ACADEMIC PRESS

Available online at www.sciencedirect.com
SCIENCE DIRECT®

NeuroImage

NeuroImage 19 (2003) 555–564

www.elsevier.com/locate/ynimg

Age dependency of the hemodynamic response as measured by functional near-infrared spectroscopy

Matthias L. Schroeter,* Stefan Zysset, Frithjof Kruggel, and D. Yves von Cramon

Max-Planck-Institute of Cognitive Neuroscience, Stephanstrasse 1A, 04103 Leipzig, Germany

Received 30 October 2002; revised 5 February 2003; accepted 3 March 2003

Abstract

Aging reduces cerebral blood flow in association cortices during rest. However, the influence of age on functional brain activation is still controversial. The aim of our study was to examine age dependency of brain activation in primary and association cortices. Therefore, changes in the concentration of oxy- and deoxyhemoglobin as well as changes in the redox state of cytochrome-c-oxidase (Cyt-Ox) were measured by functional near-infrared spectroscopy (fNIRS) in the lateral prefrontal and motor cortices during an event-related Stroop interference task. Fourteen young (23.9 ± 3.1 years old) and 14 elderly subjects (65.1 ± 3.1) participated in the study. Data revealed two effects of aging on brain activation: (1) Elderly and young subjects used the lateral prefrontal cortex to cope with interference during the Stroop task. In young subjects, the vascular response was higher during incongruent than neutral trials in the entire examined lateral prefrontal cortex. However, in the elderly, all lateral prefrontal regions showed a hemodynamic response but not necessarily a specific interference effect. (2) The hemodynamic response was reduced in elderly subjects in the lateral prefrontal association cortex, but obviously not in the motor cortex. We propose that calculating effect sizes is the only reliable approach to analyze age-related effects in fNIRS studies, because they are independent from the assumed differential pathlength factor. In summary, our findings suggest that aging decreases the hemodynamic response in the frontal association cortex during functional activation, omitting the primary motor cortex.

Keywords: Aging; Near-infrared spectroscopy; Stroop

Introduction

Recent studies reported altered cerebral blood flow (CBF) in elderly in comparison with young adults. During rest, regional CBF decreases with advancing age in both association and limbic cortex as shown by positron emission tomography (PET) (Martin et al., 1991) and single-photon emission computed tomography (SPECT) (Nakano et al., 2000) (age ranges 30–85 and 18–87 years, respectively). Further, in functional magnetic resonance imaging (fMRI) studies, fewer voxels were activated in elderly (>60 years) in comparison with young adults (<40 years) during a motor task (Mehagnoul-Schipper et al., 2002), a simple reaction time task (D'Esposito et al., 1999), and visual stimulation (Huettel et al., 2001). However, the amplitude of the hemodynamic response was equal in both age groups. Two fMRI studies (Ross et al., 1997; Buckner et al., 2000) demonstrated that the amplitude is reduced in elderly (mean 75 years) compared to young subjects (mean 24 and 21 years, respectively) during visual stimulation. Mehagnoul-Schipper et al. (2002) showed by functional near-infrared spectroscopy (fNIRS) that oxy-hemoglobin (Hb) increased less and de-oxy-Hb decreased less during finger tapping in elderly compared with young adults, which was in agreement with the smaller number of activated voxels as shown by simultaneous fMRI. Hock et al. (1995) demonstrated by fNIRS that oxy- and total Hb increased less in the anterior frontolateral cortex of elderly (mean 52 years) compared with young subjects (mean 28 years) during a calculation task,

* Corresponding author. Max-Planck-Institute of Cognitive Neuroscience, Stephanstrasse 1A, 04103 Leipzig, Germany. Fax: +49-341-99-40-221.
E-mail address: schroet@cns.mpg.de (M.L. Schroeter).

1053-8119/03/$ – see front matter © 2003 Elsevier Science (USA). All rights reserved.
doi:10.1016/S1053-8119(03)00155-1

