

# Age-related Changes in Neural Activity during Visual Target Detection Measured by fMRI

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**We used functional magnetic resonance imaging (fMRI) of a visual target detection (oddball) task to investigate age differences in neural activation for the detection of two types of infrequent events: visually simple items requiring a response shift (targets) and visually complex items that did not entail a response shift (novels). Targets activated several prefrontal regions (e.g. middle frontal gyrus), as well as deep gray matter regions (caudate, putamen, thalamus and insula). Prefrontal activation was similar for younger and older adults, whereas deep gray matter activation was relatively greater for the older adults. Novels activated occipital regions (fusiform and lateral occipital gyri), and this activation was relatively reduced for older adults. The changes in behavioral performance across the task conditions were similar for the two age groups, although the older adults' responses were slower overall. Regression analyses of the relation between neural activation and task performance (response time) indicated that whereas performance was mediated most directly by prefrontal cortex for younger adults, older adults' performance was influenced to a greater extent by deep gray matter structures. Older adults may place relatively greater emphasis on the attentional control of response regulation, in compensation for the age-related decline in visual processing efficiency.**

**Keywords:** aging, attention, neuroimaging, oddball task, perception, response time

## Introduction

Behavioral research on age-related changes in cognition indicates that a wide range of perceptual and attentional processes exhibit decline over the course of later adulthood, even in the absence of significant disease (McDowd and Shaw, 2000; Madden and Whiting, 2003). Executive control processes such as updating and maintaining information in working memory, shifting between mental sets, and intentionally inhibiting irrelevant information (Miyake *et al.*, 2000) appear to be particularly vulnerable to age-related decline, although measures of executive control also reflect the influence of other information processing components, such as the speed of elementary perceptual processes (Salthouse, 2000; Madden, 2001).

Neuroimaging research has documented substantial age-related change in the neural systems mediating visual perception. Studies using both positron emission tomography (Grady *et al.*, 1994; Madden *et al.*, 1997, 2002) and functional magnetic resonance imaging (fMRI) (Ross *et al.*, 1997; Buckner *et al.*, 2000; Huettel *et al.*, 2001) have reported that the activation of visual cortical regions is less pronounced for older adults than for younger adults. Evidence from neuroimaging research has also indicated that a decline in the structure and

function of the frontal lobe, a central component of the neural system for attention, is particularly pronounced during aging (Raz, 2000; Madden *et al.*, 2003). Little information is available, however, on age-related changes in the neural systems mediating the attentional control of responses to perceptual events. There are extensive neuroanatomical connections between frontal cortical regions and deep gray matter structures including the basal ganglia and thalamus, which form a system for the attentional control of visuomotor learning and response regulation (Poldrack *et al.*, 1999; Graybiel, 2000; Hikosaka *et al.*, 2000). These deep gray matter nuclei, especially the thalamus, may, in addition, selectively modulate task-relevant features within the visual system (Corbetta *et al.*, 1991; LaBerge, 2000). Behavioral evidence has led to the speculation that age-related change in deep gray matter structures contributes to performance declines in perceptual and attentional tasks (Hicks and Birren, 1970; Bashore, 1993; Rubin, 1999).

In this experiment we used fMRI to determine whether age-related changes in the neural activation associated with the attentional control of visual target detection could be distinguished from the neural activation for other components of task performance. Behavioral measures were obtained, during imaging, in the oddball task (Friedman *et al.*, 2001; Herrmann and Knight, 2001), which comprises several component processes. In the canonical version of the oddball task, a limited number of infrequent target items are presented during the course of an extended series of standard items, and observers respond only to the targets, either overtly or by keeping a mental count. In another version, the novelty oddball task, there are two types of infrequent events – targets and novets – interspersed among the standards, but observers respond differentially to the targets. As a result, target detection can be distinguished from the more general process of novelty detection. A variety of evidence, including different types of event-related potential (ERP) measures obtained from healthy individuals, intracranial recordings from epileptic patients, and studies of the effects of brain lesions in both humans and animals, suggests that target detection and novelty responses in the oddball task represent the functioning of widely distributed but interconnected neural systems including multi-modal posterior association cortex, hippocampus, anterior cingulate, and prefrontal regions (Knight, 1997; Knight and Grabowecy, 2000; Daffner *et al.*, 2003).

Neuroimaging studies of the oddball task using fMRI have confirmed the general pattern of differences between target detection and novelty responses reported by ERP research. McCarthy *et al.* (1997) used a canonical version of the oddball task with visual stimuli and reported that target detection led

to activation of the middle frontal gyrus bilaterally (though more extensively in the right hemisphere) and inferior parietal lobe. The pattern of activation was consistent with other electrophysiological and neuroimaging investigations of working memory tasks, suggesting that target detection in the oddball task may rely on the same neural circuitry as working memory. Kirino *et al.* (2000), using a novelty oddball paradigm, replicated the fMRI activation of the right middle frontal gyrus in response to targets. In addition, there was minimal activation for the novel items (inferior frontal gyrus of the right hemisphere), suggesting that the target-related activation was not simply an orienting response to an infrequent event. Kirino *et al.* also demonstrated that the target-related activation of the middle frontal gyrus was independent of a specific type of response, in that the activation did not vary substantially as a function of whether subjects pressed a button in response to targets or simply kept a mental count of the number of target occurrences. These authors proposed that the prefrontal activation represented the detection of stimuli requiring a differential response, which in turn depended on the active memory maintenance of the target-response rules. Huettel and McCarthy (2003) extended this account by demonstrating that target-related prefrontal activation in a variant of the oddball task was elicited by dynamic changes in response strategy, independently of changes in overt response.

In this experiment we used the same type of novelty oddball task as Kirino *et al.* (2000), in which observers make the same response to both frequent standards (squares) and infrequent novels (photographs of objects) but a different response to infrequent targets (circles). Accuracy is typically high in this task, and thus differences between the age groups in behavioral performance should be more clearly evident in response time than in accuracy. Specifically, age-related decline in the efficiency of visual encoding and response selection should lead to an overall increase in response time for older adults. Responses to the target require the greatest degree of executive control, because they involve an inhibition of a prepotent (standard) response and selection of an alternative response. Thus, a specific age-related decline in this form of attentional control would lead to a differential increase in response time for older adults' target detection responses. Novels may also require some inhibitory processing, however, because they may bias subjects away from the standard response and consequently also lead to a differential increase in older adults' response time.

We were particularly interested in potential age-related changes in the prefrontal activation for targets (Kirino *et al.*, 2000; Huettel and McCarthy, 2003). In several neuroimaging investigations of age differences, prefrontal activation has been observed to be greater in either magnitude or spatial extent for healthy older adults than for younger adults (Grady, 2000; Cabeza, 2002). This age-related increase in prefrontal activation has occurred in the context of perceptual tasks (Grady *et al.*, 1994; Madden *et al.*, 1997; Nielson *et al.*, 2002) and episodic memory tasks (Cabeza *et al.*, 1997; Madden *et al.*, 1999), although an age-related decrease in prefrontal activation has been observed in some working memory tasks (Reuter-Lorenz, 2002). The age-related increase in activation may represent a compensatory recruitment of the attentional functions mediated by the frontal lobe. In neuroimaging studies of episodic memory, for example, the older adults who exhibited the more extensive prefrontal activation were also the higher

performing individuals on the memory task (Cabeza *et al.*, 2002; Rosen *et al.*, 2002). We therefore predicted that in the present task, the prefrontal activation associated with target detection would be more pronounced for older adults than for younger adults, and that this target-related activation would be associated with faster target detection responses.

