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Comparison of sustained and transient activity in children and adults using a mixed blocked/event-related fMRI design

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The ability to make direct comparisons between adult and child neuroimaging data is important to the study of the neural basis of cognitive development. Recent fMRI studies in adults have used mixed blocked/event-related designs to extract activity consistent with separable sustained, task-related processes and transient, trial-related processes. Because brain regions with different time courses of activity may have different roles in cognitive processing, the ability to distinguish between sustained and transient signals would contribute to understanding the functional roles of regions involved in cognitive processing. The developmental profile of such activity would give insight into how cognitive processing develops over time. The purpose of this study was to assess the utility of the mixed design to detect and dissociate sustained and transient activity in children, and to determine if the time courses or magnitudes of the extracted signals differ from those extracted from adults. An fMRI experiment was performed on 10 adults and 10 children (ages 7–8) using counterphase flickering checkerboard stimuli that produced sustained, transient, and a combination of sustained and transient responses in visual cortex. Analyses were performed using the general linear model (GLM) assuming a shape for sustained effects, but not for transient effects. In visual cortex, neither transient nor sustained effects showed significant between-group differences. For both groups, flickering checkerboard stimuli produced robust responses in visual cortex contralateral but not ipsilateral to the stimulus. Results extend the feasibility of direct statistical comparison of adults and children; mixed designs provide a means to examine neural activity in both adults and children related to sustained, task-level processes, likely related to task-level control.

Keywords: fMRI; Child; Neuroimaging

Introduction

Researchers in developmental cognitive neuroscience have made advances in demonstrating that direct statistical comparisons can be made between adult and child neuroimaging data. When brains of adults and children are transformed into a common stereotactic space, anatomical differences between adults and children are small, allowing for direct between-group comparisons and reporting of data in standardized coordinates (Burgund et al., 2002; Muzik et al., 2000). Numerous recent studies have used a common stereotactic space in exploring developmental issues (e.g., Booth et al., 2003; Bunge et al., 2002; Durston et al., 2003; Kwon et al., 2002; Luna et al., 2001; Monk et al., 2003; Schlaggar et al., 2002; Shaywitz et al., 2002; Turkeltaub et al., 2003; Wilke et al., 2002).

fMRI relies upon the blood oxygenation level-dependent (BOLD) contrast signal as an indirect measure of cerebral activity (Ogawa et al., 1990). In order to make direct comparisons between adults and children or between any two groups using fMRI, the two groups must have physiologically similar BOLD responses. Unknown between-group differences in the BOLD signal might bias any between-group comparison. For example, if BOLD signals have different time courses or greater variance in children than in adults, it would be difficult to draw conclusions about age-related changes during development. Several studies have compared various components of the BOLD signal in young and old adults (D’Esposito et al., 1999; Huettel et al., 2001; Taoka et al., 1998); more recent studies have specifically compared the BOLD signal in young adults and children (Kang et al., 2003) or across the age span, including children down to age 7 (Richter and Richter, 2003). When BOLD signal responses of adults and children were compared, negligible differences in signal onset or peak magnitude were found (Kang et al., 2003; Richter and Richter, 2003), further validating direct statistical comparison between adult and child neuroimaging data.

The ability to extract separate sustained, task-related signals and transient, trial-related signals in fMRI in both adults and children is important to cognitive neuroscience. Because brain regions with different time courses of activity are likely to play different roles in

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cognitive processing, the ability to detect and distinguish between sustained and transient signals should contribute to a more complete understanding of the functional roles of the observed signals. In a cognitive fMRI experiment, neural activity related to each trial of a task might produce a transient time course associated with each trial; this "transient, trial-related activity" would reflect moment-to-moment processing related to the input, output, or intermediate processing during each trial of a task. In contrast, neural activity related to the task itself but not to individual trials might be sustained throughout performance of the task and would manifest as "sustained, task-related activity". Sustained, task-related signals could reflect several different processes related to task-level control including task maintenance, attentional state, or arousal.

In the mixed blocked/event-related design, trials are presented during task blocks, which are alternated with control blocks. The difference between a mixed design and a blocked design is that in the former, trials are presented with different intervals between them, as in rapid event-related designs. This allows estimation of the temporal profile of activity related to each trial (Dale, 1999; Dale and Buckner, 1997; Josephs et al., 1997; Miezin et al., 2000). Alternating task blocks with control blocks, as in a blocked design, allows estimation of sustained activity throughout a task block, separate from transient trial-related activity. Figs. 1A, B show a schematic of the mixed design. Recent cognitive fMRI studies using mixed blocked/event-related designs in adults have allowed researchers to examine separable sustained, task-related control processes, and transient, trial-related processes occurring during a task (Braver et al., 2003; Burgund et al., 2003; Donaldson et al., 2001; Otten et al., 2002; Velanova et al., 2003). Visscher et al. (2003) empirically tested the mixed design's ability to separate sustained and transient activity in fMRI: counterphase flickering checkerboard stimuli were used in order to produce sustained, transient, and combined sustained and transient responses in visual cortex, and appropriate separation of activity was seen in all three cases. Importantly, transient stimuli or sustained stimuli alone did not produce spurious sustained or transient time courses, respectively (Visscher et al., 2003).

