Effects of Aging on BOLD fMRI during Prosaccades and Antisaccades

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Abstract

■ Age affects the ability to inhibit saccadic eye movements. According to current theories, this may be associated with age-induced neurophysiological changes in the brain and with compensatory activation in frontal brain areas. In the present study, the effects of aging are assessed on brain systems that subserve generation and inhibition of saccadic eye movements. For this purpose, an event-related functional magnetic resonance imaging design was used in adults covering three age ranges (18–30, 30–55, and 55–72 years). Group differences were controlled for task performance. Activity associated with saccadic inhibition was represented by the contrast between prosaccade and antisaccade activation. The tasks activated well-documented networks of regions known to be involved in generation and inhibition of saccadic eye movements. There was an age-related shift in activity from posterior to frontal brain regions after young adulthood. In addition, old adults demonstrated an overall reduction in the blood oxygenation level dependent (BOLD) signal in the visual and oculomotor system. Age, however, did not affect saccade inhibition activity. Mid and old adults appear to increase frontal activation to maintain performance even during simple prosaccades. The global reduction of the BOLD response in old adults could reflect a reduction in neural activity, as well as changes in the neuronal–vascular coupling. Future research should address the impact of altered vascular dynamics on neural activation and the BOLD signal. ■

INTRODUCTION

Advances in neuroimaging techniques allow for increasingly sophisticated measurements of brain activity. Functional magnetic resonance imaging (fMRI) has proven to be a valuable tool not only for mapping of brain functions, but also for explaining behavioral differences between groups in terms of neurofunctional differences. fMRI is increasingly being used to investigate the effects of aging on brain activation. Many physiological changes occur in the brain during the transition from young to old adulthood. Many of these changes have been associated with cognitive decline. Imaging studies have investigated age-related impairments in various brain functions including memory, perception, and motor action. This study addresses the effects of aging on brain activation during execution and inhibition of saccadic eye movements.

Performance on saccade tasks declines with age. There is a linear relationships between age and the onset latencies of visually guided saccades (Olincy, Ross, Youngd, & Freedman, 1997; Tedeschi et al., 1989; Abel, Troost, & Dell'Osso, 1983; Carter, Obler, Woodward, & Albert, 1983). Elderly subjects also demonstrate impaired antisaccade performance. For the generation of antisaccades, subjects have to inhibit a saccade toward a novel peripheral stimulus and instead make a saccade in the opposite direction (Hallett, 1978). Old adults make more erroneous saccades towards the stimulus and exhibit increased onset latencies of correct antisaccades when compared to young adults (Sweeney, Rosano, Berman, & Luna, 2001; Klein, Fischer, Hartnegg, Heiss, & Roth, 2000; Nieuwenhuis, Ridderinkhof, de Jong, Kok, & van der Molen, 2000; Butler, Zacks, & Henderson, 1999; Olincy et al., 1997). Some studies only report increased onset latencies of antisaccades in elderly subjects (Eenshuistra, Ridderinkhof, & van der Molen, 2004; Munoz, Broughton, Goldring, & Armstrong, 1998; Fischer, Biscaldi, & Gezeck, 1997).

The neural substrate of the oculomotor impairment remains unknown. A widespread network has been unveiled that subserves the generation and suppression of saccadic eye movements and encompasses eye fields in all the major cortices including not only the parietal eye fields (PEFs) the frontal eye fields (FEFs), and supplementary eye fields (SEF), but also portions of the visual cortex and the basal ganglia (Desouza, Menon, & Everling, 2003; Cornelissen et al., 2002; Raemaekers et al., 2002; Kimmig et al., 2001; Matsue et al., 1994). Impaired inhibitory control over saccades in elderly subjects has been attributed to impaired function of the frontal lobes, but this notion is mainly based on

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the finding that patients with lesions affecting the dorsolateral prefrontal cortex (DLPFC) demonstrate similar deficits (Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991). The existing fMRI literature demonstrates substantial agreement with the models of the oculomotor system that are based on cell recordings in nonhuman primates (Berthoz, 1996). The extensive knowledge of this network provides a reliable background for investigating differences between age groups.

As yet, there has been no study that addressed the changes in brain activity that occur in the oculomotor system with aging. Both global and regionally specific changes may occur in the system during the life span. Elderly subjects are thought to engage compensatory mechanisms, supposedly to counteract age-induced physiological changes. A possible mechanism for compensation is described by the hemispheric asymmetry reduction in old adults (HAROLD) model (Cabeza, 2002). This model states that frontal activity tends to be less lateralized in older than in younger adults, which may reflect compensatory processes. Support for the HAROLD model has also been found for control over motor functions. During a go/no-go task, elderly subjects exhibit a more bilateral pattern of frontal recruitment during correct inhibition than do young adults (Langenecker & Nielson, 2003; Nielson, Langenecker, & Garavan, 2002).

