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RESEARCH ARTICLE

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Logarithmic transformation for high-field BOLD fMRI data

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Abstract Parametric statistical analyses of BOLD fMRI data often assume that the data are normally distributed, the variance is independent of the mean, and the effects are additive. We evaluated the fulfilment of these conditions on BOLD fMRI data acquired at 4 T from the whole brain while 15 subjects fixated a spot, looked at a geometrical shape, and copied it using a joystick. We performed a detailed analysis of the data to assess (a) their frequency distribution (i.e. how close it was to a normal distribution), (b) the dependence of the standard deviation (SD) on the mean, and (c) the dependence of the response on the preceding baseline. The data showed a strong departure from normality (being skewed to the right and hyperkurtotic), a strong linear dependence of the SD on the mean, and a proportional response over the baseline. These results suggest the need for a logarithmic transformation. Indeed, the log transformation reduced the skewness and kurtosis of the distribution, stabilized the variance, and made the effect additive, i.e. independent of the baseline. We conclude that high-field BOLD fMRI data need to be log-transformed before parametric statistical analyses are applied.

Keywords Logarithmic transformation · fMRI · BOLD · Brain

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Introduction

Traditionally, BOLD fMRI data are analyzed using parametric statistical analyses without any transformation. However, such analyses (e.g. *t*-test, ANOVA, linear regression, etc.) typically assume that the data are normally distributed, the variance is independent of the mean, and the effects are additive, i.e. independent of the baseline. However, departures from these assumptions, especially the heteroskedasticity (i.e. inequality of the variances) and nonadditivity are likely to have serious effects on the results (Snedecor and Cochran 1989, pp. 273–296). Such violations could be due to physiological factors that underlie the measurements. For example, many functional maps in the fMRI literature are presented as percentage changes from the baseline, which assumes that the effect depends on the baseline; in

other words, it is assumed that the underlying model of the response is proportional. This assumption of proportionality is expected to break down for contributions to BOLD-weighted images that come from large blood vessels, predominantly due to blood-related effects that are particularly strong at lower magnetic fields such as 1.5 T (Uğurbil et al. 1999, 2000). At higher magnetic fields of 4 T and above, however, effects associated with microvasculature become increasingly dominant (Yacoub et al. 2000, 2003; Duong et al. 2003; Uğurbil et al. 2003), in which case the proportionality assumption will be increasingly valid. This implies that the data should be transformed before applying statistical tests assuming additive effects (e.g. *t*-test, ANOVA, linear regression, etc.). However, this step is often ignored. Instead, it is common to present percentage functional activation maps together with results of *t*-tests performed on the raw, untransformed data. In this study, we investigated such issues extensively by analyzing a large set of BOLD fMRI data obtained at 4 T in a visuomotor experiment. We found that such data need to be log-transformed before parametric statistical analyses are applied to them.

Materials and methods

Subjects

Fifteen healthy, right-handed human subjects [seven women and eight men, age (mean ± SD) 25.0 ± 7.3 and 24.5 ± 2.8 years, respectively] participated in these experiments as paid volunteers. The study protocol was approved by the University of Minnesota Institutional Review Board. Informed consent was obtained from all subjects according to the Declaration of Helsinki.

Experimental paradigm

Stimuli were generated by a computer and presented to subjects via a rear-projection screen and a mirror attached to the top of the head-gradient set. The stimuli were nine shapes (equilateral triangle, isosceles triangle, square, diamond, vertical trapezoid, pentagon, hexagon, circle, and vertical lemniscate; see Lewis et al. 2003). All shapes had the same surface area and subtended ~5° of visual angle. Subjects performed three 45-s tasks for each shape in a consecutive order. In the first task, they fixated a blue spot of light in the center of a black screen; in the second task, the light changed to red and a single white shape appeared around it; and in the third task, the light changed to green (a "go" signal) and the subjects drew the shape continuously by moving an X–Y joystick with their right hand. Subjects were instructed to copy the shapes counterclockwise at their own speed; no visual feedback was provided. The same sequence was then repeated for another shape, followed by another, until the nine shapes were shown in a random order; separate randomization was done for each subject. Subjects were instructed to maintain fixation throughout the tasks. The experiment was controlled by a personal computer and the X–Y position of the joystick was sampled every 10 ms (see Lewis et al. 2003 for details). In this work, we analyzed only data from the first three 45-s tasks for the first shape shown to avoid possible effects of drifts in the BOLD signal.

