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Breath holding reveals differences in fMRI BOLD signal in children and adults

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Application of fMRI to studies of cognitive development is of growing interest because of its sensitivity and non-invasive nature. However, interpretation of fMRI results in children is presently based on vascular dynamics that have been studied primarily in healthy adults. Comparison of the neurological basis of cognitive development is valid to the extent that the neurovascular responsiveness between children and adults is equal. The present study was designed to detect age-related vascular differences that may contribute to altered BOLD fMRI signal responsiveness. We examined BOLD signal changes in response to breath holding, a global, systemic state change in brain oxygenation. Children exhibited greater percent signal changes than adults in grey and white matter, and this was accompanied by an increase in noise. Consequently, the volume of activation exceeding statistical threshold was reduced in children. The reduced activation in children was well modeled by adding noise to adult data. These findings raise the possibility that developmental differences in fMRI findings between children and adults could, under some circumstances, reflect greater noise in the BOLD response in the brains of children than adults. BOLD responses varied across brain regions, but showed similar regional variation in children and adults.

Keywords: Breath holding; BOLD contrast; Children; Adults; Noise

Introduction

The rapid cognitive and perceptual stages of development through which children progress are directly linked to brain development. Today, MRI is the most effective method available for investigating functional and structural brain maturation in children. In fact, functional magnetic resonance imaging (fMRI) is one of the most widely used methods for studying the neural basis of human cognition in and across all age groups and populations. Indeed, substantial progress has been made in understanding brain development through use of fMRI in children (Adleman et al., 2002; Booth et al., 1999, 2003; Bunge et al., 2002; Casey et al., 1995, 1997; Gaillard et al., 2000; Klingberg et al., 2002; Luna et al., 2001; Moses et al., 2002; Nelson et al., 2000; Rubia et al., 2000; Sachs and Gaillard, 2003; Schlaggar et al., 2002; Thomas et al., 1999; Turkeltaub et al., 2003), but attention to the methodological issues needs to focus future investigations using this technique (Casey, 2002; Gaillard et al., 2001; Poldrack et al., 2002; Stiles et al., 2003; Wenger et al., 2004).

One of the primary methodological issues in fMRI is that the blood oxygen level dependent (BOLD) signal is only an indirect measure of neuronal activity. Active neural circuits cause an increase in local perfusion and slight increase in oxygen consumption. BOLD signal results from changes in local oxygen tension consequent to increased perfusion in microvasculature that in turn results from increased neuronal metabolism (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992; for a review, see Logothetis, 2002). Therefore, inferences about inter-group differences in neural activity drawn from BOLD signal intensity (SI) could be distorted by group differences in hemodynamic responsiveness.

Two studies have begun to address this potential confound of inter-group vascular differences by comparing BOLD hemodynamic response in children and adults during simple visual and motor tasks (Kang et al., 2003; Richter and Richter, 2003). However, the use of tasks that require cognitive control, even simple sensory paradigms, leads to questions of reproducibility and confounds from psychophysical performance variables. In addition, such tasks only activate limited regions of the brain, thereby leaving open the question of responsivity of non-sensory regions. Alternatively, hypercapnia has been postulated to be a good surrogate for simple visual and motor tasks with less possible confound by neuronal differences. The proportionality of BOLD signal changes during hypercapnia, a state of excess CO_2 in the blood that can result from breath holding or inhaling CO_2 air mixtures, and focal neuronal activation supports this position (Bandettini and Wong, 1997; Davis et al., 1998; Riecker et al., 2003; Thomason et al., 2004). To date, no study has used hypercapnic methods to query potential differences in BOLD

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signal characteristics across the entire brain in children and adults. In the past few years, vascular challenges have been used to delineate group and individual differences in hemodynamic response by inducing state changes that do not derive from modulation of neuronal metabolism alone. Intravenous injection of acetazolamide (in its role as a vasoconstrictor) and inhalation of CO_2 gas mixtures (vasodilators in air mixtures of up to 5% CO_2) cause altered levels of cerebral blood flow (CBF) and modulate local oxygen tension (Kastrup et al., 1998a, 2002; Reich and Rusinek, 1989). In addition, breath holding (BH) causes autonomic down-regulation of heart rate (HR) and concomitant reduction in blood flow to the brain, resulting in hypercapnia and vasodilation (Corfield et al., 2001; Kastrup et al., 1998b, 1999a,b,c; Li et al., 1999a,b; Liu et al., 2002; Nakada et al., 2001). These methods have been useful for determining differences in the BOLD effect between different brain regions within-subject (Kastrup et al., 1999b), as well as BOLD signal responsiveness between people of different ages (Kastrup et al., 1998a; Reich and Rusinek, 1989; Riecker et al., 2003; Yamamoto et al., 1980), and between patients and healthy controls (Shiino et al., 2003; Yamaguchi et al., 1980; Yamamoto et al., 1980), but never between children and adults. Good correlation between global BOLD signal intensity changes during BH and during CO_2 inhalation (Kastrup et al., 2001), as well as between acetazolamide and CO_2 inhalation (Kimoto et al., 1995), supports the essential equivalence of these approaches in depicting vascular responsiveness. BH has the advantage of being a simpler paradigm for evaluating hemodynamic responsiveness, because it requires neither an exogenous source of CO_2 nor an acetazolamide injection, making it a good non-invasive alternative for testing children. Furthermore, BOLD response to short duration BH is robust. Measured signal changes driven by BH range from 0.8% to 5.1% in a 1.5-T MR system (Kastrup et al., 1998b, 1999b), with a similar or larger effect observed at 3 T. The present study considers differences in signal and noise features of BOLD signal responsiveness between children and adults as well as between cerebral regions within groups.

While BH can readily develop global BOLD signal changes, its effectiveness as a surrogate for task activation may be questioned, and it is instructive to compare the two. In task activation, increased local perfusion in the capillary bed results from vasodilation of arterioles supplying the spatially limited region of cortex involved in the task. The vasomotor response is triggered by a (poorly understood) combination of hypercapnia, increases in [NO] and [H+], changes in [K+], [Na+], and [Ca+], and decreases in $pO2$ in response to heightened glycolysis (Roland, 1993). Whatever the exact chemical messengers, the hemodynamic perturbation from task activation is confined to a small fraction of the vascular system. By contrast, the BH task causes a modulation of CBF to the entire brain, thereby involving the complete neurovascular system. In this case, little or no cognitive or CMRO2 changes occur, and metabolic activity remains at baseline levels of the resting-state brain (Kastrup et al., 1999a). However, with reduced perfusion but continued baseline metabolic activity, the same cascade of chemical processes leads to vasodilation of arterioles characteristic of local reactivity. Thus, the BOLD response to BH is similar to task-initiated hypermetabolism in that it results identically from up-regulation of local flow. It may be dissimilar in that with all cortical regions responding to the external hypoCBF challenge, some vascular steal processes may be operative. We believe this effect is small, however, because direct comparisons of BH and task activation using a sensorimotor paradigm show good agreement of effect size (Bandettini and Wong, 1997; Davis et al., 1998; Riecker et al., 2003; Thomason et al., 2004).

Therefore, BH can be thought of as a method for inducing BOLD response in all vascularized tissue, with signal dependent on local vascular reactivity and using the same basic vasodilation mechanism for up-regulation as that in task activation, but with some potential differences in details of response. Additionally, because basal metabolism proceeds during BH, fluctuations in BOLD signal level from concomitant baseline blood flow and blood volume changes are expected to be similar to those in resting state brain experiments. The present study is not the first to use a global hypercapnic challenge to define nonneuronal contributions to altered age-related activation patterns (Kastrup et al., 1998a; Reich and Rusinek, 1989; Riecker et al., 2003; Yamaguchi et al., 1980; Yamamoto et al., 1980), but it is the first to apply this to the study of BOLD response in adults and children.