Whether it is essentially hemispheric asymmetry reduction that is reflected in these studies is unclear. The apparent hemispheric asymmetry reduction could also represent a net increase in activation in frontal brain areas with increasing age. A recent study on motor inhibition during Stroop interference reported more activation in the task-specific areas of the frontal lobe in elderly subjects (Langenecker, Nielson, & Rao, 2004; Milham et al., 2002). This indicates that elderly subjects may compensate through increasing engagement of task-specific, frontal brain areas. This implies that aging may be accompanied by changes in the anterior–posterior asymmetry instead of hemispheric asymmetry. A shift toward more frontal activation could reflect an increase in effort to maintain task performance.

In this study, we assess age-related changes in the oculomotor system by measuring blood oxygenation level dependent (BOLD) responses during saccadic eye movements in a sample of subjects covering a broad age range. Differences between the age groups are assessed for prosaccades, and the contrast between antisaccades and prosaccades (saccadic inhibition) in task-related brain areas. We expect increasing compensatory activation to arise in frontal brain areas with increasing age during either prosaccades or saccadic inhibition or during both. This additional activation would shift the anterior–posterior asymmetry. Such compensation may arise quite early in the life span as age-related increases in activation (e.g., related to working memory) have already been observed within a group of only younger adults (Adler, Holland, Enseleit, & Strakowski, 2001). To minimize the confound of differences in performance between young and old subjects, we applied an event-related paradigm that allows us to base group comparisons on correct responses only.

METHODS

Subjects

Thirty-one subjects (16 men) participated in the experiment. The subjects were evenly distributed between 18 and 72 years of age (mean, 41 years; *SD*, 19 years). For groupwise comparisons, subjects were categorized into young adulthood (18–30 years), mid adulthood (30–55 years), and old adulthood (55–72 years). All were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) (mean, 0.84; *SD*, 0.18). A history of substance abuse or major neurological illness resulted in exclusion from the experiment, as did metal implants. All subjects gave informed consent for participation (approved by the Human Ethics Committee of the University Medical Center Utrecht).

Scanning Protocol

All images were obtained with an ACS-NT 1.5T clinical scanner (Philips Medical Systems, Best, the Netherlands) with fast gradients (PT6000). The head was held in place with a strap and with padding. Structural and functional images were acquired in transverse orientation, from the same section of the brain. For functional scans, a navigated 3D-PRESTO pulse sequence (Ramsey et al., 1998; Van Gelderen et al., 1995) was used with the following parameters: TE 37 msec, TR 24 msec, flip angle 9.5°, matrix 48 × 64 × 24, FOV 192 × 256 × 96 mm, voxel size 4 mm isotropic, scan duration 1.49 sec per 24-slice volume. Immediately after functional scans, an additional PRESTO scan of the same volume of brain tissue was acquired with a high flip angle (30°, FA30) for the image coregistration routine (see below). Finally, a T1-weighted structural image was acquired.

Task Design

The fMRI design used a PC, a rear projection screen, and a video projector system for presentation. All stimuli were projected in white on a dark background. All events were time-locked to the fMRI scans. The design consisted of two tasks, that is, prosaccades and antisaccades. These two conditions had identical stimuli. During prosaccades, subjects had to make eye movements toward peripherally presented stimuli. During antisaccades, subjects were requested to suppress these stimulus-triggered eye movements and instead make saccades toward the opposite direction.

Each new trial started with the disappearance of a fixation cross (0.9° visual angle) at central view. After a 200-msec gap period, a square (0.9° visual angle) was presented semirandom 8.7° to the left or right of central fixation. The square was extinguished after 3240 msec, simultaneously with the reappearance of the fixation cross at central view. A new stimulus was triggered by the scanner every ninth scan, thereby generating a fixed stimulus interval of 13.4 sec giving stimulus-related BOLD signal time to return to baseline (Bandettini & Cox, 2000).

Instructions were given verbally prior to the start of the experiment and included the following:

1. Prosaccade: ''From central fixation look towards the square as quickly as possible when it appears. Look back to the fixation cross when the square disappears and the fixation cross reappears in the center.''
2. Antisaccade: ''When the square appears, look in the opposite direction as quickly as possible, without looking towards the square. Look back to the fixation cross when the square disappears and the fixation cross reappears in the center.''

Task instructions preceded each new block of 10 stimuli. There were four blocks per task making a total of eight, which were orderly alternated.

