SNR changes given an SNR value for a known β. To determine the dependence on β, and to understand the role of SNR in fMRI, a computer simulation was used to define the minimum SNR required for specific experimental and statistical parameters. These include the confidence level (t-value), power level (β), expected percent signal change (ΔS), and number of samples collected during the rest and active state (N).

Correlation Statistic

Another statistic widely used in the field of functional imaging is cross correlation (9). Typically this statistic is used for template matching or image comparison in signal processing applications. In fMRI, a measured time series is compared to a reference time series, which is a function of the paradigm and may be convolved with an estimate of the hemodynamic response. For the purpose of determining the SNR dependence, it is not possible to derive an analytic solution since a measured time series is required. However, it is possible to simulate the measured time series to determine how the correlation value depends on the noise and hence the SNR.

A goal of this work was to calculate a minimum SNR value required by the fMRI experimental parameters and statistical method used in order to detect an expected MR signal change associated with neuronal activation. The assumptions often employed in current fMRI statistical models, such as sample independence (in which each voxel is assumed to be independent of its neighbor), were also true for this study. This becomes more complicated if one uses spatially and temporally smoothed data. Nevertheless, the utility of the minimum SNR value is that it can be used prior to the experiment to determine the required experimental parameters (pixel size, or N) and/or during the post-processing phase to limit the regions of investigation to those with a SNR greater than SNR_{min} to improve the reliability of the functional maps.

METHODS

Computer simulations were used to determine the minimum SNR for both the *t*-test and the cross correlation statistic. Typical functional imaging experimental parameters were used to guide the simulations. To demonstrate the utility of the minimum SNR concept, the simulation results were applied to a set of clinical fMRI data to generate a BOLD sensitivity map. In the clinical BOLD sensitivity map, regions were coded white to identify zones in which BOLD signal changes could be detected. The anatomic data were merged with the BOLD sensitivity map with a threshold at specific signal changes (1% or 2%) to demonstrate which regions of the brain could be interrogated with confidence. This same data was further explored to show the sensitivity of the fMRI experiment to variations in the SNR.

Computer Simulations

A computer simulation was implemented on an HP UNIX workstation using MATLAB (Mathworks, Sherborn, MA). The simulation investigated the effects of noise on the *t*-test and the cross-correlation statistics. Random trials were created within the MATLAB programming environment, with a range of noise values giving rise to SNR values of 10 to 500. A boxcar design was modeled such that the baseline condition had a mean of 1 and a standard deviation determined by the noise value under investigation. For a given amount of signal change associated with the activation, an "active" time course was calculated centered on the new mean ($1+\Delta S$) with the same standard deviation as the rest data. The SNR was calculated over the entire time series data. To overcome errors related to random number generation, each functional experiment, consisting of N images, was repeated 10000 times (trials) at

Table 1
t-Score Required to Detect a 2% BOLD Signal Change

	N = 80	N = 112	N = 300
t with α = 5%	1.99	1.98	1.97
t with α = 1%	2.64	2.63	2.60
r = 0.3	2.71	3.23	5.33
r = 0.4	3.72	4.42	7.30
r = 0.5	4.82	5.73	9.47

Minimum t-score required to detect a 2% signal change for the number of images indicated. The lower half of the table shows the converted correlation coefficients in t-score values. For example, if N = 80 and r = 0.3, the equivalent t-score is 2.71.

each noise level. A t-score and a correlation value were calculated for each trial. The threshold values for the *t*-test were determined by choosing an alpha of 1% ($P < 0.01$) and 5% ($P < 0.05$) and the appropriate degrees of freedom based on N. The cutoff for the correlation statistic was set at r-values of 0.3, 0.4, and 0.5, which are typical for fMRI studies. Using the Fisher transformation, it is possible to calculate a Z-score for the corresponding correlation coefficient (10). When the degrees of freedom are sufficiently large (N > 40), then the t-value and Z-score are asymptotically equivalent. The converted correlation coefficients are listed in Table 1 for several values of N, allowing for comparison in terms of t-values.