Data acquisition

A 4 T whole-body system with head gradients and a homogeneous radio frequency coil [Oxford (Oxford, UK)/Varian (Palo Alto, Calif., USA)/Siemens (Erlangen, Germany)] was used. A head support system with several foam pads was used to minimize head movements during the experiment. Multi-slice axial, sagittal, and coronal anatomic images (T1—weighted) were obtained using a turbo-FLASH sequence with 5 mm slice thickness and in-plane spatial resolution of 1.55×1.55 mm. For functional imaging, a T2*—weighted, single-shot Echo-Planar Imaging (EPI) sequence was employed (TE = 25 ms). Imaging planes were axial, with 5 mm slice thickness and in-plane spatial resolution of 3.11×3.11 mm. In total, 25–29 slices were collected, covering the whole brain. The acquisition time for a single slice was 100 ms; for a complete multi-slice image, the repetition time was 3.0 s. Images were collected continuously during the experiment. The duration of each study was 20 min and 15 s. In total, 405 multi-slice images were collected in each experiment (15 during each task) per subject; however, only the first 45 images were used for the present analyses (see above). The fMRI analysis package STIMULATE (Version 5.8.1; Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, Minn., USA) was used to process the fMRI images. Images were screened for motion artifacts by measuring variation in the center of mass of functional images over the entire time course. This measurement was performed separately for the X, Y, and Z coordinates. Subject motion was further assessed by forming a cine loop of the images. Both measurements were performed using the fMRI analysis program STIMULATE and motion correction was performed using automated image registration (Cox and Jesmanowicz 1999).

Data analysis

Task periods

For these analyses, only the first 45 images were used (see above), corresponding to 15 images for each of the three consecutive tasks for just the first shape. Specifically, (1) the rest (control) period was from the onset of the fixation spot until the appearance of the shape; (2) the visual presentation period was from the onset of the

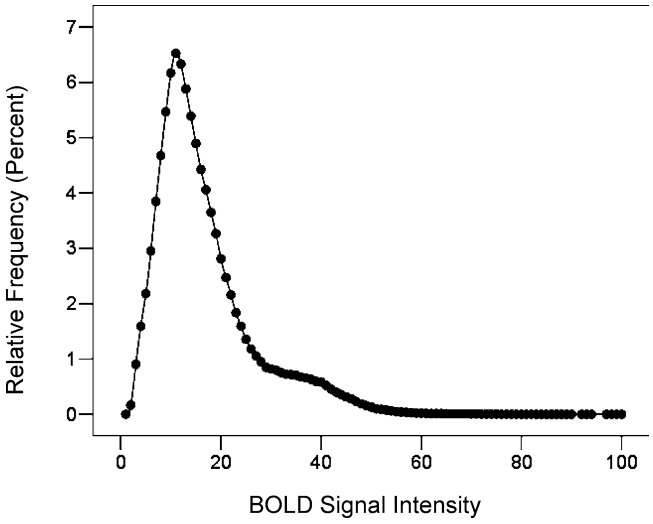

Fig. 1 Frequency distributions of whole-brain BOLD values from 15 subjects (see text for details)

shape until the onset of the go signal; (3) the copying (motor) period was from the onset of the go signal until the disappearance of the shape.

BOLD fMRI data extraction

Analyses were carried out on data from the whole brain. The data analyzed consisted of voxels for which the coefficient of variation in the control period was $\leq 5\%$, since it has been documented that the coefficient of variation is higher in the vicinity of large vessels as well as outside of the brain (Kim et al. 1994). This criterion ensured that the BOLD signal thus selected reflected activation in the brain uncontaminated from blood in large vessels.

