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Neurovascular coupling is impaired in cerebral microangiopathy—An event-related Stroop study

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Small-vessel disease or cerebral microangiopathy is a common finding in elderly people leading finally to subcortical ischemic vascular dementia. Because cerebral microangiopathy impairs vascular reactivity and affects mainly the frontal lobes, we hypothesized that brain activation decreases during an event-related color–word matching Stroop task. 12 patients suffering from cerebral microangiopathy were compared with 12 age-matched controls. As an imaging method we applied functional near-infrared spectroscopy, because it is particularly sensitive to the microvasculature. The Stroop task led to activations in the lateral prefrontal cortex. Generally, the amplitude of the hemodynamic response was reduced in patients in tight correlation with behavioral slowing during the Stroop task and with neuropsychological deficits, namely attentional and executive dysfunction. Interestingly, patients showed an early deoxygenation of blood right after stimulation onset, and a delay of the hemodynamic response. Whereas the amplitude of the hemodynamic response is reduced in the frontal lobes also with normal aging, data suggest that impairments of neurovascular coupling are specific for cerebral microangiopathy. In summary, our findings indicate frontal dysfunction and impairments of neurovascular coupling in cerebral microangiopathy.

Keywords: Cerebral microangiopathy; Near-infrared spectroscopy; Neurovascular coupling; Small-vessel disease; Stroop

Introduction

Vascular dementia is the second most common type of dementia (Roman et al., 2002). The subcortical ischemic form, which constitutes 36% to 67% of all vascular dementias, frequently causes cognitive impairment in elderly people. It is clinically homogenous, and results from small-vessel disease, or cerebral microangiopathy (CMA). Two main pathophysiological pathways are involved (Fig. 1). In the first, occlusion of the arteriolar lumen leads to the formation of lacunes resulting in a lacunar state. In the second, critical stenosis and hypoperfusion of multiple medullary arterioles cause widespread incomplete infarction of deep (periventricular) white matter leading to leukoaraiosis with a clinical picture of Binswanger's disease. In practice, the two clinical pathways overlap. Etiologically, CMA is characterized by a degeneration of the cerebral microcirculation mainly due to arterial hypertension and diabetes (Caplan, 1995; Corry and Tuck, 2002; de Leeuw et al., 2002; Roman et al., 2002). Walls of the small penetrating arteries and arterioles are thickened and often hyalinized (Caplan, 1995). Fibrosis, loss of smooth muscle cells, and splitting of the internal elastic membrane can lead to increased vessel stiffness (Tanoi et al., 2000).

Consequently, vasomotor reactivity is reduced as shown by positron emission tomography (Roman et al., 2002), near-infrared spectroscopy (NIRS), transcranial Doppler sonography (Schroeter et al., 2005; Terborg et al., 2000), and functional magnetic resonance imaging (MRI; Hund-Georgiadis et al., 2003). Interestingly, the frontal lobes are primarily affected. More precisely, white matter lesions, reductions in glucose metabolism, impairments of vascular reactivity and cerebral blood flow (CBF) during rest are most pronounced in this brain region (Hund-Georgiadis et al., 2003; Terborg et al., 2000; Tullberg et al., 2004; Yoshikawa et al., 2003). Finally, these changes lead to a variety of clinical symptoms and neuropsychological abnormalities, which are dominated by a dysexecutive syndrome and reductions in information processing speed (McPherson and Cummings, 1996; Prins et al., 2005; Roman et al., 2002).

Recently, we showed that aging leads to a specific reduction of the hemodynamic response in the frontal lobes during a color–word matching Stroop task (Schroeter et al., 2003). As discussed above, CMA accelerates aging-related changes, namely vessel stiffness (Caplan, 1995; Roman et al., 2002; Schroeter et al., 2004b, 2005; Tanoi et al., 2000) and frontal lobe dysfunction (Hund-Georgiadis et al., 2003; Terborg et al., 2000; Tullberg et al., 2004; Yoshikawa et al., 2003). Accordingly, we measured brain activation in the frontal lobes of patients with CMA during a color–word matching Stroop

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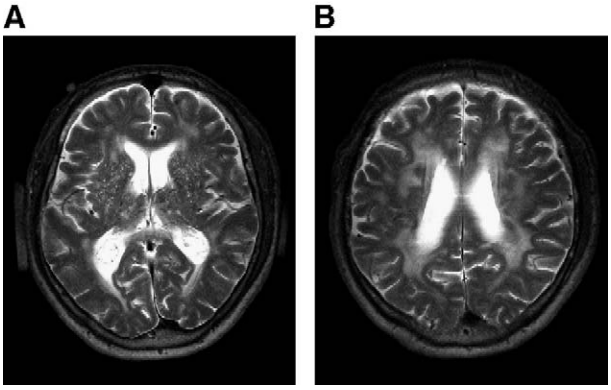

Fig. 1. Structural changes in cerebral microangiopathy visualized with high-resolution magnetic resonance tomography at 3 Tesla in T2-weighted sequence. Characteristic abnormalities are (A) lacunar state of the basal ganglia and (B) periventricular white matter disease (according to Schroeter et al., 2005).

task, and hypothesized that brain activation further declines in CMA compared with age-matched controls. We applied functional NIRS (fNIRS), because it is particularly sensitive to the microvasculature (Liu et al., 1995a, 1995b), and can measure changes in the concentration of oxy-, and deoxy-hemoglobin (Hb) specifically (Hoshi et al., 2003; Obrig and Villringer, 2003; Schroeter et al., 2004a; Schroeter, 2006; Strangman et al., 2002).