The number of trials exceeding the significance threshold for each statistic was calculated. The level of detection of true positives, or power (beta) was set at 99% or 95%. The minimum SNR was determined to be the point at which 9900 or 9500 trials were greater than the threshold value for each statistical condition. Simulations were run for the different experimental parameters of trial length (N = 80 (simple clinical fMRI experiment), 112 (standard for our research work), and 300), and activation-related BOLD signal change (0.5%, 1%, 2%, and 5%). A minimum SNR value was calculated for the *t*-test (two levels) and for the cross correlation (three different thresholds).

Functional Imaging Application

Based on the results from the *t*-test and cross-correlation simulations, a minimum SNR was determined for a typical clinical experimental design: 8 blocks of 7 active and 7 baseline images, for a total of 112 images. The subject was an individual who had a cavernous malformation in the left parieto-occipatal region, which had bled in the last 3 months. A small amount of residual blood products was present and caused susceptibility artifacts on the functional images, thus reducing the SNR in the ROI. The imaging protocol allowed the MR signal to reach steady state prior to collecting the 112 images. A single shot, susceptibility-weighted EPI sequence was implemented on a Siemens Vision 1.5T scanner using the standard circularly polarized head coil. The imaging parameters used for functional imaging were TR = 4.35 sec, TE = 40 msec, readout bandwidth = 133kHz, voxel size = 3.75 × 3.75 × 4 mm, and matrix size = 64 × 64. A vacuum pillow was used to control head motion (11) and the functional data were motion corrected using SPM96 (7,8,12). The SNR of the functional time-series data was calculated for the re-

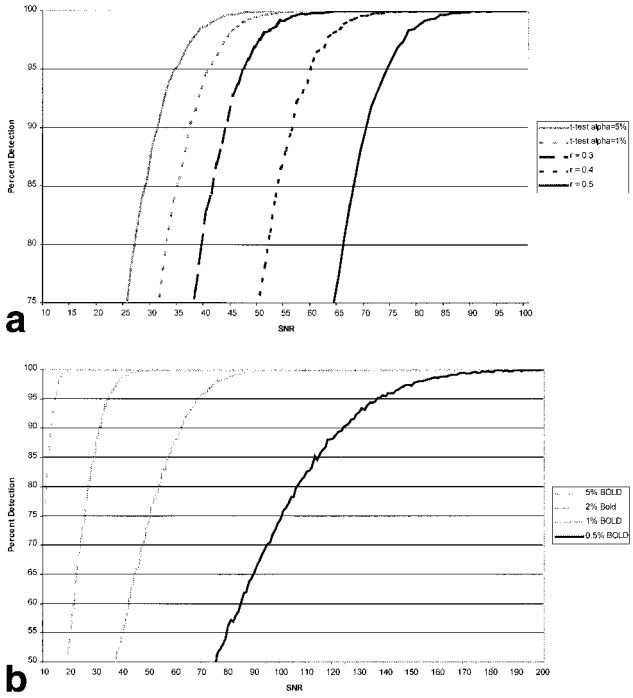

FIG. 1. The plot in **a** demonstrates the required minimum SNR value for an expected 2% signal change and *N* = 112 images. For the *t*-test with a 5% alpha and beta value of 95%, the minimum SNR is 34. As the required confidence increases, so does the minimum SNR value. Note that in general the SNR requirements for typical correlation values are higher than those of typical *t*-test parameters. **b** demonstrates the effect of an expected BOLD signal change on a specific statistical test, *t*-test with an alpha of 5% and *N* = 112. Note that the large signal changes (5%, small gray dashed line) are easier to detect because the required SNR is so low (SNR = 14). However, if smaller changes (<1%) are expected, the required SNR is much larger (SNR >70).

aligned time series and a spatially smoothed (6 mm FWHM Gaussian) version of the realigned data. An average signal change map was calculated for both sets of data. An SNR volume was created for each time series. The BOLD sensitivity map was created by thresholding the SNR volume at a level determined by SNR_{min} for a specific expected signal change. This data could be further processed such that several sensitivity maps could be displayed on a single anatomic image and different colors used to label ranges of BOLD signal change. Since the sensitivity maps

Table 2
Minimum SNR Required for a 1% Signal Change

	N = 80	N = 112	N = 300
t with α = 5%	82	69	39
t with α = 1%	96	83	46
r = 0.3	100	95	82
r = 0.4	126	120	106
r = 0.5	154	148	135

The values in the table represent the minimum SNR value needed to detect a 1% BOLD signal change with a detection rate (beta) of 95%. Note the decrease in the required SNR as the number of images in the time series is increased. This is particularly true for the *t*-test.