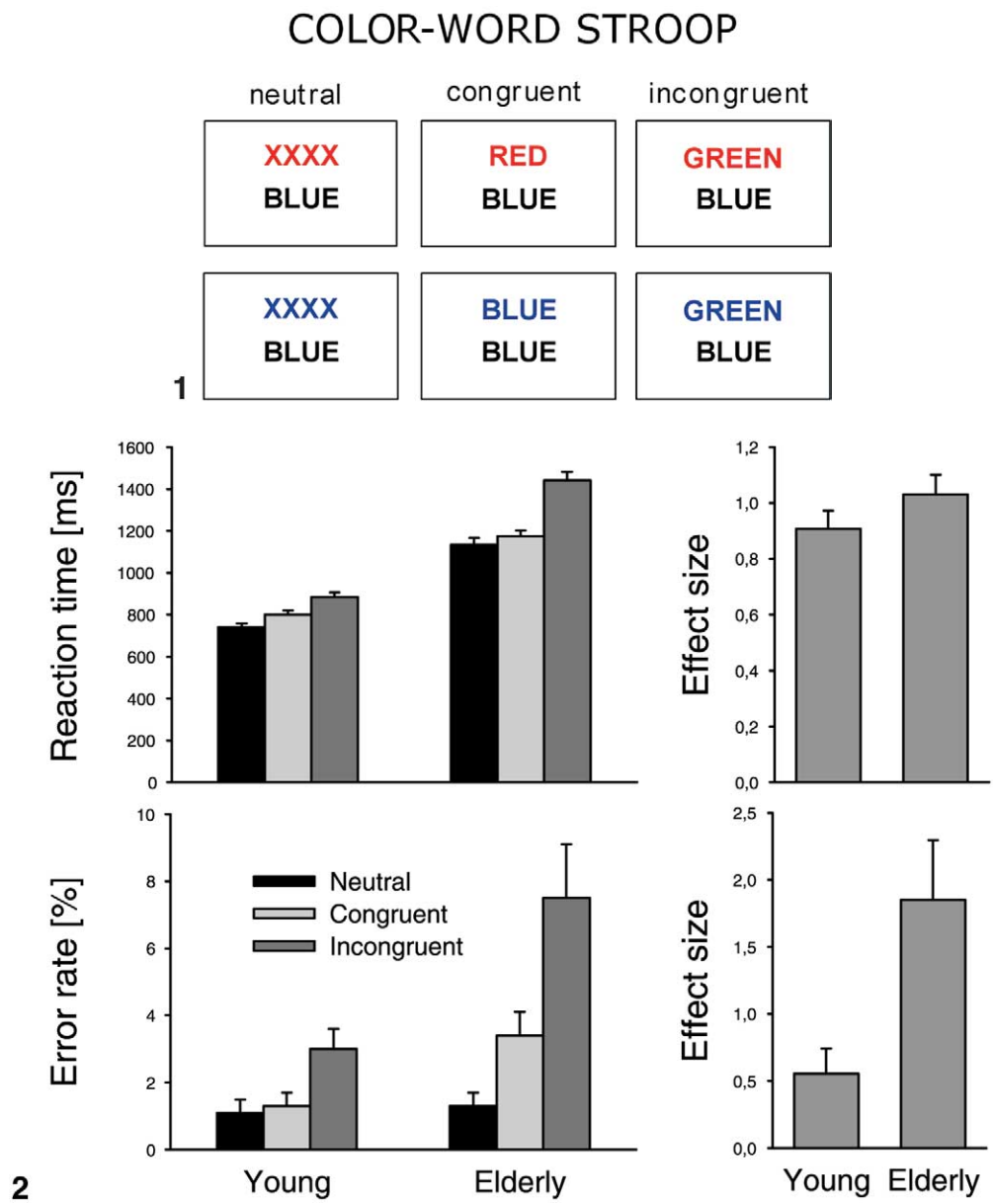

Fig. 1. Examples of single trials for the neutral, congruent, and incongruent condition of the color-word matching Stroop task. "Does the color of the upper word correspond with the meaning of the lower word?" For the top three examples, the correct answer would be "NO"; for the bottom three examples, the correct answer would be "YES" (according to Zysset et al., 2001).

Fig. 2. Reaction time, error rate, and effect size of the Stroop interference effect (incongruent vs. neutral condition), averaged over all young and elderly subjects. Mean ± SEM.

although they did not correct for the age dependency of the differential pathlength factor (DPF) (Duncan et al., 1996).

The aim of our study was to investigate the age dependency of brain activation in primary and association cortices. fNIRS is particularly appropriate to examine brain function in elderly people, because it is relatively insensitive to movement artifacts in comparison with other imaging methods, such as fMRI. Therefore, changes in the concentration of oxy- and deoxy-Hb as well as changes in the redox state of cytochrome-c-oxidase (Cyt-Ox) were measured by fNIRS in the lateral prefrontal cortex during performance of an event-related Stroop task (Stroop, 1935; color-word matching Stroop task modified according to Zysset et al., 2001). Moreover, we examined age dependency of brain activation in the motor cortex.

Materials and methods

Subjects

Fourteen young (mean age 23.9 ± 3.1 years, range 19–29 years; 8 women) and 14 elderly subjects (65.1 ± 3.1

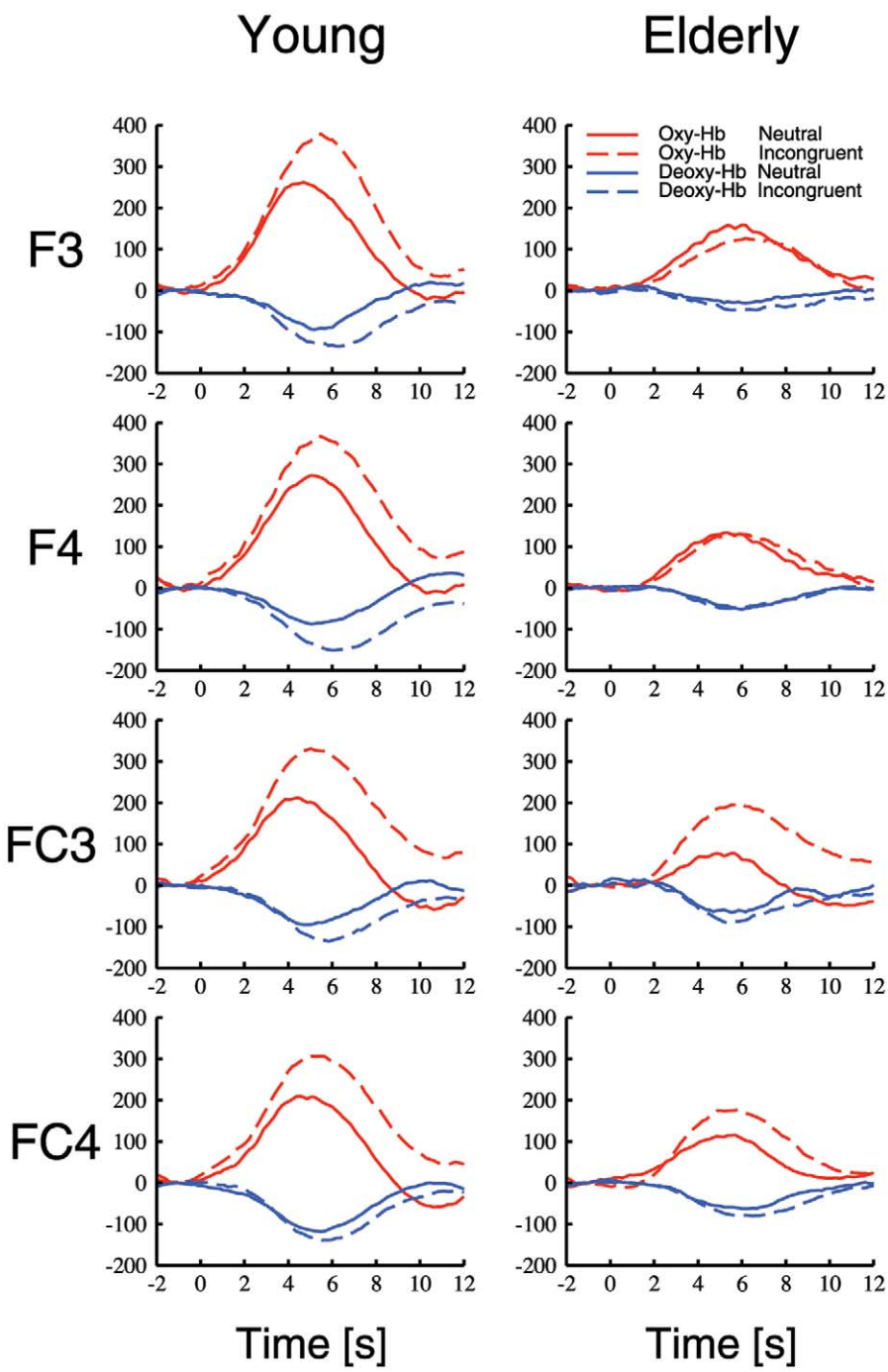

Fig. 3. Time courses for concentrations of oxy- and deoxy-hemoglobin (Hb) in nM in the dorsolateral prefrontal cortex (F3/4 and FC3/4) during the neutral and incongruent conditions of the Stroop task. The Stroop task started at 0 s. Average across 14 young and elderly subjects. Running averages over 2 s.

years, range 62–71 years, 7 women) participated in the study. Written informed consent was obtained from all subjects after complete description of the study prior to the session. The research protocol was approved by the ethics committee of the University of Leipzig and was in accordance with the latest version of the Declaration of Helsinki. All subjects had normal or corrected-to-normal vision and normal color vision, were native German speakers, and were right-handed. No subject had a history of neurological or psychiatric disorder. Subjects were not under any psychotropic medication.