Materials and methods

Subjects

12 Caucasian patients with CMA and 12 age-matched Caucasian control subjects participated in the study (group characteristics see Table 1). Patients were treated in the Day Clinic of Cognitive Neurology of the University of Leipzig. They had previously been diagnosed with CMA on the basis of anatomical MRI or computer tomography scans and a comprehensive clinical examination. Although five patients suffered additionally from macroangiopathy (atherosclerosis), it did not influence results, and none of the patients had related lesions. Controls had no history of neurological or psychiatric disorders. 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, were native German speakers, and were right-handed.

MRI scoring for structural abnormalities in CMA

Imaging was performed at 3 T on a Bruker Medspec 30/100 system (Bruker Medical, Ettlingen, Germany) (Hund-Georgiadis et al., 2002). For staging CMA a MRI score was calculated on the basis of T2-weighted axial scans as proposed by Hund-Georgiadis et al. (2002). Criteria for scoring were the presence of lacunar infarctions and periventricular white matter lesions (Fig. 1). The presence and severity were graded according to their extent and their uni- or bilateral distribution. The maximum theoretical score was 21 points and ranged in the patient group from 8 to 18 (mean 13.3±3.3).

Neuropsychological test battery

The neuropsychological battery assessed cognitive performance for attention, executive functions, and memory in the patient group. Alertness and divided attention were tested by the test battery for the assessment of attention (TAP) (Zimmermann and Fimm, 1993). Impairment in executive functions was assessed by the behavioral assessment of the dysexecutive syndrome (BADS) and a modified Stroop paradigm (Wilson et al., 1996; Wolfram et al., 1986). Memory functions were assessed by digit span and block span of the Wechsler memory scale (WMS-R) (Haerting et al., 2000), for short-term, and by the verbal and visual memory quotient (WMS-R) and by the California verbal learning test (CVLT) (Delis et al., 1987) for long-term memory, respectively. A score (0 'unimpaired' to 3 'severely impaired') was calculated for each domain (attention, executive functions, learning and spans). Hence, the sum score ranged from 0 to 12 points. Mean scores for neuropsychological impairments were 0.82±0.98 (attention), 1.27±1.19 (executive function), 0.82±1.25 (learning), 0.73±0.79 (span), and 3.64±3.53 for the sum score.

Data acquisition by fNIRS

Changes in the concentration of oxy- and deoxy-Hb were measured by a NIRO-300 spectrometer (Hamamatsu Photonics K. K.) and are expressed in nanomolar (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 and CBF, respectively (Tsuji et al., 1998). Although we also measured changes in the redox state of cytochrome *c* oxidase, we generally did not report these

Table 1
Clinical characteristics and therapy of the patients with cerebral microangiopathy and controls

	Patients (n=12)	Controls (n=12)
Mean age (years±SD)	61.2±4.9	64.5±2
Age range (years)	54–68	62–67
Sex (male/female; n)	10/2	5/7
Additional medical diagnoses		
Arterial hypertension (n)	10	5
Type II diabetes (n)	5	0*
Hypercholesterolemia (n)	7	1*
Medication		
Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers (n)	9	4
Beta-adrenergic blockers (n)	4	2
Calcium channel blockers (n)	5	1
Diuretics (n)	4	0
Antidiabetic agents (n)	2	0
Statins (n)	5	1
Inhibitors of thrombocytic aggregation (n)	10	1*
NO donators (n)	0	1

Sex, other diagnoses and medications not different between groups ($p>0.05$). No difference of mean age ($p>0.05$; two-tailed unpaired Student's t-test).

* Significant difference according to Fisher's Exact Test (df=1, two-sided $p<0.05$).

results, because cross-talk effects might have mimicked them, i.e., a change in Hb concentration might yield an artifactual change in the cytochrome *c* oxidase (Heekeren et al., 1999; Uludag et al., 2002). 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 (Schroeter et al., 2006; Villringer and Chance, 1997; no difference of emitter–detector spacing between patients and controls according to Fisher's Exact Test). It is known from literature that the differential pathlength factor is age-dependent and might be calculated by the formula $5.13+0.07*(age^{0.81})$ (Duncan et al., 1996). Precise formulas for the differential pathlength factor in subjects over 50 years of age are currently unknown. Therefore, we set the differential pathlength factor generally to 6.79, representing the value 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, and 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. 2). Response was given by a button press with the index (YES response) and middle (NO response) fingers of the right hand except in two subjects, who responded with the left 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 incongruent trials, the top row consisted of the color words "RED", "GREEN", "BLUE", and "YELLOW" 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 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. We excluded congruent trials from analysis as discussed in Schroeter et al. (2004c). Words remained on the screen until the response was given. The screen was blank between the trials.

Optodes were placed symmetrically over the lateral prefrontal cortex (centered at F3/4, F7/8, and FC3/4 of the international 10/20 system; emitter caudal and detector cranial) (Okamoto et al., 2004). An experimental run was carried out at each position (total time of 18 min). The order of the different positions was counterbalanced. For F3/4 and FC3/4, one control subject had to be excluded from analysis due to severe movement artifacts. Although we measured brain activation during the Stroop task also at F7/8, the signal-to-noise ratio was low presumably due to a long distance between the surface of the skin and cortex (Okamoto et al., 2004), making a detection of event-related activations impossible and leading, accordingly, to no significant results. Accordingly, we do not report these data.

