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The Effect of Normal Aging on the Coupling of Neural Activity to the Bold Hemodynamic Response

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The use of functional neuroimaging to test hypotheses regarding age-related changes in the neural substrates of cognitive processes relies on assumptions regarding the coupling of neural activity to neuroimaging signal. Differences in neuroimaging signal response between young and elderly subjects can be mapped directly to differences in neural response only if such coupling does not change with age. Here we examined spatial and temporal characteristics of the BOLD fMRI hemodynamic response in primary sensorimotor cortex in young and elderly subjects during the performance of a simple reaction time task. We found that 75% of elderly subjects (n = 20) exhibited a detectable voxel-wise relationship with the behavioral paradigm in this region as compared to 100% young subjects (n = 32). The median number of suprathreshold voxels in the young subjects was greater than four times that of the elderly subjects. Young subjects had a slightly greater signal:noise per voxel than the elderly subjects that was attributed to a greater level of noise per voxel in the elderly subjects. The evidence did not support the idea that the greater head motion observed in the elderly was the cause of this greater voxel-wise noise. There were no significant differences between groups in either the shape of the hemodynamic response or in its the within-group variability, although the former evidenced a near significant trend. The overall finding that some aspects of the hemodynamic coupling between neural activity and BOLD fMRI signal change with age cautions against simple interpretations of the results of imaging studies that compare young and elderly subjects. © 1999 Academic Press

Key Words: **functional MRI; aging; BOLD; hemodynamic response**

INTRODUCTION

The application of blood oxygenation level dependent (BOLD), functional magnetic resonance imaging (fMRI) relies upon the observation that a change in neural activity produces a change in local deoxyhemoglobin concentration and hence local magnetic inhomogeneity. This change in local magnetic inhomogeneity can be detected through its effect on the T2*-weighted magnetic resonance imaging (MRI) signal (Ogawa *et al.*, 1992; Kwong *et al.*, 1992). Therefore, local changes in neural activity cause local changes in this aspect of the MRI signal, allowing the latter to be used as an indirect marker for the former.

A number of functional imaging studies have sought to identify age-related changes in the neural substrates of cognitive processes. Those studies that in a quantitative manner directly compare changes in fMRI signal intensity across age groups rely upon the assumption of age-equivalent coupling of neural activity to fMRI signal in time and space. There are motivations to test this general assumption. First, histological studies of cerebral microvasculature have demonstrated considerable age-related variability in the organization of intercerebral arterioles, capillaries, and venules. Fang (1976), for instance, observed age-related increases in the winding, coiling, and number of "blind-ends" in the cerebral vascular microlattice, most notably in the arteriole-venous-capillary bed. Because the BOLD fMRI signal has been shown to have a significant contribution from the capillary bed (Menon *et al.*, 1995) these age-related differences in vasculature could conceivably produce age-related differences in BOLD fMRI signal responsiveness.

Differences in experimentally induced fMRI signal change between young and elderly subjects are indicative in general of differences in neural activity only if the coupling between neural activity and fMRI signal does not change with age. The age-equivalence of this coupling can be assessed in part by measuring the temporal and spatial characteristics of the fMRI hemodynamic response in young and elderly subjects to equivalent neural input. Differences in the hemodynamic response between age groups in either time or space would indicate a failure of the age-equivalence assumption. In performing such a test, one must assume an identical spatiotemporal pattern of neural activity. Therefore, we made the provisional assumption of identical neural activity in healthy young and

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elderly subjects in sensorimotor cortex associated with a fixed-paced, simple reaction time task. This assumption is supported by the observation of similar movement-related electrical potentials in samples from these two populations under similar conditions (Cunnington *et al.*, 1995).

METHODS

Subjects

We studied 32 "young" subjects (20 men, 12 women; mean age = 22.9, range 18–32) and 20 "elderly" subjects (8 men, 12 women; mean age = 71.3, range 61–82). All subjects were right handed. Data from the younger subjects have been previously reported (Aguirre *et al.*, 1998). Younger subjects were recruited from the undergraduate and medical campuses of the University of Pennsylvania. Healthy elderly subjects were recruited from the community. Subjects were excluded if they had any neurological or psychiatric illness or if they were taking any centrally acting medication. All elderly subjects performed within normal limits (score $\geq$26) on the Mini-Mental Status Exam (Folstein *et al.*, 1975). All subjects gave informed consent.

MRI Technique

Imaging was carried out on a 1.5T SIGNA scanner (GE Medical Systems) equipped with a fast gradient system for echo-planar imaging. A standard radiofrequency (RF) head coil was used with foam padding to comfortably restrict head motion. High resolution sagittal and axial T1-weighted images were obtained in every subject. A gradient echo, echoplanar sequence (TR = 2000 ms, TE = 50 ms) was used to acquire data sensitive to the BOLD signal (Kwong *et al.*, 1992; Ogawa *et al.*, 1992). Resolution was 3.75 $\times$ 3.75 mm in plane, and 5 mm between planes, with no skip in between planes (18 axial slices were acquired). Twenty seconds of gradient and RF pulses preceded the actual data acquisition to allow tissue to reach steady-state magnetization.