Data acquisition by fNIRS

Changes in the concentration of oxy- and deoxy-Hb as well as the redox state of the Cyt-Ox were measured by a NIRO-300 spectrometer (Hamamatsu Photonics K.K.) and are expressed in nM. Values were calculated according to

Cope and Delpy (1988). Moreover, we calculated changes in the concentration of total Hb (sum of oxy- and deoxy-Hb) and hemoglobin difference (HbD; oxy- minus deoxy-Hb) as a measure for changes in cerebral blood volume (CBV) and CBF, respectively (Tsuji et al., 1998). Two channels were measured at a sampling frequency of 6 Hz in reflection mode. The emitter–detector spacing was 4 or 5 cm, depending on specific light attenuation and allowing a depth penetration of approximately 2 cm (Villringer and Chance, 1997). It is known from literature that the DPF is age-dependent (Duncan et al., 1996). Accordingly, the DPF was calculated by the formula $5.13 + 0.07(\text{age}^{0.81})$ in the young subjects. Precise formulas for the DPF in subjects over 50 years of age are currently unknown. Therefore, we set the DPF to 6.79 in the elderly, representing the DPF of the oldest age group examined by Duncan et al. (1996). For all experiments, subjects were seated in an electroencephalography chair in a quiet dimmed room. The probes were protected from ambient light by black cloth.

Psychophysical procedures and data analysis

The color-word matching Stroop task (Stroop, 1935; Treisman and Fearnley, 1969; modified according to Zysset et al., 2001; Schroeter et al., 2002) was used in an event-related version. Two rows of letters appeared on the screen and subjects were instructed to decide whether the color of the top row letters corresponded to the color name written in the bottom row (Fig. 1). Response was given by a button press with the index (YES response) and middle (NO response) fingers of the right hand. During neutral trials, the letters in the top row were "XXXX" displayed in red, green, blue, or yellow, and the bottom row consisted of the color words "RED," "GREEN," "BLUE," and "YELLOW" shown in black. For congruent trials, the top row consisted of the color words "RED," "GREEN," "BLUE," and "YELLOW" printed in the congruent color. For the incongruent condition, the color word was displayed in a different color to produce interference between color word and color name. To shift visual attention to the top word, it was presented 100 ms before the bottom word (MacLeod, 1991). In half of the trials in all conditions the color in the top row corresponded to the color name of the bottom row. An experimental run consisted of 30 trials (10 neutral, 10 congruent, and 10 incongruent trials) in random order with an interstimulus interval of 12 s. Words remained on the screen until the response was given with a maximum time of 2 s. The screen was blank between the trials.

Optodes were placed symmetrically over the lateral prefrontal cortex (F7/8, F3/4, and FC3/4 of the international 10/20 system), intraparietal sulcus (P3/4), primary visual cortex (O1/2), and motor cortex (C3/4) (Fig. 4; Homan et al., 1987; Steinmetz et al., 1989). An experimental run was carried out at each position (total time of 36 min). The order of the different positions was counterbalanced. For some subjects and positions a signal could not be obtained because of strong light attenuation (at C3/4 for one elderly subject and at P3/4 for one young and one elderly subject). Data at O1/2 were not analyzed because differences between the conditions of the Stroop task were not expected (Schroeter et al., 2002). Artifacts owing to swallowing and movements were removed manually in the elderly subjects before data analysis. Thereafter, the mean of the signal intensity during the "baseline" (2 s before trial onset) and the "vascular response" (3–8 s after trial onset) was calculated for each subject, condition, and position. The interval from 3 to 8 s after the stimulus was chosen because the vascular response occurred during this interval in all conditions of the Stroop task (Fig. 3). Differences between the mean of the "vascular response" and the "baseline" revealed a measure of the hemodynamic response for every condition. Thereafter, the incongruent condition was compared with the congruent and neutral one by paired Student's t tests for both age groups separately. At positions C3/4, the differences between the "vascular response" and the "baseline" were compared between C3 and C4 with a paired Student's t test.

Because the DPF is unknown in subjects over 50 years of age and because of methodological advantages (see Discussion), we compared effect sizes for behavioral and hemodynamic results between young and elderly subjects additionally to concentration changes of the chromophores. Effect sizes were calculated according to Winer et al. (1991) as the difference of the means of two experimental conditions divided by the standard deviation of the control condition:

$$d = (m_1 - m_2)/s.$$

Accordingly, m_1 and m_2 are the mean signal strengths during the incongruent and neutral conditions and s is the standard deviation of the neutral condition. For the motor cortex (C3/4), we calculated the effect size of the motor response. Thus, m_1 and m_2 are the mean signal strengths on the left and right sides, and s is the standard deviation on the right side. Because both the numerator and the denominator in the formula contain the same (age-dependent) DPF as a factor, it may be canceled. Therefore, effect sizes are independent from the assumed DPF. Results are generally given as mean ± standard deviation (SD), if not stated otherwise.

Results

Behavioral results

Fig. 2 illustrates the behavioral results of the Stroop task. With respect to reaction time, a repeated-measure condition (neutral vs. congruent vs. incongruent) × age (young vs. elderly) ANOVA demonstrated a significant effect for condition ($F = 208.09$, $df = 2$, $P < 0.001$), age ($F = 139.05$, $df = 1$, $P < 0.001$), and condition × age interaction ($F = 38.27$, $df = 2$, $P < 0.001$). The mean reaction time was

Table 1
Comparison of the hemodynamic response (nM) in the left and right motor cortices of the elderly subjects during the Stroop task

Chromophore	Left motor cortex	Right motor cortex	Significance[a]
Oxy-Hb	123.2 ± 97	102.7 ± 115	$P < 0.05$
Deoxy-Hb	−48.2 ± 43	−32.5 ± 37	$P < 0.01$
Total Hb	75 ± 90	70.2 ± 106	n.s.
HbD	171.3 ± 120	135.3 ± 134	$P < 0.02$
Cyt-Ox	1.7 ± 10	1.5 ± 9	n.s.

Note. Response to trials was carried out by button press with the right hand.