Analysis was performed as previously described in detail (Schroeter et al., 2002, 2003). The mean of the signal intensity during the baseline (2 s before trial onset) and the vascular response (5–8 s after trial onset for controls, and 7–10 s after trial onset for patients) was calculated for each subject, condition, and position. These time intervals were chosen, because the vascular response occurred during these intervals (Fig. 3). Differences between the mean of the vascular response and the baseline revealed a measure of the hemodynamic response for both conditions of the Stroop task. Thereafter, the hemodynamic response was compared between incongruent and neutral trials (within subject factor condition), and between patients and controls (between subject factor CMA) with a repeated measure ANOVA, followed by post hoc Student's *t*-tests adjusted for inequality of variance, if necessary. Equality of variance was tested by Levene's test.

To exclude that additional medical diagnoses or medications (Table 1) biased our results, we re-analyzed data in an ANOVA with medical diagnoses (arterial hypertension, diabetes, hypercholesterolemia), or medications (angiotensin-converting enzyme inhibitors/

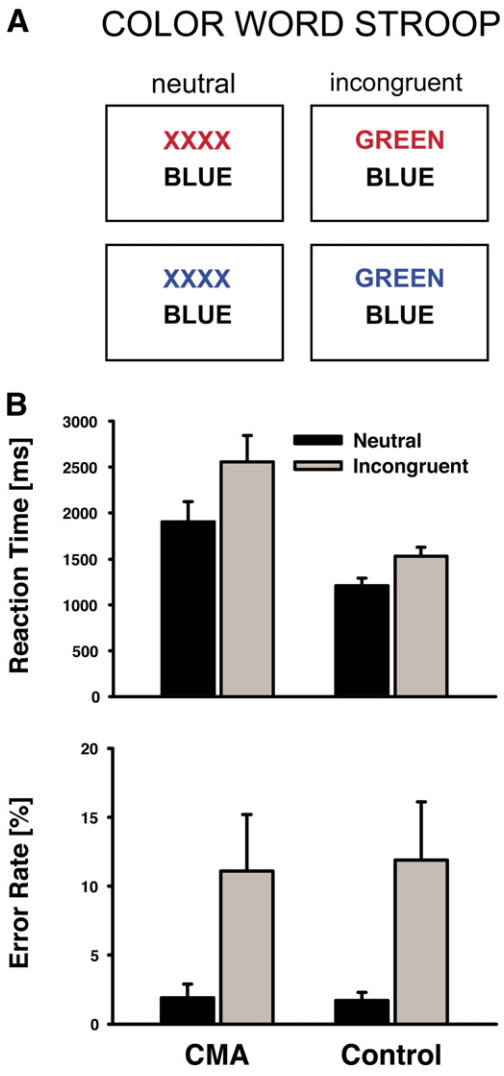

Fig. 2. (A) Examples of single trials for the neutral, and incongruent condition of the color–word matching Stroop task. "Does the color of the upper word correspond with the meaning of the lower word?" For the top two examples, the correct answer would be "NO"; for the bottom two examples, the correct answer would be "YES". (B) Reaction time, and error rate for the Stroop task, averaged across all patients with cerebral microangiopathy (CMA) and control subjects. Mean±SEM.