Behavioral Paradigm

During this task, a white fixation cross was constantly illuminated in the center of a black background. Every 16 s the cross would change briefly (500 ms) to a white circle, which would cue the subjects to make a bilateral button press, and reaction times were recorded. Therefore, the nature of the visually-cued movement was predictable both in time and space. A total of 20 such button press events were presented during a 320-s scan (160 images at TR = 2 s).

Data Analysis

Off-line data processing was performed on SUN Ultra workstations using programs written in Interactive Data Language (Research Systems, Boulder, CO). After image reconstruction and before motion correction, the data were sinc interpolated in time to correct for the fMRI acquisition sequence. This step is of particular importance for our experiment because hemodynamic responses were to be compared across slices that were obtained at different points in the acquisition sequence (and therefore at different points in time). If left uncorrected, this would have introduced variability and bias (an advance) into the hemodynamic responses. The data were then motion corrected using two methods sequentially. First, a six-parameter (three translational and three rotational), rigid-body, least squares realignment routine [part of SPM96b package (Friston *et al.*, 1996)] was applied. Second, a slice-wise motion compensation method was used that removed spatially coherent signal changes via the application of a partial correlation method to each slice in time (described in Zarahn *et al.*, 1997).

There were three major aims of this experiment: (1) to detect (in a manner not biased by previous information about hemodynamic responses from young subjects) BOLD fMRI signal change in the region surrounding and including the central sulcus temporally associated with the button-press paradigm in young and elderly subjects; (2) to compare magnitudes of voxel-wise BOLD fMRI task-related signal, noise, and signal:noise ratios between young and elderly groups as well as the spatial extent of the task-related signal change; (3) to compare the waveforms (which include both shape and magnitude information) of the BOLD fMRI hemodynamic responses between young and elderly subjects.

(1) Detection. Data were analyzed by first defining a central sulcus search region from each subject's T1 axial images. The central sulcus was identified by one of the authors (BR) as the first medial-lateral sulcus posterior to, and not in contact with, the posterior extent of the superior frontal sulcus on the superior-most slices (Talairach and Tournoux, 1988). The central sulcus search region included both the sulcus and the surrounding gray matter, yielding a mean total (left and right combined) search volume of 364 voxels (range 239–461, SD = 58) per subject in the young group and 385 voxels (range 232–568, SD = 93) in the elderly group. The rule used to guide region definition was that the sulcus and the surrounding gray matter of one voxel thickness were to be included. Due to changes in sulcal cerebrospinal fluid volume with age (e.g., Pfefferbaum *et al.*, 1994) this rule could possibly lead to systematic differences in the size of the search region between young and elderly subjects. However, there was not a significant difference in search region size

between young and elderly subject groups ($t(50) = 1.02$, $P = 0.31$). In addition, a greater volume of truly active tissue in the search regions of elderly subjects would be predicted (under the null hypothesis) to lead to opposite results from those which were observed.

A 1/f model (Zarahn *et al.*, 1997) of temporal autocorrelation specific for each subject was used in the context of the general linear model modified for serial errors (Worsley and Friston, 1995). The time series were bandpass filtered (removing information at $\leq$0.05 Hz and $\geq$0.24375 Hz). The low range of filtered frequencies has high noise (Zarahn *et al.*, 1997), while the high range (which would not be predicted to contain any task-related information) contains technical artifacts in our data. A partial F test (which took into account temporal filtering/autocorrelation; Worsley *et al.*, 1997) was performed in the central sulcus search region in each young and elderly subject to test for focal signal change temporally associated with the button-press paradigm. The reduced model contained only trial-effect covariates (i.e., trial means), while the full model also included a six-element Fourier basis set spanning the 16-s (i.e., 8 TR) trial duration (comprising sines and cosines at 0.0625, 0.125, and 0.1875 Hz; excluding the Nyquist frequency and trial mean). α was controlled in each subject at 0.05 by Bonferroni correction for the number of voxels in the search region of each subject. Voxels surpassing the appropriate F threshold in each subject are referred to as suprathreshold voxels. More details regarding this analysis method are available in Aguirre *et al.* (1998).

The use of a basis set has as an advantage in that it eliminates of most a priori constraints on the expected shape of the hemodynamic response (Friston *et al.*, 1998). Therefore, the young and elderly might have completely different shapes of hemodynamic response and yet activations in both groups would be detected equally well by this method (if the total task-induced variance relative to noise in each type of response was the same).

(2) Signal:noise characterization. In each young and elderly subject, the time series (normalized by their means) of the voxels which were suprathreshold were tabulated for estimates of noise variance (i.e., the denominator of the F statistic), signal variance (i.e., the numerator minus the denominator of the F statistic), and their ratio (i.e., signal:noise). These values were compared between young and elderly subjects using the Mann–Whitney test for two-sample location at $\alpha = 0.05$. The reason a nonparametric test was chosen is that the distributions of these data appeared to deviate from normal (as would be expected in any case as sums of squared normal deviates are not themselves normal).