Methods

Subjects

Data were collected from 36 healthy, right-handed, native English speakers (18 male, 18 female) after giving informed consent as described by the Stanford Institutional Review Board. Subjects were divided into two participant groups: children (range 7 to 12 years, 10 female, 9 male) and young adults (range 18 to 29 years, 8 female, 9 male). Three subjects were eliminated due to movement exceeding the a priori maximum movement of 2 mm (3 females, 2 children), and a fourth was removed due to flawed data collection (1 male, child). Therefore, the subjects included in all data analysis include 16 children (mean age 9.8) and 16 adults (mean age 22.8).

Experimental paradigm

Subjects performed seven repetitions of alternating 18-s blocks of breath holding and self-paced breathing. Subject compliance to task timing and ability to hold breath was measured using a pneumatic belt and by subject report. Trial timing was cued by visual stimulus which included a “rest” and “get ready” phase during self-paced breathing and a non-verbal stimulus (a circle that diminished in size during breath holding and disappeared at the end of the BH period). This visual cue undoubtedly introduced a small activation in the visual cortex but the amount was not measured.

MRI acquisition

Magnetic resonance imaging was performed on a 3.0-T GE whole-body scanner with a custom quadrature birdcage head coil. Head movement was minimized using a bite bar and foam padding. Twenty-three oblique axial slices were taken parallel to the AC–PC with 4-mm slice thickness, 1-mm skip. High-resolution T2-weighted fast spin echo structural images (TR = 3000 ms, TE = 68 ms, ETL = 12, FOV = 24 cm, 192 × 256) were acquired for anatomical reference. A T2*-sensitive gradient echo spiral in/out pulse sequence (Glover and Law, 2001) was used for functional imaging (TR = 1500 ms, TE = 30 ms, flip angle = 70°, FOV = 24 cm, 64 × 64). An automated high-order shimming procedure based on spiral acquisitions was used to reduce B0 heterogeneity (Kim et al., 2002). Spiral

in/out methods have been shown to increase the signal to noise ratio (SNR) and BOLD contrast to noise ratio in uniform brain regions as well as to reduce signal loss in regions compromised by susceptibility-induced field gradients generated near air–tissue interfaces such as PFC (Glover and Law, 2001). Compared to traditional spiral imaging techniques, spiral in/out methods result in less signal dropout and greater task-related activation in PFC regions (Preston et al., 2004). A high-resolution volume scan (128 slices, 1.2 mm thickness) was collected for every subject using an IR-prep 3D FSPGR sequence for T1 contrast (TR = 8.9 ms, TE = 1.8 ms, TI = 300 ms, flip angle 15°, FOV = 24 cm, 256 × 192 × 128).

Physiological monitoring

Previous studies have shown that the inspiration level during the BH task can have an influence on the BOLD signal (Nakada et al., 2001 as well as our own unpublished studies). In order to examine potential performance and behavioral differences in the subject populations during the BH task, respiration and cardiac rates were recorded using a data logger (PowerLab, AD Instruments, Inc. Castle Hill, NSW) connected to the scanner's monitoring system and sampling at 40 Hz. Respiration data were acquired using the scanner's pneumatic belt placed on the subject's abdomen. However, the scanner's internal autogain/offset algorithm is set to rezero the reading when there is no change in the respiration level for a few seconds, as occurs during the 18-s BH period (Fig. 4A). The resulting recorded waveforms are distorted and cannot be directly used to quantify respiration amplitude. Therefore, we measured the respiration amplitude of each BH block by recording the difference in observed respiration signal just before and after the BH transition, i.e., prior to the amplitude gain correction. The inspiration amplitude for the scan was then obtained as the average of readings for the 7 BH blocks. These measures of inspiration were averaged within groups to obtain mean inspiration amplitudes for children and adults. In order to account for systematic size differences between the two groups, a weighted average was also obtained. Subject inspiration-amplitudes, which are a linear measurement of abdominal circumference, were normalized by dividing by subject-height, and then averaged over subjects.

The respiration amplitude results were used to assess whether there were group differences in inspiration level that could account for BOLD signal changes. In addition, group average waveforms were obtained to examine temporal differences in performing the BH task (see Temporal response of BOLD signal). Differences were tested with a two-tailed t test across all subjects.

Heart rate was measured with the scanner's photoplethysmograph on the subject's index finger of the left, non-dominant hand and recorded simultaneously with the respiration waveforms with the data logger.

Anatomical data analysis

Each subject's T1-weighted 3D volume scan was segmented into grey and white matter volumes using SPM99 (Wellcome Dept of Cognitive Neurology) [feasibility of using SPM in children: Muzik et al., 2000]. Subject-specific grey and white matter volumes were used for quantification of anatomical data and were used to restrict examination of activation extent and magnitude measures to each tissue type.

fMRI data analysis

fMRI data were preprocessed using SPM99 and custom MATLAB routines. Preprocessing included time series image realignment of all images to the first time frame and correction for linear signal drift. fMRI signal during the task breath hold epochs across the 23 slices was compared to baseline activity during the normal breathing condition. Regressors for the corresponding condition blocks were modeled as a boxcar function convolved with the canonical HRF. Statistical analysis at the single-subject level treated each voxel according to a general linear model (Worsley et al., 2002). Single-subject level statistics produced t values for all brain voxels or full brain t maps. Individual subject t maps were used to calculate average t values across all grey matter and white matter. Additionally, subject activation volumes were measured at two thresholds, $P < 0.0001$, corrected for multiple comparisons, and $P < 0.001$ uncorrected. The more rigorous threshold of $P < 0.0001$ corrected was of interest for this study because BOLD response to breath holding is robust.

Regional analysis was performed to examine the response of different tissue types and different brain regions. A set of 27 spatial masks covering the area of the entire brain, as well as subject-specific grey and white matter masks, was applied to each subject's normalized, smoothed (FWHM = 8 mm) data. For the activated volume at corrected $P < 0.0001$ in each of these areas, both percent signal change and voxel counts were measured. Voxel counts were normalized to control for differences in the total area of the spatial regions being queried. The number of total activated voxels was divided by the total number of voxels in that area and voxel counts were, therefore, expressed as percentages. For voxel counts in subject-specific grey and white matter masks, percentage volumes of activation at both $P < 0.0001$ corrected and $P < 0.001$ uncorrected were tested.

The BOLD signal and noise magnitudes were computed with a Fourier analysis utilizing the first four harmonics of the task frequency. The time series were obtained from activation volumes within subject-specific segmented grey matter and white matter areas in order to distinguish responses in different tissue types for both groups. Because the block duration was short enough to sharply attenuate the harmonics beyond the fundamental, the Fourier model achieved very high correlation with the data, and the residual had virtually no task-related signal as determined from its spectral components at harmonics of the task frequency. Task-related signal change magnitude for an area averaged across trials was used as the signal estimate, and residual signal variance not explained by the model was taken as a noise estimate. Analysis of signal change and noise in grey and white matter was performed for activation volumes produced at three thresholds: (1) $P < 0.0001$ corrected, (2) $P < 0.001$ corrected, and (3) $P < 0.001$ uncorrected.

Results

Anatomical differences between groups

From the segmentation analysis, significant group differences in the number of voxels characterized as grey matter or as white matter were found. The proportion of grey to white matter in children was greater than the proportion in adults. Children exhibited a greater mean grey matter volume than adults, and a smaller mean white

matter volume than adults (Figs. 1A and B). This confirms what has been observed in past diffusion tensor imaging (DTI), histological, and MR morphology studies (Benes et al., 1994; Klingberg et al., 1999; Paus et al., 1999; Sowell et al., 1999, 2002; Yakovlev and Lecours, 1967). In order to examine the influence of absolute brain volumes on group differences, we performed a volume correction and re-estimated statistics for the transformed data. We found no significant change in grey and white matter proportions after performing volume correction.