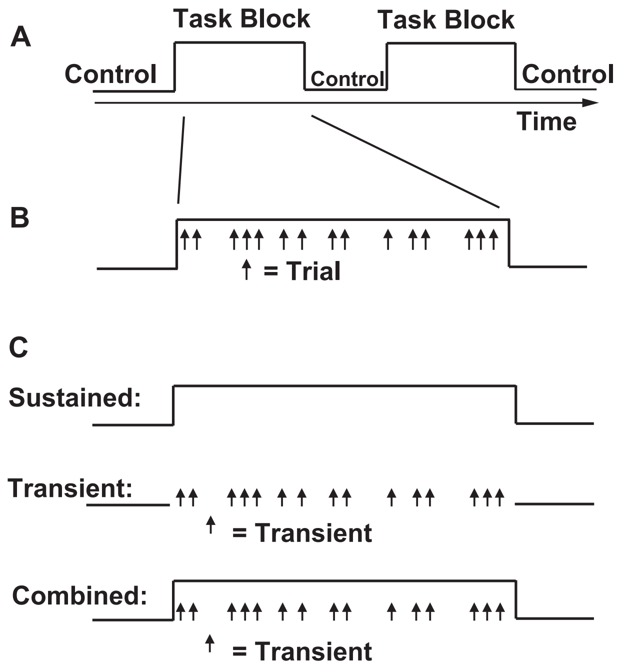

Fig. 1. Schematic of the mixed blocked/event-related design. (A) In the mixed design, task blocks are alternated with control blocks. (B) Within task blocks, individual trials (arrows) are jittered with different intervals between them. (C) The mixed design was tested in adults and in 7- to 8-year-old children in an fMRI experiment that examined sustained activity, transient trial-related activity, or combined sustained and transient activity. Schematics for a task block of each of these conditions are shown. The sustained condition comprised sustained activity through the task block, represented by the raised bar. The transient condition comprised time courses of activity that rise and fall after each trial, the onset of trials represented by the arrows. The combined condition comprised both types of activity, and is represented by the raised bar and arrows together (adapted from Visscher et al., 2003).

The goal of the present study is to extend the approach of Visscher et al. (2003) to validate the use of the mixed blocked/event-related design to compare sustained and transient activity in the visual cortex in adults and children. The hypothesis is that the extracted sustained and transient signals will not differ between adults and children in visual cortex. No significant differences in transient activity were observed in visual cortex between adults and 7- to 8-year-old children during an event-related fMRI study using counterphase flickering checkerboard stimuli (Kang et al., 2003). The present study will examine both sustained and transient activity in the context of the mixed/block event-related design. Similar responses in adults and children would further extend the feasibility of direct statistical comparison of adults and children; age-related changes in higher order cortical regions may be interpreted as reflecting differences in underlying neural activity and not differences in the ability to manifest and sustain BOLD signals.

Across the recent cognitive studies that have used the mixed design, sustained effects alone have been observed in some regions, transient trial-related signals alone in others, and both were observed together in yet other regions (Braver et al., 2003; Burgund et al., 2003; Donaldson et al., 2001; Otten et al., 2002; Velanova et al., 2003). These findings highlight the importance of a set of fMRI methods that can accurately separate activity with different time courses likely related to different cognitive processes. In this way, the mixed design also offers a potentially powerful tool for studying cognitive development; for example, the development of sustained task-related processes may follow a different developmental time course than that of transient trial-related processes. In the present study, if large between-group differences in magnitudes or time courses of sustained or transient activity are found, this might limit use of the mixed design for comparing adults and children. On the other hand, the existence of similar responses between groups in visual cortex would support the use of the mixed blocked/event-related design as a tool to study cognitive development.

Materials and methods

An fMRI experiment was performed on young adults and 7- to 8-year-old children by using stimuli that produced sustained, transient, and a combination of sustained and transient responses in visual cortex.

Subjects

Ten adults (5 female; mean age, 26.4 years; range, 19.2–28.4 years) and 10 children (7 female; mean age, 8.5 years; range, 7.6–

8.9 years) participated in return for payment. Subjects were recruited from the Washington University campus and surrounding community. All subjects reported having normal or corrected-to-normal vision and having no history of neurological problems. All subjects were screened with a questionnaire to ensure that they had no history of neurological problems or drug abuse. Children made an additional visit to the lab (before the actual scan) during which they were examined by a pediatric neurologist (author B.L.S.), completed a detailed health questionnaire to assess normal development, and were acclimated to the MRI environment in a ''mock'' scanner. Saccadic eye-movement data were collected outside the scanner for both adults and children. Informed consent was obtained from adult subjects and parents of child participants, and assent was obtained from the child participants, in accordance with the guidelines and approval of the Washington University Human Studies Committee. Data acquired from three additional child participants were not analyzed due to excessive movement or poor task compliance in the majority of imaging runs.

Equipment

Visual stimuli were presented to subjects by projecting (Sharp PG-C20XU LCD projector) the image generated from a Power Macintosh G3 (Apple, Cupertino, CA) using Psyscope software (Cohen et al., 1993) onto a screen at the back of the magnet bore. Subjects viewed the screen through a mirror attached to the headcoil. Subjects responded to the behavioral task by using a fiber-optic key press whose output was recorded by Psyscope.

Subjects' eye movements were monitored during scanning sessions by using hardware and software by Applied Science Laboratories (Model 504 LRO, Bedford, MA). A dim infrared light was reflected by a small mirror attached to the headcoil onto the subject's left eye. A video camera sensitive to infrared light monitored the subject's eye throughout the scan. The same software and similar hardware (basic Model 504 without long-range optics) were used to monitor subjects' eye movements outside the scanner.

Visual stimuli

Stimuli from visual field locations not on the vertical meridian are almost exclusively processed in the contralateral visual cortex in early visual cortex regions (Daniel and Whitteridge, 1961; Fox et al., 1986; Holmes, 1918; Holmes and Lister, 1916; Hubel and Wiesel, 1962; Inouye, 1909; Sereno et al., 1995; Tootell et al., 1998). We presented stimuli in both left and right hemifields simultaneously and treated responses in left and right visual cortex regions separately.