(3) Comparison of the shapes and magnitudes of the BOLD fMRI hemodynamic responses between young and elderly subjects. In each young and elderly subject, the time-series (normalized by their means) of a single, randomly chosen, suprathreshold voxel was averaged across trials. The reason that only a single voxel was chosen from each subject is that there were subjects with only one suprathreshold voxel. The assumption of homogeneity of variance (in the analysis to be directly described) would be expected to be violated if different subjects contributed different numbers of voxels.

These trial-averaged time series were used to compare the variability of the hemodynamic responses within age group to those between age groups. Specifically, the coefficients of a subset of the Fourier components of the trial-averaged responses (specifically, the same components as those comprising the basis set used for detection) were subjected to a multivariate analysis of variance. The multivariate nature of this analysis is due to the treatment of the coefficient of each Fourier component as a separate dependent variable. This analysis yielded a single F statistic with (number of Fourier components = 6) degrees of freedom in the numerator and (number of young subjects + number of elderly subjects $-$ 2) $*$ (number of Fourier components) degrees of freedom in the denominator. This analysis is sensitive to both (signed) magnitude differences in the Fourier components as well as phase differences. Therefore, any differences in scaling and/or shape in the hemodynamic responses would tend to be detected by this analysis.

(4) Comparison of head motion. One source of variance in fMRI time-series is bulk head motion (Friston *et al.*, 1996). If significant differences in noise were found between the young and elderly groups, we wished to test the hypothesis that one source of this difference is a tendency for greater head motion during scanning for one group as compared to the other. A measure of the path length of the center of the head was calculated for 13 randomly selected elderly and 15 randomly selected young subjects:

$$\text{Path Length} = \sum_{i=0}^{158} \sqrt{(X_{i+1} - X_i)^2 + (Y_{i+1} - Y_i)^2 + (Z_{i+1} - Z_i)^2},$$

where i indexes the 160 images obtained for each subject and X, Y, and Z are the translation parameter values returned by the motion correction algorithm. Two tests were performed upon these values. First, an unpaired Mann–Whitney test was used to test if the set of path length values obtained for the young and elderly subjects were significantly different. Second, separate Pearson product moment correlation coefficients were calculated for the young and elderly groups to examine the relationship between the movement measure and the noise variance for each subject.

RESULTS

Behavioral Performance

Accuracy rates for younger (100%) and elderly subjects (98.9%) were similar (four elderly subjects did not respond in time in 1 of the 20 trial events). Elderly subjects' mean reaction time (414.8 ms, SD = 60.6) was significantly slower than that of younger subjects (368.1 ms, SD = 68.2; $t(48) = 2.3$, $P < 0.03$; the behavioral data from two young subjects and two elderly subject were lost due to a computer error). The mean reaction time of the five elderly subjects who showed no suprathreshold activation (M = 451.1, SD = 48.6) had a trend toward being slower than that of the elderly subjects who showed suprathreshold activation (M = 400.8, SD = 57.2; $P = 0.06$) (see below). Accuracy rate for the nonresponders (98%; three of these subjects timed out on one trial) was not significantly less than that of responders (99%; two of these subjects timed out on 1 trial).

Detection

32/32 (100%) of the young subjects had suprathreshold voxels detected in their respective central sulcus search regions, while 15/20 (75%) of the elderly subjects evidenced such suprathreshold voxels. All subsequent analyses only involved those subjects that had at least one suprathreshold voxel. In this subset of the subjects, there was a significantly greater number of suprathreshold voxels in the central sulcus search regions of the young compared to that of the elderly subjects (median of the young = 30.5 voxels; median of the elderly = 6.0 voxels; $U = 60.5$; $P < 0.0001$). This difference in spatial extent of activation could not be explained by the volume of the search regions as these were slightly larger in the elderly group (385 vs 364 voxels).

Signal:Noise Characterization

The voxel-averaged noise magnitude was significantly greater in the elderly subjects than in the young ($U = 125$; $P = 0.009$), but signal magnitude was not ($U = 194$; $P = 0.29$). As expected from these results, the signal:noise was significantly greater in the young than in the elderly group (median of the young = 7.6; median of the elderly = 5.9; $U = 107$; $P = 0.002$). Examination of the averaged power spectra from the suprathreshold voxels showed that the increased noise in the elderly over the young subjects was greater in the 1/f component than in the white noise component (Fig. 1).