Movement

When making direct comparisons between children and adults using fMRI, it is critical to consider possible movement differences. Using Fourier analysis of the image realignment parameters computed by SPM99, we extracted the task-correlated movement components by calculating the movement energy at the first and second harmonics of the task frequency. In addition, we examined the average movement, the maximum extent of movement, and the root mean square (RMS) movement for each subject across the scan. Both groups exhibited the greatest average movement (mm/scan) in the Z direction (min: 0.00, max: 1.05) and greatest max extent of movement in the Z direction (min: 0.16, max: 1.53). Group means and between group statistics are provided in Table 1. Adults showed slightly greater task-related movement than children, but these differences were non-significant. Children showed significantly greater RMS values (a measure of image-to-image jitter) and maximum excursion than

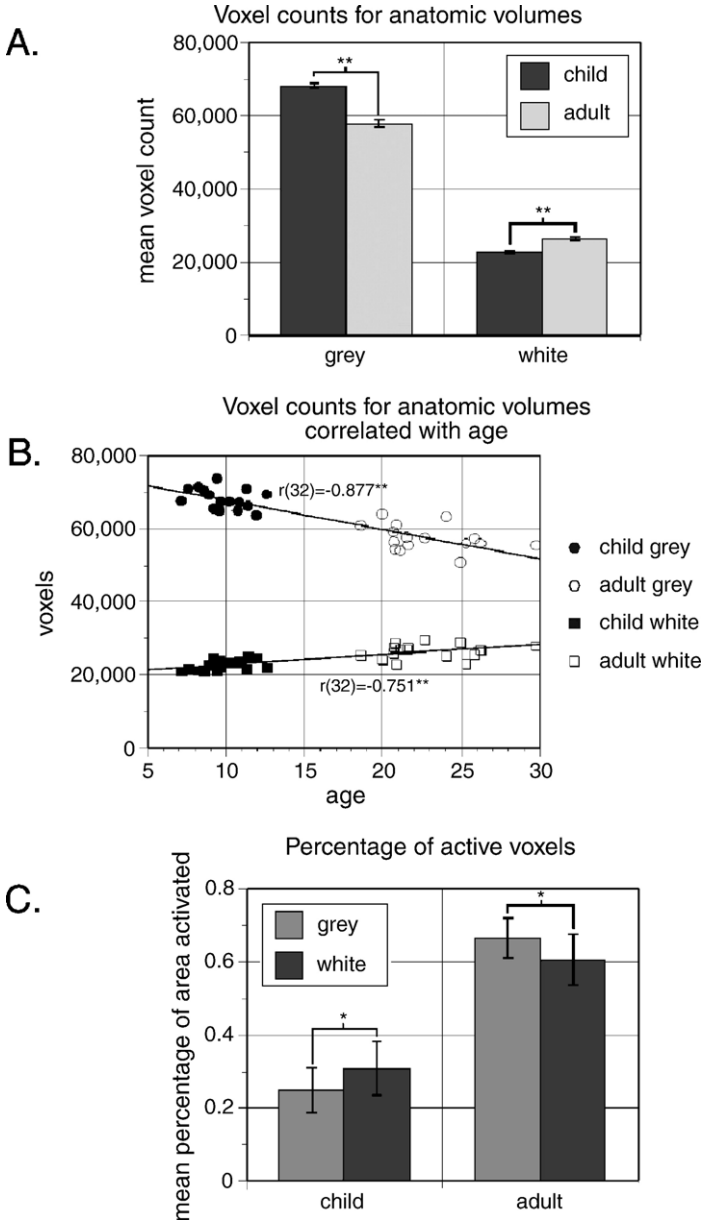

Fig. 1. Anatomic volumes (A and B) and percentage of activated voxels (C). All panels include data from 16 children and 16 adults. (A) Independent sample t tests showing the total number of voxels that were classified as grey matter versus white matter using SPM's segmentation algorithm, (B) the total number of grey and white matter voxels correlated with age, $r(32) = -0.877$, $P < 0.001$ and $r(32) = 0.751$, $P < 0.001$, respectively, (C) the amount of grey matter versus white matter that surpassed the threshold of $P < 0.0001$ corrected for multiple corrections. ($*P < 0.05$, $**P < 0.001$).

Table 1
Movement averages for each group and statistical tests (one-way ANOVA) of between group differences for $N = 32$

		Mean	Standard deviation	F	P value
Stimulus-correlated movement, arbitrary units	Child	4.165	1.916	1.866	0.182
	Adult	5.139	2.114		
Average overall movement, mm	Child	0.119	0.067	0.181	0.674
	Adult	0.130	0.082		
Maximum excursion, mm	Child	0.406	0.199	4.639	0.039
	Adult	0.280	0.120		
Average RMS movement, mm	Child	0.110	0.052	8.043	0.008
	Adult	0.068	0.030		

adults. There was no significant group difference in average overall movement.

BH task performance

The BH inspiration amplitude for children as a group was significantly smaller than that for adults (32.1 ± 13.8 versus 41.4 ± 8.6 arbitrary units, respectively, $P = 0.04$). However, when inspiration was normalized by height, there was no difference in relative inspiration levels (5.76 ± 2.51 versus 6.14 ±1.24 arbitrary units, respectively, $P = 0.6$). Therefore, to the extent that the BOLD signal depends on inspiration amplitude, the effect of group differences in inspiration would be expected to reduce or not affect BOLD signal in children.

Activation extent

Volumes of BOLD activation were compared between children and adults (Figs. 1C and 2). Children demonstrated significantly reduced activation volumes. To quantify differences in the extent of activation in children versus adults, we measured the number of voxels activated at two thresholds, $P < 0.001$ uncorrected and $P < 0.0001$ corrected, within subject-specific segmented grey and white matter images. The total number of voxels active was converted to a percentage to correct for absolute volume differences. Children's activation volumes in grey matter at both thresholds were smaller than adults, for $P < 0.001$ uncorrected, $t(30) = 5.014$, $P < 0.001$, and for $P < 0.0001$ corrected, $t(30) = 1.96$, $P = 0.059$. Children also demonstrated smaller white matter activation volumes than adults, for $P < 0.001$ uncorrected, $t(30) = 3.942$, $P < 0.001$, and for $P < 0.0001$ corrected, $t(30) = 0.93$, $P = 0.361$. Therefore, these differences were significant in volume comparisons made at $P < 0.001$ uncorrected and showed a trend toward significance in grey matter at the more stringent threshold of $P < 0.0001$ corrected. In addition, we observed a novel difference in response features for grey and white matter in which children activated a significantly larger percentage of white than grey matter in volumes created at both thresholds (for $P < 0.001$ uncorrected, $t(15) = 7.403$, $P < 0.001$; for $P < 0.0001$ corrected, $t(15) = 2.24$, $P < 0.05$ (Fig. 1C)).