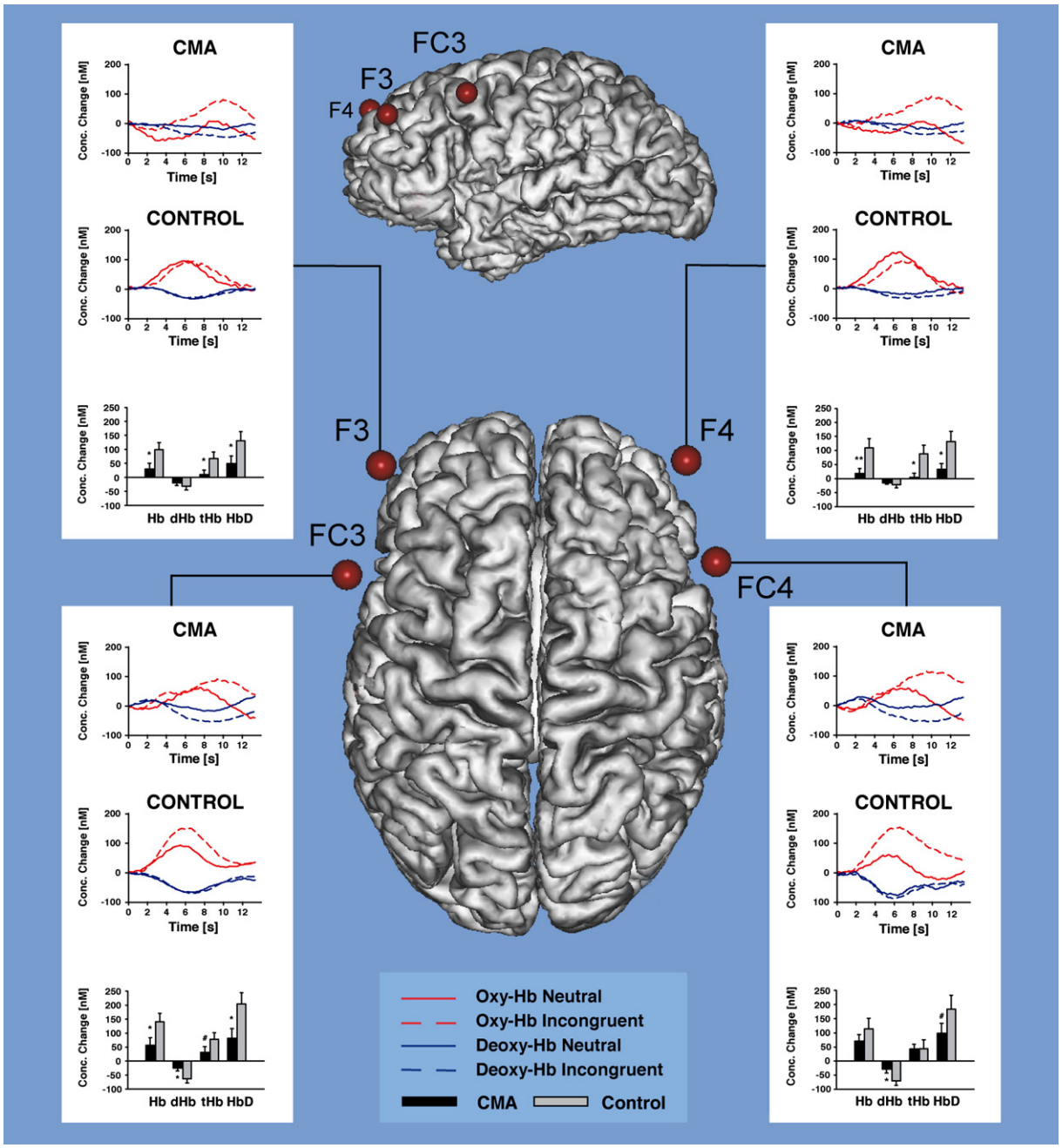

Fig. 3. Time courses for concentrations of oxy- and deoxy-hemoglobin in the dorsolateral prefrontal cortex during the neutral and incongruent conditions of the Stroop task. The Stroop task started at 0 s. Running averages over 2 s. For display purposes the mean concentration between 1 s before until 1 s after stimulation onset was set to 0 nM. The bar charts illustrate the mean hemodynamic concentration changes. Values during the neutral and incongruent condition were pooled. Generally, average across patients with cerebral microangiopathy (CMA) and control subjects is shown. Hb—hemoglobin, dHb—deoxy-Hb, HbD—Hb difference, tHb—total Hb. $^{**}p<0.01$; $^{*}p<0.05$; $^{\#}p<0.1$ ('trend') for controls vs. patients (unpaired one-tailed Student's *t*-test). Mean±SEM. Red spheres correspond with optode positions mapped onto a reference brain (Schroeter et al., 2002).

angiotensin II receptor blockers, beta-adrenergic blockers, calcium channel blockers, statins) as additional factors, because these diagnoses/drugs might influence microcirculation, and hence the vascular response (Bernardi et al., 1997; de Leeuw et al., 2002; Harrison and Ohara, 1995; Levy et al., 2001; Meyer et al., 2003; Scalia and Stalker, 2002). NO donators were excluded from this analysis, because only one control subject received it. Correlation analysis was performed according to Pearson. Results are generally given as mean±standard deviation (SD), if not stated otherwise.

One limitation of NIRS is that analysis involves the differential pathlength factor, which is age-dependent, and shows a high inter- and intra-subject variation (Duncan et al., 1996; Schroeter et al., 2003, 2004a). Furthermore, as stated above, precise formulas for the differential pathlength factor in subjects over 50 years of age are currently unknown (Duncan et al., 1996). Recently, we

suggested to apply statistical approaches that are almost independent of the assumed differential pathlength factors (Schroeter et al., 2003, 2004a). Hence, we calculated additionally individual effect sizes (d) of the Stroop interference effect according to Cohen (1988) and Schroeter et al. (2003) as the difference of the means of the incongruent (m_i) and neutral (m_n) condition divided by the standard deviation of the neutral condition (SD_n):

$$d = \frac{m_i - m_n}{SD_n}$$

Results

Behavioral results

Fig. 2 illustrates the behavioral results of the Stroop task. With respect to reaction time, a repeated measure ANOVA (including the two factors neutral vs. incongruent, and CMA vs. controls) demonstrated a significant effect for condition ($F=55.8$, $df=1$, $p<0.001$), CMA ($F=10.7$, $df=1$, $p<0.005$), and a significant interaction between both factors ($F=6.5$, $df=1$, $p<0.02$). The mean reaction time was significantly longer in the incongruent compared with the neutral condition in both groups, patients with CMA and controls ($T=5.2$, $T=8.9$, $df=11$, $p<0.001$; two-tailed paired Student's *t*-test). Generally, patients reacted more slowly than control subjects (incongruent condition $T=3.4$, $df=13.4$, $p<0.005$, neutral condition $T=2.9$, $df=13.9$, $p=0.01$; two-tailed unpaired Student's *t*-test). To analyze interaction between the factors condition and CMA we calculated the Stroop interference effect for each group separately. Patients with CMA showed a greater interference effect (difference between incongruent and neutral condition) than control subjects (657±437 ms vs. 323±126 ms; $T=2.5$, $df=12.8$, $p<0.05$; two-tailed unpaired Student's *t*-test). One may hypothesize that the difference of the interference effect is just an artifact of general slowing in CMA (Prins et al., 2005). To test this confounding factor, we calculated effect sizes of the Stroop interference effect according to Cohen (1988). Although effect sizes were high for both, patients (0.85±0.57) and controls (1.14±0.44; $T=5.2$, =8.9, $df=11$, $p<0.001$; one-tailed Student's *t*-test against 0), the difference between the groups vanished ($T=1.4$, $df=22$, $p>0.05$; two-tailed unpaired Student's *t*-test). Hence, the intergroup difference of the interference effect has to be regarded as an artifact of general slowing in CMA.