Because bulk head motion can introduce variance into fMRI data even after motion correction (Friston *et al.*, 1996), one possible cause of the greater noise in the elderly group is a tendency for greater head motion during scanning for the elderly as compared to the young. A summary motion measure (path length) that reflects the translational movement of the head during scanning was calculated for a randomly selected subset of the elderly and young subjects. Path length was found to be significantly greater in the elderly population as compared to the young (median young = 0.041 mm; median elderly = 0.074 mm; $P = 0.0008$ by Mann–Whitney U test). However, no noticeable relationship was found between the noise magnitude and the motion

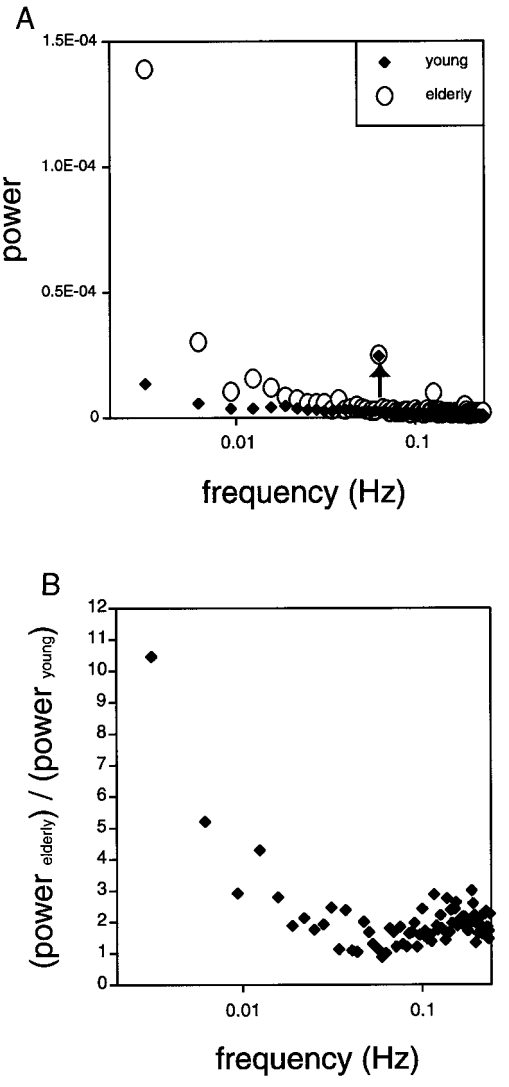


FIG. 1. (A) The average power spectrum for the young ($n = 32$) and elderly ($n = 20$) samples are shown. For each group, the spectrum is an average across subjects of the within-subject average spectra (which themselves are averages of the power spectra across all suprathreshold voxels; see Materials and Methods). It can be seen that power at the fundamental frequency of the behavioral paradigm (marked by arrow) is nearly identical in the two groups. (B) The ratio of the average elderly group power spectrum to the average young group power spectrum is shown. It can be seen that the greatest disparity between noise in the young and elderly groups is at the lowest frequencies, although the noise tends to be greater in the elderly group throughout the spectrum.

measure either within the young or elderly groups [elderly ($n = 11$), Pearson's $r = 0.32$, $P = 0.26$; young ($n = 16$), Pearson's $r = -0.17$, $P = 0.53$]. This suggests that greater noise and greater motion are both the effect of age, but that one does not cause the other (because if motion were a proximal cause for noise, then we would expect it to still have some relationship with noise after covarying for age).

Comparison of the Shapes and Magnitudes of the BOLD fMRI Hemodynamic Responses between Young and Elderly Subjects

Single voxels were randomly selected from the set of suprathreshold voxels in each young and elderly subject that evinced any such voxels. The trial-averaged time series corresponding to these voxels were tested for age differences in shape and magnitude. This test was implemented using a multivariate analysis of variance, which, for all selected Fourier coefficient (see Methods), compared the variability within each age group to the variability between age groups (with variability pooled across Fourier coefficients). A comparison of the within-group variability in the hemodynamic responses between the young and elderly groups revealed no significant difference ($F(84,186) = 1.18$, $P = 0.17$). Since there apparently was not a large[1] difference in the within-group variances, we proceeded with the between groups test which yielded a trend towards a difference between young and elderly groups in the shape and scaling of the hemodynamic response ($F(6,270) = 2.06$, $P = 0.06$). The individual and across-subject average hemodynamic responses (with each subject contributing the time series of one randomly selected voxel) for the elderly and the young groups are presented in Fig. 2.

DISCUSSION

In this study, random samples drawn from a young population (ages 18–32) and an elderly population (ages 65–82) were subjected to identical behavioral paradigms while being scanned with BOLD fMRI. The behavioral paradigm was a simple reaction time task that involved a visually cued, bilateral button press every 16 s. Therefore, the spatial characteristics (i.e., where the stimulus was to appear and what kind of movement would be required) and the temporal characteristics (i.e., when the visual cues for movement appeared) were predictable. In this study, we have made the assumption that neural activity associated with a button press is not different between young and elderly subjects. We believe that this is a reasonable assumption for two reasons. First, movement-related electrical potentials at a central scalp electrode in young and elderly subjects have been reported to be similar under conditions such as those present in our paradigm (Cunnington *et al.*, 1995). Second, there is also neuropathological evidence that primary motor cortex does not exhibit significant neuronal loss in normal aging (Haug, 1997).