Counterphase 8-Hz flickering checkerboard wedges each spanning 57° radially and spanning 2–6° in eccentricity were presented in the lower left and right quadrants of the visual field. Sample stimuli are shown in Fig. 2. The low-contrast stimulus had approximately 10% contrast and the high-contrast stimulus had 98% contrast. Both the high-contrast and low-contrast checkerboards had alternating high- and low-luminance squares. Though it may be difficult to distinguish high- and low-luminance squares in the figure for the low-contrast stimuli, they were sufficiently distinct when presented. Stimuli were shown on a gray background equal in luminance to the light squares of the low-contrast stimuli, though for clarity in Fig. 2, the background is shown in a lighter gray. Additionally, a small central fixation cross was present in all displays.

A schematic of a functional MR run is shown in Fig. 1A. Each run consisted of 29 s (11 MR frames) of fixation (control) followed by an 80-s stimulus block (task block; 30 MR frames), followed by 37 s (14 MR frames) of fixation, an 80-s stimulus block (30 MR frames), and 40 s (15 MR frames) of fixation.

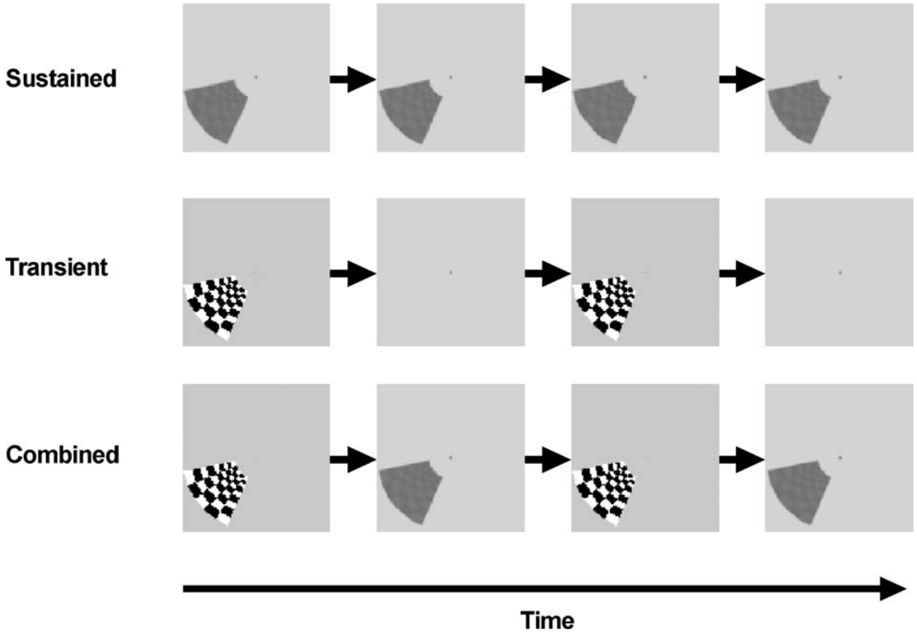

Fig. 2. Example visual stimuli. Only left hemifield stimuli are shown for simplicity. The first row shows selected frames during a block in which a sustained stimulus condition was presented in the left hemifield; the second row shows the transient condition; the third row shows the combined condition. Note that during the sustained condition, the low-contrast stimulus is present at all times. During the transient condition, high-contrast stimuli are shown intermittently and for 1.25 s at a time. During the combined condition, a sustained low-contrast stimulus is intermittently replaced with high-contrast transient stimuli.

Stimulus conditions

During each stimulus block, one of three stimulus conditions was presented in one visual field, while either the same or a different stimulus condition was presented in the other visual field. The ''sustained'' stimulus condition (Figs. 1C and 2) consisted of the low-contrast checkerboard stimulus flickering continuously at 8 Hz for the entire 80-s stimulus block. The ''transient'' stimulus condition (Figs. 1C and 2) consisted of the high-contrast checkerboard stimulus presented for 1.25 s. During the ''transient'' condition, stimuli were presented 13 or 15 times in 80 s. Intervals between transient stimuli were planned so that the time between successive stimuli varied across a block, as in rapid event-related designs (Dale, 1999; Dale and Buckner, 1997; Miezin et al., 2000). Timing between trial onsets ranged from one to three frames (2.678–8.034 s), and was more often shorter than longer (Dale, 1999). Each of four presentation timing sequences occurred equally often for blocks of each stimulus condition. Another type of stimulus condition combined transient with sustained stimuli. For the ''combined'' stimulus condition (Figs. 1C, 2), high-contrast flickering checkerboards were presented with the same duration and timing sequences as in the transient blocks described above. Additionally, low-contrast flickering checkerboards were present at all times during the block when high-contrast checkerboards were not present.

Transient or combined conditions occurring in different hemifields during the same block never shared the same presentation sequence of transient stimuli, so that the BOLD signal responses to transient stimuli could be separated in left and right visual cortex regions.

Effect types included in the general linear model

The three stimulus conditions describe four different visual stimulus responses, or visually evoked effect types. The sustained condition is modeled by a sustained effect. The transient condition is modeled by a transient effect. The combined condition is modeled by two effects: a sustained/combined effect and a transient/combined effect. Since each of these four effects can follow from stimulus conditions in the left and right hemifields, there were a total of eight different visually evoked effects.

Behavioral task

During all scans, subjects were instructed to keep their gaze on a fixation cross in the center of their field of view and to ignore the checkerboard stimuli. To maintain attention at the center of gaze as well as possible, subjects were instructed to press a button as soon as they could when the fixation cross changed from black to gray. The fixation cross dimmed at random times during the scan (on average, six times per run) for 250 ms. This task was qualitatively considered to be difficult by all subjects, as the change in luminance of the fixation cross was small.

