Cerebral Blood Flow Dynamics During Pain Processing Investigated by Functional Transcranial Doppler Sonography

Stefan Duschek, PhD,* Nicolette Hellmann,* Karim Merzoug, MD,† Gustavo A. Reyes del Paso, PhD,‡ and Natalie S. Werner, PhD*

*Department of Psychology, University of Munich, Munich; †Department of Anesthesiology, Paracelsus Hospital, Munich, Germany; ‡Department of Psychology, University of Jaén, Jaén, Spain

Reprint requests to: Stefan Duschek, PhD, Department Psychology, University of Munich, Leopoldstr. 13, 80802 Munich, Germany. Tel: 89-2180-5297; Fax: 89-2180-5233; E-mail: duschek@lmu.de.

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Abstract

Objective. Functional transcranial Doppler sonography (fTCD) enables reliable quantification of cerebral blood flow modulation during neural activation processes. Its high-time resolution, relatively simple technical arrangement, and low costs could make fTCD a useful tool in the investigation of brain activity underlying pain experience in fundamental and clinical research. The present pilot study explored the suitability of this technique to investigate cerebral hemodynamics during the processing of experimental heat pain.

Design. In 46 healthy subjects, blood flow velocities in the anterior cerebral arteries (ACA) and middle cerebral arteries (MCA) of both hemispheres were recorded, while heat stimuli of 45 and 47°C were applied to their left forearms (stimulus duration 20 seconds). Subjective sensory and affective pain intensities were assessed using visual analog scales.

Results. A biphasic right dominant blood flow increase arose in the ACA and MCA with maxima around 5 and 15 seconds after stimulus onset. The response was stronger under stimulation with 47°C with respect to 45°C, and the magnitude of the late response component correlated positively with sensory and affective pain intensity under the 45°C condition.

Conclusions. The findings suggest that fTCD measurements prove sensitive both to different levels of physical intensity of painful stimuli and to interindividual differences in nociceptive responding. fTCD may be a valuable tool in clinical pain research, for instance, when it comes to quantifying the temporal dynamics of exaggerated nociceptive responses in chronic pain, or evaluating treatment effects on nociceptive processing.

Key Words. Pain; Cerebral Blood Flow; Transcranial Doppler Sonography

Introduction

The functional coupling between neural activity and cerebral blood flow is of vast importance for the investigation of brain-behavior relationships. Neuroimaging methods such as functional magnetic resonance imaging (fMRI) or positron emission tomography register local distribution patterns of cerebral blood flow to map brain function [1]. Regarding the processing of acute pain, these methods have identified a neuromatrix of nociception including the primary and secondary somatosensory cortices, the insula, cingulate and thalamus, as well as prefrontal and parietal regions [2,3].

Like spatial distribution patterns, the dynamic dimension of the cerebral hemodynamic response has been attracting increasing interest in behavioral neuroscience. This is justified in particular by the time-dependence of the association between nerve cell and hemodynamic activity that has repeatedly been described [4,5]. In this sense, the linkage of cerebral blood flow to neural as well as psychological processes is restricted to relatively small and mostly early time frames of the hemodynamic response [6–10]. Analyses of this connection in the field of nociception are, however, still sparse [11].

Functional transcranial Doppler sonography (fTCD) is an ultrasonic technique that enables continuous non-invasive measurement of blood flow velocities in the basal cerebral arteries. Unlike most neuroimaging techniques, fTCD provides excellent time resolution and may therefore be well suited for the assessment of the time dynamics of cerebral
blood flow modulations related to nociception [12,13]. Additional advantages arise from the relatively simple technical arrangement and low costs, which could make fTCD a useful tool in the investigation of brain processes underlying pain experience in both fundamental and clinical pain research.

The objective of the present study was twofold. First, it explored the suitability of fTCD for the investigation of cerebral blood flow during the processing of acute pain. Second, it attempted to gain insight into the pattern of hemodynamic modulations in the basal cerebral arteries related to nociceptive processing. For this purpose, healthy subjects were exposed to painful heat stimuli of different intensities. During stimulation, bilateral recordings were made of blood flow velocities in the anterior cerebral arteries (ACA) and middle cerebral arteries (MCA), which supply the neuromatrix of nociception. Four hypotheses were addressed: 1) Painful stimulation was expected to cause an increase in blood flow velocities in the named vessels, which, due to contralateral processing in the central nociceptive system, is stronger in the hemisphere opposite the side of stimulation. 2) fTCD studies from the field of cognition commonly revealed biphasic hemodynamic responses beginning with a latency of around 1 second after stimulus onset [5,7,14]. Due to the relative inertness of nociceptive signal processing, however, longer latencies and stronger late response components were expected in the present case. The validity of fTCD would be supported by its sensitivity to both stimulus intensity and subjective pain experience. We therefore predicted 3) a more pronounced hemodynamic response during stronger stimulation and 4) an association between at least specific response components and pain intensity.