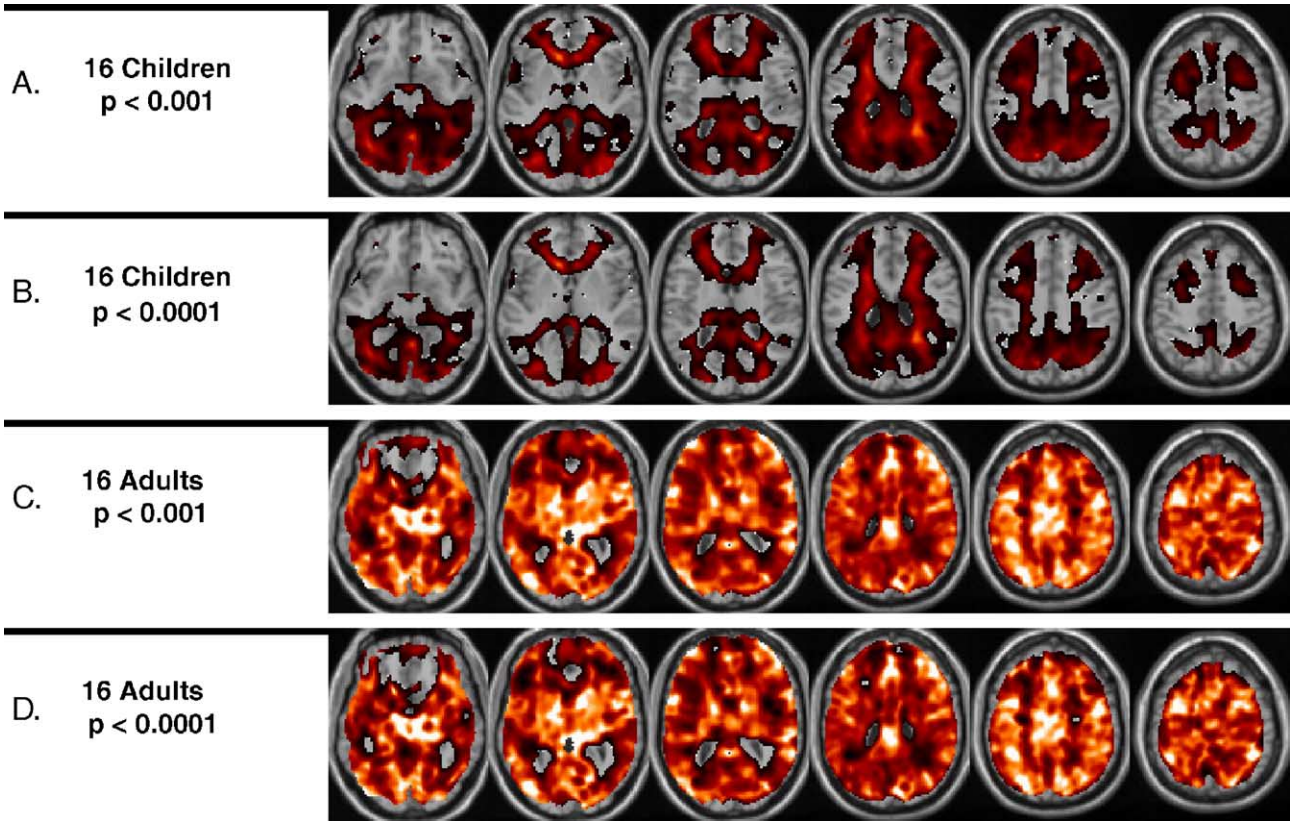

Fig. 2. Group statistical activation maps. (A) Children thresholded at $P < 0.001$, (B) children thresholded at $P < 0.0001$, (C) adults thresholded at $P < 0.001$, (D) adults thresholded at $P < 0.0001$.

In contrast, young adults activated a larger percentage of grey than white matter, consistent with prior reports (Kastrup et al., 1998b, 1999c).

Signal and noise

Signal change and noise were significantly greater in children compared to adults in grey matter; for signal $t(30) = 4.116$, $P \leq 0.001$, and for noise $t(30) = 3.449$, $P \leq 0.003$. Signal and noise were not significantly greater in children compared to adults in white matter, although a trend toward significance was observed for children greater than adults in white matter for noise; for signal $t(30) = 0.764$, $P = 0.452$ and for noise $t(30) = 2.033$, $P = 0.058$. A repeated-measures analysis of variance (ANOVA) with a between-subjects factor of age and a within-subjects factor of grey matter BOLD response (task related signal change and residual signal, or noise) yielded a significant group effect, $F(1,30) = 17.83$, $P < 0.001$. The interaction of group × BOLD effects in grey matter was also significant, $F(1,30) = 14.74$, $P \leq 0.001$. For white matter repeated-measures analysis of variance (ANOVA) with a between-subjects factor of age and a within-subjects factor of white matter BOLD response (task related signal change and residual signal, or noise), the interaction was not significant, $F(1,30) = 0.244$, $P = 0.625$.

We determined that noise, or remnant signal variance, agrees well with variance in resting state voxels for the same subject in a different scan (data not shown). In addition, we found that the residual time series had no significant signal component at the task frequency or its harmonics, supporting use of residual variance as a noise estimate even in an activated voxel. Because physiological noise is putatively attributed to basal metabolic processes (Kruger and Glover, 2001), the equivalence of our two measures of noise suggests that the underlying basal metabolism is not changed by the BH task. The results of the signal and noise analyses are displayed as maps in Fig. 3, in which signal and noise have been extracted for every voxel for every participant and averaged across groups.

The BOLD SNR for each group was estimated by grey/white segmentation of the t values obtained for all brain voxels from individual statistics estimated by SPM. t values are proportional to BOLD SNR for large degrees of freedom because they are the effect size (signal) divided by residual noise. The comparison revealed a significant between-group effect for t values. Consistent with higher noise levels, children had significantly reduced BOLD SNR averaged over all voxels. For all anatomically-defined grey matter voxels, children yielded significantly lower t values (adult mean: 8.99; child mean: 4.37) $t(30) = 5.80$, $P < 0.001$, and for all white matter voxels children yielded significantly lower t values (adult mean: 7.08; child mean: 4.90) $t(30) = 3.238$, $P \leq 0.003$, which is consistent with the differences in group activation maps shown in Fig. 2.

In order to examine whether the signal and noise differences measured in children and adults were related to the (stringent) threshold of $P < 0.0001$ corrected utilized for making activation volumes, we re-analyzed grey and white matter signal change and noise at the reduced thresholds of $P < 0.001$ corrected and $P <$