MRI data acquisition

fMRI data were acquired on a Siemens 1.5-T Vision system (Erlangen, Germany). Subjects' heads were stabilized using pillows and a thermoplastic face mask. Structural images were acquired using a sagittal MP-RAGE three-dimensional T1-weighted sequence (repetition time = 9.7 ms, echo time = 4 ms, flip angle = 12°, inversion time = 300 ms, voxel size = 1.25 × 1 × 1 mm).

Functional images were acquired using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast during visual stimulation (Kwong et al., 1992; Ogawa et al., 1992). Sequence parameters were repetition time = 2.678 s, T2* evolution time = 50 ms, flip angle = 90°, voxel size = 3.75 × 3.75 mm in-plane resolution (Conturo et al., 1996). One volume was acquired every 2.678 s, or one MR ''frame''. Subjects performed up to six functional runs. During each run, 100 frames of 16 contiguous interleaved 8-mm-thick axial slices were acquired parallel to the plane transecting the anterior and posterior commissures (AC-PC plane). This plane was defined with an automated program utilizing a low-resolution MP-RAGE image. The first four frames in each run were discarded to allow stabilization of longitudinal magnetization.

Data preprocessing

Functional images were preprocessed to remove artifacts. Each volume was corrected to account for intensity differences due to order of slice acquisition. Volumes were then motion corrected using a rigid-body rotation and translation correction that outputs the adjustments required for realignment of each image at each MR frame. This information can be used as a measure of head movement in six dimensions: translations and rotations in the x, y, and z planes (Lancaster et al., 1995; Snyder, 1996). Then each slice was temporally realigned using sinc interpolation to account for between-slice timing differences induced by their acquisition order.

Movement analysis

Measures of head movement were obtained from the output of the rigid-body translation and rotation algorithm. Translations and rotations in the x, y, and z dimensions were averaged across frames, and total rms linear and angular precision measures were calculated for each BOLD run. Runs in which a subject's total rms movement was more than 0.8 mm were excluded from further analysis. Six runs of data were included for all ten adult subjects and for six pediatric subjects, four runs for two pediatric subjects, and three runs for two pediatric subjects. Values for included runs were then averaged for each subject, and two-sample t tests performed on the two groups.

Analysis methods

Preprocessed data were analyzed on a voxel-by-voxel basis using the general linear model (GLM) (Friston et al., 1994; Josephs et al., 1997; Miezin et al., 2000; Visscher et al., 2003; Worsley and Friston, 1995; Zarahn et al., 1997) as implemented with in-house software (Miezin et al., 2000; Ollinger et al., 2001). Transient effects were coded in the GLM by delta function regressors for each of the seven frames following trial onset. Seven frames were examined because they span more than 15 s, roughly the time it takes for the hemodynamic response to decay to baseline (Boynton et al., 1996; Miezin et al., 2000). This method does not assume a response shape. A sustained effect was coded into the GLM as a single regressor with an assumed shape. This shape has a graded rise to a sustained value and a decline to zero at termination, modeled as a ''gamma'' function convolved with a boxcar function of width equal to the assumed duration of neuronal firing (Boynton et al., 1996). Here, the duration is the length of one task block. Both sustained and transient effects are coded in the GLM, as described above. Two additional regressors were coded in the

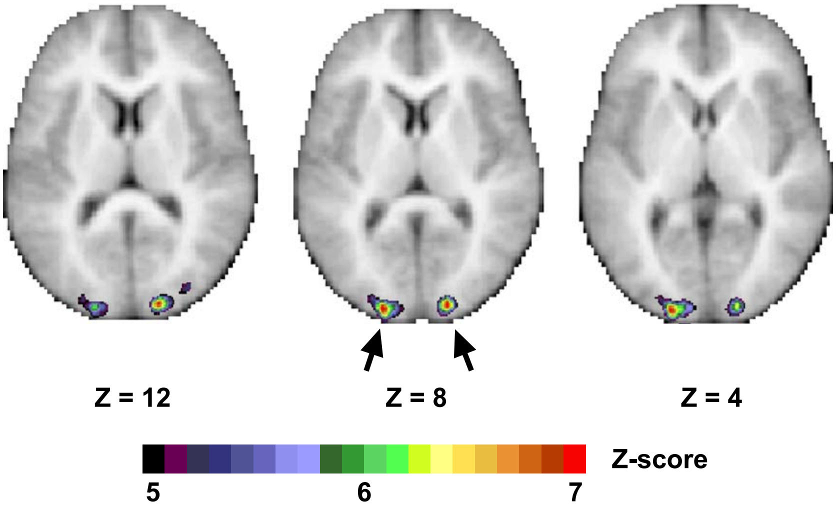

Fig. 3. *Z* statistic map of omnibus *F* statistic of voxels significantly fitting a model given by the visually evoked effects averaged over 10 children and 10 adults. Statistical image is superimposed on the averaged anatomical image for all subjects; the right side of the brain is represented on the reader's right. Pseudocolor scale shows significance in units of standard deviation (*Z* score). Transverse slices are shown in Talairach space at z = 12, 8, and 4 mm.

GLM: one for the baseline signal and one for the slope, or linear drift, in the MR signal. All effects are described in terms of percentage of the average baseline term estimated across all runs.

For analysis of data between subjects, each subject's data were placed into a standardized stereotactic atlas space (Lancaster et al., 1995; Snyder, 1996; Talairach and Tournoux, 1988) and interpolated to isotropic voxels 2 mm on a side. Data were smoothed with a Gaussian filter with full width at half maximum of two voxels.