Methods

Participants

Forty-six subjects (25 women, 21 men) with a mean age of 27.0 years (standard deviation [SD] = 7.5 years) participated. Criteria for exclusion comprised relevant physical diseases, acute or chronic pain of any kind, psychiatric disorders, as well as the use of psychoactive drugs, analgesics, or medication affecting the cardiovascular system. Health status was assessed using an anamnestic interview and a comprehensive medical questionnaire. All subjects were right-handed according to the Edinburgh Handedness Inventory [15]. Thirteen of the women in the sample were using oral contraceptives. Five subjects reported that they were having their period on the day of the experiment. For the remaining women, the time interval from the end of the latest period was 12.6 days (SD = 7.1 days). Thirty of the participants were university students, nine were employees or civil servants, and seven were self-employed.

Pain Induction and Quantification

Thermal stimulation was performed using a Thermal Sensory Analyzer (TSA II, Medoc Advanced Medical Systems, Ramat Yishai, Israel). A contact thermode (surface 30 × 30 mm) was attached to the volar surface of the left forearm. The thermode was digitally controlled using the software CoVAS (Medoc Advanced Medical Systems). Eight stimuli of 45 and 47°C, respectively, were presented in pseudorandom sequence. The temperature of 45°C is close to the pain threshold in a large portion of subjects, while 47°C is mostly above the threshold [16,17]. Stimulus duration was 20 seconds with each stimulus being preceded by a 60-second baseline of 32°C (increasing and return rate 10°C/s).

The participants’ subjective pain experience was quantified using two 10-cm visual analog scales (VAS) referring to the sensory and affective aspects of pain (“How strong/unpleasant was the pain?”). The anchor points of the scales were marked “not at all” and “extremely.” Each of the 16 stimuli was evaluated separately. In order to keep effects of motor and verbal processing on the cerebral blood flow signal at a minimum, a 15-second interval was included between stimulus end and presentation of the VAS. The average values across the trials of stimulation with 45 and 47°C, respectively, were used for the statistical analysis.

Recording of Cerebral Blood Flow

For the purpose of cerebral hemodynamic recording, a commercially available Doppler sonography device (Multi dop L2, DWL Elektronische Systeme, Singen, Germany) was used. Blood flow velocities were monitored pairwise in both ACA and MCA. The recordings were obtained through the temporal bone windows using two 2-MHz transducer probes. Insonation took place at a depth of between 60 and 70 mm for the ACA and between 48 and 54 mm for the MCA. Following vessel identification, the ultrasonic probes were fixed to the head using a head-harness [13]. The spectral envelope curves of the Doppler signal were stored at a sample rate of 28 Hz.

Procedure

The experimental sessions were conducted at a constant room temperature of 22°C. Prior to the experimental procedure, socio-demographic data were taken from the participants and their current emotional state was assessed using the “Befindlichkeits-Skalae” (Mood Scale) [18]. This is a 28-item self-rating scale including positive and negative adjectives, which are related to general aspects of well-being (e.g., cheerful, relaxed), as well as to more specific emotions (e.g., depressed, insecure). Following this, the ultrasonic probes were mounted and pain stimulation was carried out in the described form. Blood flow in ACA and MCA was recorded sequentially, i.e., the entire procedure was repeated for both pairs of arteries with half of the subjects starting with the ACA and the other half with the MCA. Subjects were requested not to smoke or drink either alcohol or beverages containing caffeine for 3 hours prior to the experimental session. The study protocol was approved by the
ethics committee of the University of Munich and all participants gave their informed consent.