[a] One-tailed paired Student's *t* test left versus right motor cortex. Hb, hemoglobin; HbD, hemoglobin difference; Cyt-Ox, cytochrome *c* oxidase. Mean ± SD of all three conditions of the Stroop task.

significantly longer in the incongruent compared with the congruent and neutral condition in both age groups ($P < 0.001$; one-tailed paired Student's *t* test). Elderly subjects reacted more slowly than young subjects during all conditions ($P < 0.001$). Concerning error rates (percentage of all respective trials), the repeated-measure condition × age ANOVA showed a significant effect for condition ($F = 17.67$, $df = 2$, $P < 0.001$), age ($F = 8.52$, $df = 1$, $P < 0.005$), and condition × age interaction ($F = 4.56$, $df = 2$, $P < 0.05$). Mean error rates were significantly higher in both age groups in the incongruent condition, when compared with the congruent and neutral ones ($P < 0.01$; one-tailed paired Student's *t* test). Further, elderly subjects made more errors than younger ones in the incongruent and congruent condition ($P < 0.01$), whereas there was no difference during the neutral condition ($P > 0.05$). In summary, behavioral results of the Stroop task are in accordance with the literature (MacLeod, 1991), as demonstrated by a clear interference effect for young (142 ms) and elderly subjects (307 ms). Verhaeghen and De Meersman (1998) demonstrated that the age sensitivity of the Stroop interference effect is an artifact of general slowing. Therefore, behavioral effect sizes were compared between young and elderly subjects (Fig. 2). Effect size of error rates was higher in the elderly subjects ($P < 0.01$; one-tailed paired Student's *t* test), whereas there was no significant difference for effect size of reaction time ($P > 0.05$). Thus, results concerning reaction times are in accordance with Verhaeghen and De Meersman (1998).

fNIRS results

As subjects responded during the Stroop task with the right index or middle finger, there was a significantly stronger vascular response in the left (C3) in comparison with the right motor cortex (C4) in elderly subjects (Table 1). Accordingly, the concentration of deoxy-Hb decreased more, whereas the concentration of oxy-Hb and HbD increased more on the left than on the right side. There were no significant differences for Cyt-Ox and total Hb. Thus, a stronger vascular response was found in the contralateral primary motor cortex during the response with the index or middle finger, in agreement with results in young subjects (Schroeter et al., 2002).

Fig. 3 illustrates the time courses for oxy- and deoxy-Hb in the lateral prefrontal cortex (F3/4 and FC3/4) of young and elderly subjects. Generally, oxy-Hb increased and deoxy-Hb decreased during the Stroop task, although the hemodynamic response was diminished in elderly subjects. To quantify this age effect we compared the mean vascular response (mean of all trials of the Stroop task) for the different optode positions. As illustrated in Table 2, the mean hemodynamic response was higher in young subjects at FC3/4, C3/4, and P3/4. At F3/4, values were also higher for young adults, although the difference was not significant. In contrast, oxy-Hb and HbD were higher in elderly subjects than in young subjects at F7/8. Interestingly, el-

Table 2
The mean hemodynamic response (nM) at the different optode positions during the Stroop task in comparison between young and elderly adults

	F7/8	F3/4	FC3/4	C3/4	P3/4
Oxy-Hb					
Young	4 ± 149	216.6 ± 256	228.7 ± 164	228.5 ± 229	189.9 ± 232
Elderly	43.9 ± 101*	110.6 ± 116	107.4 ± 141***	112.9 ± 106***	111.1 ± 148*
Deoxy-Hb					
Young	−18 ± 72	−66.9 ± 112	−95.8 ± 67	−55.8 ± 61	−5.4 ± 46
Elderly	−22.5 ± 39	−35.7 ± 50	−57.2 ± 56***	−40.4 ± 41(*)	−14.1 ± 36
Total Hb					
Young	−14 ± 181	149.6 ± 172	132.9 ± 143	172.7 ± 239	184.6 ± 240
Elderly	21.3 ± 104	74.7 ± 108	50.3 ± 111***	72.6 ± 98**	97.1 ± 160**
HbD					
Young	22 ± 149	283.5 ± 355	324.5 ± 206	284.2 ± 234	195.3 ± 233
Elderly	66.4 ± 111*	146.4 ± 143	164.6 ± 183***	153.3 ± 128***	125.2 ± 145*
Cyt-Ox					
Young	0.8 ± 14	3.2 ± 12	−2.3 ± 16	−9.5 ± 32	−15.2 ± 30
Elderly	−2 ± 12	−2.7 ± 13	1.4 ± 12(*)	1.6 ± 9**	0 ± 12***

Note. (*)$P < 0.1$ ("trend"), *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; two-tailed unpaired Student's *t* test elderly vs. young adults. Hb, hemoglobin; HbD, hemoglobin difference; Cyt-Ox, cytochrome *c* oxidase. Mean ± SD of all trials.

Table 3
The hemodynamic response (nM) in comparison between the three conditions of the Stroop-task in the elderly subjects

Position	Chromophore	Hemodynamic response (Mean ± SD)			Incongruent vs. congruent	Incongruent vs. neutral
		Neutral	Congruent	Incongruent		
F7	Oxy-Hb	59.2 ± 90	40.4 ± 122	71.5 ± 121	n.s.	n.s.
	Deoxy-Hb	−16.5 ± 48	−19.3 ± 50	−37.4 ± 37	(*)	*
	Total Hb	42.8 ± 90	21 ± 121	33.9 ± 130	n.s.	n.s.
	HbD	75.6 ± 113	59.7 ± 141	108.9 ± 123	*	n.s.
F8	Oxy-Hb	25.7 ± 87	13.8 ± 102	52.9 ± 82	(*)	n.s.
	Deoxy-Hb	−15.3 ± 30	−18.2 ± 30	−28.6 ± 33	n.s.	*
	Total Hb	10.3 ± 90	−4.4 ± 105	24.2 ± 94	n.s.	n.s.
	HbD	41 ± 93	32 ± 108	81.5 ± 82	*	(*)
FC3	Oxy-Hb	52.3 ± 146	100 ± 146	166.4 ± 140	(*)	**
	Deoxy-Hb	−49 ± 54	−54.4 ± 65	−66 ± 57	n.s.	n.s.
	Total Hb	3.2 ± 125	45.5 ± 124	100.5 ± 106	*	*
	HbD	101.2 ± 182	154.4 ± 190	232.4 ± 185	(*)	**
FC4	Oxy-Hb	90 ± 129	85.9 ± 141	150 ± 134	(*)	*
	Deoxy-Hb	−50.7 ± 45	−59 ± 48	−64 ± 71	n.s.	n.s.
	Total Hb	39.2 ± 95	27.1 ± 112	85.9 ± 89	(*)	*
	HbD	140.6 ± 168	144.9 ± 178	214 ± 195	n.s.	(*)

Note. (*)$P < 0.1$ ("trend"), *$P < 0.05$; **$P < 0.01$; n.s., not significant; one-tailed paired Student's t test. Hb, hemoglobin; HbD, hemoglobin difference.

derly subjects showed higher changes in the redox state of Cyt-Ox compared to young adults at C3/4 and P3/4 and a trend at FC3/4 ($P < 0.1$).