Deep gray matter structures including the basal ganglia, thalamus, and insula were also of interest, in view of the central role of these regions in the attentional control of motor responses. Ardekani *et al.* (2002) reported target-related activation in the thalamus and insula, as well as in a more widespread frontoparietal network, during a visual oddball task. Huettel *et al.* (2002) found that activation of the basal ganglia (caudate and putamen) occurred when the current stimulus required a change in the motor response, but not when the stimulus required the repetition of the previous response, even if the stimulus violated an expected pattern, suggesting that the basal ganglia are involved in the preparation for new motor responses. Previous neuroimaging evidence on age-related changes in response selection is limited, but behavioral evidence indicates an age-related decline in the efficiency of response selection (Hartley, 2001; Allen *et al.*, 2002). Either one of two patterns of age differences in neural activation for oddball target detection could reasonably be predicted: the activation of deep gray matter structures may be less pronounced for older adults than for younger adults, representing a decline in processing efficiency, as has been observed for occipital regions. Alternatively, if the executive control of response selection is more difficult for older adults than for younger adults, then activation in deep gray matter regions may actually be relatively greater for older adults, perhaps as the result of compensatory functioning, as has been observed for prefrontal regions.

Finally, we were also concerned with activation in visual cortical regions. The novelty oddball task provided the opportunity to compare different types of infrequent events: those that are visually similar to the standards but require a separate response (targets) and those that are more complex visually than the standards but require the same response (novels). Thus, in theory, the novels should be more effective than targets in activating occipital cortex. The Kirino *et al.* (2000) fMRI investigation, which used the same type of stimuli as the present experiment, focused primarily on issues relating to prefrontal activation, and the imaging sequence used coronal slices limited to the frontal lobe. The previous neuroimaging evidence clearly leads to the prediction of an age-related decline in occipital activation for novels, although the fMRI studies differ on whether the age-related decline is evident primarily in the amplitude (Buckner *et al.*, 2000) or spatial extent (Huettel *et al.*, 2001) of the hemodynamic response (HDR). We obtained separate estimates of the time course and spatial extent of the HDR and used a relatively fine grained scale (1 s) for the time course, so that changes in HDR peak amplitude (the early component of the HDR) could be distinguished from changes in HDR duration (the return to baseline later in the time course). In addition, the Buckner *et al.* (2000) and Huettel *et al.* (2001) studies measured activation for either passive viewing or nondiscriminative responses to visual patterns (checkerboards), and the present task provided the opportunity to investigate age differences in occipital activation when the stimuli (novels) depicted real objects and required a choice response.

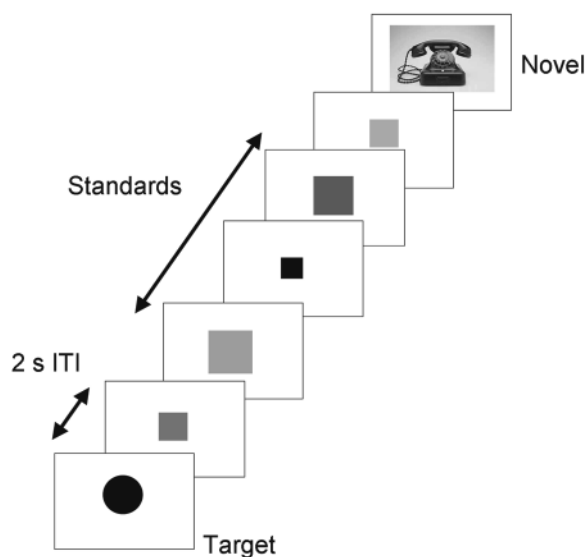
## Materials and Methods

### Subjects

The subjects were 16 younger adults (eight women) between 19 and 25 years of age (mean = 20.9 years) and 16 older adults (eight women) between 60 and 70 years of age (mean = 64.7 years). The research procedures were approved by the Institutional Review Board of the Duke University Medical Center, and all subjects gave written informed consent. All subjects were right-handed, community-dwelling individuals. The number of years of education did not differ significantly as a function of age group (younger adults' mean = 15.2 years; older adults' mean = 15.8 years). As determined by a screening questionnaire, subjects were free of significant health problems (e.g. hypertension, atherosclerosis) and were not taking medication known to affect cognition or cerebral blood flow. Subjects scored a minimum of 26 on the Mini-Mental State Exam (Folstein *et al.*, 1975), a maximum of 9 on the Beck Depression Inventory (Beck, 1978), and possessed a minimum corrected binocular acuity for near point of 20/40. The structural  $T_2$ -weighted MR images for each subject were reviewed by a neuroradiologist and found to be free of significant abnormality (e.g. atrophy, white matter hyperintensity). Response time per item in a computer version of symbol-digit substitution (Salthouse, 1992) was higher for older adults (mean = 1678 ms) than for younger adults (mean = 1184 ms), [ $t(30) = 5.0$ ,  $P < 0.0001$ ]. The raw score on the vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) did not differ significantly as a function of age group (younger adults' mean = 63.6; older adults' mean = 61.9).

### Behavioral Task

During scanning, subjects performed the version of the oddball task reported by Kirino *et al.* (2000). On each trial (Fig. 1), subjects viewed a display that contained one of three types of items: either a standard (a filled square), a target (a filled circle), or a novel (a photograph of an everyday object, e.g. telephone, bicycle). The displays were presented against a white background. To reduce habituation, the standards and targets varied across trials in fill color and size (~1–3° visual angle). The novels were ~3–9° visual angle. All displays were presented by a liquid crystal display projector with a custom throw lens, to a screen behind the scanner bore. Subjects viewed these rear-



**Figure 1.** Visual target detection (oddball) task performed during fMRI scanning. On each trial, subjects pressed the same response button at the onset of standards (squares, 87% of trials) and novels (photographs of familiar objects, 6% of trials) but pressed a different response button at the onset of targets (circles, 7% of trials). Across trials, the standards and novels varied in size and color (presented here as grayscale). Display duration was 500 ms, followed by a 1500 ms blank interval, yielding a 2 s intertrial interval (ITI).

projected displays by means of goggles with attached mirrors. Display duration was 500 ms, followed by a blank interstimulus interval of 1500 ms (i.e. display onset-to-onset interval = 2 s). Responses were collected from a two-button fiber optic response box. Subjects were instructed to make the same button-press response to standards and novels, and a different button-press response to targets. Subjects rested one finger of each hand on a response button throughout the scanning session. Thus, the novels required the same response as standards but were of greater visual complexity, whereas targets were similar in visual complexity to standards but required a different response. There were 1080 test trials in all, including 939 standards (87% of total), 66 novels (6% of total), and 75 targets (7% of total). Individual novels were not repeated within the scanning session.

In a separate session ~2 weeks before the scanning session (i.e. screening and psychometric testing), subjects performed a computer-administered version of the oddball task, which also used squares, circles, and photographs as displays. Subjects were also given an optometric examination, and a pair of lenses for the scanner goggles was ground for each subject based on his or her optometric prescription. Thus, each subject viewed the displays during scanning with his or her best corrected acuity. During the scanning session, subjects first performed one block of 90 practice trials, followed by six blocks of 180 test trials corresponding to six scanning runs. Novels and targets were separated by a minimum of five standards. Six block orders were constructed that counterbalanced the serial position of individual trial blocks, and these were varied across subjects so that each block order was used by at least one man and one woman in each age group. The right-left assignment of the two response buttons to targets versus standards/novels was alternated across subjects, with each assignment being used by at least three men and three women in each age group.

### Imaging Protocol

Scanning was conducted on a 1.5 T GE NVi SIGNA scanner with 41 mT/m gradients for fast image acquisition. Head motion was minimized with a vacuum-pack system molded to fit each subject. The  $T_1$ -weighted structural imaging included nine sagittal localizer images, spanning the midline, followed by 14 contiguous near-axial oblique slices, 5 mm thick, with no interslice gap. These latter slices were oriented for each subject so that the fourth slice from the bottom was located on the plane connecting the anterior and posterior commissures. The slices were selected to encompass the majority of the frontal, deep gray matter, and occipital cortical regions. The structural imaging of these slices used a high resolution gradient-echo sequence, with  $T_R = 450$  ms,  $T_E = 3.5$  ms, flip angle = 90°, FOV = 24 cm, and in-plane resolution = 0.94 mm<sup>2</sup>. Functional  $T_2^*$ -weighted images sensitive to the blood oxygen level dependent (BOLD) contrast were acquired at the same slice locations as the structural images (i.e. 14 contiguous slices, each 5 mm thick). The functional scans used a spiral gradient-echo sequence, with  $T_R = 1000$  ms,  $T_E = 40$  ms, flip angle = 81°, NEX = 1, FOV = 24 cm, and in-plane resolution = 3.75 mm<sup>2</sup>.