Data Analysis

The envelope curves revealed by Doppler sonography were analyzed offline using the software AVERAGE [19]. Blood flow velocities were represented by a time- and intensity-weighted “mean flow velocity index.” This score is the least susceptible to artifacts and demonstrates the highest correlation with blood volume flowing through a vessel [13]. Flow velocities were integrated over each cardiac cycle and averaged, time locked to stimulus onset, i.e., the beginning of the temperature increase. The epochs were set starting 10 seconds before stimulus onset and ending 10 seconds after stimulus offset, i.e., the beginning of the temperature decrease. The mean flow velocity during the 10 seconds prior to stimulus onset served as a baseline (FVbas). Relative (percent) changes in flow velocity during stimulation (dFV) were calculated for the left and right ACA and MCA using the formula dFV = (FV(t) - FVbas) × 100 / FVbas, where FV(t) is the flow velocity over the course of time. The values of dFV were aggregated to three predefined intervals. Based on first visual inspection of the data, two response components were identified, i.e., an early phase covering the first 10 seconds of stimulation and a late phase covering the second 10 seconds of stimulation. In addition, a recovery phase including the first 10 seconds after stimulus offset was defined.

For the purpose of statistical analysis, an analysis of variance (ANOVA) procedure was computed with the factor’s stimulus intensity (45 vs 47°C), response interval (early response vs late response vs recovery), vessel (ACA vs MCA), and hemisphere (left vs right). Relationships between subjective pain experience and cerebral blood flow responses were quantified by means of Pearson correlations between the VAS ratings and the aggregated values of dFV. VAS ratings tended to be higher in women than in men. Even though the gender effect was significant only for the 47°C condition during the recording of the MCA (sensory VAS: t[44] = 2.16, P = 0.036; affective VAS: t[44] = 2.32, P = 0.025), gender was partialled out in the computation of all correlations. Gender did not affect cerebral blood flow velocities (all t[44] ≤ 1.33, all P ≥ 0.19), nor were there significant effects of mood, use of oral contraceptives, or menstrual status on any of the dependent variables (Mood Scale: all r not significant [n.s.]; contraceptives: all t[23] ≤ 1.12, all P ≥ 0.28; presence of period: all t[23] ≤ 1.64, all P ≥ 0.12; days from latest period: all r n.s.). Therefore, no further covariates were applied in the analyses.

Results

Figure 1 displays the changes in blood flow velocities in the ACA and MCA of both hemispheres under both stimulation conditions. As a general response pattern, a biphasic flow increase was observed. A first peak occurred in the middle of the time frame defined as the early response, i.e., the first 10 seconds of stimulation and a second one in the interval of the late response, i.e., the second 10 seconds of stimulation, or close to stimulation offset. Overall, stimulation with 47°C produced a markedly stronger blood flow increase than stimulation with 45°C. Both in the ACA and in the MCA, the response was more pronounced in the right hemisphere than in the left hemisphere. The latency of the flow increase was between 2 and 3 seconds after stimulus onset and did not differ as a function of vessel, hemisphere, or stimulus intensity.

The ANOVA revealed a main effect of temperature (F[1,45] = 4.20, P = 0.046, partial eta squared = 0.085), showing that stimulation with 47°C produced a stronger response. Even though the temperature effect was somewhat more pronounced in the late phase of the response, the interaction between temperature and response component did not reach significance (F[1,45] = 2.20, P = 0.12, partial eta squared = 0.047). A main effect of hemisphere confirmed the observed laterализation (F[1,45] = 26.49, P < 0.01, partial eta squared = 0.37) and a main effect of the factor vessel (F[1,45] = 6.38, P = 0.015, partial eta squared = 0.12) indicated an overall stronger response in the MCA than in the ACA. Also, the main effect of response component reached significance (F[2,90] = 7.55, P < 0.01, partial eta squared = 0.14). Post hoc testing revealed overall significantly lower blood flow velocities during the early response compared with the late response and recovery (early vs late: F[1,45] = 19.77, P < 0.01; early vs recovery: F[1,45] = 5.60, P = 0.022).

In Figure 2 the VAS ratings on subjective pain experience are shown. The bars represent the mean values computed across all trials of the respective stimulus intensities. Concerning both the sensory and the affective pain dimensions, the ratings were markedly higher for stimulation with 47°C than with 45°C (sensory: t[45] = 27.51, P < 0.01; affective: t[45] = 29.16, P < 0.01).

Table 1 includes the correlations of the magnitudes of the cerebral blood flow changes for the early and late response components with pain experience. The late response correlated significantly positively with the ratings on sensory and affective pain during stimulation with 45°C. This holds true for the ACA and MCA of both hemispheres. None of the remaining correlations reached significance.