As shown in Fig. 3, incongruent trials led to a stronger vascular response than neutral trials at F3/4 in the young adults and at FC3/4 for both age groups. However, the hemodynamic response showed no difference between the incongruent and neutral condition at F3/4 in elderly sub-

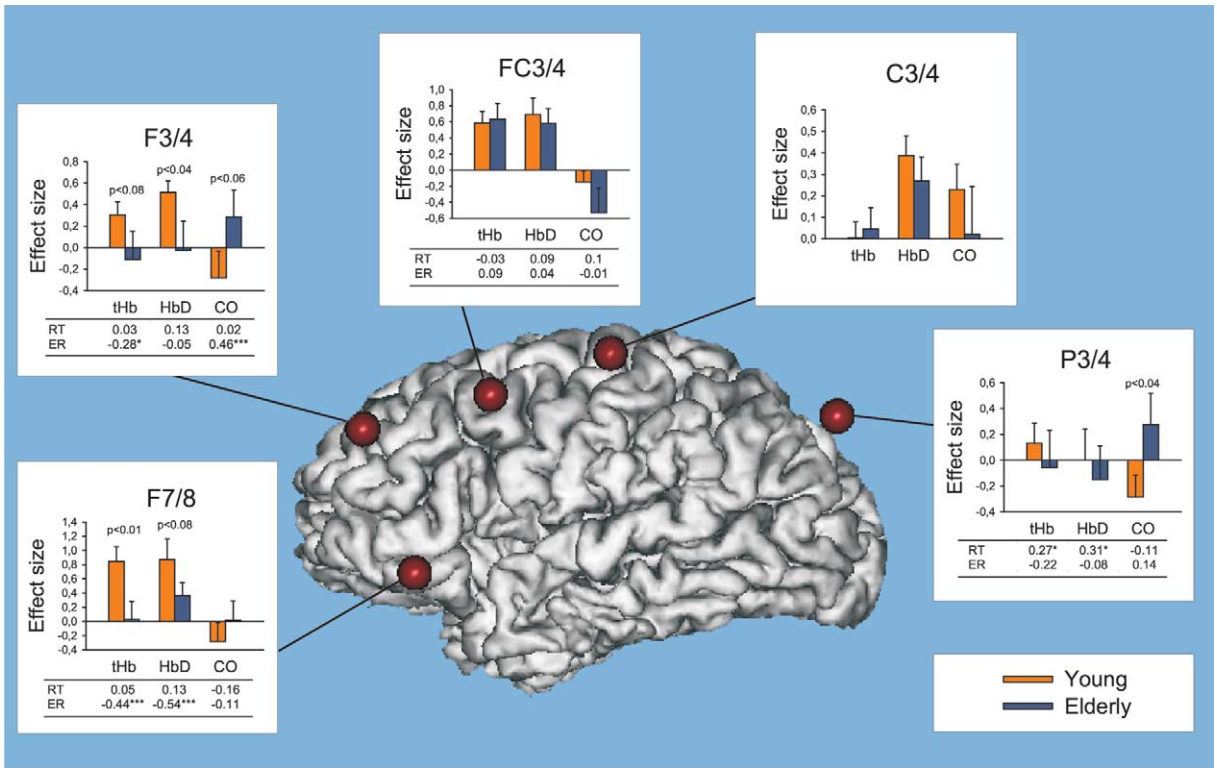

Fig. 4. Effect sizes of total hemoglobin (tHb), hemoglobin difference (HbD), and cytochrome c oxidase (CO) compared between young and elderly subjects for the different optode positions during the Stroop task. Mean ± SEM, including data from the right and left side, respectively. One-tailed unpaired Student's t test. Spearman correlation coefficients are reported for correlation between hemodynamic (tHb/HbD/CO) and behavioral effect sizes (reaction time [RT], and error rate in percent [ER]; one-tailed P). *$P < 0.05$, ***$P < 0.001$. Red spheres correspond with optode positions mapped onto a reference brain (Schroeter et al., 2002).

jects. Table 3 illustrates the results for the elderly subjects, when the hemodynamic response was compared between the three conditions of the Stroop task quantitatively. Incongruent trials led to a stronger vascular response than neutral trials, corresponding to a stronger brain activation owing to interference at FC3/4 and F7/8 in the elderly subjects (Villringer and Dirnagl, 1995; Gratton et al., 2001). At F3/4 and P3/4, changes in the concentration of oxy-Hb, deoxy-Hb, total Hb, and HbD did not differ between the neutral, congruent, and incongruent conditions in the elderly subjects (data not shown). Regarding Cyt-Ox in elderly subjects, incongruent trials led to a stronger increase in the redox state of Cyt-Ox compared with neutral trials at P3 (1.6 ± 8 vs. -7.4 ± 11 nM; $P < 0.01$) and F4 (2.7 ± 9 vs. -2.7 ± 13 nM; $P < 0.08$; one-tailed paired Student's t test), which was not the case for the other optode positions.

Summarizing our findings, the Stroop task led to a reduced mean change of the vascular response (oxy-Hb, deoxy-Hb, total Hb, and HbD) in elderly in comparison with young subjects in almost all measured positions. In contrast, the mean change of Cyt-Ox was higher in elderly than young subjects. Although elderly subjects used a lateral prefrontal network like young adults (F3/4, F7/8, FC3/4) to cope with interference, brain activation was higher during incongruent trials than in neutral trials in the elderly at F7/8 and FC3/4 only. In young subjects, this higher activation during incongruent trials was found at all examined prefrontal positions (Schroeter et al., 2002). In contrast to elderly subjects, differences between the three conditions of the Stroop task were generally not found for Cyt-Ox in young adults (Schroeter et al., 2002).