The total number of voxels differed among subjects. In order for each subject to contribute equally to the analyses, the same number of voxels ($n = 19{,}000$) from each subject was entered in the database.

Statistical analyses

The SPSS for Windows (SPSS Inc., Chicago, Ill., USA, 2000) and the BMDP/Dynamic (BMDP Statistical Software, Inc., Los Angeles, Calif., USA, 1992) statistical packages were used for statistical analyses.

Results

BOLD fMRI data follow lognormal distribution

Parametric analyses typically assume normally distributed data. The BOLD fMRI data in each of the three periods (rest, visual, and motor) showed large deviations from normality; in fact, these data were distributed in a lognormal fashion. We present detailed results from the control (rest) period, i.e. from the first 15 images. (Very similar results were obtained for the other two periods.) The distribution of the intensity of voxels during the rest period is shown in Fig. 1 ($n = 19{,}000$ voxels×15 subjects×15 images = 4,275,000 data points). It can be seen that it is severely skewed to the right and hyperkurtotic. We calculated the coefficients for skewness and kurtosis (zero values indicate perfectly normal distribution). The estimated coefficients [± standard error (SE)] were 1.49 ± 0.001187 and 2.59 ± 0.00236, for skewness and kurtosis, respectively, with corresponding ratios of coefficient/SE of 1255 and 1097. These represent very large deviations from normality, and they are especially important, given the very large number of data points on which these estimates are based. (The ratios above are essentially normal deviates, where 1.96 indicates $P = 0.05$) The departure from normality is also demonstrated in the cumulative probability (P–P) plot shown

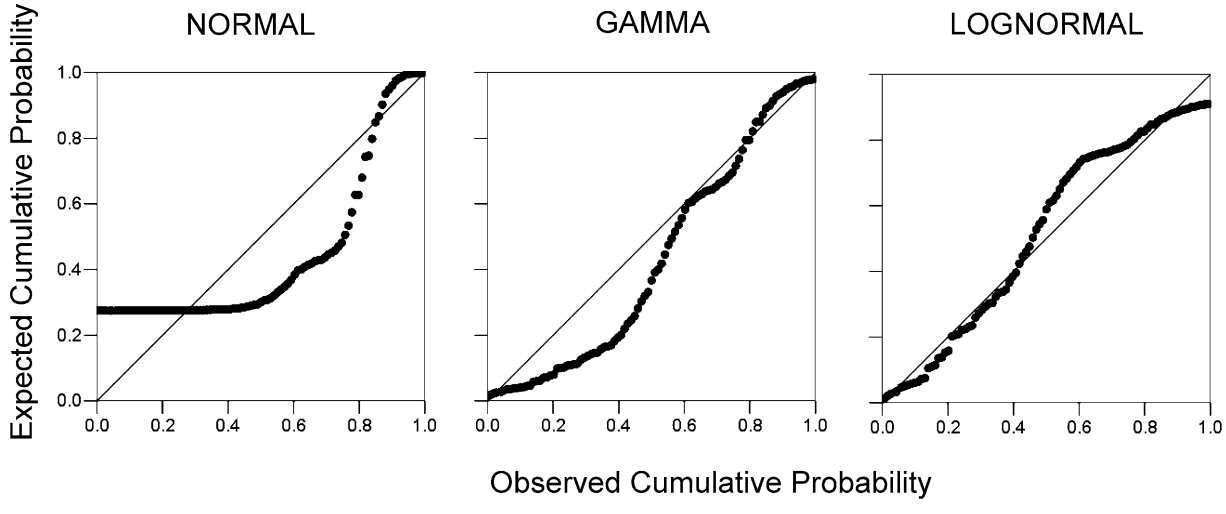

Fig. 2 Cumulative probability–probability (P–P) plots for normal, Gamma and lognormal fits for the data shown in Fig. 1