As noted, the sustained effects were modeled with a single regressor. This approach does not allow extraction of time profiles of the sustained effect. Instead, time profiles of sustained effects were obtained by using the portion of the fMRI temporal signal variance that was not explained by the model (i.e., the residual). The residual signal plus the signal associated with the modeled magnitude of a sustained effect was computed for each frame of each effect of each subject's data for each region of interest. This estimate was averaged over all occurrences of the effect for one subject, then averaged across subjects. This estimate based on the residual is reported as the time course of the sustained effect.

Region of interest (ROI) definition

GLMs coding for each of the eight effect types related to visual stimuli were created for each subject. The omnibus *F* statistic was calculated for each voxel in each subject's image. This statistic is a ratio of explained over unexplained variance for the entire GLM (Draper and Smith, 1966), including all effect types but excluding the baseline and linear drift regressors. To identify regions involved in processing the stimuli, the *F* statistic maps for each subject were transformed into stereotactic space and converted to equivalently probable z values, and maps were then averaged across subjects. Maps were smoothed with a 3-mm radius sphere, and a three-dimensional search algorithm (developed in-house by Avi Snyder) was used to automatically define region of interests (ROIs) centered on loci of peak z statistics. The algorithm consolidated peaks closer than 10 mm by coordinate averaging. Then, a sphere with a radius of 10 mm was defined around each peak. Subsequently, voxels were eliminated from each region where the z value did not reach the specified threshold of z = 5.5. This procedure resulted in two ROIs: one in the visual cortex of each hemisphere.

Significance of sustained effects was determined by using a 4-factor ANOVA with group (adults, children), stimulus hemifield (left, right), stimulus type (sustained, combined), and region (left, right) as factors. Significance of transient effects was determined by using a 5-factor ANOVA with group (adults, children), stimulus hemifield (left, right), stimulus type (sustained, combined), region (left, right), and time as factors. Based on results from these analyses, various other analyses were pursued (see below). Values for all analyses were corrected for sphericity (Box, 1954; Ollinger and McAvoy, 2000).

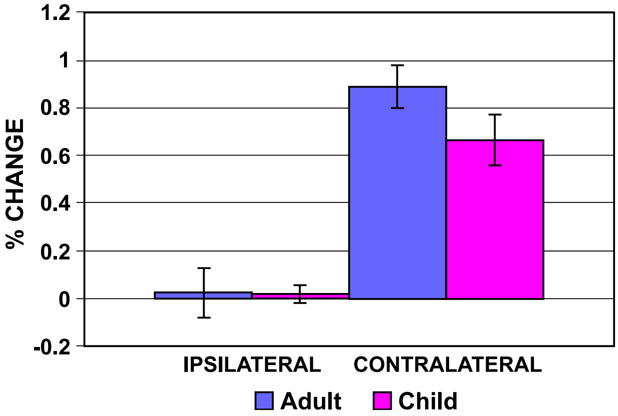

Fig. 4. Magnitude of sustained effects collapsed across region (left and right hemisphere regions) and stimulus type (sustained and combined conditions). Percent signal change with respect to baseline is shown along the y axis. Blue bars show magnitude of effects in adult subjects, and pink bars represent magnitude of effects in child subjects. The left side of the figure represents effects in the ipsilateral hemisphere (effects of left visual stimuli on the left hemisphere region and effects of right visual stimuli on the right hemisphere region); the right side of the figure represents effects in the contralateral hemisphere (effects of left visual stimuli on the right hemisphere region and effects of right visual stimuli on the left hemisphere region). For both adults and children, only the effects in the visual field contralateral to the stimulus are large and positive. Error bars represent standard error of the mean.

Results

Behavioral results

Accuracy (hits minus false alarms) did not significantly differ between adult subjects (78%) and pediatric subjects (72%) (2-factor analysis of variance [ANOVA] with group and block type as factors: $F_{1,18} = 0.499$; $P > 0.10$). However, there was an effect of block type (control vs. task block) ($F_{1,18} = 5.036$; $P = 0.0376$). Post hoc *t* tests revealed that this was due to adult subjects' significantly greater accuracy during task blocks (83%) than during control blocks (72%) (paired two-tailed *t* test: $T_9 = -3.104$; $P < 0.05$).

Reaction time (for correct responses) was significantly longer for child subjects (872 ms) than for adult subjects (700 ms) (2-factor ANOVA: $F_{1,18} = 14.686$, $P < 0.01$). Reaction time did not vary according to block type ($F_{1,18} = 0.243$; $P > 0.10$), and there was no interaction of group and block type ($F_{1,18} = 0.561$, $P > 0.10$).

Monitoring of saccadic eye movements during task performance in and out of the scanner suggested that while both adults and children maintained visual fixation the majority of the time, children made more unwanted saccades than adults.

Movement results

Children had significantly more head movement on average than adults ($T_{18} = -3.167$, $P < 0.01$), although average rms values for both groups were well under the cutoff of 0.8 (0.4 for children and 0.32 for adults). Results are in agreement with other studies showing that children exhibit more head motion during scanning than do adults (Kang et al., 2003; Poldrack et al., 2002; Schlaggar et al., 2002; Thomas et al., 1999).

Imaging results

Fig. 3 shows a statistical map averaged over all subjects highlighting voxels that showed a good fit to the model of all visually evoked effects. The two most significant peaks were in the left and right occipital cortex, respectively. The left visual cortex region of interest defined from this map comprises 131 voxels (center of mass: $x = -17$, $y = -95$, $z = 0$); the right visual cortex region of interest comprises 117 voxels (center of mass: $x = 17$, $y = -95$, $z = 10$). All subsequent analyses relate to these two regions of interest.