Preprocessing of the functional imaging data included correction for head motion and temporal order of slice acquisition within a TR, using SPM 99 software (Wellcome Department of Cognitive Neurology, London, UK). Neither additional spatial smoothing nor normalization was performed, and subsequent analyses of the BOLD signal changes were performed using custom MATLAB (Mathworks, Natick, MA) scripts, applied to anatomical regions of interest (ROIs). There were 12 ROIs in total, comprising three categories: (i) frontal regions, including the superior, middle, and inferior frontal gyri, motor cortex, and the anterior cingulate; (ii) deep gray matter structures, including the caudate, putamen, thalamus, and insula; and (iii) occipital regions, including the cuneus, fusiform gyrus, and lateral occipital gyrus. We selected these regions for their potential importance in visual perception and executive control. Other brain regions, not investigated here, including the inferior parietal lobule (McCarthy *et al.*, 1997), cerebellum (Clark *et al.*, 2000) and hippocampus (Yoshiura *et al.*, 1999) have also exhibited activation in fMRI studies of the oddball task.

Location and size of the ROIs are presented in Table 1. These regions were outlined manually on the high-resolution structural

**Table 1**  
Location and size of regions of interest

Region	Slice numbers	Slice location	Region size (voxels)	
			Younger adults	Older adults
<b>Frontal</b>				
Superior frontal gyrus	6–13	10 to 45	635 (86)	609 (77)
Middle frontal gyrus	4–13	0 to 45	795 (87)	782 (119)
Inferior frontal gyrus	2–12	–10 to 40	680 (76)	611* (69)
Motor cortex	12–13	40 to 45	497 (78)	513 (71)
Anterior cingulate cortex	4–11	0 to 35	271 (64)	238 (41)
<b>Deep gray matter</b>				
Caudate	2–9	–10 to 25	190 (26)	173 (23)
Putamen	3–7	–5 to 15	327 (39)	299* (36)
Thalamus	3–8	–5 to 20	597 (52)	599 (56)
Insula	2–9	–10 to 25	739 (87)	737 (75)
<b>Occipital</b>				
Cuneus	3–9	–5 to 25	369 (62)	389 (66)
Fusiform gyrus	2–4	–10 to 0	665 (136)	614 (116)
Lateral occipital gyrus	2–9	–10 to 25	771 (121)	742 (92)

Note. Imaging slices were near-axial oblique, 5 mm thick, with slice 4 located on the plane connecting the anterior and posterior commissures (AC–PC). Slice location is in mm from AC–PC. Region size is mean number of voxels across participants; standard deviations are in parentheses.

\*Age group comparison significant by *t*-test at  $P < 0.05$ .

images of each subject, within each cerebral hemisphere, on a slice-by-slice basis. Individual regions were identified by comparison to an MR-specific brain atlas (Damasio, 1995) and a three-dimensional reconstruction of the axial images (Analyze 3.0, AnalyzeDirect, Lenexa, KS). Either two or three trained operators outlined the regions within each category, dividing equally the subjects within each age group. Consistency among operators in region definition was assessed by having all possible pairs of operators in each category outline the same randomly selected set of regions for two younger and two older subjects. Within the selected frontal, deep gray matter, and occipital regions (510 slices total) the proportion of spatially overlapping voxels between operators was 0.80–0.85. We compared younger and older adults in region size (number of voxels) for each ROI (averaged over hemisphere), by *t*-test. The only significant differences were smaller ROIs for older adults than for younger adults in the inferior frontal gyrus [ $t(30) = 2.46, P < 0.05$ ] and putamen [ $t(30) = 2.14, P < 0.05$ ].

#### HDR Time Course and Spatial Extent of Activation

The BOLD signal time course data were obtained by extracting the epochs time-locked to the onset of each display from the continuous time series and averaging the epochs according to trial type (standard, novel or target). These averaged epochs comprised the five volumes preceding and 13 volumes following display onset (19 s total, for  $T_R = 1000$  ms). This time course of changes in the BOLD signal represents the HDR function. The majority of the displays (87%) were standards, and there was a minimum of five standards separating target and novel displays. The five-volume pre-stimulus baseline period consequently estimates the steady-state activity associated with repeated presentation of the standards. For each trial, the mean response exceeding this baseline level of activity was subtracted from the total response to allow determination of percentage signal change relative to the pre-stimulus baseline. Thus, the changes in the HDR associated with targets and novels represent display encoding, decision, and response processes beyond those occurring on the standard trials.

Voxel-wise signal changes on the target and novel trials, relative to the standards, were estimated for each combination of subject, ROI, imaging slice, cerebral hemisphere, and time point, from an empirically derived reference waveform, cross-correlated with the averaged

time series of every brain voxel (Huettel and McCarthy, 2000). *t*-statistics were derived from the resulting correlation coefficients, thresholded at  $t > 2.0$  ( $P < 0.05$ , uncorrected). To reduce variability in the time course data, the fMRI analyses were restricted to those trials on which the behavioral response was correct (Nielson *et al.*, 2002). The signal changes were analyzed within each ROI for each subject, by averaging (across slices) the time course of the activated voxels as defined by the cross-correlation procedure. Our procedure for ROI analysis replicates that of Jha and McCarthy (2000).

Separate spatial maps were created for voxels activated by targets and those activated by novels. Only voxels meeting the above threshold were included in each map. To preclude selection bias, these two maps were then combined into one final map of voxels activated by either type of trial. Thus, when activation for each type of display was estimated separately, the spatial map was not restricted to voxels thresholded for that type of trial (e.g. target activation was measured in the set of voxels activated by either targets or novels). This approach helped ensure that in the comparison of primary interest, the difference in activation between targets and novels, the results represented activation related specifically to trial type, beyond that attributable to the occurrence of an infrequent event.

The data for the HDR analyses were the spatial maps of activation, for those voxels active to either targets or novels, for each subject, as a function of ROI, trial type, hemisphere, and time point. Preliminary analyses indicated that the peak of the HDR curve occurred reliably at 5–6 s following display onset, and that the earliest return to the baseline level occurred at ~9 s from display onset. We therefore focused the HDR analyses on two measures, the percentage increase in the BOLD signal at time points 5–6 and the percentage increase in the BOLD signal at time points 9–13, relative to the pre-stimulus baseline, as estimates of the early and late components, respectively, of the HDR curve. An influence on the peak amplitude of the BOLD signal would be reflected in an increase in signal level during the early HDR component, whereas an increase in signal duration would be reflected in a signal level that remained above baseline during the late HDR component.

Within each ROI, we conducted two types of analyses for both the early (time points 5–6) and late (time points 9–13) components of the HDR: *t*-tests to determine whether activation exceeded the pre-

stimulus baseline, and ANOVAs to determine the effects of age group, trial type, and cerebral hemisphere. The *t*-tests indicated that, at the early HDR component, nearly all of the signal values were significantly greater than baseline at  $P < 0.05$ . The median *t* value was 5.8,  $P < 0.0001$ . The only exceptions were some of the individual comparisons for novel-related activation in the anterior cingulate (older adults' right hemisphere, younger adults' left and right hemispheres). When averaged across age group and hemisphere, however, novel-related activation at time points 5–6 was greater than zero [ $t(31) = 2.6$ ,  $P = 0.014$ ]. In view of the consistent activation in the early HDR component, for both targets and novels, we will therefore not report specific tests of the signal versus baseline levels for time points 5–6. We will report the individual tests for the late HDR component, because the task conditions varied with regard to whether the associated signal level decreased to the baseline at time points 9–13.

