

The development of sustained and transient neural activity

E. Darcy Burgund,^{a,*} Heather M. Lugar,^b Francis M. Miezin,^{b,c}
Bradley L. Schlaggar,^{b,c,d,e} and Steven E. Petersen^{b,d,e,f}

^aDepartment of Psychology, MS-25, Rice University, PO Box 1892, Houston, TX 77251, USA

^bDepartment of Neurology, Washington University School of Medicine, St. Louis, MO 63110, USA

^cDepartment of Radiology, Washington University School of Medicine, St. Louis, MO 63110, USA

^dDepartment of Pediatrics, Washington University School of Medicine, St. Louis, MO 63110, USA

^eDepartment of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO 63110, USA

^fDepartment of Psychology, Washington University, St. Louis, MO 63110, USA

Received 13 February 2005; revised 19 July 2005; accepted 25 August 2005

Available online 19 October 2005

Sustained and transient signals were compared in a group of 7–8-year-old children and a group of adults performing the same cognitive task using functional magnetic resonance imaging (fMRI) in conjunction with a mixed blocked/event-related design. Results revealed several regions, including a region in the right lateral inferior frontal gyrus, that exhibited opposing developmental trajectories in sustained and transient signals—in particular, decreased sustained signals and increased transient signals with age. Re-analysis of the data assuming “blocked” and “event-related” designs, as opposed to a mixed design, produced different results. In combination, these results may help to explain contradictory findings in the literature regarding the direction of neural development in frontal cortex. Moreover, these results underscore the value of separating sustained and transient signals in fMRI studies of development.

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Introduction

Understanding the functional organization of the developing human brain is a fundamental goal of cognitive neuroscience. Functional magnetic resonance imaging (fMRI) has become a useful tool for measuring and comparing brain activity in healthy individuals at different stages of development. Using fMRI to compare brain activity in children and adults during controlled cognitive tasks, many studies have observed differences in regions within the frontal lobes (Adleman et al., 2002; Booth et al., 2003, 2004; Brown et al., 2005; Bunge et al., 2002; Casey et al., 1997, 2002; Gaillard et al., 2000, 2003; Klingberg et al., 2002; Kwon et al., 2002; Luna et al., 2001; Schapiro et al., 2004; Schlaggar et al., 2002; Tamm et al., 2002; Turkeltaub et al., 2003). Despite strong support for delayed frontal lobe maturation, however, a discrepancy in the

results from many of these studies exists. In particular, some studies have reported greater activity in frontal regions in children than adults (e.g., Booth et al., 2003; Casey et al., 1997; Gaillard et al., 2000), while others have reported greater frontal activity in adults than in children (e.g., Adleman et al., 2002; Booth et al., 2004; Casey et al., 2002; Gaillard et al., 2003; Kwon et al., 2002; Luna et al., 2001; Schapiro et al., 2004; Turkeltaub et al., 2003). Indeed, even when functionally analogous tasks are examined, different studies have reported opposite effects in the same or similar frontal regions (e.g., Adleman et al., 2002; Booth et al., 2003).

Discrepant findings such as these are particularly problematic because opposing patterns of results support different theories of frontal lobe maturation. As discussed by Brown et al. (2005), theories of the relationship between cognitive and brain development may be categorized as either progressive (i.e., brain regions become increasingly involved in cognitive tasks with age) or regressive (i.e., brain regions become decreasingly involved in cognitive tasks with age). Progressive models of development emphasize increases in connectivity through synaptic growth and bias elaboration (Quartz and Sejnowski, 1997), and thus predict increases in neural activity with age, as observed in the frontal lobes in several studies (e.g., Adleman et al., 2002; Booth et al., 2004; Gaillard et al., 2003; Kwon et al., 2002; Luna et al., 2001; Schapiro et al., 2004; Turkeltaub et al., 2003). Regressive models, in contrast, emphasize the selective pruning of less active synapses (Changeux and Danchin, 1976), and consequently predict decreases in neural activity with age, as observed in the frontal lobes in other studies (e.g., Booth et al., 2003; Casey et al., 1997; Gaillard et al., 2000). While some evidence indicates that progressive and regressive patterns of development may be observed in separate regions within frontal cortex (Brown et al., 2005; Bunge et al., 2002; Schlaggar et al., 2002), reports of opposing effects in similar regions during similar tasks (e.g., Adleman et al., 2002; Booth et al., 2003) have not been reconciled.

In the present study, we examine a possible reason for this discrepancy in the literature. In particular, we hypothesize that

* Corresponding author. Fax: +1 713 348 5221.

E-mail address: dburgund@rice.edu (E.D. Burgund).

Available online on ScienceDirect (www.sciencedirect.com).

studies observing opposite patterns of activity for children and adults in frontal cortex may be sensitive to different types of neural activity present in the fMRI signal. Barring a few exceptions (e.g., Brown et al., 2005; Bunge et al., 2002; Schlaggar et al., 2002), the majority of studies observing differences between children and adults in frontal activity have used blocked, as opposed to event-related, designs. Blocked designs, it has been argued (Chawla et al., 1999; Donaldson, 2004; Donaldson et al., 2001), confound two types of neural signal-transient signals, which are time-locked to individual trials within the block, and sustained signals, which endure throughout the entire task block and are not related to individual trials. Event-related designs, in contrast, measure only transient signals, and thus ignore potential sustained signals.