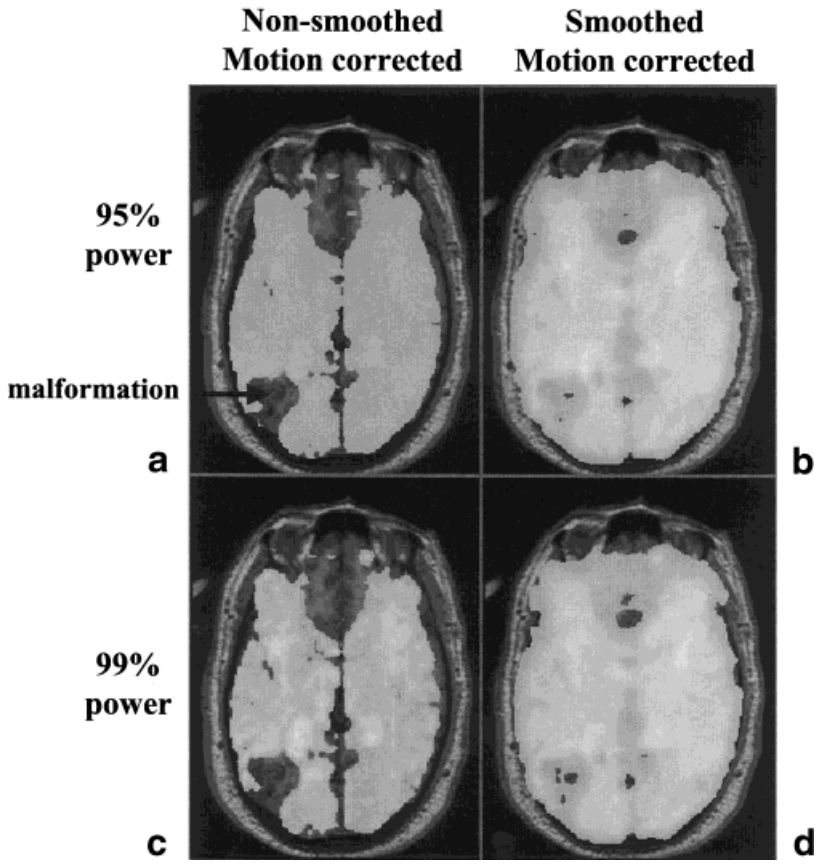

FIG. 2. This figure illustrates the importance of SNR and the impact of smoothing on the detection of BOLD signal changes. The white regions within the brain depict where it is possible to detect a 2% or greater signal change given: 5% alpha, $N = 112$ using a *t*-test. The level of confidence (power) is noted on the left side of the figure (95% or 99%). The left column is based on motion-corrected data; the right column is generated from spatially smoothed (6 mm), motion-corrected data. The region adjacent to the lesion cannot be investigated for signals smaller than 2% in the motion-corrected data. However, the smoothing dramatically improves the regions of the brain that can be tested for a 2% or greater signal change. The sinus benefits from the smoothing as well.

are based on the SNR_{min} value, larger than expected BOLD signal changes can also be detected. For example, a 3% signal change is detectable in the region labeled as 1% BOLD signal change. These BOLD sensitivity maps were then merged with the anatomical image to demonstrate the regions of the brain that were appropriate for statistical investigation. The BOLD sensitivity maps could also be merged with the original EPI data to demonstrate the effect of signal drop-out.

RESULTS

Computer Simulation Results

The results from the computer simulation are shown in Fig. 1. The percent detection (percentage of trials greater than the threshold value) is plotted vs. the SNR for both the *t*-test and cross correlation for the same experimental design (2% BOLD signal change and $N = 112$), Fig. 1a. The rapid drop-off in the number of detected trials is evident as the SNR decreases. Given the statistical parameters of a 95% detection rate and a *t*-test with an alpha of 5%, the minimum SNR for a 2% BOLD signal change is 34. For the cross-correlation statistic, the minimum SNR required at the same detection rate varies from 47 ($r = 0.3$) to 74 ($r = 0.5$). The SNR_{min} for the other experimental designs ($N = 80$, 112, or 300) are summarized in Table 2 for a BOLD signal change of 1%. Because the SNR_{min} varies linearly with signal change (Eq. [2]), it is easy to convert these data to the SNR_{min} for any expected signal change.