Sustained effects

4-Factor ANOVA: The only significant effect in the 4-factor ANOVA of sustained effects was an interaction of region and stimulus hemifield ($F_{1,18} = 60.370$, $P < 0.0001$); this finding was expected, since visual stimuli should have a large effect on the BOLD signal in the contralateral visual cortex and little or no effect in the ipsilateral visual cortex. All other effects were $P > 0.08$. There were no significant interactions with group or stimulus type, and no other significant interactions with region. The lack of effect of stimulus type is notable, as it shows that the mixed design correctly does not differentiate between sustained stimuli when presented alone, as a sustained low-contrast visual stimulus, or when combined, as a sustained low-contrast visual stimulus occasionally replaced by a high-contrast stimulus.

Post hoc significance values for each of the sustained effects were calculated individually by using two-tailed *t* tests where the null hypothesis is that the effect's magnitude is zero. Sustained effects for flickering checkerboard stimuli were large and significant for both adults and children in the contralateral hemisphere but not different from zero in the ipsilateral hemisphere (Fig. 4). Significance values for the sustained effects are shown in Table 1.

2-Factor ANOVA: Since a major goal of the study is to find any differences that might exist between adults and children, an additional analysis was done with increased power to detect group differences. Since there were no effects of region or stimulus type in the 4-factor ANOVA, the effects of all contralateral stimuli and all ipsilateral stimuli were averaged across the regions (i.e., effects of all left hemifield stimuli on the right visual cortex region were averaged with effects of all right hemifield stimuli on the left visual cortex region and vice versa). Then, a 2-factor ANOVA was run with group (adults, children), and stimulus hemifield (ipsilateral, contralateral) as factors. The only significant effect was the large effect of stimulus hemifield ($F_{1,18} = 60.372$, $P < 0.0001$). All other effects were $P > 0.10$. Importantly, there was no effect of group or significant interactions with group as a factor. Fig. 4 shows the averaged sustained effects for adults and children due to ipsilateral and contralateral stimuli.

Time courses for the sustained effects (calculated as described in Materials and methods) are shown in Fig. 5. Sustained effects for the sustained and combined conditions are shown for each group. Note that these time courses show apparently slightly higher activity at the beginning of the sustained stimulus than near the end.

Table 1
Stimulus conditions and associated visually evoked sustained effects

	Stimulus condition	Effect(s) modeled	Stimulus duration (s)	No. of regressors	*P* value			
					Adult		Child	
					Contra	Ipsi	Contra	Ipsi
Left visual field	sustained	sustained	80	1	<0.0001	0.086	<0.01	0.38
	combined	sustained/ combined	80	1	<0.0001	0.20	<0.01	0.73
Right visual field	sustained	sustained	80	1	<0.01	0.17	<0.001	0.54
	combined	sustained/ combined	80	1	0.011	0.23	<0.01	0.61

The first column lists all the stimulus conditions (in the left and right visual fields) for which a sustained effect was modeled. The second column shows the name of the effects modeled for each condition. The duration of the stimulus associated with each effect is given in the third column. The number of regressors is one for all sustained effects (since only their magnitudes are estimated by the GLM). The last four columns report significance values (*P* values) for each sustained effect in the visual cortex contralateral and ipsilateral to the stimulus for adults and children.

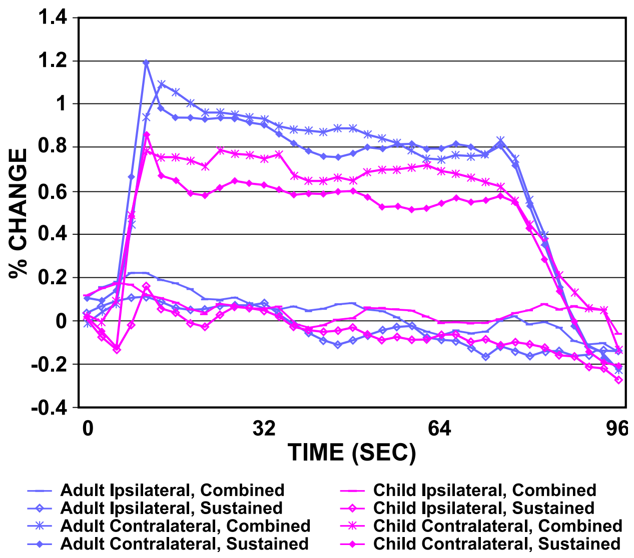

Fig. 5. Time courses of sustained effects estimated as the residual signal change (see Materials and methods) plus the estimated magnitude of the sustained effect. Percent signal change with respect to baseline is shown along the y axis, and time (in seconds) is shown along the x axis. Data are smoothed across five time points. Data shown were collapsed across region (left and right cortical regions) but not across stimulus type (sustained vs. combined conditions), and are shown separately for adults and children. Adult time courses are shown in blue, and child time courses are shown in pink. For each group, time courses evoked by ipsilateral stimuli are shown by a solid line without symbols (for the combined condition) and by an open symbol (for the sustained condition). Time courses evoked by contralateral stimuli are shown by a star (for the combined condition) and by a filled diamond (for the sustained condition). Note that for each effect, time courses are similar between adults and children.

Transient effects

5-Factor ANOVA: For transient effects, there was a significant interaction between the factors region, stimulus type, stimulus hemifield, group, and time ($F_{6,108} = 2.701$, $P = 0.022$). Due to this high-order interaction, data were not collapsed across regions as was done for sustained effects, and each region was considered separately.