Recent work with adult (Braver et al., 2003; Burgund et al., 2003, 2005; Donaldson et al., 2001; Otten et al., 2002; Velanova et al., 2003; Visscher et al., 2003) and child (Wenger et al., 2004) subjects has demonstrated that transient and sustained signals may be measured independently with fMRI using a mixed blocked/event-related design. Using this type of design, several studies have observed both transient and sustained signals in the frontal lobes (Braver et al., 2003; Burgund et al., 2003, 2005; Donaldson et al., 2001; Velanova et al., 2003). Moreover, studies examining sustained and transient signals within the same region have observed increased sustained activity paired with decreased transient activity and decreased sustained activity paired with increased transient activity in some frontal regions (Burgund et al., 2003, 2005). Thus, the same region may exhibit increased and decreased activity simultaneously, when sustained and transient signals are separated.

Although the mixed design has been validated for use with children as young as 7 years old using a low-level visual perception task (Wenger et al., 2004), to date, no studies have examined the development of sustained and transient signals during higher-level cognitive tasks that elicit frontal lobe activity in adults. Therefore, in the present study, we compared sustained and transient activity in a group of 7–8-year-old children and a group of adults during a task previously demonstrated to produce opposing sustained and transient activity in frontal cortex in adults (Burgund et al., 2005). Specifically, we examined (1) whether sustained and transient signals exhibit opposing (i.e., increasing vs. decreasing) patterns of development in frontal as well as in other regions, and (2) the consequences of blocked and event-related designs for the analysis of regions in which opposing developmental trajectories are observed. Results from this study may help inform the progressive vs. regressive controversy in the developmental literature, as well as provide insight to the dynamics of functional cerebral development.

Method

Subjects

Eighteen adult (mean age 23.91 ± 3.82 years; 9 male) and 18 child (mean age 8.14 ± 0.61 years; 9 male) volunteers from the St. Louis area participated for payment. Data from the adult subjects in the present study have been reported in greater detail in previous work (Burgund et al., 2005). All subjects were right-handed and had normal or corrected-to-normal vision. Child subjects were determined to be neurologically normal through examination by a pediatric neurologist (B.L.S.) and by completing a detailed history-of-physical-condition questionnaire. Adult subjects were screened

using another detailed questionnaire to insure that they had no history of neurological or psychiatric problems or drug abuse. Adult subjects and parents of child subjects gave informed consent, and child subjects gave assent, in accordance with the guidelines and approval of the Washington University Human Studies Committee.

Behavioral paradigm

All subjects completed four functional runs lasting approximately 6 min each. Each run was composed of alternating blocks of control and task. During the control blocks, a cross hair (+) was displayed continuously. This cross hair turned red for 2.5 s at the beginning and end of each task block in order to cue subjects to the beginning and end of the task. During each task, 24 letter pairs were presented for 500 ms each in a temporally jittered manner such that 0, 1, or 2 control frames followed each stimulus frame. Letters were presented in 36 point, Times font, in white against a black background, and subtended approximately 0.5° of widest (horizontal or vertical) visual angle individually. Letter pairs subtended approximately 2° in the horizontal dimension. The cross hair preceded each presentation and remained on the screen between stimulus frames.

During two consecutive runs, subjects matched letters according to their name. That is, subjects were instructed to respond “same” when letters within the pair had the same name (e.g., A a) and “different” when letters within the pair had different names (e.g., A B). During the other two consecutive runs, subjects matched letters according to their physical identity, responding “same” only when letters within the pair were exactly the same (e.g., A A) and “different” when they were not (e.g., A a). Subsequent analyses did not reveal any differences between the two tasks in either behavioral performance or functional activity however; thus, for the remainder of this report, we collapse across the different versions of the letter-matching task. Subjects pushed the right (or left) button on a button wand, with the index finger of their right (or left) hand, to indicate a “same” response, and the left (or right) button with the index finger of their left (or right) hand, to indicate a “different” response. The hand (left vs. right) used to indicate a “same” response was counterbalanced across subjects, as was the order in which the two different matching tasks (name match and physical match) were administered.

Data acquisition

MRI data were acquired on a Siemens 1.5-T Vision scanner (Erlangen, Germany) using the standard circularly polarized head coil. A pillow and a thermoplastic-face mask were used to minimize head movement. Headphones dampened scanner noise and enabled communication with subjects. Stimulus presentation and response measurement were controlled by a Macintosh computer and the PsyScope software package and button box (Cohen et al., 1993) with a connected button wand that was compatible with MRI. Stimuli were projected onto a screen at the head of the bore that was viewable in a mirror attached to the coil.

Anatomical images were acquired first, using a sagittal MP-RAGE three-dimensional T1-weighted sequence (Mugler and Brookeman, 1990) with a voxel size of $1 \times 1 \times 1.25$ mm (TR = 9.7 ms; TE = 4 ms; flip angle = 12° ; TI = 300 ms; and TD = 0 ms). At the beginning of each session, the main field was shimmed to a tolerance of <0.1 ppm. Functional images were acquired using an

asymmetric spin-echo, echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast ($T2^*$; TR = 2.5 s, $T2^*$ evolution time = 50 ms, flip angle = 90° , voxel size = 3.75×3.75 mm in-plane resolution). During each functional run, 134 sets of 16 contiguous 8-mm thick axial images were acquired parallel to the anterior–posterior commissure plane.

Data analysis

Imaging data from each subject were preprocessed to remove noise and artifacts, including correction for movement within and across runs using a rigid-body rotation and translation algorithm (Friston et al., 1994; Snyder, 1996). Image slices were temporally realigned (using sinc interpolation) to the midpoint of the first slice, accounting for differences in the acquisition time for each individual slice. Data were then resampled into 2-mm isotropic voxels and warped into a standardized atlas space (Talairach and Tournoux, 1988). This method has been validated for the comparison of 7- and 8-year-old children and adults at image resolutions greater than 5 mm (Burgund et al., 2002; Kang et al., 2003).