To compare the targets and novels, we conducted separate ANOVAs on the early and late HDR components, including age group (younger versus older) as a between-subjects variable, and trial type (target versus novel) and hemisphere (left versus right) as within-subjects variables. We also conducted analyses of the spatial extent of activation, by ANOVA on the percentage of voxels above threshold in each ROI, including age group as a between-subjects variable, and trial type and hemisphere as within-subjects variables.

## Results

### Behavioral Data

Median response time for correct responses was obtained for each participant in each task condition, and the means of these medians are presented in Table 2. An analysis of variance (ANOVA) of these data, including age group as a between-subjects variable and task condition as a within-subjects variable, indicated that the older adults' responses were slower than those of the younger adults [ $F(1,30) = 6.8$ ,  $P = 0.014$ ]. The task condition main effect was also significant [ $F(2,60) = 142.4$ ,  $P < 0.0001$ ], and paired comparison of the task conditions indicated that response time for novels and targets did not differ, but that response time in both of these conditions was higher than for standards [ $t(60) > 2.5$ ,  $P < 0.05$ ].

Mean accuracy on the standard and novel trials was 0.99 for both age groups. Accuracy was lower on the target trials but did not differ significantly between groups (younger adults' mean = 0.88; older adults' mean = 0.84).

### Imaging Data: HDR Curves

#### Frontal regions

The HDR data for the frontal regions are presented in Figure 2. All of the significant effects for these regions were associated with the early component (HDR peak). Analyses of these data for the superior frontal gyrus yielded a Trial Type  $\times$  Hemisphere interaction [ $F(1,30) = 7.6$ ,  $P < 0.01$ ], which occurred

because the highest signal was associated with the right hemisphere response to targets, and the lowest signal was associated with the right hemisphere response to novels. The left hemisphere signals (comparable for targets and novels) were intermediate to these.

The early component for the middle frontal gyrus also yielded a Trial Type  $\times$  Hemisphere interaction [ $F(1,30) = 12.7$ ,  $P < 0.01$ ], with a pattern similar to that of the superior frontal gyrus. The highest signal was associated with the right hemisphere response to targets, the lowest signal was associated with the right hemisphere response to novels, and the left hemisphere signal levels were intermediate to these.

Analyses of the early component for the inferior frontal gyrus yielded significant effects for trial type [ $F(1,30) = 4.4$ ,  $P < 0.05$ ] and hemisphere [ $F(1,30) = 19.5$ ,  $P < 0.001$ ], representing relatively higher signal levels for novels and for the right hemisphere, respectively. The Trial Type  $\times$  Hemisphere interaction was also significant [ $F(1,30) = 19.7$ ,  $P < 0.001$ ]. Unlike the pattern for superior and middle frontal gyri, the pattern for the inferior frontal gyrus reflected a relatively higher signal level for novels than for targets, in the left hemisphere.

The analyses of the early HDR component yielded a significant effect of trial type, with higher signal level for targets than for novels, for both motor cortex [ $F(1,30) = 6.6$ ,  $P < 0.05$ ] and the anterior cingulate [ $F(1,30) = 23.2$ ,  $P < 0.001$ ].

#### Deep Gray Matter Regions

The HDR data for these regions are presented in Figure 3. In the analysis of the caudate, the only significant effects were associated with the early HDR component. The signal level was higher for targets than for novels [ $F(1,30) = 12.1$ ,  $P < 0.01$ ] and was higher for older adults than for younger adults [ $F(1,30) = 4.9$ ,  $P < 0.05$ ].

Analyses of other regions of the basal ganglia, and insula, yielded significant effects for both the early and late components of the HDR. The putamen analysis yielded a significant trial type effect in the early component [ $F(1,30) = 10.8$ ,  $P < 0.01$ ], representing greater activation for targets than for novels. The trial type effect was also significant in the late component of the HDR, [ $F(1,30) = 5.2$ ,  $P < 0.05$ ], as a result of a higher signal level for novels than for targets, but the mean signal level at time points 9–13 did not differ significantly from the pre-stimulus baseline. In the putamen analyses, the signal level was higher for older adults than for younger adults in both of the HDR components [ $F(1,30) > 4.0$ ,  $P < 0.05$ , in each case]. In the late component, however, the signal was not significantly above baseline for either age group.

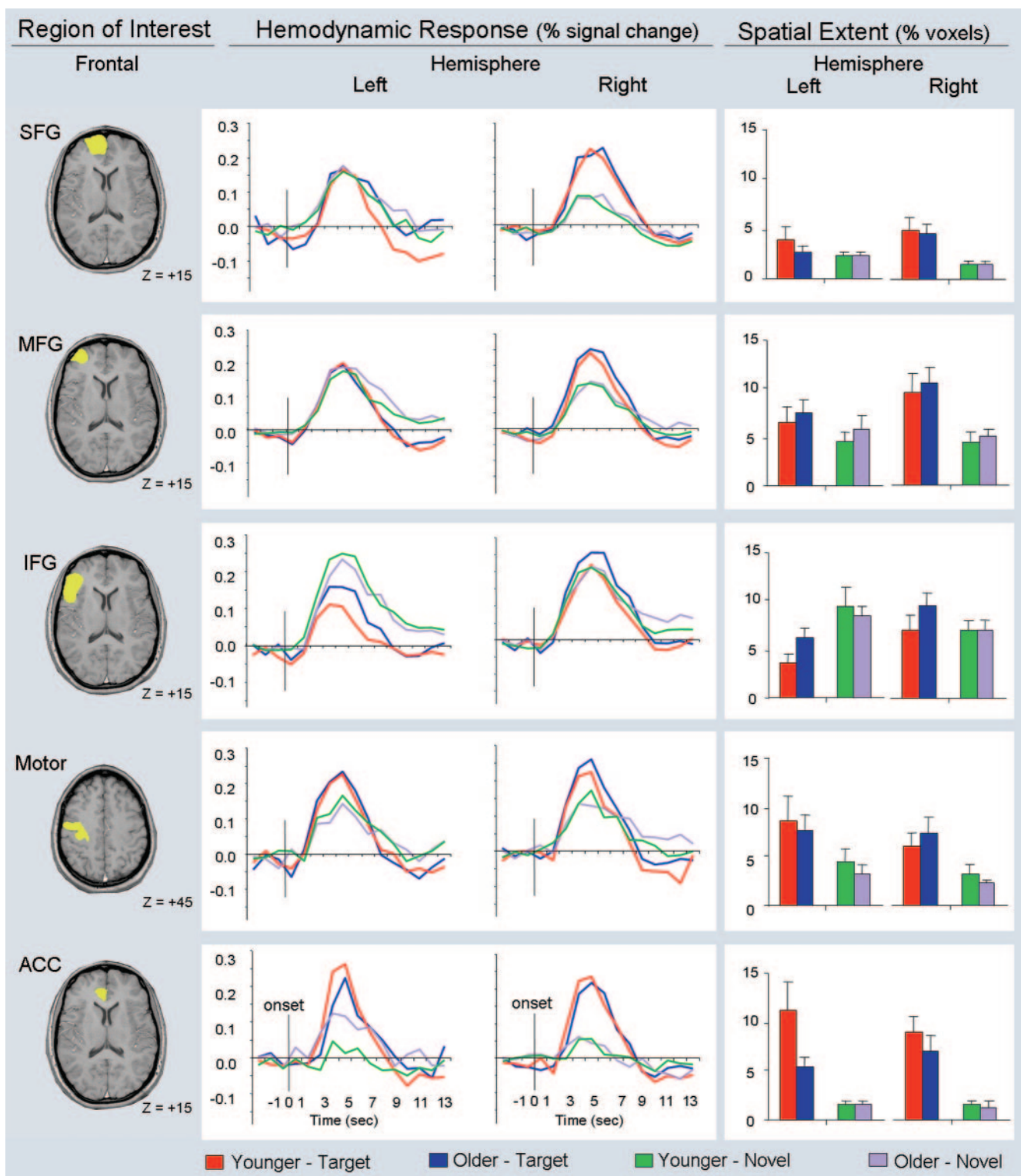
In the analysis of the early HDR component for the thalamus, there were significant main effects for age group [ $F(1,30) = 4.4$ ,  $P < 0.05$ ], trial type [ $F(1,30) = 8.5$ ,  $P < 0.01$ ] and hemisphere [ $F(1,30) = 6.2$ ,  $P < 0.05$ ], representing relatively higher signal levels for older adults, targets, and the right hemisphere, respectively. The Age Group  $\times$  Hemisphere interaction was also significant [ $F(1,30) = 4.0$ ,  $P = 0.054$ ], because the age-related increase in signal was greater for the right hemisphere than for the left hemisphere. The analysis of the late component of the thalamus HDR yielded effects for trial type [ $F(1,30) = 20.6$ ,  $P < 0.001$ ] and Age Group  $\times$  Trial Type [ $F(1,30) = 3.9$ ,  $P = 0.056$ ]. In this pattern, the older adults' activation to novels at time points 9–13 remained above baseline [ $t(15) = 2.8$ ,  $P = 0.013$ ], whereas all of the other signal values were either at or below the baseline level.