4-Factor ANOVA: Two separate 4-factor ANOVAs, one for each region, were performed with group (adults, children), stimulus hemifield (left, right), stimulus type (transient, combined), and time as factors. Both the left (L) and right (R) regions of interest showed highly significant changes over time with interactions of time and stimulus hemifield (L: $F_{6,108} = 18.259$, $P < 0.00001$; R: $F_{6,108} = 26.921$, $P < 0.00001$); time and stimulus type (L: $F_{6,108} = 2.252$, $P = 0.048$; R: $F_{6,108} = 3.1$, $P < 0.01$); and time, stimulus type, and stimulus hemifield (L: $F_{6,108} = 4.941$, $P < 0.001$; R: $F_{6,108} = 3.965$, $P < 0.01$). An interaction of time and stimulus hemifield was expected since visual stimuli should have a large effect on the BOLD signal in the contralateral visual cortex and little or no effect in the ipsilateral visual cortex. An interaction of time and stimulus type was also expected: there is a greater difference in contrast between the high contrast stimulus and the gray background (in the transient condition) than between the high contrast stimulus and the low contrast stimulus (in the combined condition), and this is reflected in the BOLD signal. Importantly, there were no significant interactions with group; effects were similar between adults and children.

Post hoc significance values for each of the transient effects were calculated individually by using one-factor ANOVAs with time as the factor. Transient effects were very large and significant in the contralateral hemisphere and very small in the ipsilateral hemisphere. As can be seen in Fig. 6, effects for contralateral

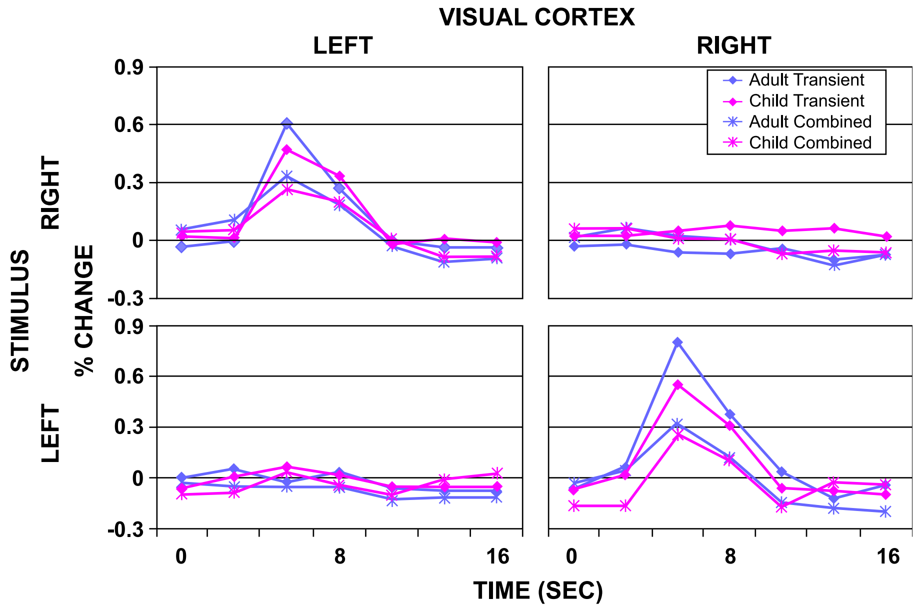

Fig. 6. Time courses of transient effects. Transient effects extracted from the left visual cortex region are plotted on the left side of the figure; transient effects extracted from the right visual cortex region are plotted on the right side of the figure. Percent signal change with respect to baseline is shown along the y axis; time (in seconds) is shown along the x axis. Effects in adult subjects are plotted in blue; effects in child subjects are plotted in pink. Transient effects from the transient condition are shown with diamonds, while transient effects from the combined condition are shown with stars. For both adults and children, only the effects in visual cortex contralateral to the stimulus (upper left and lower right panels) are large and positive.

Table 2
Stimulus conditions and associated visually evoked transient effects

	Stimulus condition	Effect(s) modeled	Stimulus duration (s)	No. of regressors	*P* value			
					Adult		Child	
					Contra	Ipsi	Contra	Ipsi
Left visual field	transient	transient	1.25	7	<0.00001	0.033	<0.00001	0.72
	combined	transient/ combined	1.25	7	<0.00001	0.037	<0.01	0.22
Right visual field	transient	transient	1.25	7	<0.00001	0.79	<0.00001	0.98
	combined	transient/ combined	1.25	7	<0.00001	0.089	<0.00001	0.085

The first column lists all the stimulus conditions (in the left and right visual fields) for which a transient effect was modeled. The second column shows the name of the effects modeled for each condition. The duration of the stimulus associated with each effect is given in the third column. The number of regressors is seven for all transient effects (since seven time points are estimated by the GLM). The last four columns report significance values (*P* values) for each transient effect in the visual cortex contralateral and ipsilateral to the stimulus for adults and children.

stimuli have time courses that follow the typical rise and fall of a hemodynamic response (Boynton et al., 1996). Transient effects for adults in the left hemisphere region for ipsilateral (left visual) stimuli were significant at the $P < 0.05$ level. However, the time courses of these effects do not resemble the typical hemodynamic response. Significance values for each transient effect are shown in Table 2.

Discussion

Summary of major findings

In the two visual cortical regions examined, time courses for transient effects were not statistically different between adults and 7- to 8-year-old children, and peak magnitudes for sustained effects were not statistically different between adults and children. For both groups, flickering checkerboard stimuli produced robust responses in the visual cortex contralateral to the stimulus, but not ipsilateral to the stimulus. Results extend the feasibility of direct statistical comparison of these groups using the mixed blocked/event-related design. Although these observations do not extend beyond primary sensory regions, the presumption seems reasonable that neurovascular coupling would be quite similar throughout the brain, so the similarity of responses in early visual cortex suggests that group differences that might be seen in higher order cortical regions reflect age or maturation, strategy, or may reflect differences in performance between groups.