Concerning error rates (percentage of all respective trials), the repeated measure condition × diagnosis ANOVA showed a significant effect for condition ($F=13.7$, $df=1$, $p=0.001$), without effects of diagnosis (CMA vs. controls $F=0.01$, $df=1$, $p>0.05$), and without significant interaction between both factors ($F=0.04$, $df=1$, $p>0.05$). Mean error rates were significantly higher in both groups in the incongruent condition, when compared with the neutral one (CMA $T=2.6$, $df=11$, $p<0.05$; controls $T=2.6$, $df=11$, $p<0.05$; two-tailed paired Student's *t*-test). Again, effect sizes of the Stroop interference effect were high for both groups (CMA 2.78±3.66, Control 4.67±6.18; $T=2.6$, =2.6, $df=11$, $p<0.05$; one-tailed Student's *t*-test against 0) without intergroup differences ($T=0.9$, $df=22$, $p>0.05$; two-tailed unpaired Student's *t*-test). Summing up behavioral results, one may conclude that patients with CMA and controls showed a clear interference effect (for reaction time and error rate) and that patients with CMA reacted more slowly than controls.

fNIRS results

Fig. 3 illustrates concentration changes of the NIRS parameters in the dorsolateral prefrontal cortex (DLPFC) during the Stroop task. Obviously, the Stroop task led to a bilateral brain activation in both, patients and controls. Control subjects showed an increase of oxy-Hb and decrease of deoxy-Hb starting at approximately 2 s after stimulation onset. The vascular response peaked at 6 s after stimulation onset and returned after 12 s to baseline values. In CMA patients, the hemodynamic response was generally delayed. Concentration of oxy-Hb decreased and concentration of deoxy-Hb increased just after stimulation onset, which lasted approximately until 3 s after the beginning of stimulation. Thereafter, oxy-Hb increased and deoxy-Hb decreased such as in controls, reaching its peak values 7–10 s after stimulation onset. The hemodynamic response returned to baseline values after ~10–13 s. Obviously, longer reaction times in CMA during the Stroop task (1 s slower) might explain the delay of the hemodynamic response in the patient group only partly (1–4 s later). Incongruent trials generally led to a stronger vascular response than neutral trials in the DLPFC due to Stroop interference, except for controls at F3/4.

Table 2 shows the results of the repeated measure ANOVA that analyzed influences of CMA and the conditions of the Stroop task (incongruent vs. neutral) on the hemodynamic response in the DLPFC. CMA had a significant influence on the hemodynamic response at every position, albeit not consistently for all NIRS parameters. The hemodynamic response was significantly different between the two conditions of the Stroop task in the right DLPFC (FC4). Generally, there was no significant interaction between the factors diagnosis and condition (not shown).

To further investigate the differences between CMA and controls, we compared the mean hemodynamic response during the Stroop task between patients and controls. Therefore, incongruent and neutral trials were pooled, because the ANOVA did not show any significant interaction between diagnosis and condition beside the main effect of diagnosis. We hypothesized that the mean hemodynamic response is reduced in CMA in the prefrontal cortex due to increased vessel stiffness (Caplan, 1995; Roman et al., 2002; Tanoi et al., 2000), and frontal lobe dysfunction (Hund-Georgiadis et al., 2003; Terborg et al., 2000; Tullberg et al., 2004; Yoshikawa et al., 2003). The post hoc analysis confirmed this hypothesis for all measured areas in the DLPFC, although not for all parameters (Fig. 3). Further, we hypothesized that the incongruent condition leads to a higher brain activation, and hence hemodynamic response, than the neutral condition, which was confirmed by post hoc tests. Namely, the vascular response was higher during incongruent compared with neutral trials at FC4 (for oxy-Hb, deoxy-Hb and HbD $T=2$, -1.9, 2.3, $df=22$, $p<0.05$, paired one-tailed Student's *t*-test). Hence, coping with Stroop interference enhanced brain activation in the DLPFC.

To exclude that additional medical diagnoses or medications (Table 1) biased our results, were analyzed data in an ANOVA with the factor CMA, and further medical diagnoses/medications as additional factors. The analysis was performed for the mean hemodynamic response, because only this parameter was significantly changed in CMA. Neither additional medical diagnoses nor medications had an effect on the results.

Until now we have shown that the mean hemodynamic response is impaired in CMA in the DLPFC during performance of a Stroop task. To validate the specificity of the effect, we conducted a correlation analysis relating the mean hemodynamic

Table 2
Hemodynamic response in the dorsolateral prefrontal cortex during the neutral and incongruent condition of the Stroop task—effects of condition and cerebral microangiopathy, and effect sizes of the Stroop interference effect