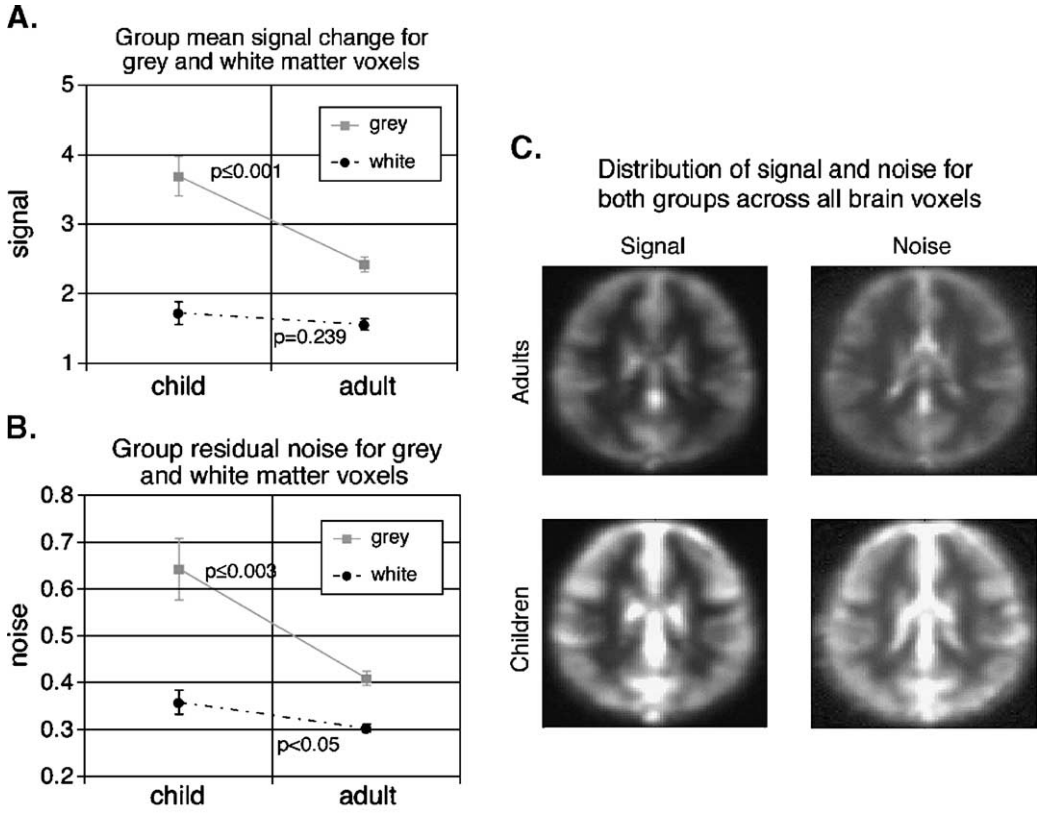

Fig. 3. Mean signal and noise measures for children and adults (percent of raw signal). Line graphs of group means and standard error for (A) signal change and (B) noise in grey and white matter activation volumes show both groups have greater signal and noise in grey matter. (C) Group averages of signal and noise values for every voxel in the brain coded on a greyscale with arbitrary units where white depicts the highest values and black the lowest values. Noise represents the residual standard deviation after signal variance has been removed.

0.001 uncorrected. Results for the entire cohort of 32 subjects were similar at the 3 thresholds. Grey matter signal change and noise extracted from volumes activated at three different thresholds are summarized in Table 2. Consistency at different thresholds was further confirmed by within-subject correlation analysis between signal change estimates derived at $P < 0.0001$ and $P < 0.001$ corrected. The correlation value for percent signal change in grey matter was $r(31) = 0.998$, $P < 0.001$ and the correlation value for percent noise in grey matter was $r(31) = 0.726$, $P < 0.001$.

With a task like BH that elicits global signal change, some of the significant group differences in BOLD signal and noise demonstrated above could potentially have resulted from differences in motion characteristics not corrected by the image realignment algorithm. We performed two additional analyses to examine the effects of movement on BOLD signal and noise in our groups, even though our motion analysis demonstrated very small group differences and small overall movement (Table 1). First, we assessed the degree to which group noise and signal measurements in grey and white matter correlated with movement parameters, and found none of the correlations were significant. Second, we performed a post hoc analysis of a subset of 14 children and 14 adults where movement parameters did not differ for overall movement, stimulus-correlated noise, and maximum excursion. This analysis was of interest because if the small movement differences between our groups contribute to the BOLD signal effects we observed, then for this subset of subjects significance would be reduced. We found that even with non-significant differences in three critical movement measures, adults still demonstrated a significantly greater number of activated voxels than children, and children demonstrated significantly greater signal and noise values than adults. Maintenance of the major effects of this study in a subset where movement is even more closely matched reduces the likelihood that movement differences between groups contributed to the observed signal and noise effects.

Table 2
Group averages for grey matter percent signal change and noise obtained from activation volumes defined at three different statistical thresholds

	Group	Mean	Standard deviation	F	P value
p0001-corrected signal change, %	Child	3.691	1.161	17.833	<0.001
	Adult	2.420	0.422		
p0001-corrected residual noise, %	Child	0.642	0.265		
	Adult	0.408	0.063		
p001-corrected signal change, %	Child	3.599	1.079	18.878	<0.001
	Adult	2.387	0.423		
p001-corrected residual noise, %	Child	0.625	0.237		
	Adult	0.405	0.058		
p001-uncorrected signal change, %	Child	3.362	0.877	24.042	<0.001
	Adult	2.258	0.435		
p001-uncorrected residual noise, %	Child	0.592	0.171		
	Adult	0.395	0.053		

Repeated measures ANOVA (within subjects factors: grey matter signal change and noise, between subjects factor: age group) was applied to data at each threshold for $N = 32$.
F values given for between group differences in signal and noise in grey matter.

Temporal response of BOLD signal

We examined overall latency differences in BOLD response using a cross correlation technique. Group-averaged time series measured in children for grey matter and white matter were cross-correlated against the corresponding time series for adults. The offset of the peak in the cross correlation function was utilized to calculate latency between the series. To account for potential performance differences between adults and children, we used the same method to estimate latency in average respiration and cardiac waveforms measured by pneumatic belt and pulse oximetry, respectively. The precision of this cross correlation method depends on the task period, number of time frames, and the SNR of the waveforms. In our case with 36 s period, 168 time frames, and SNR of ~50 in the group average, a precision of ~25 ms was expected.

These analyses revealed (Fig. 4) that the respiratory and cardiac waveforms in adults lagged those of children by 0.44 ± 0.05 s and 0.10 ± 0.08 s, respectively. Because the BH latencies (respiration) between groups differed significantly, we subtracted these performance latencies from the estimation of signal latency for grey and white matter. The corrected activation response in grey matter in children is 0.75 ± 0.05 s faster than adults. Similarly, white matter response in adults lagged response in children by 0.20 ± 0.05 s. It is noteworthy that latency differences in grey matter are greater than those observed in white matter. The finding that children exhibit a faster signal response is complementary to other studies that have examined BOLD signal hemodynamic response in different age groups. Younger subjects have shown faster return to baseline than older subjects (Buckner et al., 2000; D'Esposito et al., 1999; Richter and Richter, 2003).

Heterogeneity of brain response

One of the advantages of utilizing a global state change like BH for studying BOLD signal responsiveness (neurovascular response) is the availability of information about how a uniform stimulus can affect regions of the brain differently. A repeated-measures analysis of variance (ANOVA) with a between-subjects factor age-group and a within-subjects factor brain region (regional divisions are outlined in Figs. 5A–C) showed a significant difference between groups in number of voxels activated across the brain regions interrogated, $F(1,30) = 26.03$, $P < 0.001$, as well as significant difference between regions, $F(6,180) = 16.20$, $P < 0.001$ (Fig. 5D). In both groups, the relative difference in extent of activation between these brain regions was similar, although the overall quantity of voxels was greater for adults. A second repeat measures ANOVA was run for signal change across these regions, between groups, and a similar result was observed (Fig. 5E). These results of voxel counts and signal change agree with previous BH studies that demonstrate regional differences in brain responsiveness (Kastrup et al., 1999b). However, this is the first time the regional effect has been tested for consistency between different age groups. Group means in Fig. 5D show consistency in activation patterns across brain areas between groups. These data support a model of regional brain heterogeneity with stability between middle childhood and young adulthood.