Eye Movements

Eye movements were recorded during the entire oculomotor task using an MR-compatible eyetracker (Cambridge Research Systems Ltd., Rochester, UK; Kimmig, Greenlee, Huethe, & Mergner, 1999) in combination with Labview (National Instruments Corporation, Austin, TX) acquisition software on a PC with a multifunctional I/O board (National Instruments Corporation). This acquisition PC was linked to the stimulus PC by a parallel cable to synchronize the eye recordings and the task presentation. Calibration and adjustment of the sensor were done during a 5-min period prior to scanning. The sample frequency of the recording was 500 Hz. For each saccade in the time window of 200 msec before until 600 msec after the stimulus presentation, the latency and the direction were determined using a custom nonautomated analysis program in IDL (Research Systems Inc., Boulder, CO).

Analysis

Data analysis of fMRI scans was done with custom-written programs in IDL. The last functional volume was registered to the FA30 volume. Next, all fMRI volumes where registered to the (now registered) last functional volume using a least squares differences criterion (Thevenaz, Ruttimann, & Unser, 1998). The structural scan was also registered to the FA30 scan thereby providing spatial alignment between the structural scan and the functional volumes. A 3-D gaussian filter (8 mm full width at half maximum) was applied to all fMRI volumes.

Preprocessing of Individual Subject Data Sets

Next, a standard linear multiple regression analysis was conducted for each subject. Several factors were generated for each subject individually, based on trial type (prosaccade/antisaccade), accuracy of the trials (first saccade in correct/incorrect direction), whether a potentially false saccade was corrected by a saccade toward the opposite direction, and anticipation (first saccade before or after 100 msec). This resulted in a maximum of six factors per condition (Figure 1). Two separate factors represented the eye movement that returned the view to central gaze for the two conditions. All events in the design matrix were convolved with a predefined hemodynamic response function (Friston, Frith, Turner, & Frackowiak, 1995). Additional factors included the average intensity of each scan, and 88 discrete cosine functions forming a high-pass filter with a cutoff at 3.73×10^{-2} Hz to correct for low-frequency scanner and physiological artifacts but also for differences in baseline activation between conditions. After voxelwise regression analysis, 3-D volumes were created of the regression coefficients. Only the volumes containing the regression coefficients representing the activation during the different trial types were included in further analysis. Subsequently, these volumes were spatially normalized in Talairach orientation to enable groupwise comparisons (Collins, Neelin, Peters, & Evans, 1994). To assess brain activation for the different conditions in the entire group, voxelwise t tests were performed using the normalized volumes containing the regression coefficients and the pooled standard deviation (Worsley, 1994). Bonferroni correction for the number of tests resulted in a critical t value of 4.52 for each voxel.

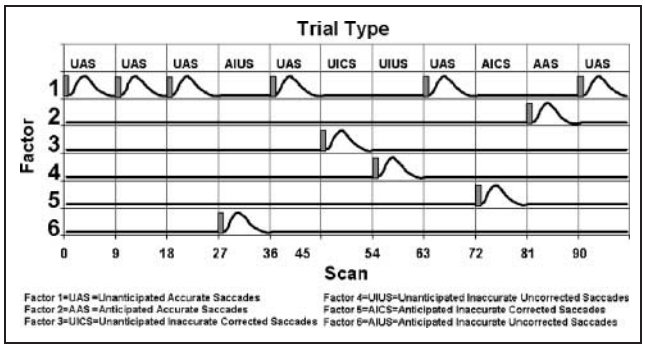

Figure 1. Schematic of the factors for one condition. Results per trial were subdivided in six categories. These categories represented the six different behavioral outcomes per trial (see the abbreviations). The different categories were subsequently represented in separate factors in the regression model.

Groupwise Analyses

To assess age-related changes in brain activation, two different strategies were employed. The first strategy involved a voxel-based analysis of aging effects. For this analysis, an independent variable was created that contained the age in days for all the subjects. This independent variable was used as a regressor in a voxelwise regression analysis of age over the volumes containing the regression coefficients of correct prosaccades, and the contrast between prosaccades and antisaccades (saccadic inhibition). Subsequently, the two regression coefficients were tested for significance. The resulting statistical t maps represent the linear effects of age on regional brain activation for prosaccades and saccadic inhibition.

The second strategy was a region of interest (ROI)-based approach. Two sets of ROIs were defined, one for prosaccades and one for saccade inhibition.