Position	Parameter	Hemodynamic response (nM; mean±SD)				ANOVA		Effect size (mean±SD)	
		CMA		Control		Condition (df=1)	Diagnosis (df=1)		
		Neutral	Incongruent	Neutral	Incongruent			CMA	Control
F3	Oxy-Hb	22.6±87.1	37.2±127.2	100.3±131.9	96.9±114.6	n.s.	*	0.17±1.94	−0.03±1.36
	Deoxy-Hb	−6.8±40.2	−32.1±54.1	−28.1±50.9	−35.6±39.6	n.s.	n.s.	−0.63±1.58	−0.15±0.54
	Total Hb	15.8±86.1	5.1±98.6	72.2±124.3	61.3±111.9	n.s.	#	−0.12±1.72	−0.09±1.41
	HbD	29.4±104.9	69.3±168.8	128.5±156.6	132.5±130	n.s.	#	0.38±1.98	0.03±1.2
F4	Oxy-Hb	−3.8±77.3	40.5±101.1	127.1±203.8	93.2±194	n.s.	*	0.57±1.73	−0.17±1.65
	Deoxy-Hb	−8.8±20.1	−21±32.7	−11±49.2	−33±46.9	n.s.	n.s.	−0.61±1.94	−0.45±1.29
	Total Hb	−12.6±81.1	19.5±83.8	116.1±228.3	60.2±185.4	n.s.	*	0.4±1.52	−0.25±1.59
	HbD	4.9±78.6	61.6±124.7	138.1±189.3	126.2±212.9	n.s.	*	0.72±1.96	−0.06±1.7
FC3	Oxy-Hb	49±109.3	64.4±124.9	117.6±142	164.1±87.6	n.s.	*	0.14±1.31	0.33±0.91
	Deoxy-Hb	−14.6±40.4	−35.5±52.3	−62.3±43.8	−63.5±62.1	n.s.	*	−0.52±1.59	−0.03±1.03
	Total Hb	34.5±95.3	28.9±96.9	55.3±113.7	100.7±71.5	n.s.	n.s.	−0.06±1.37	0.4±1.0
	HbD	63.6±134.5	100±165.2	179.9±176.7	227.6±134	n.s.	*	0.27±1.34	0.27±0.89
FC4	Oxy-Hb	50.5±110.2	90.6±121.7	66.3±174.2	161.3±111.5	#	n.s.	0.36±1.51	0.54±0.87
	Deoxy-Hb	−4.7±42.1	−51.6±89.1	−57.9±70.1	−82±65.2	#	#	−1.11±2.32	−0.34±1.24
	Total Hb	45.8±101.7	39±67.9	8.5±148.9	79.2±107	n.s.	n.s.	−0.07±1.24	0.48±1.04
	HbD	55.2±132.3	142.1±202.2	124.2±219.9	243.3±148	*	n.s.	0.66±1.83	0.54±0.87

*$p<0.05$; #$p<0.1$ ('trend'). Results of the repeated measure ANOVA including the within subject factor condition (incongruent vs. neutral) and the between subject factor diagnosis (CMA vs. controls). CMA: cerebral microangiopathy. Hb: hemoglobin. HbD: Hb difference (oxy-Hb minus deoxy-Hb). n.s.: Not significant. Effect sizes were calculated as the difference of the means of the incongruent and neutral condition divided by the standard deviation of the neutral condition.

response during the Stroop task to the behavioral performance of the subjects (neutral and incongruent trials pooled, respectively) and neuropsychological deficits. We hypothesized that a stronger vascular response is related to more efficient behavioral performance and less neuropsychological deficits (Schroeter et al., 2003). For the Stroop task, the mean hemodynamic and mean behavioral response (reaction time) were highly correlated (F3 oxy-, deoxy-Hb, HbD $r=-0.36$, $=0.42$, $=-0.43$, $p<0.05$; F4 oxy-, deoxy-Hb, HbD $r=-0.34$, $=0.39$, $=-0.4$, $p=0.05$, <0.05, <0.05; FC3 deoxy-Hb $r=0.37$, $p<0.05$; FC4 deoxy-Hb $r=0.32$, $p=0.07$; Pearson, one-tailed p). The analysis confirmed further our hypothesis with regard to neuropsychological deficits, particularly for attentional and executive dysfunction, which were also correlated with the amplitude of the vascular response (attention: F3 oxy-, deoxy-, total Hb, HbD $r=-0.77$, $=0.64$, $=-0.56$, $=-0.79$, $p<0.005$, <0.05, <0.05, <0.005; F4 oxy-, deoxy-, total Hb, HbD $r=-0.7$, $=0.49$, $=-0.58$, $=-0.74$, $p<0.01$, $=0.06$, <0.05, <0.005; FC3 deoxy-Hb $r=0.64$, $p<0.05$; FC4 total Hb $r=0.75$, $p<0.05$; executive function: F3 deoxy-Hb $r=0.54$, $p<0.05$; F4 deoxy-Hb $r=0.78$, $p<0.005$; learning: F4 deoxy-Hb $r=0.61$, $p<0.05$; span: FC4 total Hb $r=-0.54$, $p<0.05$). Generally, there was no significant correlation between the severity of CMA as scored in MRI scans and neuropsychological deficits or the mean hemodynamic response during the Stroop task (only total Hb at FC4 $r=0.75$, $p<0.05$; Pearson, one-tailed p).

Furthermore, we analyzed the hemodynamic Stroop interference effect specifically by calculating its effect size for each optode position (Table 2). Effect sizes of the interference effect were significant different from 0 at FC4 (controls: oxy-Hb, total Hb, HbD $T=2.1$, $=1.5$, $=2.1$; $p<0.05$, $=0.08$, <0.05; patients: deoxy-Hb $T=-1.7$, $p=0.06$) and F3 (patients: deoxy-Hb $T=-1.4$, $p<0.1$; one-tailed Student's t-test against 0). There were no significant differences between the two groups at any of the measured positions as tested by two-tailed unpaired Student's t-tests ($p>0.05$, respectively). Regarding the relation between hemodynamic and behavioral effect sizes of the interference effect, we hypothesized that a higher Stroop-specific brain activation leads to more successful inhibition of competing responses and, hence, a smaller behavioral interference effect (Schroeter et al., 2003). This was indeed the case for reaction time (F4 oxy-Hb $r=-0.31$, $p=0.08$, total Hb $r=-0.32$, $p=0.07$, HbD $r=-0.28$, $p=0.1$; Pearson, one-tailed p). Furthermore, hemodynamic effect sizes were correlated with the neuropsychological deficits of the patient group, particularly attention and executive dysfunction, confirming the assumption that higher Stroop task-specific brain activations are related to smaller neuropsychological deficits (attention: F3 oxy-, total Hb, HbD $r=-0.57$, $=-0.56$, $=-0.53$, $p<0.05$; F4 oxy-, total Hb, HbD $r=-0.63$, $=-0.61$, $=-0.61$, $p<0.05$; FC4 HbD $r=-0.43$, $p<0.1$; executive function: F3 oxy-, total Hb, HbD $r=-0.48$, $=-0.45$, $=-0.45$, $p=0.07$, $=0.08$, $=0.08$; F4 oxy-Hb, HbD $r=-0.46$, $=-0.48$, $p=0.08$, $=0.07$; span: F4 oxy-Hb, HbD $r=-0.43$, $=-0.47$, $p=0.09$, $=0.07$). Again, there was no significant correlation between hemodynamic effect sizes and the severity of CMA as scored in MRI scans ($p>0.05$).