Discussion

As a main result of the study, fTCD revealed marked biphasic increases in blood flow velocities in the ACA and MCA during stimulation with painful heat. Stimuli of 47°C, which are believed to be above the pain threshold in most individuals, elicited a significantly stronger blood flow response than moderate stimuli of 45°C. The magnitude of the late response component correlated positively with the intensity of subjective sensory and affective pain under the 45°C condition. These observations suggest that fTCD measurements are sensitive to the physical intensity of painful stimulation as well as interindividual differences.
in subjective pain experience and thus support the utility of the technique in the assessment of cerebral blood flow modulations related to nociceptive processing.

The blood flow modulations may be ascribed to neural activation processes within the neuromatrix of nociception. The perfusion territory of the MCA mainly comprises lateral parts of the cortex. Among the structures involved in nociception, this area includes the fraction of the primary somatosensory cortex representing the forearm, the inferior parietal lobe, as well as the insular cortex. The ACA supplies medial regions of both hemispheres including the cingulate cortex. The prefrontal cortex is supplied by both the ACA and the MCA [2,3,20]. Blood flow responses were more pronounced in the hemisphere opposite the side stimulated than in the ipsilateral hemisphere. This is in accordance with the predominantly contralateral processing of nociceptive information. Thermal pain is transmitted by A delta and C fibers of the anterolateral tract, which cross the spinal cord close to their origin in the dorsal horn [17].

**Figure 1** Relative changes of blood flow velocities in the anterior cerebral arteries (ACA) and middle cerebral arteries (MCA) of both hemispheres in the course of stimulation (grand average).

**Figure 2** Visual analog scale (VAS) ratings on sensory and affective pain intensity (bars represent standard errors of the mean).
Early response Left ACA 0.00
Right ACA 0.08
Left MCA 0.13
Right MCA 0.15

Late response Left ACA 0.29*
Right ACA 0.33*
Left MCA 0.38**
Right MCA 0.40**

* $P < 0.05$; ** $P < 0.01$.

ACA = anterior cerebral artery; MCA = middle cerebral artery.

Table 1  Correlations between changes in cerebral blood flow velocities and visual analog scale (VAS) ratings on sensory and affective pain (Pearson correlations with gender partialled out)

<table>
<thead>
<tr>
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<th>45°C Sensory Pain</th>
<th>45°C Affective Pain</th>
<th>47°C Sensory Pain</th>
<th>47°C Affective Pain</th>
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<td>Early</td>
<td></td>
<td></td>
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<tr>
<td>response</td>
<td>Left ACA 0.00</td>
<td>–0.03</td>
<td>–0.04</td>
<td>–0.17</td>
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<td></td>
<td>Right ACA 0.08</td>
<td>0.04</td>
<td>0.05</td>
<td>–0.10</td>
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<td></td>
<td>Left MCA 0.13</td>
<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td></td>
<td>Right MCA 0.15</td>
<td>0.09</td>
<td>–0.06</td>
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<td>Late</td>
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<tr>
<td>response</td>
<td>Left ACA 0.29*</td>
<td>0.32*</td>
<td>–0.13</td>
<td>–0.23</td>
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<tr>
<td></td>
<td>Right ACA 0.33*</td>
<td>0.30*</td>
<td>–0.05</td>
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<td></td>
<td>Left MCA 0.38**</td>
<td>0.28*</td>
<td>0.24</td>
<td>0.22</td>
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<tr>
<td></td>
<td>Right MCA 0.40**</td>
<td>0.33*</td>
<td>0.18</td>
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More intense heat stimulation appears to have led to stronger neurovascular activation. In the current temperature range, there is an almost linear rise in firing rate of temperature-sensitive nociceptors with respect to stimulus intensity [21]. While warmth receptors are also active with stimulation at 45°C, their discharge frequency drops away at higher temperatures [17]. It is thus justified to attribute the stronger blood flow response at 47°C to increased nociceptive afferent input and higher central nociceptive activity. The more pronounced response observed in the MCA than the ACA may indicate higher pain-related activity in the perfusion territory of the former. However, one should bear in mind that the suitability of fTCD for the localization of foci of brain activation is confined to tight limits. The perfusion territories of the basal cerebral arteries partially overlap and may differ between individuals; hence, the spatial resolution of fTCD is commonly considered to be rather low [13].