Prosaccade ROI Analyses

The first set was based on the t map for the group during prosaccades. A mask was created by applying a threshold of $z = 3.5$ ($p < .0005$, uncorrected) on this t map, yielding the ROIs for further analyses. Borders between interconnected regions were drawn using a watershed algorithm and a priori knowledge of functional localization. The resulting ROIs are displayed in Figure 2A. Magnitude of activation within each ROI was calculated for each subject by averaging the regression coefficients of prosaccades over the voxels within the ROIs. Group differences between the three age groups during prosaccades (i.e., young, mid, and old adults) were estimated using a repeated measures General Linear Model (GLM) that included one within-subject factor (the activation during prosaccades in the ROIs for prosaccades).

Saccadic Inhibition ROI Analysis

The second set of ROIs was based on the t map for saccadic inhibition (antisaccades vs. prosaccades). ROIs were defined using the same procedure as for prosaccades. The resulting ROIs are displayed in Figure 2B. The magnitude of activation in each subject was calculated for prosaccades and antisaccades by separately averaging the regression coefficients for the two conditions over the voxels within the ROIs. The repeated measures GLM included two within-subject factors (the activation during prosaccades and during antisaccades in the ROIs for saccadic inhibition).

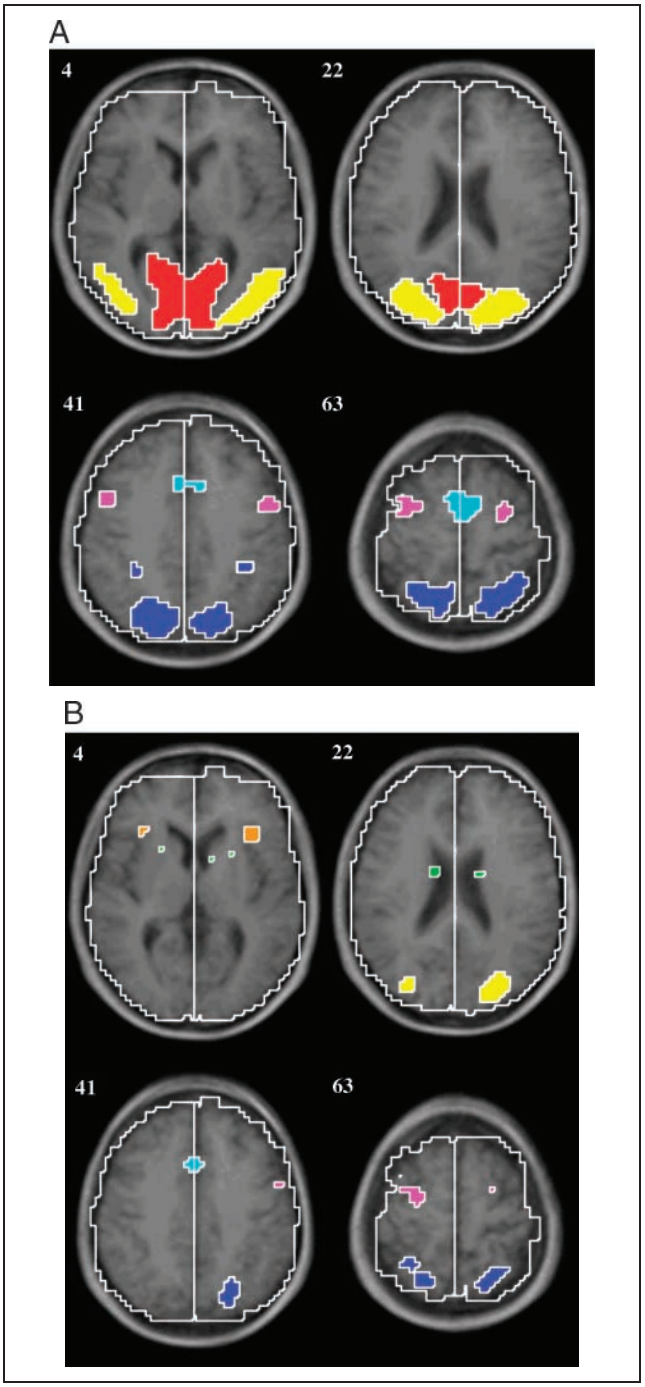

Figure 2. ROIs based on the voxels activated during prosaccades (A) and during saccadic inhibition (B) for all subjects ($z > 3.5$). ROIs are projected on an averaged anatomical image. The ROIs include V1&V2 (red), V5 (yellow), SPL&IPS (blue), FEF (purple), SEF (cyan), insula (orange), and the striatum (green). ROIs are separated for the right and left hemisphere for prosaccades, but not for saccadic inhibition. Talairach z coordinates are displayed on the top left of each slice.