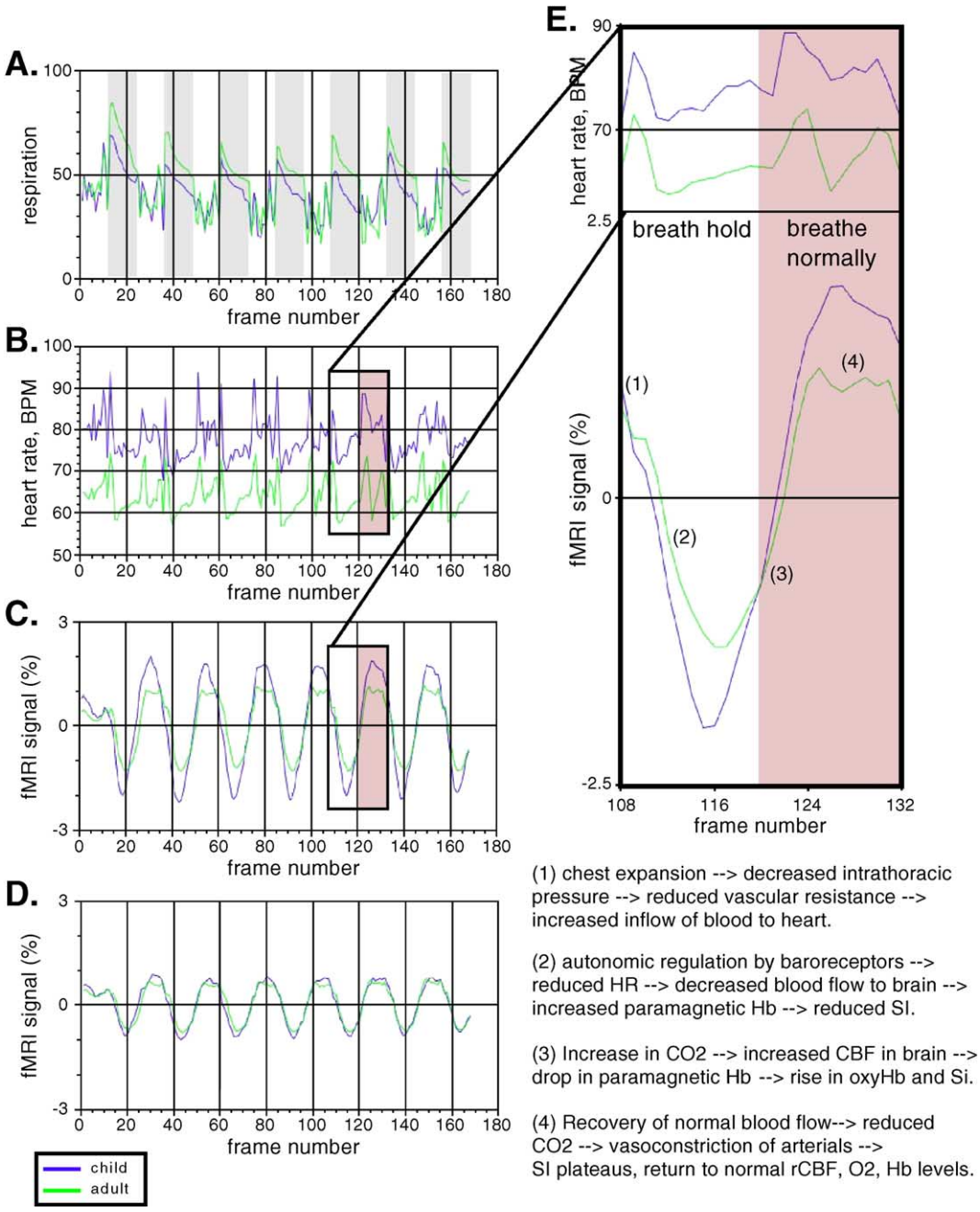

Fig. 4. Group-averaged time courses. Time courses for 16 children (purple) and 16 adults (green) show (A) respiration (arbitrary units), (B) heart rate (HR), and BOLD signal intensity (SI) in (C) grey matter and (D) white matter. (E) Expanded view of traces from frames 108–132 showing detailed relationship of respiration, HR, and SI (see text for description). Task timing is indicated by the respiration trace. Shaded areas are periods of breath holding. Abbreviations: cerebral blood flow (CBF), oxyhemoglobin (oxyHb), hemoglobin (Hb).

In order to study regional effects in more detail, we divided the brain into 18 areas combining neighboring Brodmann's areas (BAs). Our rationale for these divisions was to cover the entire cortex in this number of approximately evenly sized units. We examined both BOLD signal magnitude and activation volumes for these regions, as shown in Fig. 6. Again, relative differences between regions were consistent between groups. Children have a smaller extent of activation and greater BOLD signal change in all of these areas, but between our subjects groups, patterns of regional heterogeneity were highly consistent. It is apparent that fMRI signal responsiveness is not uniform across different regions of the brain. Importantly, however, similarity between groups in features of the response in different areas supports the feasibility of direct comparisons between groups.

Noise simulation

Finally, to verify the effects of noise on activation maps, we performed simulations where Gaussian-distributed noise was added to the pre-processed time series BH data for a typical adult subject and the model was re-run. Our goal was to increase the noise level of an adult's data to the level of the group average in

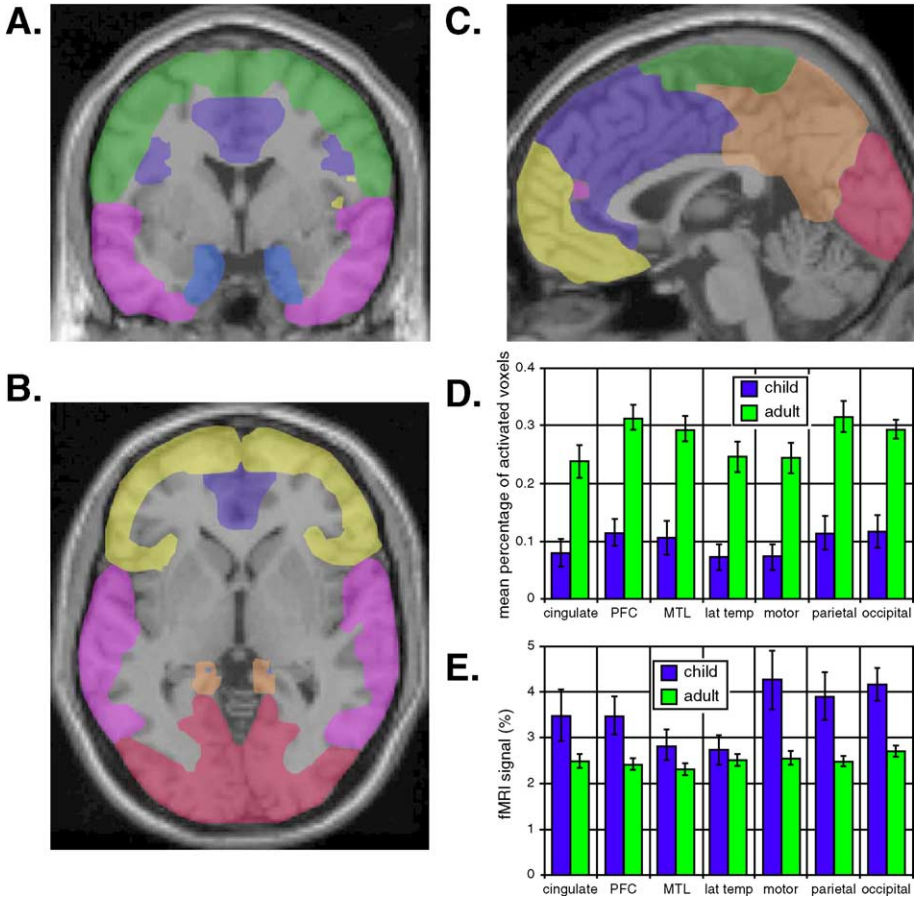

Fig. 5. ROI definition and group results for both signal and voxel counts. (A–C) T1-weighted image template in (A) coronal, (B) axial, and (C) sagittal sections defining cingulate cortex (purple), prefrontal cortex (yellow), medial temporal lobe (MTL) (blue), lateral temporal lobe (lat temp) (magenta), motor cortex (green), parietal cortex (orange), and occipital cortex (red) regions of interest (ROIs). (D) The percentage of voxels for each group in each ROI that surpassed the threshold for activation at $P < 0.0001$ corrected. (E) Signal change for each group for each ROI.

children, and test the effect of that manipulation on the resulting activation maps. Fig. 7 shows an adult subject at two noise levels compared to his baseline to which no noise was added and compared to a child to which no noise was added. This simulation demonstrates, as expected, that noise like that observed in our children can reduce the number of activated voxels dramatically even though the BOLD signal is the same. This supports our conclusion that the noise levels we observed in children can account for differences between children and adults in absolute activation volumes.