**Table 2**

Response time (ms) in the oddball task as a function of age group and task condition

Age group	Task condition		
	Standards	Novels	Targets
Younger adults	339 (45)	440 (73)	461 (67)
Older adults	384 (62)	518 (78)	509 (75)

*Note.* Values are means (across participants) of median response time for correct responses in each condition; standard deviations are in parentheses.

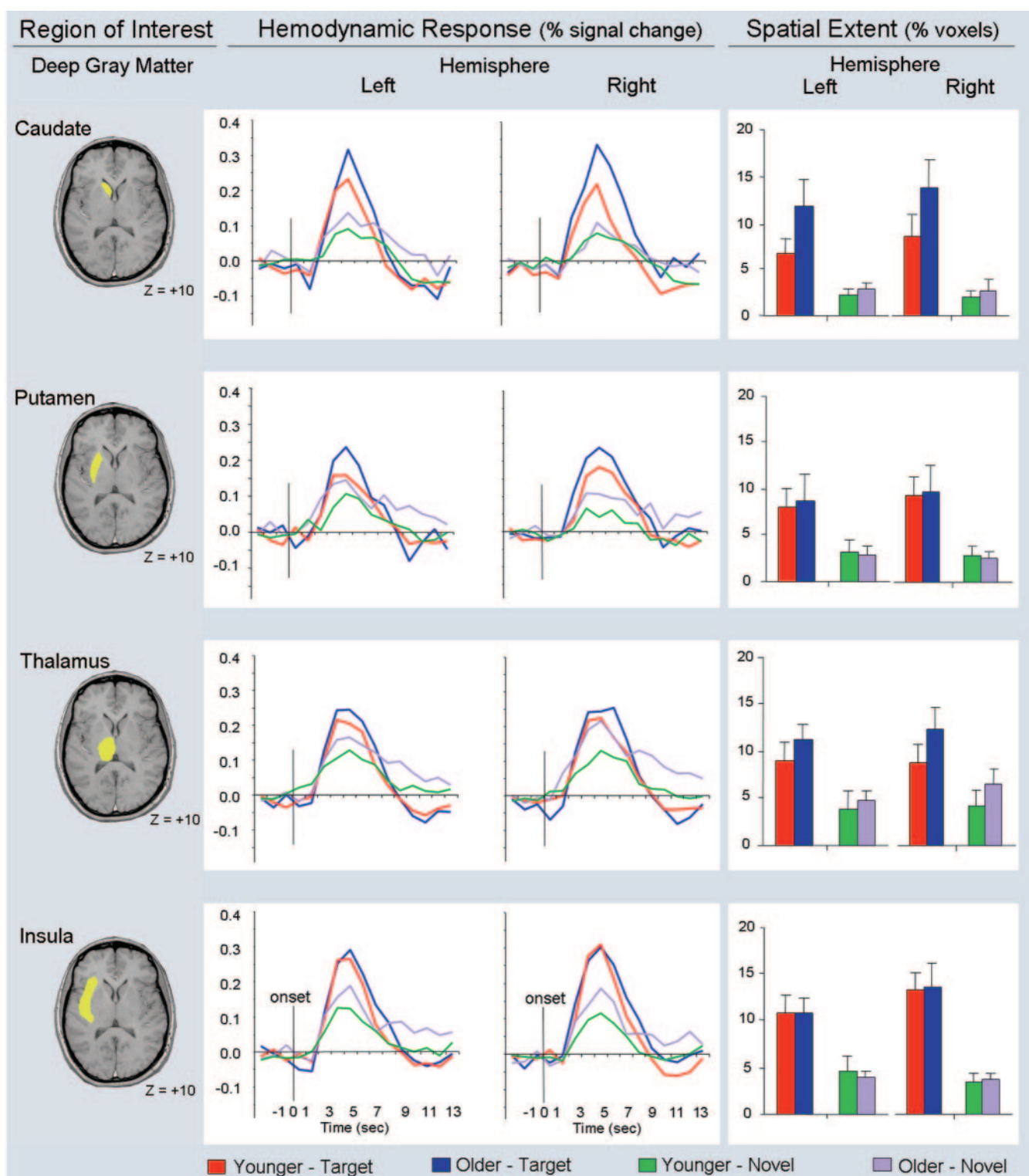


**Figure 2.** Time course and spatial extent of HDR for frontal ROIs, as a function of age group, trial type, and hemisphere. For each ROI, an example is displayed of one representative  $T_1$ -weighted MR slice, with  $Z$  value (in mm) for location of this slice relative to the plane connecting the anterior and posterior commissures. The time course and spatial extent data were averaged across all slices within an ROI. SFG = superior frontal gyrus; MFG = middle frontal gyrus; IFG = inferior frontal gyrus; Motor = motor cortex; ACC = anterior cingulate cortex.

The analysis for the insula yielded a significant effect of trial type during the early HDR component [ $F(1,30) = 12.4$ ,  $P < 0.01$ ], with a higher signal level for targets than for novels.

The trial type effect was also significant in the late HDR component [ $F(1,30) = 6.7$ ,  $P = 0.014$ ], because activation at time points 9–13 was slightly above baseline for novels [ $t(31) =$