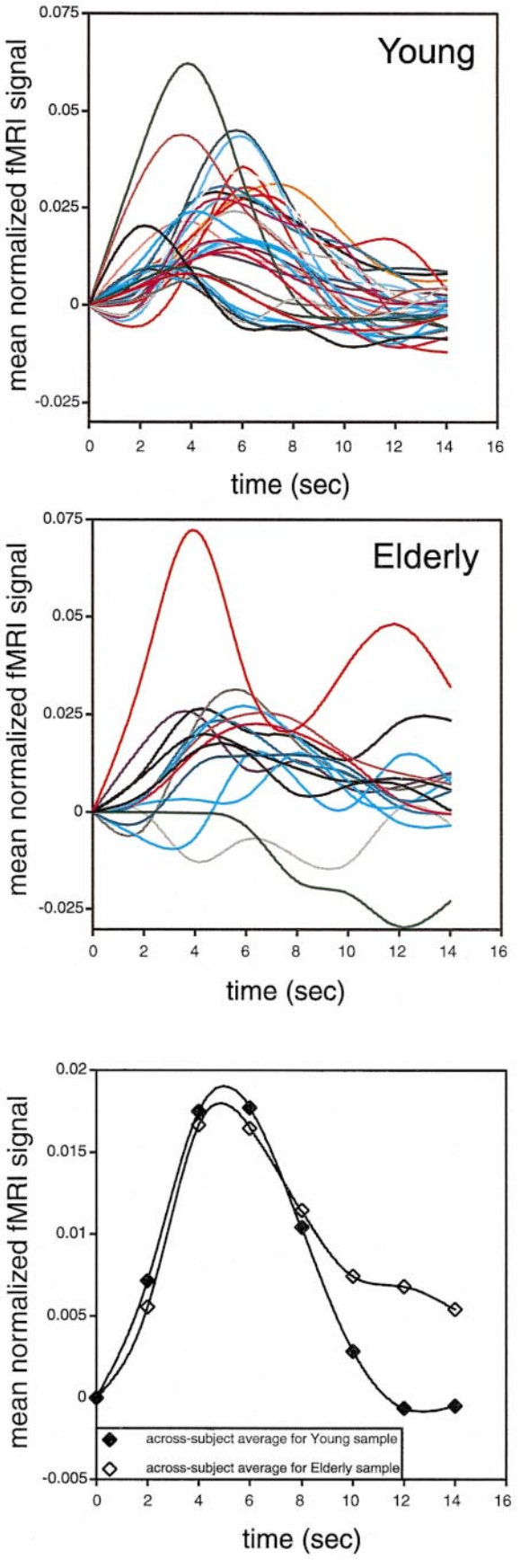
This study identified several important similarities and differences between age groups in BOLD fMRI signal within a search region confined to the central sulcus and its surrounding parenchyma. First, 25% (5/20) of the sample of elderly subjects exhibited no detectable voxel-wise relationship with the behavioral paradigm in this region, compared to 0% of the sample of young subjects. In those subjects that did exhibit some significant relationship with the task, the young subjects had a slightly greater signal:noise per voxel than the elderly subjects. This difference in signal to noise between groups was apparently due to a greater level of noise per voxel in the elderly. Although one possible source of greater noise in the elderly is greater head motion, we failed to detect any significant correlation between head motion and noise magnitude after covarying for age group.

We also found a marked disparity in the number of detected voxels between age groups, with the median number of suprathreshold voxels in the young subjects being greater than four times than that of the elderly subjects. Interestingly, the magnitude of voxel-wise task-related signal per se (taking into account noise) was not detectably different between the age groups.

Methodological Implications of the Results with an Assumption of Equal Neural Activity in the Young and Elderly Groups

One way to interpret the results of this study is to assume that the spatiotemporal pattern and intensity of neural activity in the vicinity of the central sulcus is the same between the populations from which the young and elderly groups were sampled (as supported, though not proven, by references cited above). Given this assumption, any difference between groups in the spatial and temporal fMRI results would be attributable to differences in hemodynamic coupling between neural activity and BOLD fMRI signal change and/or other factors that can affect the BOLD fMRI signal (such as motion). There are a few possible explanations for changes in coupling between neural activity and BOLD signal in normal aging. One hypothesis would be that age differences in the spatial properties of the

[1] A "large" difference in variance is one that would invalidate the false positive rate to an unacceptable extent. We would have not performed the analysis if there was greater than or equal to a 50% difference in within-group variance between the young and elderly groups. We note that unequal sample sizes, as used here, makes ANOVA less robust to such violations (Kleinbaum *et al.*, 1988).



vascular bed (Fang, 1976) causes changes in the spatial properties of this coupling. Another hypothesis would link vascular pathology (known to increase with normal aging, Bohl and Hori, 1997) with spatial extent. We note that our conclusions regarding age-related changes in the hemodynamic coupling of neural activity to fMRI signal do not necessarily generalize to other blood flow based imaging methods such as PET. In fact, one study comparing fMRI and PET suggests that the transform between blood flow to imaging signal between these methods may differ (Rees *et al.*, 1997).