RESULTS

Behavioral Results

Separate ANOVAs, with age (three groups) as an independent variable and the measures of task performance as the dependent variables, revealed no significant effect of age on saccade onset latencies during prosaccades, $F(2,28) = 1.54$; $p = .233$, nor during antisaccades, $F(2,28) = 1.98$; $p = .157$ (Table 1). The same was true

Table 1. Averages with Standard Deviations of the Behavioral Results

	Young Adults (n = 12)	*Mid Adults (n = 9)*	*Old Adults (n = 10)*
Reaction times (msec)			
Prosaccades	178.4 (18.3)	176.3 (32.5)	195.0 (27.9)
Antisaccades	250.4 (33.7)	245.6 (43.4)	281.8 (54.6)
Errors (%)			
Prosaccades	0.0 (0)	1.1 (2.1)	2.1 (4.0)
Antisaccades	24.9 (15.7)	24.2 (20.6)	35.7 (26.7)

for the effect of age on the error rates during prosaccades, $F(2,28) = 1.73$; $p = .196$, and during antisaccades, $F < 1$ (Table 1).

However, there was a near-significant correlation between age and the onset latencies of prosaccades ($r = .29$; $p = .055$ one tailed; effect size $d = .64$) and a moderate positive correlation between age and saccade onset latencies of antisaccades ($r = .34$; $p = .030$ one tailed; $d = .72$). The number of errors on prosaccade trials increased with age ($r = .35$; $p = .027$ one tailed; $d = .75$). We did not find a relationship between age and number of errors on antisaccade trials ($r = .21$; $p = .126$ one tailed; $d = .43$).

Brain Imaging Data

Voxel-based Analysis

For all fMRI analyses, group comparisons were based only on correct responses. To test whether brain activation was adequately measured, the group results for prosaccades were inspected. The task activated an extensive network of brain areas known to be involved in visual and oculomotor processing. These regions included extensive portions of the visual cortex, superior and inferior parietal areas, and the medial and lateral premotor cortex (Figure 2A). In the voxel-based analysis, we found no brain regions that exhibited a linear relationship between age and level of activation during correct prosaccades nor during correct saccadic inhibition at the significance threshold of $p < .05$ (corrected).

ROI Analysis

Prosaccades

Ten ROIs were derived from the group results for prosaccades. The ROIs included the combination of V1 and V2, an area within Brodmann's area 19 corresponding to V5, a combination of the superior parietal lobe and the intraparietal sulcus (SPL&IPS), the frontal eye fields (FEF), and the supplementary eye fields (SEF). These five regions were separated for the left and right hemisphere (Figure 2A). A multivariate repeated measures analysis of variance (ANOVA) of the prosaccade data, with region (10 levels) as a within-subject factor and age-group membership as between subject factor (3 levels), revealed a modest interaction effect between region and group, $F(18,42) = 1.86$; $p = .05$, indicating a difference between the groups in the distribution of activation across the ROIs. Subsequently, the group differences in anterior–posterior asymmetry were tested by contrasting activation in the frontal regions (FEF, SEF) to the posterior (V1&V2, V5, IPS&SPL) regions (average activity across ROIs) (Figure 3A). A one-way ANOVA revealed a significant effect of group, $F(2,28) = 3.93$; $p = .03$. Further tests indicated that this effect could be explained by relatively more posterior compared to frontal activation in young adults than in the two older groups, $t(30) = 2.31$; $p = .03$; $d = .88$. In addition, there was an effect of group, $F(2,28) = 6.52$; $p = .005$, indicating a difference between the groups in the average activation in all the ROIs. Using the post hoc Tukey Honestly Significant