As a general response pattern in the four arteries under investigation, a biphasic course of blood flow arose with reaction maxima at 5 seconds and 15–18 seconds after stimulation onset. Biphasic blood flow modulations are well-known from fTCD studies conducted in the field of cognition, e.g., verbal, arithmetic, or attentional processing [5,14,22]. This pattern has been ascribed to initial cerebral activation and following adaptation and counter-regulation at neural and vascular levels [14]. The time course during painful stimulation, however, differed in two respects from the former observations. First, the latency of the present response was at 2–3 seconds relatively long. Even when considering the fact that the contact thermode reached its maximal temperature more than 1 second after the onset of the increase, the observed latency markedly exceeded that in cognition, where latencies of less than 1 second are commonly reported [7,22,23]. This may be explained by the relative inertness of the nociceptive system, particularly resulting from the involvement of slowly conducting unmyelinated C fibers in signal trans-

mission [21]. A second contrast to previous findings is the dominant late response component, which points toward an increase in nociceptive activity through stimulation. While sensory modalities other than pain show response attrition over time, nociception sensitization is well-known to occur at peripheral, central nervous, and behavioral levels [17].

The magnitude of the late response correlated positively with the VAS ratings on pain intensity. This held true for each of the four insonated arteries and the scales for both sensory and affective pain. The linkage of fTCD measures of neurovascular activation with subjective pain experience underlines the technique’s suitability also in detecting interindividual differences in nociceptive processing. The restriction of the correlation between blood flow and subjective pain to the late response contrasts with previous findings in cognitive processing, suggesting a specific association between early hemodynamic modulation and behavior. The closest associations between blood flow and cognitive performance have consistently been shown for the first 3 seconds of activation [6–9]. This divergence may relate to specific time course characteristics of cognitively induced hemodynamic responses including a steep initial rise and maximum within the first 5 seconds. One may thus conclude that, in addition to the specific course of the hemodynamic response, the time dynamics of the association between cerebral blood flow and behavior strongly depends on the neurobehavioral function under study. The findings thereby highlight the importance of the dynamic aspect in the investigation of cerebral blood flow in behavioral neuroscience and emphasize the suitability of research techniques enabling high time resolution analyses.

The present finding is in accordance with an fMRI study by Chen et al. [11]. They investigated the time course of the BOLD signal in the somatosensory cortices of four healthy volunteers obtained during noxious heat stimulation.
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(45–46°C, stimulus duration 10 seconds). Just as in the present study, a biphasic signal change was observed with peaks at around 5 and 15 seconds after stimulus onset. The magnitude of the second maximum far exceeded that of the first one. Continuous pain ratings, which were obtained in a separate psychophysical experiment, showed a time course of subjective pain intensity similar to that obtained for blood flow in the somatosensory cortices. Interestingly, in both studies, comparable time courses of cerebral blood flow modulations arose even though stimulus duration was only half as long in the fMRI study. One may conclude that the hemodynamic reaction pattern to short-term noxious stimulation is, to some extent, independent of stimulus duration and its maximum may even occur after the end of stimulation. Unfortunately, in the study of Chen et al., correlations between blood flow and pain ratings are not reported; hence, no information is available as to the degree to which BOLD reactions prove sensitive to interindividual differences in nociceptive responding. In contrast, in the present study, information about the time course of the subjective pain response and its possible resemblance to blood flow changes is missing. Nonetheless, the similarity of the findings of both studies is remarkable, particularly taking into account that fMRI and fTCD record different phenomena representing cerebral blood flow, i.e., the cerebral oxyhemoglobin–deoxyhemoglobin ratio in fMRI and cerebral blood flow velocities in fTCD.

In terms of a more general comparison between fMRI and fTCD in experimental pain research, the main advantage of fMRI arises from its high spatial resolution, which—in contrast to fTCD—enables the description of blood flow changes in circumscribed parts of the neurormatrix of nociception. fTCD is superior with respect to the time dimension. While the technique’s temporal resolution is usually limited to the duration of a heart cycle, by means of refined techniques such as the coupling of stimulus presentation to the heart cycle, response times can be measured with an accuracy of about ±100 milliseconds [11]. This allows precise analyses of the temporal dynamics of blood flow reactions to different stimulation conditions. Also, the practical advantages of fTCD should not be overlooked. Ultrasound measurements can be carried out more easily and less expensively than fMRI scans and the application of fTCD is much less stressful for the subject. Due to the relatively simple technical arrangement of fTCD, stimulus presentation and assessment of reactions of the participants (e.g., language or motor responses) are hardly restricted.