Preprocessed data were analyzed using the General Linear Model (GLM; Friston et al., 1994; Josephs et al., 1997; Miezin et al., 2000; Worsley and Friston, 1995; Zarahn et al., 1997), and

estimates of the magnitude of effects were derived from the model. Sustained effects were modeled in the GLM as a square wave that started 7 time points (17.5 s) after the cue at the beginning of the task block, and ended at the cue at the end of the task block. The rationale for this coding procedure is described in a previous work in which the same strategy was used (Burgund et al., 2005). In brief, the sustained signal was coded to begin 17.5 s after the task began to ensure that any transient response to the cue that appeared at the beginning of each task block was not misattributed to the sustained signal measurement. No shape was assumed for the transient effects. Instead, these effects were modeled in the GLM by the 7 time points (i.e., image acquisitions) immediately following each stimulus onset. In addition, factors were coded to account for the cues at the beginning and end of each block and for the within-run linear trend (linear drift and a constant term). All effects were modeled simultaneously in the GLM for each subject.

Two voxel-wise analyses were performed to identify regions exhibiting activity differences between children and adults. Sustained activity was analyzed by an independent t test with age (child vs. adult) as the independent variable. Transient activity was analyzed by a two-way, repeated-measures ANOVA in which time (at the seven measured time points) and age (child vs. adult) were the independent variables. Statistical images produced by these analyses were smoothed with a 4-mm radius hard sphere

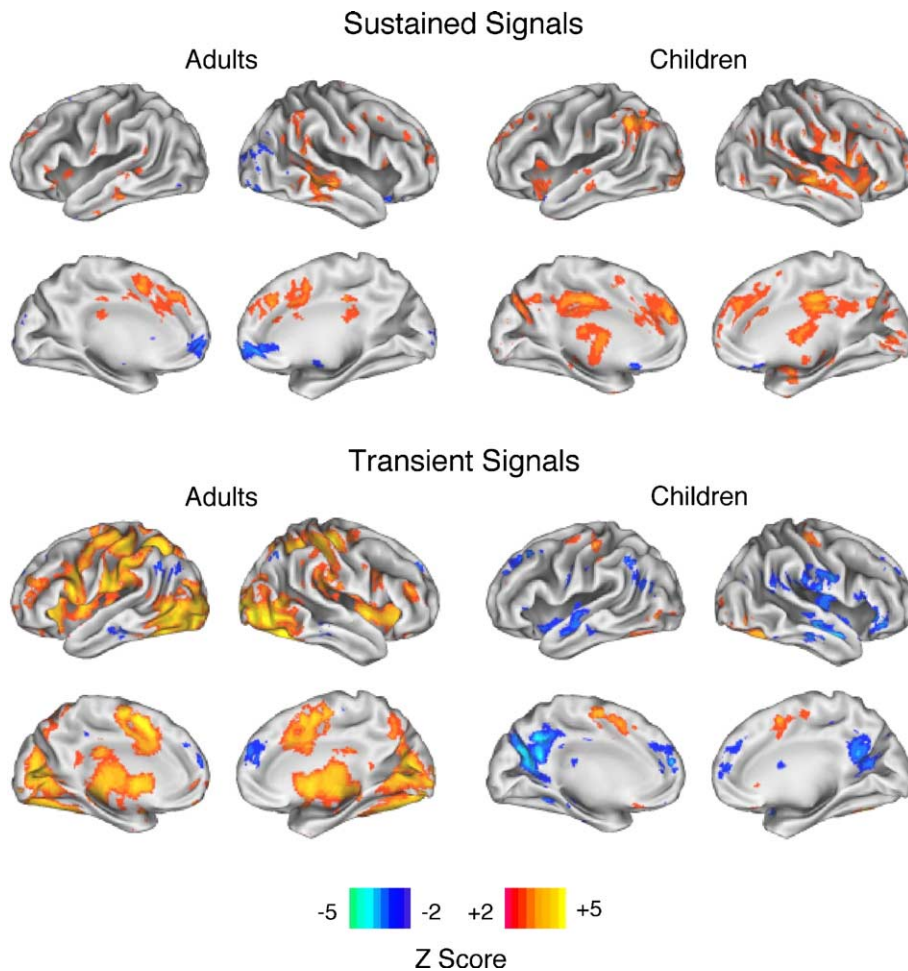


Fig. 1. Statistical images displaying sustained and transient activity separately for adults and children. Images were derived from one-way t tests computed on values averaged across the entire task block (sustained signals) or on values averaged across the third and fourth time point (transient signals). Surface-rendered images were created using CARET software and surface-based atlases (Van Essen, 2002; Van Essen et al., 2001).

kernel, and a peak (local extremum) search algorithm was used to identify the coordinates (Talairach and Tournoux, 1988) of activation peaks ($P < 0.001$ and $P < 0.0001$ for sustained and transient images, respectively¹) in the smoothed images. Peaks separated by less than 10 mm in each image were consolidated by coordinate averaging, and spheres (10-mm radius) were centered on each peak. Finally, spherical regions were masked to exclude voxels that did not meet a statistical threshold of $P < 0.005$ for sustained activity, or $P < 0.0005$ for transient activity. Voxels within each region were averaged and used as the dependent measure in subsequent region-based analyses.