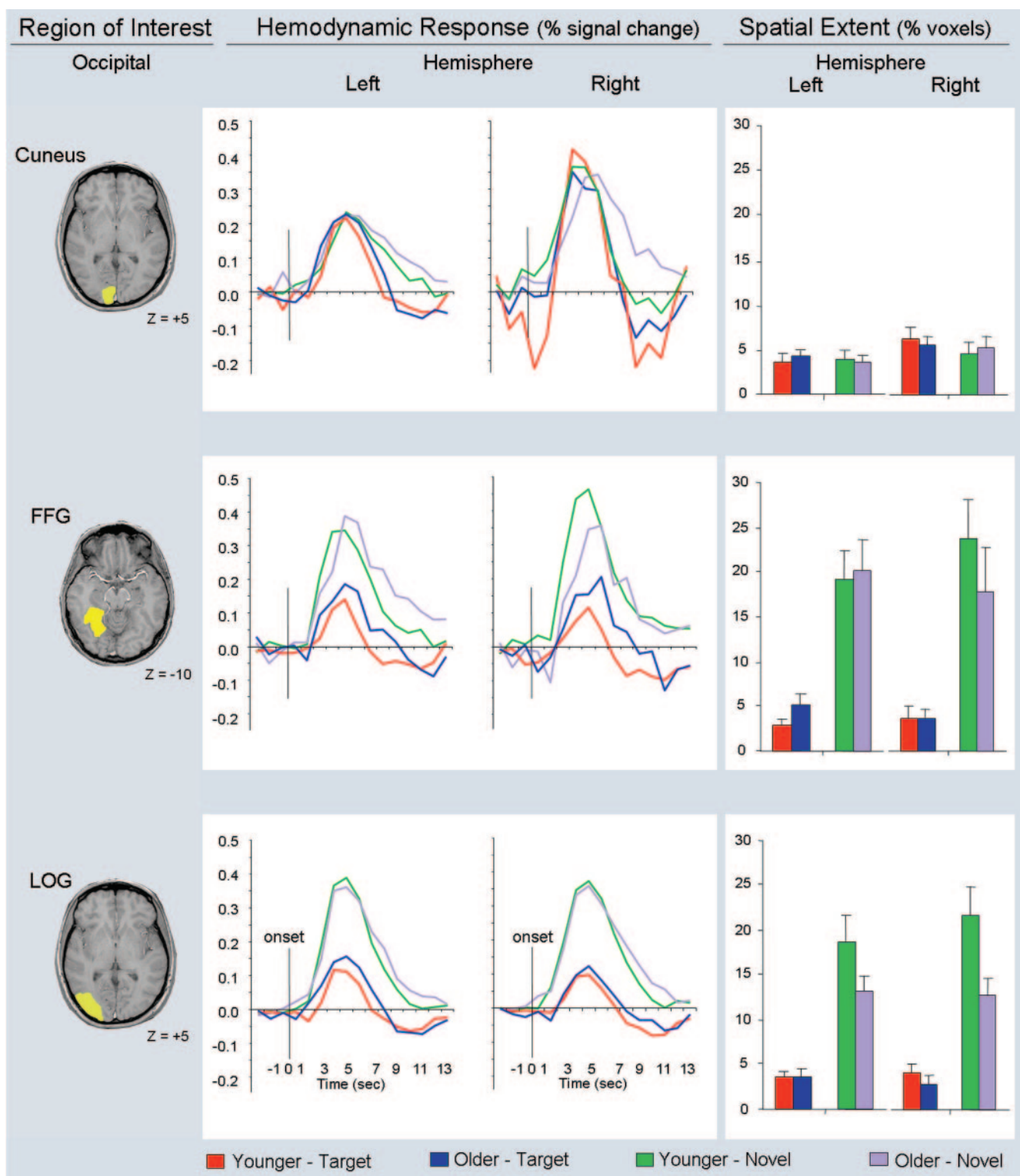


**Figure 3.** Time course and spatial extent of HDR for deep gray matter ROIs, as a function of age group, trial type, and hemisphere. An example of each ROI is displayed, as described in the legend to Figure 2.

2.0,  $P = 0.055$ ], but was below baseline for targets. The effect of age group, reflecting higher signal for older adults than for younger adults, was evident in both the early and late components of the insula HDR [ $F(1,30) = 4.0$ ,  $P < 0.05$ , in each case]. At the late component, however, the signal was not significantly different from the pre-stimulus baseline for either age group.

#### Occipital Regions

The HDR data for the occipital regions are presented in Figure 4. In the analysis of early HDR component for the cuneus, only the effect of hemisphere was significant [ $F(1,30) = 13.3$ ,  $P = 0.001$ ], representing a higher signal level in the right hemisphere than in the left hemisphere. In the late component of



**Figure 4.** Time course and spatial extent of HDR for occipital ROIs, as a function of age group, trial type, and hemisphere. An example of each ROI is displayed, as described in the legend to Figure 2. FFG = fusiform gyrus; LOG = lateral occipital gyrus.

the cuneus HDR, signal was higher for novels than for targets [ $F(1,30) = 11.2, P < 0.01$ ], and the novel-related activation remained above baseline [ $t(31) = 2.1, P < 0.05$ ], whereas the target-related activation was below baseline.

The analysis of the fusiform gyrus yielded a significant effect for trial type, reflecting a higher signal level for novels than for targets, in both the early and late HDR components [ $F(1,30) > 23.0, P < 0.001$ , in each case]. In the late component, the novel-



related activation was above the pre-stimulus baseline [ $t(31) = 3.9$ ,  $P < 0.0001$ ], whereas the target-related activation was below baseline. The Age Group  $\times$  Trial Type  $\times$  Hemisphere interaction was also significant in the early component [ $F(1,29) = 5.1$ ,  $P < 0.05$ ]. (A reduction in denominator degrees of freedom occurred because there were no voxels above threshold in this ROI for one hemisphere of one subject.) In the Age Group  $\times$  Trial Type  $\times$  Hemisphere interaction, although activation was greater for novels than for targets for both age groups, the highest signal level for the novels was associated with the younger adults' right hemisphere values, and this right-hemisphere advantage for the novel-related activation was not evident for the older adults.

For the lateral occipital gyrus, there was a significant effect of trial type in both the early and late components of the HDR [ $F(1,30) > 29.0$ ,  $P < 0.001$ , in each case], reflecting the higher signal level for novels than for targets. As was the case for both the cuneus and fusiform gyrus, the novel-related activation in the lateral occipital gyrus remained above baseline at time points 9–13 [ $t(31) = 3.46$ ,  $P < 0.01$ ], whereas the target-related activation was below baseline.

### Imaging Data: Spatial Extent

#### Frontal Regions

In the analysis of the spatial extent data for the frontal regions (Fig. 2), the superior frontal gyrus yielded significant effects for trial type [ $F(1,30) = 12.6$ ,  $P < 0.01$ ] and Trial Type  $\times$  Hemisphere [ $F(1,30) = 6.7$ ,  $P < 0.05$ ]. The spatial extent of activation was greater for targets than for novels in both hemispheres, but this difference was more pronounced for the right hemisphere than for the left.

A similar pattern was evident in the data for the middle frontal gyrus. There were significant effects for trial type [ $F(1,30) = 15.8$ ,  $P < 0.001$ ], and hemisphere [ $F(1,30) = 9.1$ ,  $P < 0.01$ ], as well as for the Trial Type  $\times$  Hemisphere interaction [ $F(1,30) = 11.3$ ,  $P < 0.01$ ], reflecting the greater spatial extent of target-related activation in the right hemisphere than in the left hemisphere.

The inferior frontal gyrus data yielded a Trial Type  $\times$  Hemisphere interaction [ $F(1,30) = 17.9$ ,  $P < 0.001$ ]. For this region, the activation extent was greater for targets than for novels in the right hemisphere but was greater for novels than for targets in the left hemisphere.

The trial type effect was the only significant effect in the analyses of both the motor cortex and anterior cingulate [ $F(1,30) > 16.0$ ,  $P < 0.001$ , in each case], representing the more extensive activation for targets than for novels.

#### Deep Gray Matter Regions

In the analyses of the spatial extent of activation in deep gray matter regions (Fig. 3), the main effect of trial type was significant for the caudate, putamen, and thalamus [ $F(1,30) > 13.0$ ,  $P < 0.001$ , in each case], reflecting the greater spatial extent of activation for targets than for novels. For the insula, both the trial type main effect [ $F(1,30) = 26.9$ ,  $P < 0.001$ ] and the Trial Type  $\times$  Hemisphere interaction [ $F(1,30) = 9.3$ ,  $P < 0.01$ ] were significant. In the insula, activation was more extensive for targets than for novels in both hemispheres, but the difference was more pronounced in the right hemisphere than in the left.