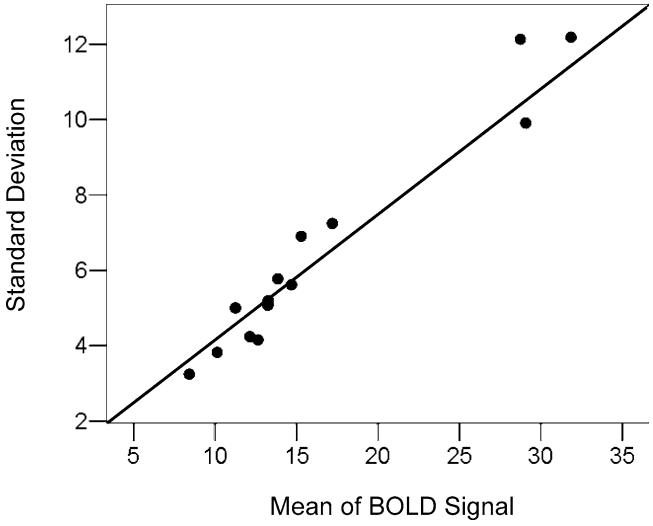

Fig. 3 Scatter plot of standard deviation against mean for the rest period for the original data ($n = 15$ subjects)

at the left panel of Fig. 2, as a substantial deviation of the observed points from the main diagonal. It can also be seen in the middle panel of this figure that a Gamma distribution was also a poor fit to the data.

The shape of the distribution in Fig. 1 is typical of a lognormal distribution; indeed a lognormal *p–p* plot (Fig. 2, right panel) shows a much closer, although not perfect, placement of the observed cumulative probabilities near the diagonal. We log-transformed the raw data and calculated the skewness and kurtosis coefficients, as above. The skewness coefficient became -0.16 ± 0.00122 (slight skewness to the left) and the kurtosis coefficient 0.2 ± 0.0023. Although statistically significantly differing from perfect normality (skewness and kurtosis absolute ratios of 131 and 87, respectively), the log transformation obviously effected a very substantial improvement towards normality: for skewness, the absolute value of its coefficient and its coefficient/SE ratio were reduced by almost a order of magnitude (9.3× and 9.6×, respectively), whereas for kurtosis these reductions exceeded an order of magnitude (12.9× and 12.6× for its coefficient and corresponding coefficient/SE ratio, respectively).

Heteroskedasticity: Relation of the standard deviation (SD) to the mean

A second, fundamental assumption in parametric statistical testing is the stability of the variance over different levels of the mean, i.e. that the variance is independent of the mean. As discussed succinctly by Snedecor and Cochran (1989, p. 290), this assumption is particularly important when different groups are considered in hypothesis testing (e.g. analysis of variance). To assess this problem, we calculated the mean BOLD signal for each one of the three periods and the SD of these mean values across the 19,000 voxels for each subject. For all periods, there was a highly significant linear increase of the SD with the mean. Figure 3 shows this finding for the rest period. The correlation coefficient between SD and mean (across subjects) was as follows for the three task periods: rest, 0.976 ($df = 13$, $P < 10^{-9}$); visual, 0.975 ($P < 10^{-9}$); motor, 0.974 ($P < 10^{-9}$). This dependence of the SD on the mean disappeared following log-transformation of the data (Fig. 4); the new correlation coefficients were as follows: rest, 0.179 ($df = 13$, $P = 0.524$); visual, 0.179 ($P = 0.524$); motor, 0.187 ($P = 0.504$). These findings demonstrate that a log transformation is appropriate for the data in all three periods.