Regardless of these hypotheses, the assumption of equal spatiotemporal patterns of neural activity in the two populations in conjunction with the result of less spatial extent in the elderly would lead to a rather clear methodological conclusion: comparisons between task-related fMRI activations in young and elderly groups using statistical parametric mapping (SPM; (Friston, 1994/1995)) cannot be expected to yield null-hypothesis results when the null-hypothesis is true in terms of neural activity. This is because differences in spatial extent of activation translate into differences in intensity after spatial smoothing. To illustrate this point, we performed a group analysis on our data and observed greater "activation" in primary sensorimotor cortex in the young subjects as compared to the old subjects (Fig. 3). If the results of Cunnington *et al.* (1995) are reliable, and evoked related potentials are a reliable measure of spatially averaged neural activity, then this is an example of a positive fMRI result in the presence of a null neural result.

In addition to the differences in spatial extent between groups (in those subjects that had a detectable fMRI response), the observation that there was a substantial proportion of subjects in the elderly group that did not evince detectable responses bolsters the conclusion of the above paragraph. That is, it is not likely that these subjects had no neural activity near the central sulcus associated with the button presses. Rather (based on prior information), it seems more likely that there was a greatly weakened, or perhaps nonexistent, coupling between neural activity and fMRI signal in these subjects. The potential explanations for

FIG. 2. Shown are trial-averaged hemodynamic responses from the (A) elderly ($n = 20$) and (B) young ($n = 32$) samples. These hemodynamic responses are from single voxels which were randomly selected from amongst the suprathreshold set (contained in the central sulcus search region) in each subject (only one hemodynamic response is shown from each subject). The hemodynamic responses are expressed as a fraction of the mean signal from within that voxel. The value at time = 0 peristimulus was subtracted from the time series for display. The values of the hemodynamic responses at 2-s sampling intervals (starting at time 0) are actual data, while the intermediate values were obtained from these data by sinc interpolation. The across-subject averages of the data shown in (A) and (B) are presented in (C).

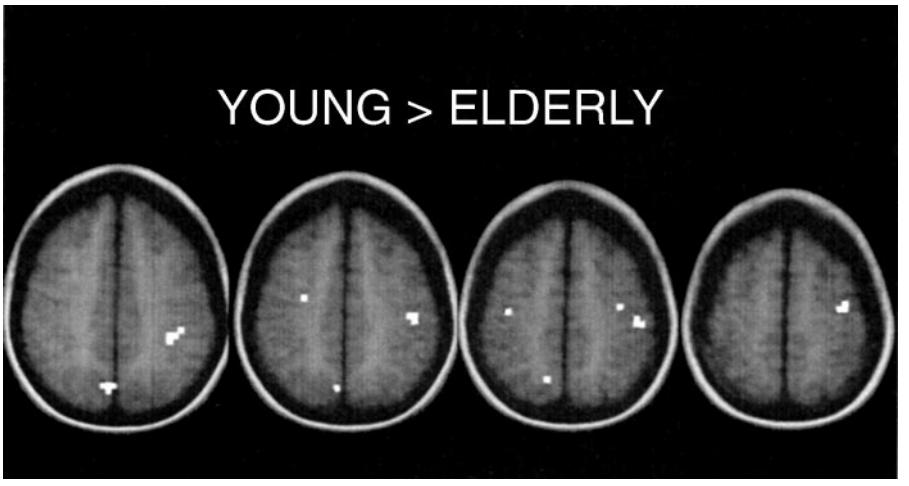


FIG. 3. Random effects SPM[*t*] of Young motor response vs Elderly motor response. The data from 11 elderly and 11 young subjects were analyzed using a modified GLM (Worsley and Friston, 1995). The covariate of interest was constructed with the first eigenvector obtained from a principal components analysis of hemodynamic responses from a separate group of subjects (Aguirre *et al.*, 1998). Additional nuisance covariates were generated using the second and third eigenvectors. An SPM[*t*], evaluating this covariate of interest, was generated for each subject. These maps were then normalized to standard Talairach space, smoothed with a three-dimensional Gaussian kernel (FWHM = 7 mm), and used to generate a new SPM[*t*], which assessed the difference in task effects between young and elderly groups. This map, which treated the task effect in each subject as a random effect, was thresholded at a $t = 5.2$, corresponding to an $\alpha = 0.05$ (20 *df*, two-tailed, corrected for multiple comparisons (Worsley, 1994)).

this finding clearly need to be addressed in future studies. Furthermore, the possibility that these apparent "nonresponders" are not really such, but rather just instances (due to random fluctuations), where the signal did not reach threshold in a few truly activated pixels should be entertained. This possibility, however, makes little difference to our methodological conclusion regarding SPM.