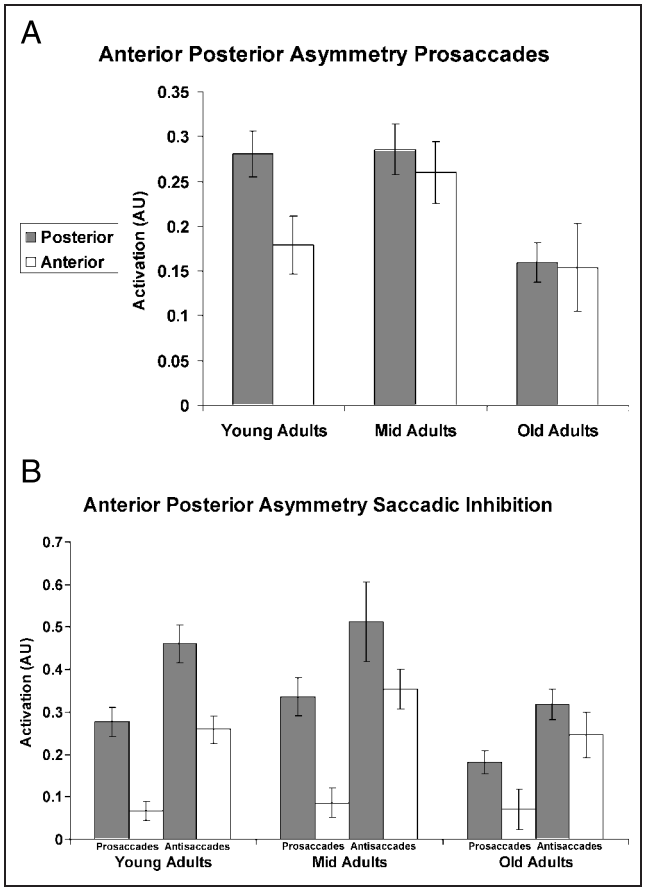

Figure 3. (A) Average activation during prosaccades in the posterior (V1&V2, V5, SPL&IPS) and the anterior (FEF&SEF) prosaccade ROIs in the three age groups. (B) Average activation during prosaccades and antisaccades in the posterior (V5, SPL&IPS) and anterior (FEF, SEF, striatum, insula) saccadic inhibition ROIs in the three age groups. Bars indicate standard errors.

Differences (HSD) method, we found that elderly subjects had lower overall activation than young adults ($p = .036$) and mid adults ($p = .005$) (Figure 4). To test whether this reduction could have arisen as a result of a difference in goodness of fit with the canonical Hemodynamic Response Function (HRF) between the groups, we correlated the averaged BOLD response over all the ROIs with the canonical HRF. The correlation was high for all three groups ($r = .99$ for young, $r = .97$ for mid, and $r = .96$ for old adults). The differences between these correlations are too small to explain the nearly 40% reduction in signal that was observed between old adults and the two younger groups. The use of ROIs and smoothing of the statistical maps could also have contributed to group differences due to effects of partial voluming. Therefore we reanalyzed the data without spatial smoothing and tested the average peak activations in the 10 ROIs between the groups. This also revealed a reduction in old adults compared to the two younger groups ($t = 2.46$; $p = .02$).

Saccadic Inhibition (Antisaccades vs. Prosaccades)

ROIs were also defined for the saccadic inhibition contrast (antisaccades vs. prosaccades). There was no activation in the V1&V2 region in this contrast. However, there was additional activation in the striatum and the anterior parts of the insula, making a total of six ROIs (Figure 2B). A repeated measures GLM was conducted to check for lateralization effects in these ROIs. As this test revealed no differences between the groups in hemispheric asymmetry for separate ROIs, $F(2,28) = 1.287$; $p = .263$, nor for all ROIs combined, ($F(2,28) = .195$; $p = .824$, we collapsed ROIs across hemispheres to increase statistical power of the GLM. The multivariate test for saccadic inhibition included task as an additional within-subject factor (two levels, i.e., prosaccades and antisaccades). Average regression coefficients were calculated for both correct prosaccades and correct antisaccades within the ROIs for saccadic inhibition. None of the interactions with group were significant, indicating that age did not significantly affect the distribution of activation. We also did not find any difference between the groups in the anterior–posterior asymmetry, that is, the difference between prosaccades and antisaccades in the contrast V5, SPL&IPS vs. FEF, SEF, striatum, and insula, $F(2,28) = .370$; $p = .694$ (Figure 3B). There was, however, a significant overall effect of group, $F(2,28) = 4.04$; $p = .02$. Post hoc tests using the Tukey HSD method revealed that activation in the mid adulthood group was higher in the saccadic inhibition areas than in the old adult group ($p = .023$).

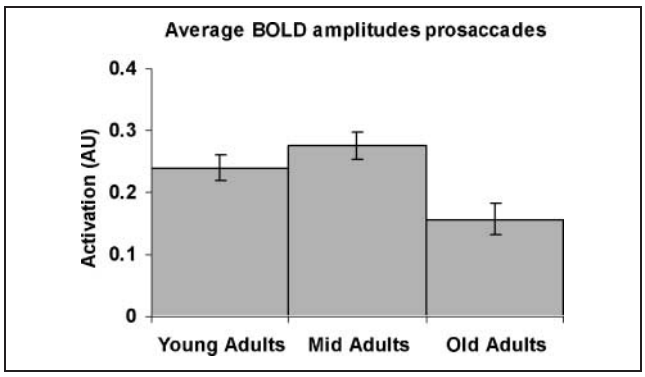

Figure 4. Average activation in all the prosaccade ROIs in the three groups. Bars indicate standard errors.