Proportionality of the effect

All parametric statistical analyses assume additivity of the effect produced by a treatment, namely that the *difference* between the mean value under a treatment and a baseline level is independent of the baseline. If, instead, this difference depends on the baseline (e.g. when it is a constant percentage of the control), the effect is not linear but *proportional*. In this case, parametric statistics are not valid but a log transformation of the data can linearize the effect so that standard analyses can be performed. Consider, for example, a case with baselines of 10, 100 and 1000 (arbitrary units), and a constant treatment effect of 10 units; this would be a linear effect, since it is independent of the particular baseline. Now, consider the case with effects of 1, 10, and 100 units, for baselines of 10, 100 and 1000 units, respectively; this effect is not linear but proportional since it is a constant proportion of the baseline ($1/10 = 10/100 = 100/1000 = 0.1 = 10\%$). Parametric additive statistical analyses are not valid in this latter case. They can be used following a log transformation of the data, which will linearize the effect (i.e. produce a constant effect across baselines). Thus, in our data, the crucial question is whether changes from the baseline were proportional to the baseline itself. We found that the effect was clearly proportional, as shown in Fig. 5, which plots the average change of the BOLD signal during copying from the preceding baseline period (i.e. visual presentation) ($r = 0.884$, $df = 13$, $P < 10^{-4}$). Therefore, a log transformation was indicated. Indeed, such a transformation resulted in an additive effect, such that the change from baseline now became independent of the baseline (Fig. 6) ($r = 0.39$, $P = 0.151$).

Additivity of the effect

A more exact, general quantitative method to (a) test for non-additivity, and, if so, (b) suggest an appropriate transformation to make the effect additive, was provided by Tukey (1949) (Snedecor and Cochran 1989, pp. 282–284). We calculated Tukey's test for nonadditivity in a repeated measures ANOVA setting, where the means of the BOLD signal during rest, visual presentation, and

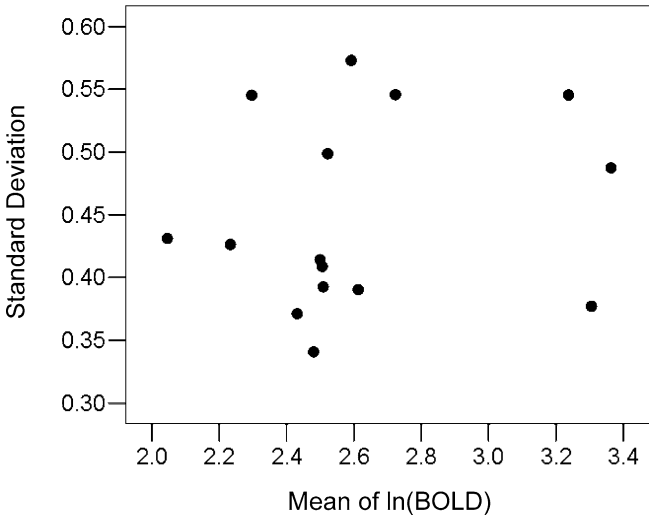

Fig. 4 Scatter plot of standard deviation against mean for the rest period for log-transformed data ($n = 15$ subjects)

copying periods were the within-voxel factors. We found the following. First, the test was very highly significant ($P < 10^{-20}$) which demonstrated that the effects among periods are extremely nonadditive. And second, the exponent to which data should be raised for the effects to become additive was 0.057; this is practically equivalent to a log transformation. This finding fully corroborated the results described in the preceding sections, all arguing for a log transformation.

Discussion

Strong, clear and consistent evidence from the analyses described above demonstrated the need for a logarithmic transformation of the data, in keeping with previous