Region-based analyses were performed to assess the statistical effects observed at the voxel level at a regional (averaged voxel) level. Thus, results from these analyses should be viewed as descriptive or confirmatory. As in the voxel-wise analyses, sustained activity was analyzed by an independent t test with age (child vs. adult) as the independent variable, and transient activity was analyzed in a two-way, repeated-measures ANOVA with time (at the seven measured time points) and age (child vs. adult) as the independent variables. To evaluate whether children and adults exhibited significant sustained or transient activity independently of each other, one-way t tests assessing the magnitude of the sustained or transient signal in children and adults were computed. For sustained signals, one-way t tests were computed on values averaged across the entire task block. For transient signals, one-way t tests were computed on values averaged across the third and fourth time point (the peak of the response).

The potential consequences of blocked and event-related designs for signal measurement in children and adults were examined by reanalyzing the data using GLMs that assumed these types of design. Thus, for each subject, two additional GLMs were created. In one GLM, data were coded as if a blocked design had been used; that is, a single effect that lasted the duration of the task block was coded. In the other GLM, data were coded as if an event-related design had been used; that is, effects were modeled by the 7 time points immediately following each stimulus onset, and no effect of task block was modeled. Factors accounting for the cues at the beginning and end of each block and for the within-run linear trend were modeled similarly in both GLMs. Region-based analyses were then performed on all regions defined in the voxel-wise analyses described above. Blocked GLMs were analyzed by an independent t test comparing children and adults. Event-related GLMs were analyzed by a two-way, repeated-measures ANOVA with time (at the 7 measured time points) and age (child vs. adult) as the independent variables.

Response times and error rates during the letter-matching task were analyzed separately by independent t tests assessing the effect of age (child vs. adult).

Results

Development of sustained and transient signals

Statistical images reflecting sustained and transient activity separately for adults and children are displayed in Fig. 1. Voxel-

wise analyses revealed 24 regions (shown in Fig. 2) that exhibited differences between groups in sustained activity, transient activity, or both. Results from region-based analyses assessing the effect of age in sustained and transient activity for each of these regions are listed in Table 1.

Several regions, shown in green in Fig. 2, exhibited opposing developmental trajectories in sustained and transient activity. Of particular interest, a region within the right lateral inferior frontal gyrus exhibited greater sustained activity in children than adults, and greater transient activity in adults than in children (see Fig. 3A). t tests assessing the magnitude of each type of signal in each group revealed positive sustained activity in children paired with no sustained activity in adults, and positive transient activity in adults paired with negative transient activity in children (see Table 1).

Opposing developmental trajectories were observed more posteriorly as well, in left lingual and parietal-occipital cortex, the left putamen, and the right postcentral gyrus. Patterns of activity in the left parietal-occipital and right precentral regions were similar to those observed in the right lateral inferior frontal region described above. In the left lingual and putamen regions, positive sustained activity was observed in children and negative sustained activity was observed in adults, whereas positive

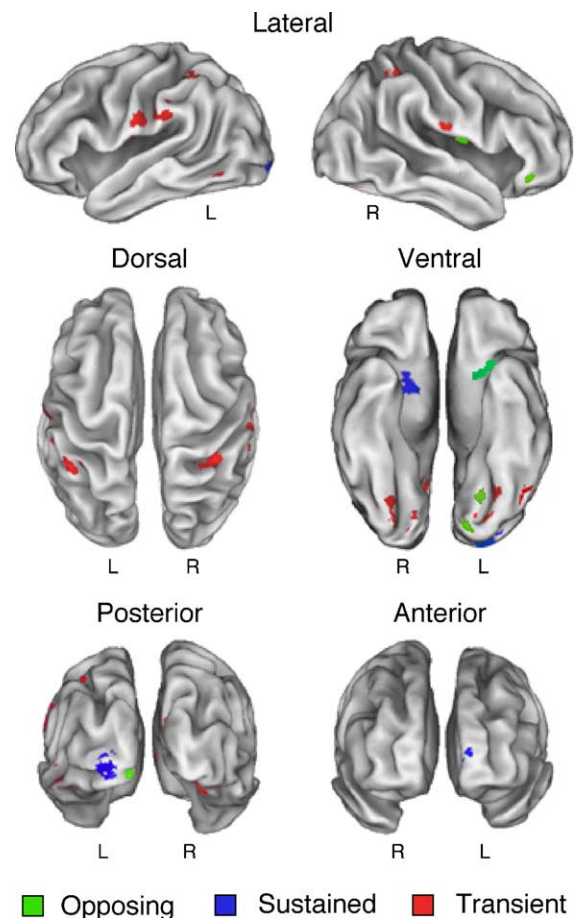


Fig. 2. Regions in which differences between children and adults were observed. Regions exhibiting opposing developmental differences in sustained and transient signals are shown in green; regions exhibiting developmental differences in sustained signals only are shown in blue; regions exhibiting developmental differences in transient signals only are shown in red. L = left hemisphere; R = right hemisphere.

¹ All P values associated with the analyses of transient signals were corrected for sphericity to account for errors caused by the inclusion of time as a repeated measure.