DISCUSSION

This study addressed effects of age on brain activation during the generation and suppression of saccadic eye movements. Behavioral results demonstrated a moderate increase in reaction times for both prosaccades and antisaccades with increasing age. The number of errors increased for prosaccades, but not for antisaccades. Analysis of the fMRI data acquired during generation of prosaccades demonstrated a (well-documented) network of visual and saccade-related brain areas (Raemaekers et al., 2002). Generation of antisaccades gave rise to additional signal increases in the FEF, SEF, PEF, striatum, anterior parts of the insula, and V5. An ROI analysis revealed that for prosaccades, the distribution of brain activation shifted with age. Old and mid adults demonstrated elevated activation in frontal brain areas relative to posterior brain areas as compared to young adults. This relative enhancement of frontal activation during prosaccades was accompanied by an overall attenuation of brain activation in old adults in comparison to the two younger groups. Mid adults exhibited higher levels of activation in the brain areas associated with saccadic inhibition during generation of prosaccades as well as antisaccades. There were no differences between the age groups in brain activity associated with saccadic inhibition.

The observed effects of age on behavioral measures of prosaccades and antisaccades are smaller than what has been reported in other studies (Klein et al., 2000; Olincy et al., 1997). This may be associated with circumstances that are specific to this experiment, namely, having to lie in an MRI scanner in darkness and with the loud noise generated by the scanner gradients, and the use of a long intertrial interval (13.4 sec). This may differentially affect individual performance, thereby increasing the standard deviations of the mean estimates of the groups. Alternatively, the inclusion criteria of this fMRI experiment may have been more stringent than for behavioral experiments, which would disproportionally affect the elderly group in the sense that they are overall healthier than in behavioral studies. With regard to performance differences on the antisaccade trials, it is not quite clear what we should have expected. Support for a behavioral saccadic inhibition deficit in elderly subjects is

equivocal, suggesting that the effect is rather small (see Sweeney et al., 2001; Klein et al., 2000; Nieuwenhuis et al., 2000; Butler et al., 1999; Olincy et al., 1997, and also Eenshuistra et al., 2004; Munoz et al., 1998; Fischer et al., 1997). Thus, elucidation of effects of age on saccade inhibition performance may require studies with large sample sizes to obtain adequate statistical power for the apparent small effect size.

The fMRI experiment demonstrated a shift in the anterior–posterior asymmetry from mid adulthood on (Cabeza, Anderson, Locantore, & McIntosh, 2002). More specifically, the FEF and SEF increased in activity relative to the regions in the occipital and parietal lobes. The FEF and SEF have been associated with more cognitively demanding eye movements such as antisaccades (Raemaekers et al., 2002; Muri et al., 1998; Sweeney et al., 1996)and newly learned sequences of saccades (Grosbras et al., 2001). Such an altered pattern of activation may therefore indicate compensatory processes or increased effort to maintain performance at least for a relatively simple task. Surprisingly, this shift towards frontal brain areas was not present for saccadic inhibition. It may be the case that increased compensatory frontal activation (with age) is not only present when cognitive demands are high, but also when the task is easy to perform. Even prosaccades may require more effort, or are executed in a more controlled manner, from mid adulthood on. The increased brain activation in saccadic-inhibition areas in mid adults may represent a similar process. As these brain areas represent a neuronal substrate of motor control, elevated activation towards mid adulthood in these areas could be indicative of increased reliance on controlled motor behavior.

In this study we did not find evidence for compensation through frontal hemispheric asymmetry reduction, but the oculomotor paradigm gave rise to little hemispheric asymmetry to begin with. It is still uncertain what the asymmetry reduction of the HAROLD model actually represents. Asymmetry could also be reduced as a result of a net increase in frontal activation in elderly subjects. Such a net increase may meet ceiling effects in the dominant, but not in the other hemisphere. Furthermore, it has been found for language that increasing the statistical threshold of the activation maps increases hemispheric asymmetry (Rutten, Ramsey, van Rijen, & van Veelen, 2002). Higher net activation could thus result in reduced hemispheric asymmetry.

The described effects of age on brain activity in essence reflect a reduced amplitude of the BOLD response following a saccade in old adults. Given that the amplitude can only be estimated with HRF functions, factors that affect the shape of the response could confound the results. However, we found that the amplitude reduction was not due to differences in shape of the BOLD response between the groups. We also show that the age effect is not due to partial voluming in the statistical maps, a potential confound that has been reported by others (Aizenstein et al., 2004). It is therefore likely that the effect of age indeed evidences an overall attenuation of activation. Others have also reported similar effects. Using a similar PRESTO technique, a negative correlation between age and the number of activated voxels in the motor cortex was found during a simple finger tapping task (Hesselmann et al., 2001). D'Esposito et al. (1999) have reported that younger subjects demonstrated more than four times the number of suprathreshold voxels in the primary sensory motor cortex compared to elderly subjects during a simple motor reaction time task. Similar observations have been reported for visual processing during checkerboard presentation (Huettel et al., 2001) and perception of emotional faces (Iidaka et al., 2002).