As shown in Fig. 1b, the effect of the BOLD signal change on the minimum SNR was investigated. The percent detection is plotted vs. SNR for a family of percent signal changes expected with constant experimental and statistical parameters of $N = 112$ and a *t*-test with an alpha of 5%. From this plot, it can be seen that the minimum SNR varies from a very high SNR ($SNR_{min} = 138$) for a 0.5% signal change to an SNR_{min} of 14 for a 5% change. The SNR_{min} varies with an inverse linear relationship to the expected BOLD signal change when all other parameters are held constant, as predicted by Eq. [2]. Below the SNR_{min} level, it is not possible to achieve the confidence level (beta) for detecting activation for the given imaging parameters.

Clinical fMRI Example

The results of a language functional imaging task performed on a patient with a cavernous malformation were used to demonstrate the impact of SNR. Figures 2 and 3 demonstrate the effect of smoothing and statistical power for different levels of the expected BOLD signal change with all other parameters held constant. In Fig. 2, the threshold for the BOLD sensitivity map was set at 2%, which depicts regions in which the SNR is sufficient to detect a 2% or greater BOLD signal change as white on the merged image. The first column of data is from non-smoothed, motion-corrected data; the second is from the smoothed time-series data. The top row of data is constrained to have a 95% power level, and the bottom reflects

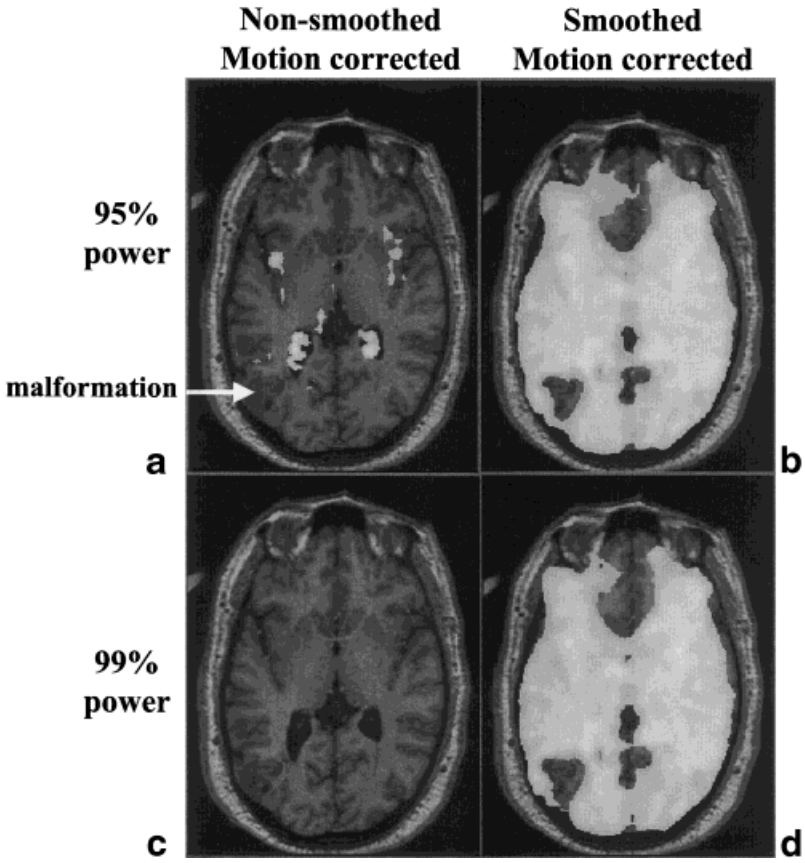

FIG. 3. This is similar to Fig. 2 except that the white regions demonstrate where it is possible to detect a 1% or greater BOLD signal change. No voxels survive the 99% confidence threshold for the motion-corrected data (**c**). There is a small number of voxels available for the 95% confidence level, and none in the region of the lesion. In contrast, the smoothed data (right column) includes most of the brain. Again, the regions of the sinus and lesion are not appropriate for investigation.

a 99% power level. The lesion produces a void in the BOLD sensitivity map, which is easily seen in Fig. 2a and c. By increasing the confidence level, the regions that can be investigated shrink. Figure 2b and d demonstrates the utility of spatially smoothing the data. The smoothed data maintains uniform coverage of the entire brain even at a 99% power level.