With regard to the age-related differences found in this study, the relatively small magnitude increase in white noise in the elderly over the young is difficult to explain physiologically, but could be due to aliasing of higher frequency physiological effects. That is, it is possible that there are greater cardiac and respiratory fMRI effects in the elderly and that these effects were observed at other frequencies because of temporal under-sampling. It is unlikely that differences in scanner noise contributed to the white noise difference between groups as the young and elderly subjects were scanned in a fairly random fashion over the course of a year. The larger 1/f component of the noise in the elderly could also be due to physiological effects, though this is all purely speculative as the specific mechanism(s) responsible for the 1/f noise in fMRI data are not understood. We observed greater head motion for the elderly as compared to the young subjects, but results did not support the hypothesis that this head motion is responsible for the increase in the 1/f component.

Outlier Hemodynamic Responses in the Elderly Group

Though the analysis of variance revealed only a trend toward a difference in the shape of the hemodynamic response with age (in voxels that evinced a significant relationship with the task), there were several apparent outliers (at least from the perspective of a Gaussian distribution) in the elderly group (see Fig. 2). These subjects would seem to indicate that the normality assumption of the analysis was violated. It might be hypothesized that these subjects are also outliers in some other unmeasured variable which is causally related to the hemodynamic response (e.g., vascular pathology). Nevertheless, the failure to detect a difference between young and elderly samples still lends credence to the conclusion that no highly consistent age difference exists in the shape of BOLD fMRI hemodynamic responses.

Previous Neuroimaging Studies of Normal Aging

One previous study has examined age-related changes in fMRI signal response using a blocked stimulation design (Ross *et al.*, 1997). In this study, subjects passively viewed periodically emitted diode-generated light. Over a 256-s period, light appeared and disappeared periodically in 60-s cycles. Examining significantly activated pixels in Brodmann areas 17 and 18, they observed significant attenuation in response amplitude (as indexed by percent signal change). They observed no change, however, in the spatial extent of the activation (as indexed by the number of pixels exceeding threshold). These findings differ from ours, but the reason behind such differences is not clear.

Another study measured the time lag of the BOLD fMRI signal in precentral gyrus between the start and end of a hand grasping task (which lasted 10 s), and

correlated signal changes across 40 subjects ranging in age from 20 to 76 years old (Taoka *et al.*, 1998). As indexes of the kinetics of fMRI signal change, the authors measured the time for the signal to reach half of the maximum ratio (T-incr) and the time for the signal to reach the initial level after ceasing the task (T-dec). The average T-incr and T-decr was quite variable across decades of age. However, subjects older than 50 years had a larger mean T-incr (3.67 s vs 2.45 s) but no difference between younger and older subjects was found in mean T-dec (6.95 s vs 6.34 s). There was also a positive age correlation for T-inc but not for T-dec. The authors postulated that if the temporal lag in BOLD fMRI signal is due to delayed vascular changes to local brain activation, then the increase in T-incr with aging may be due to diminishment of local vascular reactivity in normal aging. They also propose that arteriolar change such as narrowing due to endothelial proliferation, fibrinoid necrosis, and atherosclerosis and stiffening, could be the cause of T-incr prolongation. The lack of difference in T-decr, they propose may due to passive mechanisms in decreasing cerebral blood flow after brain activation that are not affected in normal aging.

The findings by Taoka *et al.* (1998) using a boxcar design are intriguing. Unfortunately, we cannot address this issue with our data. The reason is twofold. First, both the rising and falling phases of a linear system's response to a boxcar (when the duration of the boxcar is greater than the duration of the impulse response function) depends on the whole impulse response function, not just its rising phase or falling phase. Therefore, the rising and falling phases of a response to a relatively long duration boxcar are not equivalent to the rising and falling phase of an impulse response function (i.e., in this context the fMRI hemodynamic response). Second, and perhaps more fundamentally, the finding of differences between the rising and falling phases would suggest a nonlinearity in the fMRI system. In the current study, however, we could not detect such nonlinearities as our data correspond only to the rising phase of the study of Taoka *et al.* (1998).

The nature of the inference when comparing two different groups via neuroimaging is currently, at least, a tenuous enterprise with many contingencies and unknowns. In one scenario, a comparison of activation of young and elderly subjects during a cognitive task may show less activation by elderly (as compared to young subjects) in some brain regions, but greater activation in other regions (see PET studies by Grady, 1996). In this scenario, it is unlikely that regional variations in the hemodynamic coupling of neural activity to imaging signal would account for such age-related differences in patterns of activation. In another scenario, a comparison of young and elderly subjects may show less activation by elderly (as compared to young subjects) in some brain regions, but no evidence of greater activation in any other region (see PET study by Madden *et al.*, 1996). In this case, it is possible that the observed age-related differences are not due to differences in intensity of neural activity, but rather to other nonneuronal contributions to the imaging signal, i.e., hemodynamic coupling.