Table 1
Developmental effects in sustained and transient signals

Region	x	y	z	Peak Z	Vox	Sustained			Transient		
						Age Z	A t	C t	Age Z	A t	C t
<i>Opposing differences</i>											
R inferior frontal _(S)	40	21	−1	3.47	111	4.28 ^a	.33	6.16 ^a	4.25 ^a	4.13 ^a	−3.61 ^b
R postcentral _(T)	57	−14	21	4.32	139	2.28 ^c	0.75	2.86 ^c	5.32 ^a	2.59 ^c	−4.07 ^a
L putamen _(S)	−20	−1	−3	3.12	187	3.51 ^a	−2.48 ^c	2.98 ^b	2.62 ^c	6.12 ^a	−0.66
L parietal–occipital _(T)	−14	−65	18	3.81	164	2.42 ^c	−0.24	2.71 ^c	4.39 ^a	2.19 ^c	−4.47 ^a
L lingual _(S)	−9	−91	−10	3.10	129	3.79 ^a	−3.15 ^b	3.04 ^b	3.78 ^a	5.80 ^a	−0.99
<i>Sustained differences</i>											
L medial frontal _(S)	−10	61	13	3.11	98	3.87 ^a	−4.37 ^a	1.41	1.32	2.49 ^c	0.74
R putamen _(S)	21	0	−3	3.18	153	3.55 ^a	−2.43 ^c	3.11 ^b	0.96	4.24 ^a	.55
L middle occipital _(S)	−21	−98	−3	3.27	178	4.06 ^a	−2.26 ^c	4.10 ^a	0.98	5.41 ^a	0.67
<i>Transient differences</i>											
R thalamus _(T)	8	−11	7	3.77	58	1.18	0.27	1.94	4.96 ^a	6.24 ^a	−0.47
R middle temporal _(T)	41	−11	−6	4.01	85	1.40	−0.94	1.09	4.53 ^a	0.47	−3.88 ^b
L postcentral _(T)	−55	−17	23	5.06	256	1.41	−0.06	1.60	5.74 ^a	7.37 ^a	−1.70
R inferior parietal _(T)	55	−30	24	4.76	248	1.28	0.25	1.58	5.36 ^a	4.84 ^a	−2.41 ^c
L inferior parietal _(T)	−54	−32	27	4.39	202	1.51	−1.20	1.16	4.94 ^a	5.85 ^a	−1.58
R superior parietal _(T)	33	−43	51	4.64	273	0.07	0.62	0.24	5.71 ^a	5.19 ^a	−0.88
L superior parietal _(T)	−40	−48	50	4.66	173	1.25	0.53	2.10	5.94 ^a	6.67 ^a	−0.66
R posterior cingulate _(T)	9	−55	20	4.14	101	1.25	−0.18	1.43	4.43 ^a	−0.28	−3.59 ^b
R precuneus _(T)	15	−60	40	3.98	144	0.98	0.68	1.30	4.74 ^a	4.59 ^a	−2.19 ^c
R parietal–occipital _(T)	12	−67	19	4.20	131	1.35	0.26	1.58	4.56 ^a	5.18 ^a	−2.36 ^c
R fusiform _(T)	17	−70	−13	4.16	123	0.15	0.30	0.41	5.14 ^a	4.79 ^a	−0.77
R fusiform _(T)	26	−78	−13	4.22	149	1.26	0.25	1.91	5.26 ^a	6.02 ^a	−0.21
L fusiform _(T)	−21	−80	−13	3.74	83	1.33	−0.85	1.07	4.86 ^a	6.12 ^a	0.13
L fusiform _(T)	−45	−66	−12	4.23	124	0.56	−0.62	0.19	5.52 ^a	6.98 ^a	0.00
R cerebellum _(T)	26	−65	−14	3.86	126	1.30	0.01	1.80	4.75 ^a	6.38 ^a	0.99
L cerebellum _(T)	−21	−64	−14	4.14	100	0.70	−0.20	0.75	4.85 ^a	6.29 ^a	0.15

Peak locations (x, y, z in mm) in the Talairach and Tournoux (1988) atlas with associated significance (Peak Z) and number of voxels (Vox). Sustained and transient columns display statistics from region-based analyses. Age Z indicates the significance of the relevant age effect (t test assessing the effect of age in the sustained effects; ANOVA assessing the interaction of age × time in the transient effects). A t and C t indicate the significance of the one-way t tests assessing the magnitude of the sustained or transient signal in adult and child groups independently. For sustained signals, one-way t tests were computed on values averaged across the entire task block. For transient signals, one-way t tests were computed on values averaged across the third and fourth time point (the peak of the response). Alpha values associated with each effect are denoted ^a = P < 0.001, ^b = P < 0.01, and ^c = P < 0.05 (uncorrected). Regions defined from the voxel-wise analysis of sustained activity are denoted _(S); regions defined from the voxel-wise analysis of transient activity are denoted _(T).

transient activity was observed in adults and no transient activity was observed in children (see, for example, lingual gyrus in Fig. 3B).

Other regions exhibited differences between children and adults in sustained signals only (shown in blue in Fig. 2) or in transient signals only (shown in red in Fig. 2). For example, a region in the left medial frontal gyrus exhibited negative sustained activity in adults and no sustained activity in children, but did not exhibit group differences in the transient signals (see Fig. 3C). A region in the left fusiform gyrus exhibited increased transient activity in adults and no transient activity in children, but did not exhibit group differences in the sustained signals (see Fig. 3D).

Consequence of blocked and event-related designs

Data were recoded assuming “blocked” and “event-related” designs, as opposed to a mixed design, and region-based analyses were performed for each of the 24 regions identified above (see Table 2). Not surprisingly, regions exhibiting opposing developmental trajectories in sustained and transient signals exhibited different patterns in the “blocked” and “event-related” designs. In the “blocked” design, differences between children and adults

were no longer observed; in the “event-related” design, differences between groups that were similar to those exhibited by the transient signals were observed (see Figs. 4A–B).

Regions exhibiting developmental differences in either sustained or transient signals when the mixed design was analyzed also produced different patterns in the “blocked” and “event-related” designs. Results from these regions depended on whether developmental differences were present in the sustained or transient signals in the mixed design. For example, in the left medial frontal region, in which a developmental difference was present in the sustained signals, a difference between groups was observed in the “blocked” design but not in the “event-related” design (see Fig. 4C). In a region within the fusiform gyrus, in which a developmental difference was present in the transient signals, both “blocked” and “event-related” designs revealed a difference between groups (see Fig. 4D).