Figure 3 is structured in the same fashion as Fig. 2 but uses a 1% BOLD signal change as the threshold. In this experiment, it is not possible to detect a 1% signal change with a 99% power level in the motion-corrected data (Fig. 3c). Even for the 95% power level it is only possible to detect a 1% BOLD signal change in very limited regions. Conversely, in the smoothed time-series data it is possible to detect these changes in nearly all of the brain. Only regions directly surrounding the lesion and the sinuses are excluded.

To further demonstrate the importance of the SNR on fMRI, Fig. 4 depicts the signal change, BOLD sensitivity, and the functional map from the same clinical case. In Fig. 4a, the percent signal change while the subject performed a semantic decision task of synonym detection (13) is shown in shades of blue. The light blue color represents a 0.5% signal change; the darker the blue, the more intense the signal change. The BOLD sensitivity map for this slice is shown in Fig. 4b with shades of red. The light red regions represent areas in which it is possible to detect a 0.5% or larger BOLD signal change. The darker red regions require a larger BOLD signal change in order to be detected. The activation map shown in Fig. 4c was derived from SPM96 using an uncorrected threshold of $P < 0.001$ ($Z > 3.09$). Note that the percent signal changes (Fig. 4a, white arrow) are equal to or greater than those needed (Fig. 4b) in the region of the activation (Fig. 4c). This is not true for the region involving the lesion (Fig. 4, green arrow). The detected signal change does not meet the required level of BOLD signal change. It is quite possible that these regions were neuronally active but the SNR was lower than what was required to detect it.

DISCUSSION

Functional imaging demands high SNR images to reliably measure brain activation. In many fMRI studies, a significant amount of activation is displayed at the edges of the brain. These voxels may be incorrectly identified as active due to motion correlated signal changes. Spurious activations are also present in areas near susceptibility artifacts such as the sinus and temporal bone regions. These types of erroneous activations could be avoided by preprocessing (masking) the functional activation maps based on the BOLD sensitivity map for the type of statistic and experimental parameters used. The sensitivity map can also be used to evaluate whether specific regions of the brain meet the SNR requirements. This is useful for the development of paradigms and experiments, especially for fMRI projects investigating regions in the temporal lobes, orbito-frontal regions, and the cerebellum, since these brain regions are the most sensitive to signal loss in the EPI images.