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REFERENCES

Aguirre, G. K., Zarahn, E., and D'Esposito, M. 1998. The variability of human, BOLD hemodynamic responses. *Neuroimage* **8:**360–369.

Bohl, J. R. E., and Hori, A. 1997. Vascular changes. In *Principles of Neural Aging* (S. U. Dani, A. Hori, G. F. Walter, Eds.), Elsevier, Amsterdam.

Cunningham, R., Iansek, R., Bradshaw, J. L., and Phillips, J. G. 1995. Movement-related potentials in Parkinson's disease. Presence and predictability of temporal and spatial cues. *Brain* **118:**935–950.

Fang, H. C. H. 1976. Observations on aging characteristics of cerebral blood vessels, macroscopic and microscopic features. In *Neurobiology of Aging* (S. Gerson and R. D. Terry, Eds.), Raven, NY.

Folstein, M., Folstein, S., and McHugh, P. 1975. "Mini mental state": A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* **12:**189–198.

Friston, K., Williams, S., Howard, R., Frackowiak, R., and Turner, R. 1996. Movement-related effects in fMRI time-series. *Magn. Reson. Med.* **35:**346–355.

Friston, K. J. 1994/1995. Statistical Parametric Maps in functional imaging: A general linear approach. *Human Brain Map.* **2:**189–210.

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., and Turner, R. 1998. Event-related fMRI: characterizing differential responses. *NeuroImage* **7:**30–40.

Grady, C. L. 1996. Age-related changes in cortical blood flow activation during perception and memory. *Ann N.Y. Acad. Sci.* **777:**14–21.

Haug, H. 1997. The aging human cerebral cortex: Morphometry of areal differences and their functional meaning. In *Principles of Neural Aging* (S. U. Dani, A. Hori, and G. F. Walter, Eds.), Elsevier, Amsterdam.

Kleinbaum, D. G., Kupper, L. L., and Muller, K. E. 1988. *Applied Regression Analysis and Multivariable Methods*, Duxbury Press, Belmont, CA.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., and Turner, R. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc. Natl. Acad. Sci. USA* **89:**5675–5679.

Madden, D. J., Turkington, T. G., Coleman, R. E., Provenzale, J. M., DeGrado, T. R., and Hoffman, J. M. 1996. Adult age differences in regional cerebral blood flow during visual world identification: Evidence from H215O PET. *Neuroimage* **3:**127–142.

Menon, R. S., Ogawa, S., Hu, X., Strupp, J. P., Anderson, P., and Ugurbil, K. 1995. BOLD based functional MRI at 4 Tesla includes a capillary bed contribution: Echo-planar imaging correlates with previous optical imaging using intrinsic signals. *Magn. Reson. Med.* **33:**453–459.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J., Kim, S.-G., Merkle, H., and Ugurbil, K. 1992. Intrinsic signal changes accompanying

sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* **89:**5951–5955.

Pfefferbaum, A., Mathalon, D. H., Sullivan, E. V., Rawles, J. M., Zipursky, R. B., and Lim, K. O. 1994. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to adulthood. *Arch. Neurol.* **51:**874–887.

Rees, G., Howseman, A., Josephs, O., Frith, C. D., Friston, K. J., Frackowiak, R. S., and Turner, R. 1997. Characterizing the relationship between BOLD contrast and regional cerebral blood flow measurements by varying the stimulus presentation rate. *Neuroimage* **6:**270–278.

Ross, M. H., Yurgelun-Todd, D. A., Renshaw, P. F., Maas, L. C., Mendelson, J. H., Mello, N. K., Cohen, B. M., and Levin, J. M. 1997. Age-related reduction in functional MRI response to photic stimulation. *Neurology* **48:**173–176.

Talairach, J., and Tournoux, P. 1988. *Co-Planar Stereotaxic Atlas of the Human Brain*, Thieme, NY.

Taoka, T., Iwasaki, S., Uchida, H., Fukusumi, A., Nakagawa, H., Kichikawa, K., Takayama, K., Yoshioka, T., Takewa, M., and Ohishi, H. 1998. Age correlation of the time lag in signal change on EPI-fMRI. *J. Comput. Assist. Tomogr.* **22:**514–517.

Worsley, K. J. 1994. Local maxima and the expected euler characteristic of excursion sets of chi-squared, f and t fields. *Adv. Appl. Prob.* **26:**13–42.

Worsley, K. J., and Friston, K. J. 1995. Analysis of fMRI time-series revisited—Again. *Neuroimage* **2:**173–182.

Worsley, K. J., Poline, J. B., Friston, K. J., and Evans, A. C. 1997. Characterizing the response of PET and fMRI data using multivariate linear models. *Neuroimage* **6:**305–319.

Zarahn, E., Aguirre, G. K., and D'Esposito, M. 1997. Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. *NeuroImage* **5:**179–197.