#### Occipital Regions

In the analysis of the spatial extent of occipital activation (Fig. 4), only the main effect of hemisphere was significant in the cuneus [ $F(1,30) = 9.8$ ,  $P < 0.01$ ], reflecting the more extensive activation for the right hemisphere than for the left hemisphere. In both the fusiform and lateral occipital gyri, however, the trial type effect was significant, as a result of a greater extent of activation for novels than for targets [ $F(1,30) > 30.0$ ,  $P < 0.001$ , in each case]. The lateral occipital gyrus data also yielded significant findings for the age group main effect [ $F(1,30) = 4.3$ ,  $P < 0.05$ ], and the Age Group  $\times$  Trial Type interaction [ $F(1,30) = 5.2$ ,  $P < 0.05$ ]. Both age groups exhibited more extensive activation for novels than for targets, but this effect was more pronounced for younger adults than for older adults. Alternatively, this interaction reflects the fact that the increased spatial extent of activation for younger adults, relative to older adults, was more clearly evident for novels than for targets.

#### Relation Between HDR Amplitude and Response Time

As noted in the Introduction, some age-related changes in neural activation, especially those involving an increased level of activation for older adults, have been interpreted in terms of a compensatory recruitment of cognitive processes. To explore the potential role of compensation in the present data, we conducted regression analyses of response time for correct responses in the oddball task, using the HDRs from all of the 12 ROIs as predictors. If neural activation does have a compensatory role, then we would expect that those individuals with higher levels of activation would exhibit faster correct responses (Cabeza *et al.*, 2002; Rosen *et al.*, 2002).

To minimize the number of predictor variables, we used only the peak amplitude of the HDR (the mean of time points 5 and 6) from each ROI, averaged across hemisphere and trial type, as a predictor. Within each age group, the median response times for the three task conditions were highly correlated (0.73–0.90), and we therefore used each subject's average of the response times for the three task conditions as the dependent variable. We used a stepwise regression analysis in which predictor variables entered the model successively on the basis of the strength of their relation to the dependent variable (response time), covaried for the effects of variables previously entered. Model estimation ended when no other variable met the criterion for entry ( $P = 0.15$ ).

Results of three stepwise regression analyses are presented in Table 3. The first model included all of the subjects, and age group (coded as a categorical variable) was forced to enter as the first predictor. This model also included a predictor for the interaction of each of the ROI amplitudes with age group. The final step of this model yielded two significant predictors. The first one was the middle frontal gyrus, and the regression coefficient for this predictor was negative, indicating that increasing HDR amplitude in this region was associated with faster responses (decreasing response time). The second predictor was the interaction between the putamen and age group, which indicated that the relation between the putamen HDR amplitude and response time differed for the two age groups. These two variables combined accounted for 49% of the variance in response time, [ $F(3,28) = 9.1$ ,  $P < 0.001$ ]. In a second regression analysis conducted on the younger adults'

**Table 3**  
Stepwise regression of response time using HDR amplitudes as predictors

Variable	<i>t</i>	<i>P</i>	Beta	<i>r</i> <sup>2</sup>	Model <i>R</i> <sup>2</sup>
Model 1: all subjects					
Age group	-0.99	0.332	-0.374	0.184	
Middle frontal gyrus	-4.09	0.001	-0.634	0.197	
Age Group × Putamen	2.50	0.019	0.991	0.113	0.494
Model 2: younger adults					
Middle frontal gyrus	-3.16	0.007	-0.645	0.416	0.416
Model 3: older adults					
Thalamus	-2.70	0.018	-0.867	0.191	
Putamen	1.85	0.087	0.594	0.168	0.360

*Note.* Response time is the mean of median response time for the three task conditions. HDR amplitude is percentage change in the BOLD signal at 5–6 s after display onset. Three stepwise regression models were estimated: one for all subjects combined, and one for each age group

data separately, the final model included only the middle frontal gyrus, which was related negatively to response time and accounted for 42% of the variance, [ $F(1,14) = 9.98, P < 0.01$ ]. For the third analysis, applied to the older adults' data separately, the final model included both the thalamus and putamen, which together accounted for 36% of the variance in response time, [ $F(2,13) = 3.7, P = 0.055$ ]. In the older adults' model, the thalamus HDR was related negatively to response time, whereas the putamen HDR was related positively to response time.

## Discussion

The design of the present version of the novelty oddball task resembled that of Kirino *et al.* (2000), in which subjects made one response to both standards and novels, and a different response to targets. The behavioral data replicated closely the Kirino *et al.* results. As in their study, we found that response time for correct responses was lowest to standards and increased equally for novels and targets (Table 2). This increased response time represents the detection of an infrequent event, which occurred on both target and novel trials, as well as more specific processes of executive control. In the case of targets these included switching to a different response (while inhibiting the standard response), and in the case of novels there would be both additional visual processing and some inhibition of a tendency to switch responses at the occurrence of a novel event (Huettel and McCarthy, 2003). The hit rate was near ceiling (0.99) for both standards and novels but lower (0.86) for targets, reflecting the additional attentional demands associated with switching to the target response.

Older adults' responses were slower overall than those of the younger adults, but the changes in response time across the task conditions were similar for younger and older adults, and error rate was comparable for the two age groups. Although age-related decline in performance has been observed in some visual attention tasks relying heavily on executive control (McDowd and Shaw, 2000; Madden and Whiting, 2003), there was no evidence in the behavioral data of age differences related to specific task demands. The present results thus represent either an age constancy in executive control, or task demands that were not sufficient to challenge the limits of attentional capacity. It is likely that age-related decline in the

efficiency of both visual encoding and response selection processes contributed to the overall increased response time for older adults relative to younger adults.

Analyses of the time course and spatial extent of changes in the BOLD signal indicated that, independent of age group differences, there was a widespread effect of novelty detection in this sample of ROIs. For both targets and novels, the peak amplitude of the HDR (i.e. early component) was significantly above the pre-stimulus baseline level in nearly all of the ROIs. There were consistent differences between targets and novels, however, in the regional pattern of neural activation (Figs 2–4). Activation was greater for targets than for novels in prefrontal and deep gray matter regions, whereas activation was greater for novels than for targets in occipital regions. The direct comparison of targets and novels yielded target-specific increases in both HDR peak amplitude and spatial extent of activation in the superior and middle frontal gyri, motor cortex, anterior cingulate, caudate, putamen, and insula. The HDR peak amplitude and spatial extent of activation in the thalamus were greater for targets than for novels. Novels, in comparison, were associated with increases in both the early and late components of the HDR, as well as in the spatial extent of activation, in the fusiform and lateral occipital gyri. The late component of the HDR in the cuneus was higher for novels than for targets. Less reliable effects of trial type were evident in the inferior frontal gyrus, which exhibited a novel-related increase in HDR amplitude and spatial extent, in the left hemisphere, but a target-related increase in the extent of activation in the right hemisphere.

The target-related activation of prefrontal regions, including the superior and middle frontal gyri and anterior cingulate, is consistent with the proposal that these regions are part of an executive control network engaged by the detection of the infrequent targets (Yoshiura *et al.*, 1999; Clark *et al.*, 2000; Ardekani *et al.*, 2002). This network includes other regions not investigated in the present study, including the inferior parietal lobule (Daffner *et al.*, 2003; McCarthy *et al.*, 1997), cerebellum (Clark *et al.*, 2000) and hippocampus (Yoshiura *et al.*, 1999). The target-related activation that we observed in the middle frontal gyrus, in particular, replicates fMRI results reported by McCarthy *et al.* (1997), Kirino *et al.* (2000) and Huettel and McCarthy (2003). All of these authors also found a right-hemisphere bias to target-related activation of the middle frontal gyrus and proposed that this region has a central role in mediating the executive control of detecting and responding to targets. Kirino *et al.* (2000) also reported that there was some tendency, as in the present data, towards novel-related activation in the inferior frontal gyrus. This latter result may reflect the identification or semantic encoding of the photographs of objects used as the novel items (Gabrieli *et al.*, 1998).