In addition to the calculated concentration changes of the chromophores, we compared age-independent effect sizes for the hemodynamic responses (total Hb and HbD) and changes in Cyt-Ox during the Stroop task between young and elderly subjects. Calculation of effect sizes included data from the right and left sides, because the vascular response was roughly symmetrical during the Stroop task (Fig. 3, Table 3; no significant differences between left and right sides except for FC3/4, where the effect size was higher on the left side than on the right side in young and elderly subjects; total Hb $P < 0.05$, HbD $P < 0.01$, two-tailed paired Student's t test). We hypothesized a smaller vascular response in elderly compared with young subjects (Hock et al., 1995; Mehagnoul-Schipper et al., 2002). Accordingly, as illustrated in Fig. 4, effect sizes for total Hb and HbD were reduced in elderly subjects in comparison with young subjects at F3/4 and F7/8 above the lateral prefrontal cortex. There were no age-related differences at FC3/4, the lateral parietal cortex (P3/4), and the primary motor cortex (C3/4). Thus, it may be concluded that CBV and CBF were specifically reduced at F3/4 and F7/8 above the lateral prefrontal cortex of elderly compared to young subjects (Tsuji et al., 1998). Interestingly, effect sizes for Cyt-Ox were higher for elderly subjects compared to young subjects at P3/4 and tended to be higher at F3/4.

So far we have shown that age significantly affects effect sizes of the Stroop task concerning either the hemodynamic response or behavioral data. If changes in CBF and CBV at F3/4 and F7/8 are specific for the Stroop task, one may assume that behavioral effect sizes (reaction time and error rate) are correlated with the calculated hemodynamic effect sizes. Accordingly (Fig. 4), effect size of error rate was negatively correlated with hemodynamic effect sizes (tHb at F3/4; tHb and HbD at F7/8) and positively correlated with effect size of Cyt-Ox (F3/4) in the lateral prefrontal cortex. Moreover, effect size of reaction time was positively correlated with hemodynamic effect sizes at P3/4 (tHb and HbD).

Discussion

In both young and elderly subjects, the lateral prefrontal cortex was involved in coping with interference during the Stroop task. Thus, our data are in accordance with fMRI (Banich et al., 2000; Carter et al., 2000; Leung et al., 2000; Zysset et al., 2001; Milham et al., 2002; Fan et al., 2003) and PET studies (George et al., 1994; Carter et al., 1995; Taylor et al., 1997). Some of these studies reported also activations in the anterior cingulate cortex owing to interference, which might not be examined by fNIRS because of limited depth penetration (Villringer and Chance, 1997). Therefore, we selected a color-word matching Stroop task that did not activate this brain region (Zysset et al., 2001). In elderly subjects the incongruent condition resulted in a higher hemodynamic response than the neutral one at F7/8 and FC3/4 only, whereas the young subjects showed the interference effect additionally at F3/4 (Schroeter et al., 2002). Our analysis of hemodynamic effect sizes shows that CBF and CBV are specifically reduced in the lateral prefrontal cortex (F3/4 and F7/8) of elderly subjects compared to young subjects during the Stroop task. These data are in agreement with PET, SPECT, and fMRI studies reporting altered CBF in elderly adults in comparison with young adults. Martin et al. (1991) and Nakano et al. (2000) found a reduction of regional CBF in association and limbic cortices with advanced age during rest by PET and SPECT. We show that age reduces CBF in the prefrontal association cortex, whereas it is unaltered in the primary motor cortex. Kawahata et al. (1997) and Slosman et al. (2001) demonstrated by SPECT a decrease in global CBF with aging during rest (age range 50–99 and 18–71 years, respectively). However, this effect resolved after correction for partial-volume effects from cerebral atrophy (Meltzer et al., 2000; age range 19–76 years). In accordance with Kawahata et al. (1997) and Slosman et al. (2001) we found that mean vascular response were smaller in elderly subjects in comparison with young subjects at most of the examined optode positions. Analyzing effect sizes resolved this effect for P3/4 (lateral parietal), C3/4 (motor), and FC3/4 (prefrontal cortex, roughly on the border to the premotor cortex;

Fig. 4), whereas the effect was confirmed for F3/4 and F7/8 above the lateral prefrontal cortex. Thus, our data may support the assumption that a reduction in CBF with aging is regionally limited and not a global phenomenon. The negative correlation between the effect size of error rate and hemodynamic response in the lateral prefrontal cortex in our study may support the specificity of the aging effect. Interestingly, Raz et al. (1997) reported a substantial decline in prefrontal gray matter volume in subjects from 18 to 77 years of age, in contrast to the precentral (primary motor) cortex and the pericalcarine (primary visual) cortex. Tisserand et al. (2002) confirmed these results and located the decline particularly to the lateral and orbital frontal gray matter in subjects from 21 to 81 years of age. Further, dendrites of pyramidal layer V neurons start to shrink in the prefrontal cortex from the fifth decade onward (de Brabander et al., 1998). These alterations were described for Brodmann areas 9 and 46, which are roughly located beneath the optode positions F3/4 and F7/8 (Homan et al., 1987; Steinmetz et al., 1989). Thus, reductions of CBF and CBV in the lateral prefrontal cortex as found in our study might be caused by this region-specific decline in cortical thickness and shrinkage of neuronal dendrites.

Further, fMRI and fNIRS studies reported that the hemodynamic response is altered during functional activation by age. Comparing age-dependent hemodynamic responses between fMRI and fNIRS studies is complicated, because fNIRS measures the whole volume beneath the optodes and, therefore, might not distinguish between changes of amplitude and number of activated voxels like fMRI. On the other hand, fNIRS measures changes of several chromophores and (indirectly) CBV and CBF. Combining our results and reports from literature one may suppose that the hemodynamic response declines in association cortices starting from roughly 50 years of age. The results of Hock et al. (1995) and our results support this hypothesis for the (prefrontal) association cortex, as they demonstrate a reduction of the hemodynamic response in subjects with mean ages of 52 and 65 years, respectively. However, the fNIRS study by Hock et al. had methodological limitations as they did not correct for the age-dependency of the DPF (Duncan et al., 1996), measured the hemodynamic response at only one location, and used a block design in contrast to the event-related design of our study, which is advantageous for cognitive studies (Pollmann et al., 2000).

For the primary motor cortex we did not find influences of age when effect sizes of the hemodynamic response were compared. Thus, one may assume that the hemodynamic response declines in primary cortices after 65 years of age. First, the number of activated voxels decreases with age as shown by fMRI, which might be caused by a higher variability or a smaller active brain volume in the elderly. Concomitantly, the hemodynamic response as measured by fNIRS may be reduced (Huettel et al., 2001; D'Esposito et al., 1999; Mehagnoul-Schipper et al., 2002; Buckner et al., 2000; mean ages 66, 71.3, 73, and 75 years, respectively). Later, starting from roughly 75 years of age, the amplitude of the hemodynamic response declines in the primary cortex, at least in visual areas (Ross et al., 1997; Buckner et al., 2000).