The origin of the observed global reductions in fMRI signal remains unclear as yet. A number of possible causes may constitute such a global attenuation of fMRI signal change. First, loss of neural tissue may explain a part of the reduction, as there is evidence for cerebral atrophy in normal aging (Aizenstein et al., 2004; Scahill et al., 2003; Ge et al., 2002). Tissue loss may place a ceiling on the total amount of neural activation. However, considering the magnitude of the reduction in the fMRI signal we observed, it is unlikely it can be explained by loss of neural tissue only. Second, a reduction in total cerebral blood flow may play a role. There are several indications provided by other studies that support this notion. For instance, a reduction of nearly 40% in total cerebral blood flow has been reported in aging subjects (80–88 years) as compared to young adults (19–29 years) using ungated two-dimensional phase-contrast MR angiography (Buijs et al., 1998). Smaller reductions have been reported using single-photon emission tomography (Larsson et al., 2001). That reduced Cerebral Blood Flow (CBF) in the elderly may indeed attenuate the BOLD response is demonstrated by a reduced increase in total hemoglobin during finger tapping, measured over the motor cortex with a combination of fMRI and near-infrared spectroscopy. In that study, corresponding fMRI images showed smaller areas of cortical activation in elderly subjects (Mehagnoul-Schipper et al., 2002). Third, the cerebrovascular response to metabolic demands may be reduced due to arteriosclerotic changes such as reduced elasticity and compliance of vessels, which attenuate the dynamic range of vascular reactivity in elderly subjects (D'Esposito, Deouell, & Gazzaley, 2003). Fourth, neural activity may be reduced in elderly for instance by reduced motivation. Our results do not support this, given that there were no differences in compliance or performance between the age groups. Furthermore, one would expect similar levels of neural activity at least in the brain regions that are involved in stimulus perception, such as V1 and V2, but these regions also showed a marked reduction in fMRI signal. Nevertheless, theoretically they may process stimuli in a more efficient

manner. In summary, there is indirect evidence from multiple studies to indicate that aging may be accompanied by a change in cerebrovascular dynamics that, in turn, may affect the BOLD response. Whether such changes actually affect the neuronal–vascular coupling is yet unclear. Direct proof can only be obtained with an experiment where neuronal activity is measured and quantified directly, and is then compared to fMRI measures of hemodynamics. Obviously, this cannot be achieved with fMRI only, where behavioral output is the only available estimate of neural activity.

As in all cross-sectional studies, the results of this study could be confounded by group differences that result from historical influences such as educational opportunity, cultural factors, and socioeconomic status. Unfortunately, it is very difficult to control for these factors adequately, and they tend to result in overestimation of the age-related differences between groups (Hedden & Gabrieli, 2004). Differences in intellectual ability between the groups could have arisen due to these factors. However, the significance of this for our study is not clear, given that intellectual ability does not affect saccadic reaction times and only moderately influences the number of errors during antisaccades (Evdokimidis et al., 2002). Differences in the number of errors were further controlled for by the use of event-related fMRI and analysis of correct responses only. Another issue is the possible incidence of mild cognitive impairment (MCI) or early dementia in the old adulthood group. Although all subjects clearly understood task instructions and performance was not severely impaired, the possibility remains that a few affected subjects in the elderly group caused the differences between the groups in behavioral and fMRI results. As yet, it is not known how MCI affects oculomotor functioning, but there is evidence that impaired saccadic inhibition is the most specific oculomotor measure for Alzheimer's disease (Shafiq-Antonacci, Maruff, Masters, & Currie, 2003). Nevertheless, although the impairment in saccade inhibition in the elderly group in this study was mild at best, influences of MCI on fMRI results cannot be ruled out.

In summary, our study suggests that changes in brain function occur during aging even in the execution of simple eye movements. These changes appear to start during mid adulthood and involve relative increases in activation in frontal brain areas of the oculomotor system. This increase does not appear to be specific for one particular oculomotor task. In addition, we argue that neuronal–vascular coupling may be altered in elderly subjects, although the present study does not provide direct evidence for this notion. Future studies are therefore warranted to further explore the influences of age-related changes in vascular dynamics on the BOLD signal and to subsequently develop techniques to account for these effects when comparing fMRI activation in subjects of different ages.

Acknowledgments

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The data reported in this experiment have been deposited with the fMRI Data Center (www.fmridc.org). The accession number is 2-2005-1208X.

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