Behavior

Children took longer to respond correctly and made more errors than adults when performing the letter-matching task. The effect of age was highly significant in both response time, $t(1, 34) = 11.89$,

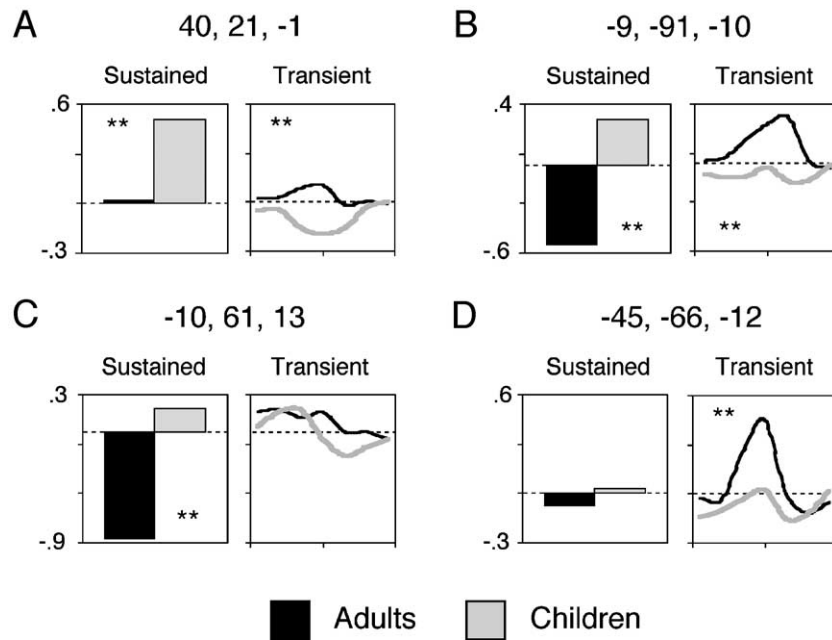


Fig. 3. Results from the region-based analyses of sustained and transient activity in the lateral inferior frontal gyrus (A), the lingual gyrus (B), the medial inferior frontal gyrus (C), and the fusiform gyrus (D). Percent signal change is plotted as a function of age for the sustained signals and as a function of age and time (at the seven estimated time points) for the transient signals. ** and * indicate a significant effect of age or age \times time at the $P < 0.001$ and $P < 0.05$ levels (uncorrected), respectively.

$P < 0.0001$, and error rate analyses, $t(1, 34) = 4.76$, $P < 0.0001$. Descriptive statistics for both measures in children and adults are listed in Table 3.

Discussion

In the present study, sustained and transient neural activity was compared in a group of 7–8 year old children and a group of young adults during a letter-matching task. Results revealed several regions, including a region in the right lateral inferior frontal gyrus, that exhibited opposing developmental trajectories in sustained and transient signals—in particular, decreased sustained signals and increased transient signals with age. Re-analysis of the data assuming “blocked” and “event-related” designs, as opposed to a mixed design, produced different results. Regions with opposing developmental trajectories in sustained and transient activity did not exhibit differences between children and adults in the “blocked” design; however, in the “event-related” design, differences similar to those exhibited by the transient signals were observed between groups. In combination, these results may help to explain some of the contradictory findings in the literature regarding the direction of functional development in frontal cortex. Moreover, these results underscore the value of separating sustained and transient signals in fMRI studies of development.

Explanation for contradictory findings

As noted in the Introduction, studies using fMRI to examine neural development have observed opposing directions of developmental change, particularly in the frontal lobes. Specifically, some studies have observed increased frontal activity with age (e.g., Adelman et al., 2002; Booth et al., 2004; Casey et al., 2002;

Gaillard et al., 2003; Kwon et al., 2002; Luna et al., 2001; Schapiro et al., 2004; Turkeltaub et al., 2003), while others have observed decreased frontal activity with age (e.g., Booth et al., 2003; Casey et al., 1997; Gaillard et al., 2000). Critically, these studies have used either blocked or event-related designs, which do not allow the separation of sustained and transient signals. In the present mixed-design study, we observed increased *transient* activity with age and decreased *sustained* activity with age in a region within the right lateral inferior frontal gyrus, as well as in other, more posterior regions. Furthermore, results from our “blocked” and “event-related” analyses indicate that blocked and event-related designs are differentially sensitive to sustained and transient signals. Thus, opposing patterns of development may be observed depending on the type of signal (transient or sustained) to which a particular design is most sensitive.

This hypothesis may help to explain contradictory developmental effects in the literature. In particular, studies observing decreased activity with age (e.g., Booth et al., 2003; Casey et al., 1997; Gaillard et al., 2000) may be especially sensitive to sustained signals, whereas studies observing increased activity with age (e.g., Adelman et al., 2002; Booth et al., 2004; Casey et al., 2002; Gaillard et al., 2003; Kwon et al., 2002; Luna et al., 2001; Schapiro et al., 2004; Turkeltaub et al., 2003), may be especially sensitive to transient signals. As noted in the Introduction, the majority of studies have used blocked designs to investigate neural development with fMRI. These designs, which confound sustained and transient signals, may produce different patterns of results depending on their relative sensitivity to sustained or transient signals. Therefore, contradictory findings in the literature may be due, in part, to differential sensitivity to sustained and transient signals across different blocked-design studies. “Event-related” designs in the present study revealed results that were similar to those observed in the transient signals in the mixed design. Thus, while only a few studies have used event-related designs to investigate