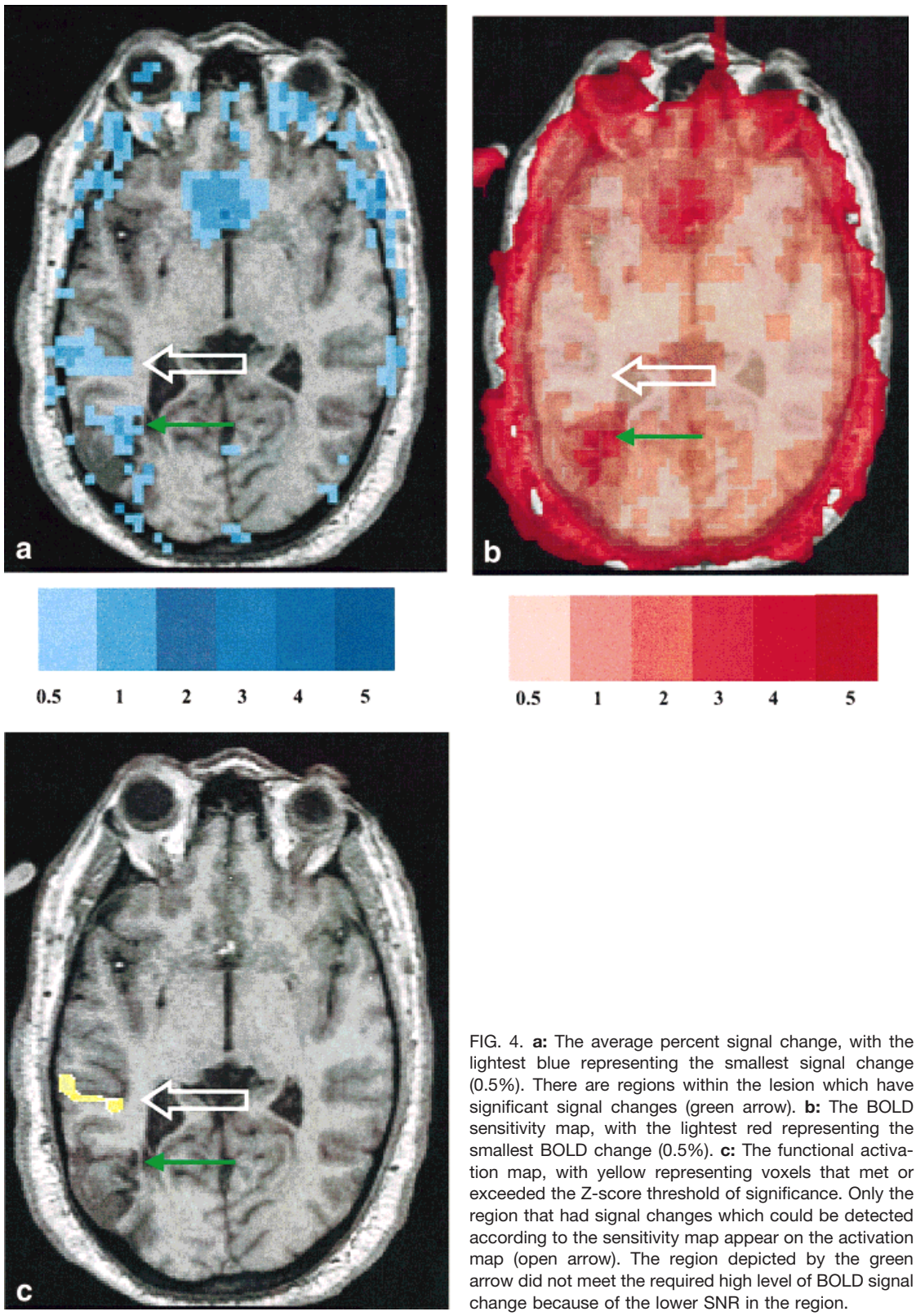

FIG. 4. **a:** The average percent signal change, with the lightest blue representing the smallest signal change (0.5%). There are regions within the lesion which have significant signal changes (green arrow). **b:** The BOLD sensitivity map, with the lightest red representing the smallest BOLD change (0.5%). **c:** The functional activation map, with yellow representing voxels that met or exceeded the Z-score threshold of significance. Only the region that had signal changes which could be detected according to the sensitivity map appear on the activation map (open arrow). The region depicted by the green arrow did not meet the required high level of BOLD signal change because of the lower SNR in the region.

An example of the utility of calculating an SNR map is the evaluation of the effectiveness of motion correction. A comparison of the time-series data was made before and after applying a rigid body motion correction scheme without corrections for spin history (7,8,12,14). The bulk of the brain, including the deep structures, had a small increase in SNR of 0–7%. However, the regions of the brain at the periphery, adjacent to the sinuses and ventricles, and other regions sensitive to motion had large increases in SNR of 20–120%. The increase in SNR was accomplished

by reducing the noise due to motion. The interpolation algorithm used to create the new, realigned images may introduce some smoothing by including information from surrounding voxels, which would further reduce the noise. However, since the motion from image to image is typically subvoxel (< .1 mm), this smoothing is not expected to be detrimental. The increase in SNR is substantial in regions of the brain that are sensitive to motion, and improves the sensitivity to BOLD signal changes.

An important role of the BOLD sensitivity map is quality control in clinical applications of fMRI as well as in neuroscience experiments. The act of overlaying the functional map on the anatomic data conceals the areas of signal loss. Identifying those regions with an SNR below the acceptable minimum value enables the investigator to visualize the impact of low SNR on the activation map. Specifically, if the regions not included in the BOLD sensitivity map were hypothesized to be active no conclusion could be made, due to insufficient SNR. This is important for clinical studies in which the physician is relying on the information to make a clinical decision. If the ROI in the brain is not included in the BOLD sensitivity map, no information can be gained from the imaging study and it should be repeated with the SNR improved in some way.