As mentioned above patients with CMA showed an early decrease in oxy-Hb and increase in deoxy-Hb in the DLPFC in the first 3 s right after stimulation onset, which was not the case for controls (Fig. 3). It is well known that vasomotor reactivity is impaired in CMA (Bäzner et al., 1995; de Reuck et al., 1999; Hund-Georgiadis et al., 2003; Rossini et al., 2004; Schroeter et al., 2005; Terborg et al., 2000). Hence, one might hypothesize that neurovascular coupling is impaired and, accordingly, brain activity leads to net blood deoxygenation immediately after stimulation onset before regional CBF increases overproportionally causing net blood oxygenation as described above. To examine the significance of the effect we calculated the difference between the early changes of oxy-/deoxy-Hb (mean concentration changes between 1 and 2 s after stimulation onset) and the respective baseline values

(2 s before trial onset) and conducted again a repeated measure ANOVA that analyzed influences of CMA and the conditions of the Stroop task. The ANOVA procedure revealed no significant effect of condition (incongruent vs. neutral) and no significant interaction between condition and diagnosis for any parameter (not shown). Hence, the early changes right after stimulation onset did not differ between both conditions of the Stroop task. However, as suggested by the timelines (Fig. 3), there was a significant effect of CMA (F3: oxy-Hb $F=11.1$, $p<0.001$, deoxy-Hb $F=0.6$, $p>0.05$; F4: oxy-Hb $F=7.5$, $p<0.01$, deoxy-Hb $F=0.0$, $p>0.05$; FC3: oxy-Hb $F=10.2$, $p<0.001$, deoxy-Hb $F=6$, $p<0.05$; FC4: oxy-Hb $F=8.5$, $p<0.01$, deoxy-Hb $F=10.7$, $p<0.001$; $df=1$, respectively).

To further investigate the differences between CMA and controls, we compared the mean early concentration changes during the Stroop task between patients and controls by pooling incongruent and neutral trials (unpaired one-tailed post hoc Student's *t*-tests). Indeed, patients with CMA showed in the early time period higher increases in deoxy-Hb and stronger decreases in oxy-Hb compared with controls, confirming our hypothesis of impaired neurovascular coupling in CMA (F3: oxy-Hb -57.2 ± 49.3 vs. 9.5 ± 46.5, $T=3.3$, $p<0.005$; F4: oxy-Hb -49.9 ± 59.1 vs. 15.5 ± 54.8, $T=2.7$, $p<0.01$; FC3: oxy-Hb -60.9 ± 63.1 vs. 20.1 ± 57.9, $T=3.2$, $p<0.005$, deoxy-Hb 26.4 ± 28.9 vs. -4.4 ± 31.6, $T=-2.4$, $p<0.05$; FC4: oxy-Hb -68.1 ± 65.8 vs. 7.8 ± 58.2, $T=2.9$, $p<0.005$, deoxy-Hb 30.7 ± 29.8 vs. -6.1 ± 23.4, $T=-3.3$, $p<0.005$; $df=21$, respectively). The difference between CMA and controls for the early period was related only to significant decreases of oxy-Hb and increases of deoxy-Hb in CMA patients (F3: oxy-Hb $T=-4$, $p=0.001$; F4: oxy-Hb $T=-2.9$, $p<0.01$; FC3: oxy-Hb $T=-3.3$, $p<0.005$, deoxy-Hb $T=3.2$, $p<0.005$; FC4: oxy-Hb $T=-3.6$, $p<0.005$, deoxy-Hb $T=3.6$, $p<0.005$; one-tailed Student's *t*-test against 0; no significant effects for controls). Interestingly, there was almost no significant correlation of the mean concentration changes in the early period with neuropsychological test scores (only deoxy-Hb at FC3 with attention $r=-0.64$, $p<0.05$, and oxy-Hb at F4 with span $r=-0.72$, $p<0.05$; correlation coefficients according to Pearson, two-tailed p).