Table 2
Developmental effects in “blocked” and “event-related” designs

Region	x	y	z	Blocked			Event-related		
				Age Z	A t	C t	Age Z	A t	C t
<i>Opposing differences in mixed</i>									
R inferior frontal _(S)	40	21	-1	0.41	3.69 ^b	1.12	3.35 ^b	5.63 ^a	-1.05
R postcentral _(T)	57	-14	21	0.70	-1.21	-1.36	4.83 ^a	3.90 ^b	-2.77 ^c
L putamen _(S)	-20	-1	-3	0.86	-0.09	1.15	1.79	3.19 ^b	1.65
L parietal-occipital _(T)	-14	-65	18	1.32	-2.18 ^c	-2.49 ^c	3.92 ^a	2.71 ^c	-3.45 ^b
L lingual _(S)	-9	-91	-10	0.06	-0.59	-0.69	2.53 ^c	1.58	0.64
<i>Sustained differences in mixed</i>									
L medial frontal _(S)	-10	61	13	2.15 ^c	-2.29 ^c	0.72	1.19	-1.22	1.64
R putamen _(S)	21	0	-3	2.27 ^c	-1.34	1.96	0.66	1.58	2.77 ^c
L middle occipital _(S)	-21	-98	-3	0.89	0.74	2.09	0.39	4.31 ^a	2.98 ^b
<i>Transient differences in mixed</i>									
R thalamus _(T)	8	-11	7	0.22	1.47	0.89	4.68 ^a	6.49 ^a	0.83
R middle temporal _(T)	41	-11	-6	2.30 ^c	-2.55 ^c	-3.97 ^b	4.25 ^a	-0.47	-3.58 ^b
L postcentral _(T)	-55	-17	23	0.84	2.22 ^c	0.38	5.49 ^a	7.89 ^a	-0.54
R inferior parietal _(T)	55	-30	24	1.70	0.22	-1.98	4.97 ^a	4.97 ^a	-1.76
L inferior parietal _(T)	-54	-32	27	0.31	0.13	-0.29	4.62 ^a	4.74 ^a	-0.95
R superior parietal _(T)	33	-43	51	1.67	1.51	-1.05	5.91 ^a	5.43 ^a	-1.00
L superior parietal _(T)	-40	-48	50	1.37	3.80 ^b	0.84	5.81 ^a	6.44 ^a	1.81
R posterior cingulate _(T)	9	-55	20	0.76	-2.78 ^c	-2.56 ^c	4.13 ^a	-0.60	-3.55 ^b
R precuneus _(T)	15	-60	40	0.98	0.40	-0.92	4.48 ^a	5.03 ^a	-1.55
R parietal-occipital _(T)	12	-67	19	1.02	-0.70	-1.63	4.24 ^a	5.01 ^a	-1.51
R fusiform _(T)	17	-70	-13	1.56	0.04	-2.12 ^c	5.30 ^a	4.78 ^a	-0.81
R fusiform _(T)	26	-78	-13	0.78	1.09	0.09	5.21 ^a	7.17 ^a	1.79
L fusiform _(T)	-21	-80	-13	1.70	1.56	-1.05	4.51 ^a	6.20 ^a	0.92
L fusiform _(T)	-45	-66	-12	3.47 ^b	2.97 ^b	-2.58 ^c	5.59 ^a	8.71 ^a	0.03
R cerebellum _(T)	26	-65	-14	0.19	0.83	0.37	4.66 ^a	6.86 ^a	2.58 ^c
L cerebellum _(T)	-21	-64	-14	0.60	-0.05	-0.67	4.96 ^a	7.62 ^a	0.57

See note for Table 1. Blocked and event-related columns display statistics from region-based analyses assuming each type of design.

neural development (Brown et al., 2005; Bunge et al., 2002; Schlaggar et al., 2002), unlike blocked designs, they may provide relatively unbiased measures of transient activity.

Of course, other reasons for contradictory results across studies exist. For one, blocked designs may produce different results when non-equivalent control tasks are used for comparison to the

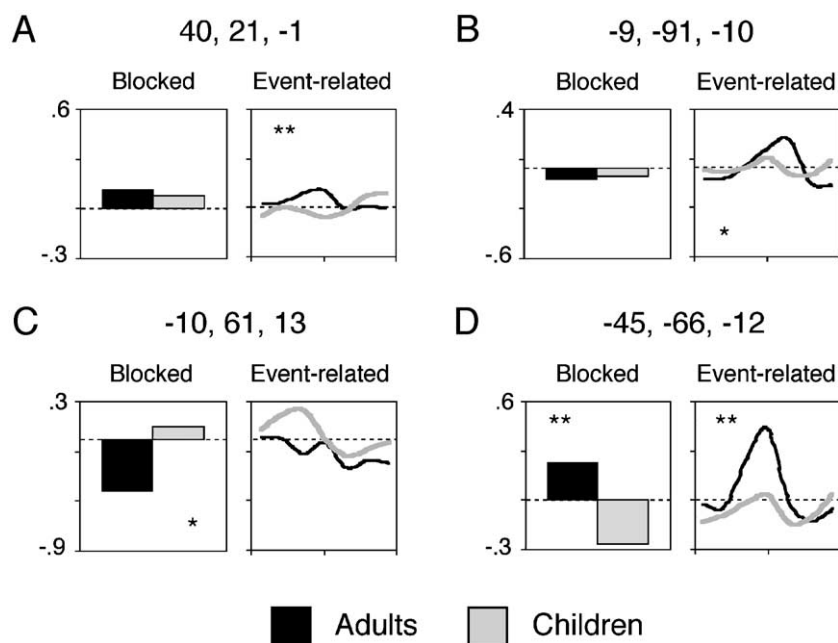


Fig. 4. Results from region-based analyses of data recorded assuming “blocked” and “event-related” designs. See note for Fig. 3.