Discussion

We have found that in BOLD response to BH: (1) children show reduction in the number of voxels activated compared to adults, (2) children activate more white matter than grey matter, and this is reversed in adults; (3) BOLD signal intensity and noise are higher in children versus adults in regions that are activated above a common statistical threshold; (4) BOLD SNR as represented by average t score is lower for children than for adults; (5) BOLD response to BH in children is faster than for adults; and (6) while vascular responsiveness is heterogeneous across the brain, these patterns are very similar in children and adults. Therefore, children and adults show similar patterns of activation, but relative signal and noise levels impact between-group activation comparisons because of differences between groups and tissue types. This suggests that with increased utilization of this technique, group effects should be considered by combining information including BOLD signal change, variance in time course data, and activation maps.

Activation volumes were shown to be greater for adults than children (Fig. 2), which at first glance seems contradictory to greater signal change observed in children. However, activation volumes are representations of test statistics (like z, F, or t), dependent on signal as well as noise. Our results demonstrate that during BH the signal is higher in children, yet activation volumes are smaller, because of greater noise in children, a result not previously demonstrated. Physiological noise has been shown to be lower in white matter than in grey matter, presumably from reduced vascularity (Kruger and Glover, 2001), causing the influence exerted by noise to be larger in the grey matter. Thus, noise has relatively less impact on activation volumes (or test statistics) in the white matter, allowing children to maintain white matter BOLD response. Both adults and children show greater noise in the grey matter, but the present study shows that this effect is greater in children. Indeed, the BOLD SNR measured by average t score is significantly lower in children than adults, and this is consistent with the greatly reduced extent of activation volume measured in children's grey matter.

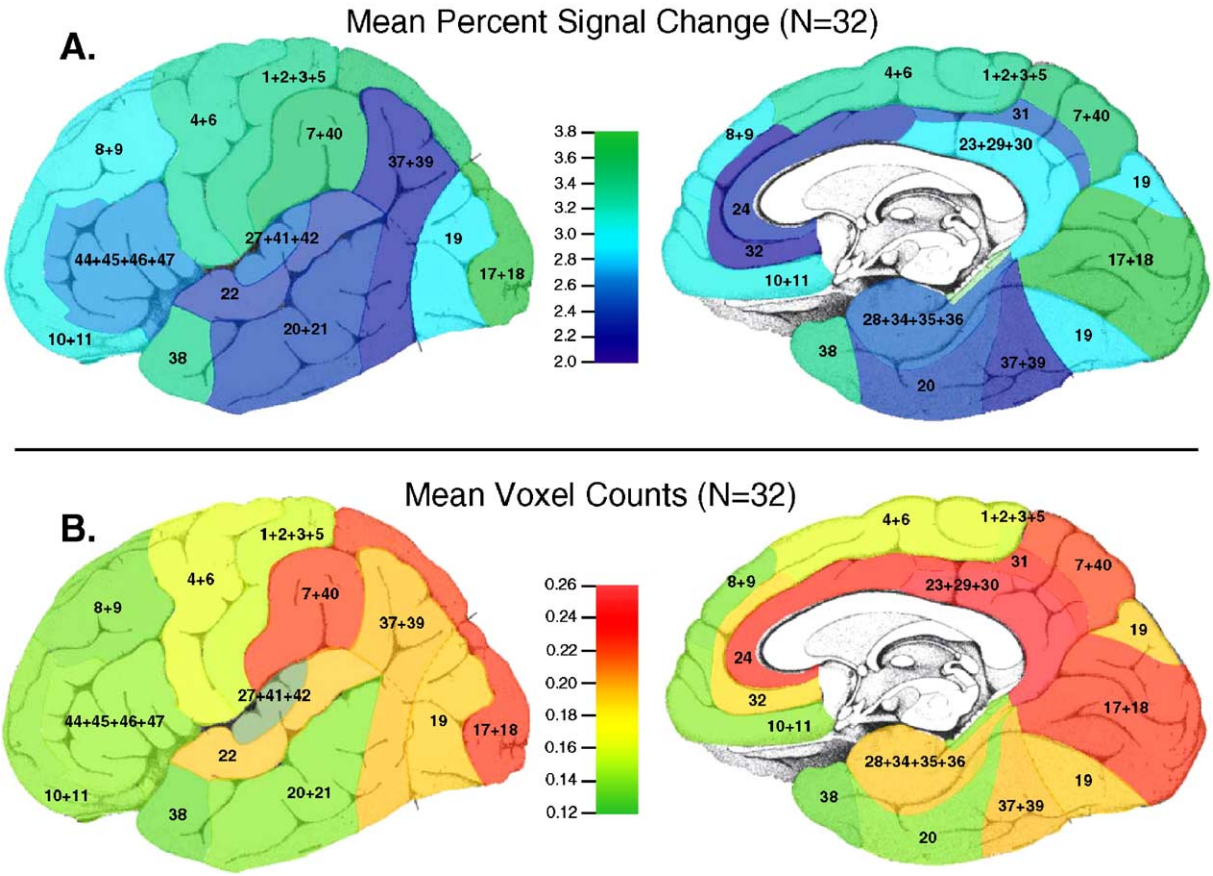

Fig. 6. Regional brain differences. Colors represent means across regional boundaries for (A) percent signal change and (B) number of activated voxels for breath holding. Each of the 18 ROIs is labeled by the combined Brodmann's areas that they encompass. Areas were selected in an effort to create approximately equal partitions covering the brain. Values for each area were determined for each subject and averaged over all subjects (N = 32).

This is the first study to demonstrate higher grey matter amplitude BOLD SI following vascular challenge in children than in adults. This finding is likely to relate to blood kinetics and oxygen extraction. For example, basal oxygenation levels or rates of O_2 consumption could differ between adults and children, and this could exert an effect on BOLD signal change following both neuronal events and physiological state changes. If children have a higher metabolic rate of O_2 and $CMRO_2$, they would be expected to show greater signal change such as that observed in the present study, by the mechanisms modeled in Fig. 4. In addition, if they have a higher rate of oxygen extraction, the brain would exhaust stores of O_2 faster during BH, again giving larger signal changes. It could also be that re-oxygenation in the lung is different in children such that more O_2 enters the blood in inspiration, leading to higher signal changes during BH. Furthermore, greater signal would be expected if children breathed more deeply; however, our un-normalized measurements showed just the opposite, or no difference when inspiration amplitudes were adjusted for subject height. A final possibility is that because the BOLD signal timing is faster in children (Fig. 4E), their hemodynamic response will reach a greater degree of equilibration in the 18 s blocks, leading to greater observed signal change.