Discussion

Patients and controls utilized the DLPFC to cope with Stroop-related interference in agreement with recent imaging studies with fMRI (Banich et al., 2000; Carter et al., 2000; Fan et al., 2003; Leung et al., 2000; Milham et al., 2002; Ruff et al., 2001; Zysset et al., 2001), positron emission tomography (George et al., 1994; Taylor et al., 1997) and fNIRS (Ehlis et al., 2005; Schroeter et al., 2002, 2003). We detected three main differences between patients suffering from CMA and controls regarding brain activation in the DLPFC during a Stroop task. (i) Most interestingly, patients with CMA showed an early deoxygenation before regional CBF increased overproportionally. (ii) The vascular response was delayed in CMA exceeding behavioral slowing. (iii) The mean vascular response was reduced in patients with CMA. However, the last difference disappeared, when effect sizes of the Stroop interference effect were regarded. These differences between patients with CMA and controls may be discussed in the context of changes of neurovascular coupling. Generally, an increase in brain activity leads to a rapid early small deoxygenation of blood (increase of deoxy-Hb and decrease of oxy-Hb; 'initial dip' of the blood oxygenation level-dependent signal of fMRI) in the first 3 s as oxygen consumption increases without changes in regional CBF and blood volume (Villringer and Dirnagl, 1995). Up to now, this phenomenon has been shown for optical measurements directly on the brain surface only, but not for measurements through the skull (Malonek and Grinvald, 1996; Mayhew et al., 2000; Suh et al., 2006). Thereafter, regional CBF increases overproportionally causing net blood oxygenation by oversupplying oxygenated blood and washing out deoxygenated blood (Schroeter et al., 2006; Villringer and Dirnagl, 1995). The latter phenomenon is known as neurovascular coupling. Whereas controls did not show a (detectable) early deoxygenation of blood in our study, patients with CMA displayed a significant effect, indicating impaired neurovascular coupling that might require a relatively high oxygen extraction rate as it was reported for CMA (de Reuck et al., 1998).

Interestingly, CMA is characterized by specific alterations of the microvasculature, namely loss of smooth muscle cells, and increased vessel stiffness that might attenuate vascular reactivity and, consequently, neurovascular coupling (Caplan, 1995; Roman et al., 2002; Tanoi et al., 2000). Indeed, vasomotion, which regulates capillary perfusion by a myogenic pacemaker mechanism in terminal arterioles, is reduced in CMA (Bäzner et al., 1995; Schroeter et al., 2005). Moreover, vascular reactivity is diminished in CMA after application of azetazolamide (de Reuck et al., 1999), and during hypo- and hypercapnia (Hund-Georgiadis et al., 2003; Terborg et al., 2000), which is most pronounced in the frontal lobes (Hund-Georgiadis et al., 2003; Terborg et al., 2000). CBF is reduced particularly in the frontal lobes even during rest (Yoshikawa et al., 2003). Most interestingly, although the hemodynamic response as elicited by stimulation is reduced, the neuronal activation seems to be preserved in CMA (Rossini et al., 2004). This assumption might be supported by absent behavioral differences between patients with CMA and controls in our study beside reductions in speed of information processing. Particularly, we did not find any behavioral difference between both groups in the effect size analysis that examined the Stroop interference effect specifically.

In sum, impairments of neurovascular coupling may explain (i) the early blood deoxygenation, and, at least partly, (ii) the delay of the vascular response in the DLPFC of CMA patients during the Stroop task in our study. The assumption of disturbed neurovascular coupling might be further supported by a prolonged cerebral transit time of blood in CMA (Puls et al., 1999).

As discussed above, CMA affects primarily the frontal lobes (Hund-Georgiadis et al., 2003; Terborg et al., 2000; Tullberg et al., 2004; Yoshikawa et al., 2003). Correspondingly, it is neuropsychologically characterized by attentional and executive dysfunction (McPherson and Cummings, 1996; Prins et al., 2005; Roman et al., 2002). Impairments in glucose metabolism in the DLPFC may even predict cognitive decline over the following years (Reed et al., 2001). Our study applied a Stroop paradigm known to be related to frontal lobe function, namely interference resolution and response inhibition (Schroeter et al., 2002; Zysset et al., 2001). We hypothesized that brain activation declines in the DLPFC in CMA during the Stroop task, if compared with age-matched controls. Indeed, (iii) the mean vascular response was reduced in patients with CMA in correlation with slower behavioral performance and neuropsychological deficits. Although this group difference disappeared for the effect size analysis of the Stroop interference effect, brain activation in the DLPFC was still highly correlated with behavioral performance and with neuropsychological deficits, namely attentional and executive dysfunction that are specific for CMA (McPherson and Cummings, 1996; Prins et al., 2005; Roman et al., 2002). In contrast, there was no consistent correlation between

hemodynamic responses during the Stroop task and structural abnormalities on MRI. These results are in agreement with Hund-Georgiadis et al. (2002), and Sabri et al. (1998, 1999), who reported that neuropsychological deficits correlate with functional imaging parameters but not morphological changes in CMA. Our study supports the assumption of frontal lobe dysfunction in CMA, although we did not measure brain activation in other cortical areas to underline the regional specificity of the effect such as in our previous study on aging (Schroeter et al., 2003).

Recently, it was suggested that aging is related to microvascular dysfunction in frontal–subcortical regions (Pugh and Lipsitz, 2002). Indeed, we could show that exactly the same Stroop paradigm elicited a smaller vascular response in the frontal cortex of elderly subjects compared with young ones (Schroeter et al., 2003). However, we did not find hints for early blood deoxygenation or a delay of the vascular response. One may conclude that impairments of neurovascular coupling during functional stimulation are specific for CMA in contrast to normal aging.

Conclusion

The study measured brain activation in the frontal cortex of patients with cerebral microangiopathy during a Stroop task. Patients showed an early blood deoxygenation right after stimulation onset, and a delay and reduction of the vascular response. The latter was highly correlated with behavioral performance and neuropsychological deficits. Results indicate that neurovascular coupling and frontal lobe function are impaired in cerebral microangiopathy.

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