Interestingly, we detected a hemodynamic response in the ipsilateral motor cortex of the young (Schroeter et al., 2002) and elderly subjects (Table 1), although it was smaller than in the contralateral motor cortex. Detection of the motor response might be confounded by the prefrontal activation owing to the relatively large sampling volume of fNIRS. However, calculation of effect sizes may resolve that influence. Differences between our results and Mehagnoul-Schipper et al. (2002) can be explained by the different mean age of the subjects. On the other hand, designs (event-related vs. block) and fNIRS analysis methods also contribute to differences. Mehagnoul-Schipper et al. (2002) showed that oxy-Hb increased less and deoxy-Hb decreased less during finger tapping in the motor cortex of elderly compared with young adults. Interestingly, we found also a smaller mean vascular response in elderly in comparison with young subjects in the primary motor cortex. However, when effect sizes were calculated, the age-related difference disappeared. We suggest that effect sizes are the only valid approach for analyzing age-related effects in fNIRS studies because of four reasons: (1) The age-dependent DPF is currently not known for subjects older than 50 years (Duncan et al., 1996). (2) This factor has generally a high intersubject (Essenpreis et al., 1993) and intrasubject variation (Zhao et al., 2002). (3) Partial volume effects may change with aging as cortical thickness decreases at least in specific brain regions (Raz et al., 1997; Tisserand et al., 2002). (4) Effect sizes as a measure of the signal-to-noise ratio are independent from the assumed DPF and may correct for these partial volume effects (see Materials and methods). Therefore, by calculating effect sizes, one may avoid these pitfalls for all fNIRS studies investigating changes during aging. Further, this approach might be feasible for patient studies and fNIRS studies, which do not measure the individual DPF. Although we found significant age-dependent effects for Cyt-Ox we do not discuss these results because of methodological limitations: The spectral resolution of the NIRO-300 is poor as it measures at only four wavelengths. Thus, results may be biased by cross talk, i.e., a change in Hb concentration might yield an artifactual change in the Cyt-Ox signal (Heekeren et al., 1999; Uludag et al., 2002). Further, cross-talk may be altered with age, because the tissue's optical properties change (Duncan et al., 1996; Uludag et al., 2002).

Conclusion

Our experiments reveal two effects of aging on brain activation during a color-word matching Stroop task. (1) Elderly and young subjects use the lateral prefrontal cortex to cope with interference. A hemodynamic interference ef-

fect was found in the elderly at F7/8 and FC3/4 only, whereas it was detected in the young subjects at all prefrontal positions. (2) The hemodynamic response is reduced in elderly in comparison with young subjects in the lateral prefrontal (association) cortex in contrast to the (primary) motor cortex. Thus, combining our results and reports from literature one may hypothesize that the hemodynamic response declines in association cortices starting from roughly 50 years of age and declines in primary cortices after 65 years of age.

References

Banich, M.T., Milham, M.P., Atchley, R., Cohen, N.J., Webb, A., Wszalek, T., Kramer, A.F., Liang, Z.P., Wright, A., Shenker, J., Magin, R., 2000. fMRI studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. J. Cogn. Neurosci. 12 (6), 988–1000.

Buckner, R.L., Snyder, A.Z., Sanders, A.L., Raichle, M.E., Morris, J.C., 2000. Functional brain imaging of young, nondemented, and demented older adults. J. Cogn. Neurosci. 12 (6 Suppl. 2), 24–34.

Carter, C.S., MacDonald, A.M., Botvinick, M., Ross, L.L., Stenger, V.A., Noll, D., Cohen, J.D., 2000. Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. Proc. Natl. Acad. Sci. USA 97, 1944–1948.

Carter, C.S., Mintun, M., Cohen, J.D., 1995. Interference and facilitation effects during selective attention: an $H_2{}^{15}O$ PET study of Stroop task performance. NeuroImage 2, 264–272.

Cope, M., Delpy, D.T., 1988. System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infra-red transillumination. Med. Biol. Eng. Comput. 26, 289–294.

Cottrell, D.A., Blakely, E.L., Johnson, M.A., Ince, P.G., Borthwick, G.M., Turnbull, D.M., 2001. Cytochrome c oxidase deficient cells accumulate in the hippocampus and choroid plexus with age. Neurobiol. Aging 22, 265–272.

De Brabander, J.M., Kramers, R.J.K., Uylings, H.B.M., 1998. Layer-specific dendritic regression of pyramidal cells with ageing in the human prefrontal cortex. Eur. J. Neurosci. 10, 1261–1269.

D'Esposito, M., Zarahn, E., Aguirre, G.K., Rypma, B., 1999. The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. NeuroImage 10, 6–14.

Duncan, A., Meek, J.H., Clemence, M., Elwell, C.E., Fallon, P., Tyszczuk, L., Cope, M., Delpy, D.T., 1996. Measurement of cranial optical path length as a function of age using phase resolved near infrared spectroscopy. Pediatr. Res. 39, 889–894.

Essenpreis, M., Elwell, C.E., Cope, M., van der Zee, P., Arridge, S.R., Delpy, D.T., 1993. Spectral dependence of temporal point spread functions in human tissues. Appl. Optics 32 (4), 418–424.

Fan, J., Flombaum, J.I., McCandliss, B.D., Thomas, K.M., Posner, M.I., 2003. Cognitive and brain consequences of conflict. NeuroImage 18, 42–57.

George, M.S., Ketter, T.A., Parekh, P.I., Rosinsky, N., Ring, H., Casey, B.J., Trimble, M.R., Horwitz, B., Herscovitch, P., Post, R.M., 1994. Regional brain activity when selecting a response despite interference: an $H_2{}^{15}O$ study of the Stroop and an emotional Stroop. Hum. Brain Mapp. 1, 194–209.

Gratton, G., Goodman-Wood, M.R., Fabiani, M., 2001. Comparison of neuronal and hemodynamic measures of the brain response to visual stimulation: an optical imaging study. Hum. Brain Mapp. 13, 13–25.

Heekeren, H.R., Kohl, M., Obrig, H., Wenzel, R., von Pannwitz, W., Matcher, S.J., Dirnagl, U., Cooper, C.E., Villringer, A., 1999. Noninvasive assessment of changes in cytochrome-c oxidase oxidation in human subjects during visual stimulation. J. Cereb. Blood Flow Metab. 19, 592–603.

Hock, C., Müller-Spahn, F., Schuh-Hofer, S., Hofmann, M., Dirnagl, U., Villringer, A., 1995. Age dependency of changes in cerebral hemoglobin oxygenation during brain activation: a near-infrared spectroscopy study. J. Cereb. Blood Flow Metab. 15, 1103–1108.