BOLD signal time series in activated volumes were significantly noisier in children than adults in BH, which may be attributed to differences in the underlying physiology or to aspects of the measurement. Because children are passing through significant stages of development and have highly variable brain structures (Wilke and Holland, 2003), developmental differences are expected, and these may lead to greater signal variation or residual noise. For example, it has been shown that metabolic rates in children this age rise to a peak and then decline to adult levels (Chugani et al., 1987). It is thought that changes in metabolic rates accompany neuronal maturational processes, such as synaptic pruning and myelination, and it is expected that variations in metabolic rates would impact the BOLD signal. Additionally, decreases in electroencephalograph (EEG) waveforms for delta, theta, alpha, and beta frequencies with age have been described in children (Gasser et al., 1988; Wada et al., 1996). Because the BOLD signal is shown to correlate with electrical activity (Heeger et al., 2000), developmental differences in electrical activity (increased levels in children) may contribute to noisier BOLD signal measurements. A second potential contribution to differences in noise may be related to data collection. Non-correlated, physical head motion during a scan session would have a tendency to reduce the number of activated voxels, as opposed to correlated motion, which would induce artifactual activation at the brain surface. In addition to the average movement statistics traditionally reported, the present study included between-group statistics for stimulus-correlated noise, maximum excursion, and root mean square jitter. Groups were well-matched across these measures. Also, a subset of 28 subjects where movement was more closely matched showed that significance of signal and noise effects was maintained even with the reduced power that resulted from removing subjects. The lack

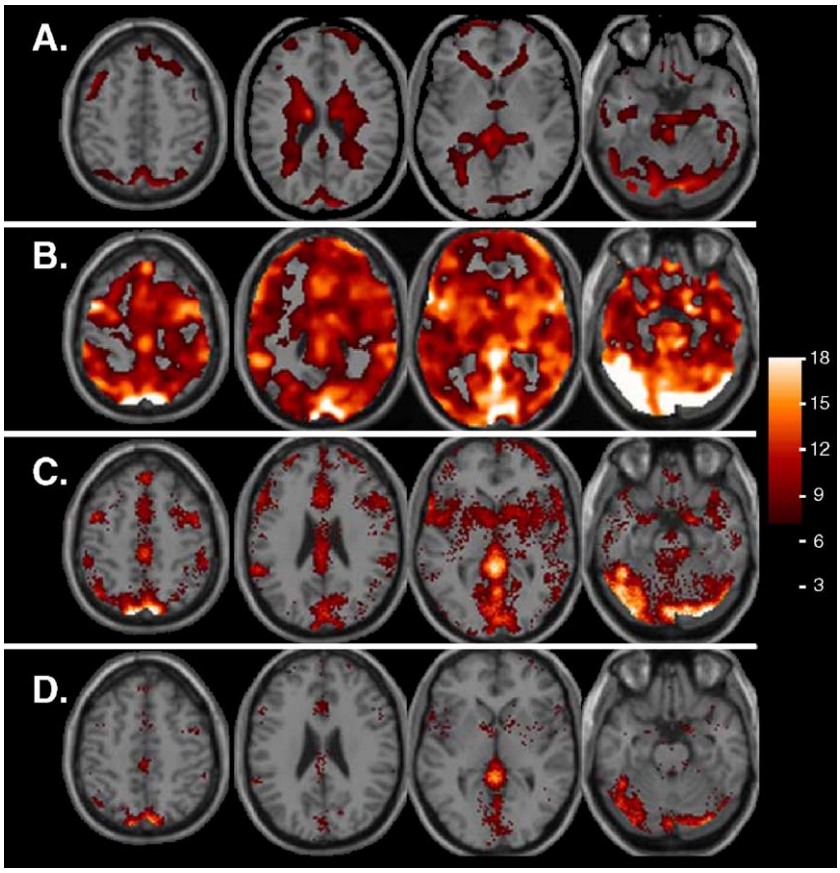

Fig. 7. Noise simulation. (A) Activation map for a typical child subject, no noise added, noise level = 0.98%, (B) activation map for a typical adult subject, no noise added, noise level = 0.38%, (C and D) activation maps for same adult subject with the addition of randomly distributed noise. For simulations, noise was added to 168 preprocessed functional volume files spanning the scan and models were re-run, resulting in two new data sets differing only in noise levels. (C) Adult subject, total noise level = 1.04%, (D) adult subject, total noise level = 2.03%. Similar extent in panels A and C, most closely matched for noise level, shows remarkable consistency in activation when noise is held constant between groups.

of motion-related differences is not unexpected, given the use of head stabilization with a bite bar and image realignment. A third possibility is that physiological contributions from vascular pulsatility and breathing-related magnetic field changes are greater for children than adults. Changes in magnetic field in the brain due to movement of lungs and diaphragm can cause additional noise in EPI or spiral imaging (Van de Moortele et al., 2002). Children consistently demonstrate higher respiration rates, heart rates, and variability in heart rate, which may add to the residual variance in their BOLD time series. However, our measurements of inspiration showed that children take smaller breaths than adults, and since children are systematically smaller than adults, these breathing-related physiological noise effects were expected to be lower, not higher for children.

The present study suggests that when making direct comparisons between adults and children in BOLD fMRI certain cautions may need to be exercised. Comparisons are facilitated by the remarkable similarity in activation patterns across brain regions during BH. Regional differences are consistent across groups, suggesting a similar distribution of response to BH across cortical and subcortical regions. However, this study provides evidence that hemodynamic responsiveness, upon which the BOLD signal is reliant, has relatively more variability, or noise, in children. Further, noise estimates are consistent within a subject across scans (data not shown). Significant differences in noise between groups during BH suggest that direct comparisons made between adults and children using fMRI need to measure noise as well as signal in both groups to determine equivalence of variance. It may not be sufficient to consider only activation volumes or BOLD signal change. Moreover, test statistics are reliant upon correction for between-group differences in variance, where assumptions of equal variance between groups are not met. If basal metabolic and other physiological noise is greater for one group, then studies and analyses should be designed in consideration of this feature. For example, a signal amplitude map as well as a map of time series standard deviation, in addition to a conventional t map, may be useful in comparing groups that have different noise features. Additionally, recruiting additional child subjects in studies of development, or increasing N, will likely combat the reduction in power introduced by noise, but comparative statistics still need to take the noise differences into account. Alternatively, noise quantification may be used to determine the appropriate age-related thresholds for the detection of activation (Gaillard et al., 2000). Because noise cannot be modeled, or therefore removed from the data, this approach may be the best way to weaken its impact on interpretation of results.

Potential methodological limitations of the present study include the observation that hemodynamic response to BH can be complicated by individual subject differences in performance

of the BH maneuver. Although we measured inspiration levels, this measure is not sensitive to potential differences in the internal posturing of the muscles that contributes to aspects of the BH response like intrathoracic pressure. However, inclusion of large groups of subjects by fMRI standards reduces the likelihood that individual differences in strategy interfered with our between-group findings. In addition, our data (Table 1) and clinical practice show no evidence that BH strategy differs between children and adults. In fact, clinical tests of heart dysfunction for both children and adults are routinely accomplished using the Valsalva maneuver, which involves expiratory effort against a closed glottis, that in turn increases pressure within the thoracic cavity and thereby impedes venous return of blood to the heart. The response in these groups is similar enough that this procedure is a medically established standard for determining heart damage for both groups. Also, the timing of the BH task maneuver between our groups was similar, as demonstrated by the temporal analysis of respiration traces, increasing our confidence in similarity in performance between our groups.

Finally, this study suggests that a BH task may be useful for calibration between groups of different developmental ages, between patients and healthy volunteers in clinical studies, between centers in multi-site studies, and within individual subjects with regional injury or isolated brain damage. Calibration is essential because it is possible that fMRI effects reported between groups do not reflect differences in neural activity, but instead reflect differences in the vascular response to neural events. Differences in microvascular anatomy and baseline cerebral blood volume could contribute to between-group differences that may be mistakenly interpreted as the effect of neural differences (Chugani et al., 1987; Gaillard et al., 2001; Martin and Marcar, 2001). Differences in neurovascular response may occlude, or spuriously pronounce, the measured timing and location of neural activity for all persons by the simple fact that all brains differ slightly, and some more significantly than others from group averages.

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