The present study suggested that stimulation of moderate intensity is more appropriate than stronger stimulation when it comes to analyzing interindividual differences in cerebral blood flow dynamics during pain processing. The low correlations between blood flow and subjective pain in the case of the 47°C stimulation may relate to limited reactivity of the physiological systems adjusting cerebral blood flow to neural activation. Extreme stimulation may lead to maximum blood flow responses in many participants. This implies reduced reliability of the measurement due to a ceiling effect, which, in turn, may account for the low correlations with the pain ratings. During moderate stimulation, regulatory systems do not operate close to their limits; hence, interindividual differences in blood flow responses may be more reliably detected. Similar observations were reported for other types of stressful stimulation. Interindividual differences in cardiovascular reactivity to psychological stress, for instance, can more reliably be quantified using moderate instead of extreme stimuli [24,25]. Stimulus temperatures lower than 45°C may lead to confusion between nociceptive and somatosensory processing. Warmth-sensitive receptors exhibit their maximal discharge rate between 40 and 45°C. The pain-induced blood flow response may therefore be superimposed by that related to thermosensation. Other techniques of pain induction may complement the present research. Methods providing higher increasing rates, i.e., minimal intervals between stimulus onset and maximal stimulation, would allow a more precise determination of hemodynamic response latencies. In this regard, mechanical, electrocutaneous, or infrared laser stimulation would certainly be helpful.

A limitation of the study concerns the restriction of pain stimulation to two intensity levels. The use of a broader intensity range as well as finer gradation in future studies may yield additional information about the accuracy of discrimination of fTCD and thus enhance the generalizability of the results. Another restriction relates to the fact that individual pain thresholds were not assessed. Even though average values of thermal pain threshold of around 45°C are commonly reported [16,17], it has to be taken into account that thresholds vary considerably between individuals. The design does not provide an objective measure indicating to which degree the pain stimuli actually exceeded thresholds of the current participants. It also did not enable us to ensure that the observed blood flow responses exclusively related to nociceptive processing. In particular cognitive processes, for instance, the shift of attention toward the pain stimuli may have affected the pattern of hemodynamic modulation as well. A final limitation is due to the missing assessment of blood pressure as a possible confound. At least extreme values of blood pressure impact both nociception and cerebral hemodynamic regulation [16,26,27].

Clinical pain research is a tempting application of fTCD-based analyses of cerebral hemodynamics. Certainly, the present results may not immediately be generalized to patient populations and the methods, i.e., stimulation and recording procedures, may have to be adjusted. Exaggerated subjective responses to experimental pain have repeatedly been documented in patients with chronic pain syndromes [28–30]. As a physiological correlate of the hyperalgesia related to chronic pain, enhanced activity of the central nociceptive system stands to reason. This is supported by fMRI studies showing increased local blood flow in the neurormatrix of nociception during painful stimulation [31,32]. However, due to the relative low time resolution of fMRI, not much is known about the dynamic characteristics of this hyper-reactivity [33]. Detailed fTCD
analyses of the time course of the hemodynamic response could therefore complement neuroimaging studies. Aberrant response dynamics in chronic pain may include, for example, reduced latency, prolonged duration, delayed return to baseline, or increased amplitudes of specific response components. fTCD analyses may also be beneficial in quantifying effects of pharmacological, physical, or psychological interventions on nociceptive processing in acute and chronic pain. Besides clinical research, numerous applications of fTCD are conceivable in basic research, for instance, concerning the analysis of biological and psychosocial determinants of inter- and intra-individual variations in pain processing.

Conclusions
The study yielded evidence that fTCD is suitable for quantifying cerebral blood flow modulations related to the processing of experimental pain. The method proved sensitive both to different levels of physical intensity of pain stimuli and to interindividual differences in nociceptive processing. The study furthermore showed that the course of the pain-related hemodynamic response, as well as the time dynamics of the association between cerebral blood flow and behavior differ from those observed in other neurobehavioral processes. fTCD may be a valuable tool in numerous applications in basic and clinical pain research.

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