Homan, R.W., Herman, J., Purdy, P., 1987. Cerebral location of international 10–20 system electrode placement. Electroenc. Clin. Neurophysiol. 66, 376–381.

Huettel, S.A., Singerman, J.D., McCarthy, G., 2001. The effects of aging upon the hemodynamic response measured by functional MRI. NeuroImage 13, 161–175.

Kawahata, N., Daitoh, N., Shirai, F., Hara, S., 1997. Reduction in mean cerebral blood flow measurements using ^{99m}Tc-ECD SPECT during normal aging. Kaku Igaku 34 (10), 909–916.

Leung, H.C., Skudlarski, P., Gatenby, J.C., Peterson, B.S., Gore, J.C., 2000. An event-related functional MRI study of the Stroop color word interference task. Cereb. Cortex 10, 552–560.

MacLeod, C.M., 1991. Half a century of research on the Stroop effect: an integrative review. Psychol. Bull. 109, 163–203.

Martin, A.J., Friston, K.J., Colebatch, J.G., Frackowiak, R.S.J., 1991. Decreases in regional cerebral blood flow with normal aging. J. Cereb. Blood Flow Metab. 11, 684–689.

Mehagnoul-Schipper, D.J., van der Kallen, B.F.W., Colier, W.N.J.M., van der Sluijs, M.C., van Erning, L.J.T.O., Thijssen, H.O.M., Oeseburg, B., Hoefnagels, W.H.L., Jansen, R.W.M.M., 2002. Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. Hum. Brain. Mapp. 16, 14–23.

Meltzer, C.C., Cantwell, M.N., Greer, P.J., Ben-Eliezer, D., Smith, G., Frank, G., Kaye, W.H., Houck, P.R., Price, J.C., 2000. Does cerebral blood flow decline in healthy aging? A PET study with partial-volume correction. J. Nuclear Med. 41, 1842–1848.

Milham, M.P., Erickson, K.I., Banich, M.T., Kramer, A.F., Webb, A., Wszalek, T., Cohen, N.J., 2002. Attentional control in the aging brain: insights from an fMRI study of the Stroop task. Brain Cogn. 49, 277–296.

Nakano, S., Asada, T., Matsuda, H., Uno, M., Takasaki, M., 2000. Effects of healthy aging on the regional cerebral blood flow measurements using ^{99m}Tc-ECD SPECT assessed with statistical parametric mapping. Nippon Ronen Igakkai Zasshi 37 (1), 49–55.

Pollmann, S., Dove, A., von Cramon, D.Y., Wiggins, C.J., 2000. Event-related fMRI: comparison of conditions with varying BOLD overlap. Hum. Brain Mapp. 9, 26–37.

Raz, N., Gunning, F.M., Head, D., Dupuis, J.H., McQuain, J., Briggs, S.D., Loken, W.J., Thornton, A.E., Acker, J.D., 1997. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cereb. Cortex 7, 268–282.

Ross, M.H., Yurgelun-Todd, D.A., Renshaw, P.F., Maas, L.C., Mendelson, J.H., Mello, N.K., Cohen, B.M., Levin, J.M., 1997. Age-related reduction in functional MRI response to photic stimulation. Neurology 48, 173–176.

Schroeter, M.L., Zysset, S., Kupka, T., Kruggel, F., von Cramon, D.Y., 2002. Near-infrared spectroscopy can detect brain activity during a color-word matching Stroop task in an event-related design. Hum. Brain Mapp. 17, 61–71.

Slosman, D.O., Chicherio, C., Ludwig, C., Genton, L., de Ribaupierre, S., Hans, D., Pichard, C., Mayer, E., Annoni, J.M., de Ribaupierre, A., 2001. ^{133}Xe SPECT cerebral blood flow study in a healthy population: determination of T-scores. J. Nuclear Med. 42, 864–870.

Steinmetz, H., Fürst, G., Meyer, B.U., 1989. Craniocerebral topography within the international 10–20 system. Electroenc. Clin. Neurophysiol. 72, 499–506.

Stroop, J., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol. 18, 643–662.

Taylor, S.F., Kornblum, S., Lauber, E.J., Minoshima, S., Koeppe, R.A., 1997. Isolation of specific interference processing in the Stroop task: PET activation studies. NeuroImage 6, 81–92.

Tisserand, D.J., Pruessner, J.C., Arigita, E.J.S., van Boxtel, M.P.J., Evans, A.C., Jolles, J., Uylings, H.B.M., 2002. Regional frontal cortical volumes decrease differentially in aging: an fMRI study to compare volumetric approaches and voxel based morphometry. NeuroImage 17, 657–669.

Treisman, A., Fearnley, S., 1969. The Stroop test: selective attention to colours and words. Nature 222, 437–439.

Tsuji, M., Duplessis, A., Taylor, G., Crocker, R., Volpe, J.J., 1998. Near infrared spectroscopy detects cerebral ischemia during hypotension in piglets. Pediatr. Res. 44, 591–595.

Uludag, K., Kohl, M., Steinbrink, J., Obrig, H., Villringer, A., 2002. Cross talk in the Lambert-Beer calculation for near-infrared wavelengths estimated by Monte Carlo simulations. J. Biomed. Opt. 7 (1), 51–59.

Verhaeghen, P., De Meersman, L.D., 1998. Aging and the Stroop effect: a meta-analysis. Psychol. Aging 13 (1), 120–126.

Villringer, A., Chance, B., 1997. Non-invasive optical spectroscopy and imaging of human brain function. Trends Neurosci. 20, 435–442.

Villringer, A., Dirnagl, U., 1995. Coupling of brain activity and cerebral blood flow: basis of functional neuroimaging. Cerebrovasc. Brain Metab. Rev. 7, 240–276.

Winer, B.J., Brown, D.R., Michels, K.M., 1991. Statistical Principles in Experimental Design, 3rd ed. McGraw–Hill, New York.

Wobst, P., Wenzel, R., Kohl, M., Obrig, H., Villringer, A., 2001. Linear aspects of changes in deoxygenated hemoglobin concentration and cytochrome oxidase oxidation during brain activation. NeuroImage 13, 520–530.

Zhao, H., Tanikawa, Y., Gao, F., Onodera, Y., Sassaroli, A., Tanaka, K., Yamada, Y., 2002. Maps of optical differential pathlength factor of human adult forehead, somatosensory motor and occipital regions at multi-wavelengths in NIR. Phys. Med. Biol. 47, 2075–2093.

Zysset, S., Müller, K., Lohmann, G., von Cramon, D.Y., 2001. Color-word matching Stroop task: separating interference and response conflict. NeuroImage 13, 29–36.