Table 3
Responses times and error rates as a function of age during letter matching

Group	Response times (ms)	Error rates (%)
Adults	780 ± 119	2 ± 5
Children	1295 ± 140	13 ± 9

± indicates the standard deviation from the mean.

experimental task of interest. As observed by Palmer et al. (2004), many developmental studies compare the difference between the experimental and control tasks in children to the difference between the experimental and control tasks in adults, and interpret the results as a comparison between experimental tasks in the two groups. This interpretation rests on the assumption that the control tasks are equal in the two groups, which may be erroneous. In addition, the use of different control tasks across previous blocked-design studies of development hinders the direct comparison of results from these studies. Thus, differences between the methods used to assess activity, as well as the particular experimental and control tasks used, likely contribute to many of the contradictory findings in the developmental literature.

Although results from the mixed design used in the present study may help to resolve some of the controversy regarding the direction of neural developmental in the frontal lobes, it should be noted that this type of design has its own set of limitations. In particular, the considerable number of fixation relative to experimental trials that is needed in order to reduce the correlation between transient and sustained signals decreases the sensitivity of the mixed design to both types of signal. Indeed, estimates of sustained signals may be affected disproportionately because long inter-stimulus intervals may attenuate signals that are difficult to maintain during prolonged periods without stimulation. Consequently, the “blocked only” model will not fit data from a mixed design as well as data from a traditional blocked design in which stimuli are presented in rapid and regular succession. Thus, our failure to observe effects of age in the “blocked” analysis in some of the regions could have been due, in part, to poor estimates of the block mean. Careful consideration of a signal’s temporal characteristics is essential for determining the type of design most suited for use in fMRI experiments.

Progressive and regressive development

The terms “progressive” and “regressive” have been used to describe increasing and decreasing neural activity with age (e.g., Brown et al., 2005). The characterization of development as progressive or regressive is appropriate for activity in some of the regions observed in the present study. For example, transient activity in the lingual gyrus exhibited a progressive pattern of development—children exhibited no activity while adults exhibited increased activity (see Fig. 3B). Likewise, sustained activity in the right lateral inferior frontal gyrus exhibited a regressive pattern of development—children exhibited increased activity while adults exhibited no activity (see Fig. 3A). In other regions, however, characterization of activity as progressive or regressive may not be appropriate. In particular, transient activity in the right lateral inferior frontal gyrus was negative in the children and positive in the adults (see Fig. 3A), indicating that this region contributed to processing in both age groups, albeit in different ways. Similarly, sustained activity in the lingual gyrus was positive in the children and negative in the adults (see Fig. 3B), indicating a role for this

region in both age groups. Thus, while changes in neural activity clearly occur with development in regions such as these, these changes are neither progressive nor regressive per se.

As noted above, sustained signals in the right lateral inferior frontal gyrus exhibited a regressive pattern of development; that is, activity was increased in children and absent in adults. Results from a previous study examining sustained activity in the same adult subjects as in the present study (Burgund et al., 2005) may provide further insight to this regressive pattern of development. In the Burgund et al. (2005) study, increased sustained activity was observed in the name letter-matching task but not in the physical letter-matching task in two regions within the right lateral inferior frontal cortex that were very close to the region observed in the present study, suggesting that sustained activity in this region was sensitive to the particular task being performed. In the present study, differences between the name and physical letter-matching tasks did not interact significantly with age, and thus, data from the two tasks were collapsed for our primary analyses. However, the lack of sustained activity observed in the collapsed adult data may have been due to the canceling out of name and physical-matching signals.

To examine this possibility, we performed a post hoc analysis comparing sustained signals during the name-matching task to signals during the physical-matching task in the right lateral inferior frontal region from the present study. In the adult subjects, sustained activity was greater during the name-matching task than during the physical-matching task, $t(1, 17) = 2.30$, $P < 0.05$, as observed in the regions from Burgund et al. (2005). In the child subjects, however, sustained activity did not differ between the two tasks, $t(1, 17) = -0.23$, $P > 0.82$. Therefore, the regressive pattern of development in sustained activity in this region may be due to increased specialization of processing with age. That is, with development, sustained activity may become increasingly sensitive to subtle differences in task demands, such as the difference between name and physical matching, such that overall activity across tasks is decreased in older compared to younger subjects. Of course, this hypothesis requires further research to examine fully.

Conclusions

In summary, results from the present study demonstrate opposing differences between adult and child neural activity in sustained and transient signals within the same region. These results may help to resolve discrepancies in the literature regarding the direction of functional–neuroanatomical developmental changes in the frontal lobes, as different design types may be sensitive to different combinations of sustained and transient signals. Furthermore, results from the present study underscore the value of separating sustained and transient neural activity in fMRI studies of development, as different patterns of neural activity may be observed when these two signals are confounded.

Acknowledgments

The authors would like to thank Abraham Snyder for invaluable technical assistance. B.L.S. is a scholar of the Child Health Research Center of Excellence in Developmental Biology at Washington University School of Medicine (HD01487). Other support for this research was provided by the McDonnell Center

for Higher Brain Function (BLS), by the National Institute of Health, NS32979 (SEP), NS51733 (SEP), NS55582 (BLS), and LM06858 (SEP), and by the Social Sciences Division at Rice University (EDB).

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