Activation of deep gray matter structures (caudate, putamen, thalamus, and insula) specific to targets has been noted in previous fMRI studies of the oddball task (Ardekani *et al.*, 2002), especially when an overt response to the target is required. It is likely that this activation represents the preparation for the shift in the motor response associated with the occurrence of the target (Hikosaka *et al.*, 2000; Huettel *et al.*, 2002). The thalamus activation may in addition result from subjects maintaining an attentional set for the visual features (circles) signaling the occurrence of the targets (Corbetta *et al.*, 1991; LaBerge, 2000).

The increased activation of the occipital regions in response to the novels suggests that subjects were responding to the additional visual complexity of these displays (photographs of familiar objects), relative to the more simple squares and circles that were used as standards and targets, respectively. Activation specific to the novels was more pronounced in the fusiform and lateral occipital gyri than in the cuneus, indicating that higher-order visual processing of object features was involved. All subjects viewed the displays with their best optical correction, thus minimizing effects due to visual acuity. The previous fMRI study of the oddball task that included these types of displays (Kirino *et al.*, 2000) was concerned primarily with frontal lobe activation, and occipital regions were not included in the imaging sequence. Clark *et al.* (2000) conducted whole-brain imaging during a novelty oddball task, but all of the displays were single letters, and the novels did not elicit activation consistently. One interesting difference between the patterns of activation associated with the novels and targets in the present study is that only the novel-related activation remained above the pre-stimulus baseline level during the late component of the HDR. This result may indicate that, in this version of the oddball task, the neural processes of visual object identification are sustained over a longer period of time than are the executive control processes mediated by the prefrontal and deep gray matter regions.

In contrast to our initial predictions, the prefrontal activation associated with visual target detection was comparable for younger and older adults, in both amplitude and spatial extent. We did not observe the age-related increase in prefrontal activation that has been reported in some memory tasks (Cabeza, 2002; Grady, 2000). An age-related increase in HDR amplitude was evident, however, in the early (peak) component for all of the deep gray matter ROIs (caudate, putamen, thalamus, and insula). The age group effect was less apparent in the late component of the HDR. In view of the clear target-related activation in the deep gray matter ROIs, and the central role of the basal ganglia in response preparation (Huettel *et al.*, 2002), it is likely that the age-related increase in HDR peak amplitude for these regions is related to the older adults devoting more attention than younger adults to the control of the motor response. The age effect in the early component of the HDR for the deep gray matter ROIs did not reliably interact with trial type, however, and thus the age-related increase in HDR peak amplitude may also be due to more general alerting and orienting processes associated with novelty detection. The late component of the thalamus HDR did exhibit an interaction between age group and trial type, specifically an age-related increase in activation to novels, which may represent a more sustained attentional response on these trials for older adults, although behavioral performance on these trials was not differentially slowed for older adults.

In the occipital regions, the age group effects interacted reliably with trial type, specifically as an age-related decrease in activation evoked by the novels. There were two aspects to this age-related change in occipital activation. First, the spatial extent of novel-related activation in the lateral occipital gyrus was reduced for older adults relative to younger adults. This result supports previous neuroimaging investigations suggesting an age-related decline in the information processing efficiency of visual cortical regions (Madden *et al.*, 2003). The occipital ROI data also extend previous fMRI studies of age differences in visual perception (Buckner *et al.*, 2000; Huettel

*et al.*, 2001) that had analyzed responses to checkerboard patterns rather than to photographs of actual objects. Secondly, the peak amplitude of novel-related activation in the right-hemisphere fusiform gyrus was lower for older adults than for younger adults. That is, the degree of right-hemisphere lateralization for the visual processing of the novels was relatively less pronounced for the older adults (cf. Cabeza, 2002). Both of the age-related effects occurred in extrastriate regions rather than in the cuneus, suggesting that the observed age-related decline reflects higher-order visual feature processing.

The stepwise regression analyses (Table 3) used the HDR amplitudes from all of the ROIs as predictor variables in accounting for the variance in response time. The results of these analyses provided additional information regarding the pattern of age-related change in the HDR data. In the analysis of all subjects combined, the amplitude of activation in the middle frontal gyrus was correlated significantly with response time, consistent with the central role of this region in attentional control during the oddball task (Kirino *et al.*, 2000; Huettel and McCarthy, 2003). This correlation was in addition negative, indicating that individuals with higher levels of middle frontal gyrus activation exhibited faster responses (i.e. lower response time). Analyses conducted within each age group, however, demonstrated that the middle frontal gyrus was significant as a predictor only for the younger adults. Thus, although the magnitude of the middle frontal gyrus activation was comparable for the two age groups, the relation of the activation to response time was more clearly evident for younger adults than for older adults. The within-group analyses demonstrated in addition that activation in the putamen and thalamus was more highly correlated with response time for older adults than for younger adults.

In view of the relatively small sample sizes, we consider these regression analyses as preliminary data for further investigation. The results are nevertheless valuable in extending the HDR findings in several ways. For this version of the oddball task, the component of the attentional network mediating motor learning and response regulation was more prominent for older adults than for younger adults. The deep gray matter regions for which the HDR amplitude was correlated significantly with the older adults' behavioral performance (putamen and thalamus) had also exhibited an age-related increase in HDR amplitude, in the time course analyses. Whereas for younger adults task performance may be mediated directly from the top-down control initiated by the prefrontal component of the attentional network (middle frontal gyrus), for older adults it may be necessary to activate the deep gray matter structures specialized for control of the motor response (Hikosaka *et al.*, 2000; Huettel *et al.*, 2002).

This pattern of results is very different from the age-related increase in prefrontal activation that has been interpreted as a compensatory function in some perceptual and memory tasks (Grady *et al.*, 1994; Cabeza *et al.*, 1997; Madden *et al.*, 1997; Nielson *et al.*, 2002; but cf. Reuter-Lorenz, 2002). Although we observed that an increase in prefrontal activation was associated with faster responses, which is generally consistent with the pattern reported by Cabeza *et al.* (2002) and Rosen *et al.* (2002) for memory performance, in the present experiment the prefrontal activation was actually less prominent as a predictor of the older adults' response time. The differential influence of the putamen and thalamus activation on the older adults' response times may represent a different form of

compensation, in which an age-related decrease in the activation of visual cortical regions leads to increased influence from a later stage of information processing related to response regulation. This account would be consistent with behavioral data suggesting that response selection is particularly vulnerable to age-related decline (Hartley, 2001; Allen *et al.*, 2002). Activation of deep gray matter structures, especially the thalamus, may in addition help to offset the age-related decline in the activation of occipital cortex, by enhancing target-relevant features relayed for visual processing (Corbetta *et al.*, 1991; LaBerge, 2000). The overall pattern of results points to the importance of the basal ganglia and related deep gray matter structures as one component of an attentional network that is a locus of age-related change (Bashore, 1993; Hicks and Birren, 1970; Rubin, 1999).

In summary, in this version of the oddball task, the detection of novel events and attentional control of responding was qualitatively similar, at the behavioral level, for younger and older adults. Response time was relatively higher overall for older adults, but the changes in response time and accuracy across the task conditions were similar for the two age groups. Analyses of the time course and spatial extent of neural activation in frontal, deep gray matter, and occipital ROIs demonstrated that both age groups exhibited increased target-related activation in prefrontal and deep gray matter regions, and increased novel-related activation in occipital regions. Although the prefrontal activation did not vary significantly as a function of age group, activation for both targets and novels within deep gray matter structures (caudate, putamen, thalamus, and insula) was relatively greater for older adults, whereas the activation for novels in occipital regions (fusiform and lateral occipital gyri) was relatively reduced for older adults. Regression analyses of the relation between HDR amplitude and response time demonstrated that activation in the middle frontal gyrus was the best predictor of response time for younger adults, whereas activation of deep gray matter structures (putamen and thalamus) were the best predictors for older adults. The age-related increase in activation in these regions may result from older adults' increased reliance on an attentional network mediating visuomotor learning and response selection.

## Notes

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