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DISSERTATION

Neurovascular coupling studied in a rat model during pathophysiological states: implications for functional brain imaging in patients

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Abstract

Functional magnetic resonance imaging (fMRI) with BOLD (blood oxygen level-dependent) has become a standard tool for psychological and neurological research. It relies on the local adaptation of blood flow to increased neuronal activity - a phenomenon known as neurovascular coupling. The effects of pathophysiological conditions on neurovascular coupling and its corresponding BOLD signal are largely unknown, restricting its implementation as a clinical tool for research and diagnosis.

This PhD-thesis summarizes findings relevant to this issue from three studies each exposing neurovascular coupling in the rat somatosensory cortex to a different pathophysiological challenge. As common experimental procedure, anesthetized rats underwent surgical preparation of a closed cranial window over the somatosensory cortex. Using Laser Doppler Flowmetry and optical spectroscopy, changes in cerebral blood flow (CBF), cerebral blood volume, deoxygenated hemoglobin (deoxy-Hb) and cerebral metabolic rate of oxygen were measured during electrical forepaw stimulation. Neuronal activity was monitored by somatosensory evoked potentials.

The first study evaluated the effect of hypothermia. Cooling down the brain by 10 °C preserved neurovascular coupling. Functional brain imaging (e.g. fMRI or near infrared spectroscopy) therefore offers the potential to evaluate neurovascular function in a patient undergoing hypothermia. The second study investigated pharmacological blocking of the neurovascular coupling response employing the cyclooxygenase (COX)-inhibitor indomethacin and the adenosine-receptor-inhibitor theophyllin, medications commonly used in patients. While CBF responses were reduced by 70 - 80 %, the deoxy-Hb response (correlate of the BOLD signal) was abolished. It was shown that medications potentially can interfere with neurovascular coupling, thereby rendering BOLD-fMRI impossible. The third study explored the influence of raised intracranial pressure (ICP). A stepwise ICP elevation to 28 mmHg reduced and eventually reversed the deoxy-Hb response to somatosensory activation. In addition, the post-stimulus response of deoxy-Hb regularly detectable at physiological conditions was abolished by increased ICP. Intracranial hypertension, a common condition in patients with an intracranial lesion or disease, can seriously disturb neurovascular coupling and preclude reliable brain mapping with fMRI. Future studies investigating these pathophysiological states in patients should be performed prior to an establishment of fMRI in the clinical setting.

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List of abbreviations

aCSF	artificial Cerebro-Spinal-Fluid
$BaCl_2$	Barium Chloride
BOLD	Blood Oxygen Level-Dependent
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CI	Confidence Interval
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
COX	Cyclooxygenase
CYP450	Cytochrome P450
ΔT	Delta T, Temperature difference
deoxy-Hb	Deoxygenated Hemoglobin
℃	Degree Celsius
EEG	Electroencephalogram
fMRI	functional Magnetic Resonance Imaging
g	Gram
Hz, kHz	Hertz, Kilohertz
ICP	Intracranial Pressure
i.v.	Intravenous
KCl	Potassium Chloride
Kir-channel	Inward rectifier potassium ion channel
LDF	Laser Doppler Flowmetry
L-NNA	N-Nitro-L-Arginine
mA	Milliampere
mmHg	Millimeter Mercury
MS-PPOH	N-Methylsulfonyl-6-(2-propargyloxyphenyl)hexanamide
min	Minutes
µm, nm	Micrometer, Nanometer
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
Oxy-Hb	Oxygenated Hemoglobin
%	per cent
r	Pearson's correlation coefficient
s, ms	Seconds, Milliseconds
SEP	Somatosensory Evoked Potentials