Direct statistical comparison of child and adult neuroimaging data

This study adds to the growing body of research showing that adult and child neuroimaging data may be directly statistically compared. Spatial normalization is a powerful tool that allows direct voxel-wise comparison of data between subjects or between subject groups (Fox et al., 1985). Spatial normalization refers to the process of transforming individual subjects' brain images to match a standardized image or template. If all brains are transformed to the same template, direct between-subject or between-group comparisons can be made, and results can be reported in standardized coordinates.

Concerns about children's brains being smaller (Caviness et al., 1996; Giedd et al., 1996; Reiss et al., 1996), proportionally different in brain region size (Lange et al., 1997), or having different ratios of gray to white matter (Courchesne et al., 2000; Giedd et al., 1999; Pfefferbaum et al., 1994; Sowell et al., 1999) have brought into question the validity of similar transformations in both groups. Studies directly addressing this question, however, have concluded that at least down to the age of 7, such normalization is appropriate for group comparisons using the typical resolution of fMRI or PET (Burgund et al., 2002; Muzik et al., 2000; Kang et al., 2003). Numerous recent studies have successfully taken advantage of a common stereotactic space in exploring developmental issues (e.g., Booth et al., 2003; Bunge et al., 2002; Durston et al., 2003; Kwon et al., 2002; Luna et al., 2001; Monk et al., 2003; Schlaggar et al., 2002; Shaywitz et al., 2002; Turkeltaub et al., 2003; Wilke et al., 2002).

One other prerequisite for the direct comparison between adult and child neuroimaging data is that the two groups have physiologically similar BOLD responses. Kang et al. (2003) pursued this question in an event-related fMRI experiment in which adults and 7- to 8-year-old children pressed buttons in response to a visual stimulus. Brains were transformed into a common stereotactic space, and it was demonstrated that there were negligible differences in foci of functional activation in visual or motor cortex, in peak amplitudes, and in time courses of transient trial-related activity between adults and 7- to 8-year-old children (Kang et al., 2003). Other researchers have examined the BOLD response parametrically across an age span or compared the BOLD response between groups of young and old adults (D'Esposito et al., 1999; Huettel et al., 2001; Taoka et al., 1998; Richter and Richter, 2003). Further research into the etiology of the BOLD response and possible changes in the BOLD response across the life span is needed; results from such studies must guide the interpretation of any age-dependent neuroimaging findings.

The present study extends this work to examine BOLD signals with both transient and sustained temporal profiles after transformation of adult and child data into a common stereotactic space. The results of this study indicate that BOLD signals of both transient and sustained temporal profiles may be compared directly in adults and children down to 7 years of age. It is possible that differences in the BOLD signal would be evident had we looked at younger children. Thus, further studies on younger populations need to be done in order to determine empirically the age range at which direct comparisons cease to be valid for both anatomical and functional data.

Behavioral differences between children and adults

While we tried to control for task performance by using a relatively simple task, behavioral results show that there were some differences in task performance, maintenance of visual fixation, and head movement. Despite these differences, however, for the early visual cortical regions examined, there were no statistically significant group differences between children and adults in either the analysis of sustained effects (magnitudes) or transient effects (time courses). It is possible that greater head movement in children than in adults resulted in slight attenuation of BOLD signal magnitude in children in a region-wise analysis (this was a trend but, again, no significant differences were found). While BOLD responses in the examined early visual cortical regions seem robust to performance differences between adults and children, this might not necessarily hold true for between-group comparisons of other brain regions. While addressing the performance confound is critical for understanding group effects, the performance discrepancy in the present experiment does not interfere with interpreting our results. Specifically, sustained and transient signals are detected (statistically) identically for adults and children.

Decreasing temporal profile of sustained activity

The time courses of the sustained effects in both groups appeared to decrease slightly over time (Fig. 5). Contrast adaptation is known to occur in early visual areas in cats and primates (Carandini and Ferster, 1997; Heinrich and Bach, 2001; Sclar et al., 1989). Adaptation could feasibly contribute to the decrease in activity seen in response to sustained stimuli.

This observation raises the importance of examining time courses resulting from analyses in addition to the statistical images generated. For example, in cognitive experiments, time courses of sustained effects could also vary over time. Knowing the time course of activity would lend insight into the potential underlying processes. Furthermore, “spurious” statistically significant results might be uncovered. In the present study, there is a statistically significant effect of an ipsilateral transient stimulus in the left cortical region for the adult data. A closer examination reveals that these time courses do not resemble the typical rise and fall of the hemodynamic time course. However, without examining the time courses, one might be misled into classifying all significant results similarly (see Visscher et al., 2003 for further discussion).

Potential use of the mixed design in studying cognitive development

The present study has shown that the mixed design can be used to examine sustained task-related activity and transient trial-related activity in both adults and children. The study also suggests that there are likely minimal physiological differences underlying the BOLD signal between adults and children, and that BOLD signals are reliably similar despite issues such as poorer performance, more saccadic eye movement, and greater head movement in children.

The brain comprises a large number of processing pathways that must be organized for the performance of a particular task. How specific pathways are selected and organized is uncertain, but some researchers have proposed models with top-down task control processes (Bundesen, 1990; Desimone and Duncan, 1995). It is reasonable to posit that task control mechanisms might be reflected in signals with a sustained temporal profile (Braver et al., 2003; Burgund et al., 2003; Donaldson et al., 2001; Otten et al., 2002).

The ability to dissociate and examine sustained activity by using the mixed design has the potential to advance the study of cognitive development, both typical and atypical. For example, the development of sustained task-related signals reflecting top-down control processes might not have the same developmental profile as that of transient trial-related signals. The mixed design provides means to investigate the development of sustained and transient signals.

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