In fMRI data analysis, smoothing of the data both spatially and temporally has been used to improve the SNR at the expense of localization of the activation (7,8,15). The effect of spatial smoothing on BOLD sensitivity is evident in Figs. 2 and 3. The smoothing tends to spread out the activation and decrease its overall amplitude (smaller BOLD signal change) but substantially decreases the noise, thus making it easier to detect the activation-induced signal changes. The method described in this work allows one to visually investigate the effect of smoothing on the ability to detect BOLD signal changes. Once the images have undergone smoothing (6 mm FWHM Gaussian), the specific anatomical details are harder to identify based on the SNR. Nevertheless, the SNR values are significantly increased in Fig. 2b and d and Fig. 3b and d. This is seen by the increase in the regions colored white, which indicates where it is appropriate to investigate the experimental hypothesis. The regions that benefit the most from smoothing include the sinus region and the area surrounding the lesion. The tradeoff for an increase in SNR is the lack of specificity of the location of the activation.

The method used in this study is equivalent to evaluating the statistic (*t*-test or correlation) at a single point (alpha or beta) on the receiver operating characteristic (ROC) curve under conditions with varying SNR. Typically, the ROC curve is used to identify which test has the best overall performance. It is not the goal of this work to find the optimal operating point (alpha or beta) for fMRI, but to find the optimal SNR value given the constant constraint of the allowed true (beta) and false (alpha) positive rates. The values for the false positive rate are typically described with the statistic used. The detection rates are not usually mentioned, but they are assumed to be high. For presurgical clinical use, fMRI demands a detection rate of >99%, which implies that the SNR of the time-series data needs to be quite high.

A drawback to this method is the use of two simple statistics. There are many data analysis methods used in fMRI and all of these need to be explored in a similar manner in order to characterize the sensitivity to SNR. More complex models of the signal response will account for components of the noise, thus reducing the required SNR to detect the specific signal change. Voxel clustering is a good example. If an activated voxel has a neighbor that has a subthreshold statistical value, the voxel clustering-based algorithm would reward the neighbor voxel by lowering the required threshold or increasing its statistical value. The result is that the voxel is labeled active despite the lower level of BOLD signal change or SNR. The BOLD sensitivity maps derived in this study do not account for this type of modeling, but it could be modified to incorporate any model.

It is important to note that the values calculated in the computer model are independent of field strength, coil type, MR manufacturer, or other physical parameters. The computer model calculates the required minimum SNR to detect a given BOLD signal change. At higher field strengths there is more signal and the BOLD signal change may be larger for a particular paradigm, but the SNR still needs to be greater than the calculated minimum in order to detect it. The temporal stability of the MR signal is very important for the detection of small signal changes.

CONCLUSIONS

In this study, a method for calculating the minimum SNR for a given level of statistical confidence was developed. The concept of a BOLD sensitivity map was introduced which depicts regions in which a minimum signal change is required in order to be detected for a specific set of experimental parameters. In the clinical study, a region was identified that had a signal change on the order of the BOLD response; however, the SNR was not high enough to detect it. This region was adjacent to the lesion, thus demonstrating the clinical importance of SNR when conducting an fMRI experiment. In this example, the region around the lesion had sufficient SNR to detect signal changes greater than 1%. However, BOLD signal changes of 1% or smaller could not be detected near the lesion. Ideally, the protocol could be changed to increase the SNR in the region around the lesion to ensure that the lack of neuronal activation is real. This is especially important for presurgical planning applications.

The method introduced in this work allows the quantitative and qualitative comparison of fMRI imaging methods based on the SNR of the time-series data. It can also be used prior to the experiment to determine if the protocol will allow the detection of the expected BOLD signal changes. Using the minimum SNR value calculated from the computer model, a BOLD sensitivity map can be generated for use in conjunction with the functional maps. The application of this sensitivity map will improve the quality of the activation maps as well as increase confidence in the conclusions made about them.

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