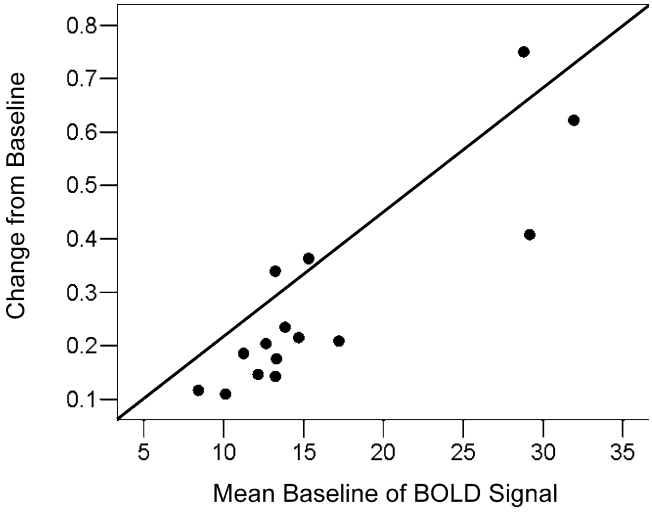

Fig. 5 Scatter plot of the effect (i.e. change from baseline) during copying against baseline for the original data. ($n = 15$ subjects; see text for details)

results (Georgopoulos et al. 2001). With respect to the kind of BOLD distribution, previous studies have underscored the non-gaussian (i.e. non-normal) distribution of these data (Hanson and Bly 2001; Chen et al. 2003; Luo and Nichols 2003). In a study of BOLD distribution for data obtained at 1.5T (Hanson and Bly 2001), a gamma distribution was found to be a more accurate fit to the data than a lognormal distribution. However, in our data, the lognormal distribution was clearly superior to the gamma (Fig. 2). It is possible that this discrepancy might reflect the different magnetic field strengths in the two studies.

Studies on task effects based on fMRI activation rarely, if ever, report on data transformations, nor do they report on the distributional properties of the raw data, the stability of the variance, and the proportionality of the observed effects. These omissions are somewhat surprising since such considerations are routine in many branches of science, including neuroimaging based on positron emission tomography (PET) (Pawlik and Thiel 1996; Ruttimann et al. 1998). Given the obvious departure from normality, instability of the variance, and proportionality of the BOLD effects reported here, a concern can be raised regarding parametric analyses performed on raw (untransformed) BOLD data in many studies. It is likely that the properties we found above are peculiar to data acquired at high magnetic fields (~4 T or greater) and that data acquired at lower fields (e.g. 1.5 T) will possess different properties. Such a difference could arise from the significantly different nature of the BOLD signal at different field strengths. Numerous studies have demonstrated that BOLD fMRI maps obtained at low magnetic fields arise mainly from blood-related effects associated with large blood vessels, whereas contributions from more densely distributed capillaries are essentially undetectable (Lai et al. 1993; Boxerman et al. 1995; Song et al. 1996; Oja et al. 1999; Hoogenraad et al. 2001). In this case, the source of the fMRI signal is not necessarily co-localized with the actual volume of increased neuronal activity but is restricted to the interior and immediate vicinity of the blood vessels. Consequently, the difference between the mean values under a treatment and a baseline will not necessarily be proportional to the signal intensity of the voxel. This implies that decreasing the voxel size will result in larger *percent* differences between baseline and treatment conditions until the voxel size becomes comparable to the blood vessel size and distribution; this effect is well documented at lower magnetic fields (Hyde et al. 2001), but is generally less applicable at 4 T or above (Yacoub et al. 2003), where capillary contributions increase and blood-related effects decrease. For capillary contributions, BOLD signal changes (ΔS) will be directly proportional to the baseline signal (i.e. S, which is directly proportional to voxel volume) until voxel dimensions become comparable or smaller than the intercapillary distance, which is ~25 μm and well beyond any present human fMRI studies. Therefore, capillary or small venule related BOLD signals will

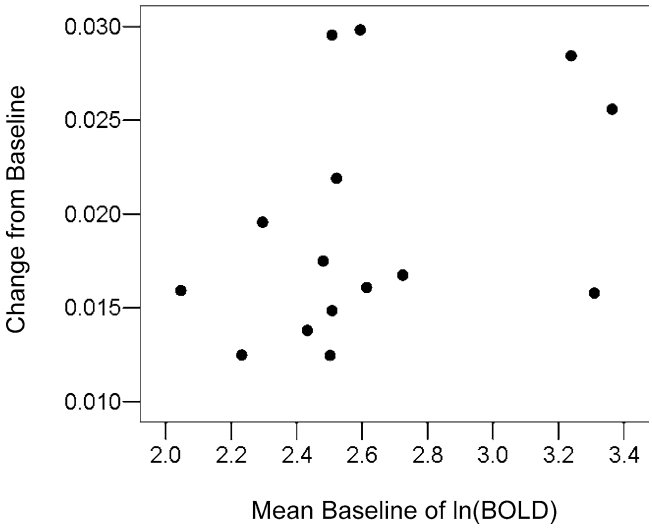

Fig. 6 Scatter plot of the effect (i.e. change from baseline) during copying against baseline for the log-transformed data. ($n = 15$ subjects; see text for details)

exhibit proportional behavior. At high fields, there are still partial volume effects due to gray-white matter admixture within voxels when voxel volumes are large, and due to residual blood effects in gradient recalled echo based BOLD images, so that the *percent* differences between control and treatment states are still somewhat dependent on voxel size (Pfeuffer et al. 2002; Yacoub et al. 2003); however, this dependence is smaller than that at lower magnetic fields where percent changes appear to go from a few percent to 100% or more with decreasing voxel size (Hyde et al. 2001). These considerations would predict a continuum in the strength of the dependence of a treatment effect on its baseline, with such a dependence increasing as a function of field magnitude either for gradient-echo or spin-echo based BOLD fMRI data. At a very high field strength such as 7 T, where blood-related effects can be virtually completely suppressed at echo times that exceed ~20–25 ms, the dependence of the treatment effect on the baseline will increase going from gradient-echo to spin-echo fMRI, and as a function of resolution even for spin-echo fMRI until gray–white matter partial volume effects are suppressed. These predictions remain to be evaluated.

In conclusion, the results of these analyses strongly suggest that a log transformation should be routinely applied to BOLD fMRI data acquired at high fields. This realization is especially timely since the use of higher fields (e.g. 3 T) is becoming increasingly common. Finally, our findings make a clear case for fMRI studies based on BOLD signals to provide information concerning the distribution, stability of variance and additivity of the effects in their data in order for the results obtained to be properly evaluated. As discussed lucidly by Snedecor and Cochran (1989, pp. 273–296), failures in the assumptions of normality, homoskedasticity, and additivity will affect adversely the outcomes of parametric statistical analyses. In spite of the frequent emphasis on, and concern with, the normality assumption (Hanson and Bly 2001; Chen et al. 2003; Luo and Nichols 2003), this assumption is the least troublesome, since most parametric tests are relatively robust. In contrast, the homoskedasticity assumption (i.e. the stability of the variance across different levels of means) is more serious, and failure in that assumption is likely to lead to errors of omission; that is, in missing effects that are really present. Finally, the additivity assumption is the most important one because it underlines all statistical analyses based on general linear modeling (i.e. linear = additive). In fact, assuming additivity when the underlying effects are proportional means that the wrong model is used and is inappropriate. To our knowledge, this study is the first to evaluate all of these issues in a large database. Although this database came from the whole brain, to be all-inclusive, the same analyses applied to specific areas (e.g. parietal cortex and cerebellum) yielded the same conclusions (Lewis et al. 2002, 2003).

In practical applications, the specific consequences stemming from failures in the assumptions above will depend to some extent on (a) the strength of the effect, and (b) the magnitude of deviation from the assumptions: Strong effects with small violations of the assumptions will be less problematic than weak effects with large violations of the assumptions. With respect to current fMRI work, many studies are indeed investigating cognitive processes frequently, if not typically, involving small effects. The net result in failure of the assumptions in those studies would be the omission of true effects, leading, e.g. to restricted brain activations when the true activation is more widespread. The results of the present study point to a simple solution to these problems, namely a logarithmic transformation of the data. This will make the distribution symmetric and closer to normal, will stabilize the variance and make it independent of the mean, and, most importantly, will confer additivity to the effects. In addition, it is a transformation that is pervasive in many fields and is easily applied.

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