1. Introduction

For more than one decade, functional magnetic resonance imaging (fMRI) with BOLD (blood oxygen level-dependent) has been used to localize activated brain areas. This imaging technique does not rely directly on neuronal activity but on concentration changes in deoxygenated hemoglobin (deoxy-Hb) which in turn originate from the local interaction between cerebral blood flow (CBF), cerebral blood volume (CBV) and the increase in oxygen consumption of the tissue ($CMRO_2$). This phenomenon is known as neurovascular coupling. Its mediation is not completely resolved but it presumably involves metabolic (e.g. CO_2, K^+, adenosine) or neurogenic factors (e.g. neurotransmitters, NO), translating neuronal activity into a change in CBF and CBV (Estrada and DeFelipe, 1998; Iadecola and Nedergaard, 2007; Metea and Newman, 2007). It has long been suggested that the CBF increase is triggered by the demand of the tissue for oxygen and glucose, but local $CMRO_2$ does not increase to the same extent as local CBF and glucose consumption of the tissue (Fox and Raichle, 1986). Hitherto, neither the exact mechanisms nor the evolutionary advantages of such a CBF response are known. However, the resulting $CBF/CMRO_2$ mismatch causes a localized hyperoxygenation during increased neuronal activity with a decrease in deoxy-Hb which provides the basis for BOLD fMRI. While the kinetics of the CBF response is related to neuronal activity, its local distribution is limited by vascular properties and by hemodynamic interactions and therefore distorted and displaced. In addition, neuronal activity is one parameter among others in CBF regulation, and CBF is one parameter among others in deoxy-Hb signaling. Signal transduction from neuronal activity to BOLD fMRI can therefore be disturbed not only at the level of neurovascular, but also of CBF - deoxy-Hb interaction.

It is currently unclear whether pharmacological interventions or pathophysiological changes of neurovascular coupling parameters modify deoxy-Hb signaling for brain mapping although functional MRI techniques are being used in patients with severe brain diseases (Monti et al., 2010) and intracranial tumors (Schreiber et al., 2000; Holodny et al., 2000). This PhD-thesis summarizes three studies that expose the same animal model of neurovascular coupling to different pathophysiological challenges including hypothermia, pharmacological intervention and intracranial hypertension.

Induced hypothermia improves neurological outcome in patients after cardiac arrest (Geocadin et al 2006, Green and Howes 2005) and is being investigated as a potential neuroprotective treatment in ischemic stroke (Gisselsson et al., 2005, Sacco et al., 2007). Understanding the relationship between brain temperature decrease and changes in the metabolic-vascular response coupled to functional activation appears relevant since optical imaging of neurovascular coupling is gaining importance in the clinical setting (Hillman, 2007). It has great potential in monitoring the infant brain (Hebden et al 2002, Hintz et al 2001), while induced hypothermia is an established therapy in children who remain comatose after resuscitation. Therefore, in a first study, the effect of hypothermia on neurovascular coupling was investigated.

The second study focused on pharmacological intervention since many patients that might in future undergo BOLD-fMRI receive medications possibly influencing neurovascular coupling. Specifically, the COX-inhibitor indomethacine and the adenosine-receptor-antagonist theophyllin, commonly used drugs in patients, were part of a pharmacological cocktail used to block the CBF response.

The third study used intracranial hypertension, i.e. raised intracranial pressure (ICP) as a challenge to neurovascular coupling. It has long been known that ICP has a strong influence on cerebrovascular dynamics (Kety et al., 1948). The influence of ICP on BOLD fMRI has not been studied so far. Indirect conclusions can be drawn from studies that report an alteration of BOLD fMRI in patients with an intacranial tumor (which is often accompanied by an increased ICP). Schreiber et al. (2000) showed that a glial tumor reduced the ipsilateral BOLD-activity, whereas a non-glial tumor did not cause a significant change.

The following paragraph summarizes the aims of the PhD-thesis and its three different studies.

2. Aims

The aim of this PhD-thesis was to clarify the influence of clinically relevant pathophysiologies on neurovascular coupling parameters in order to identify confounding factors when establishing the corresponding brain imaging methods like BOLD fMRI in the clinical setting.

The first study investigated the impact of induced hypothermia on neuronally coupled changes in CBF and $CMRO_2$. Additionally, the temperature dependency of $CMRO_2$ was quantified to estimate the Q_{10} value. The Q_{10} value served to validate an optical approach for $CMRO_2$ calculation based on CBF, CBV and deoxy-Hb measurements.

The second study focused on the combined inhibition of specific pathways mediating the CBF response to functional activity. It was tested whether a reduction of the CBF response can affect neuronal activity, $CMRO_2$, or the oxygenation state of the microvasculature. In the context of this PhD-thesis, specifically indomethacin as COX-inhibitor and theophyllin as adenosin-receptor-antagonist are relevant because of their frequent use in the clinical routine.

The third study explored the influence of ICP elevation on functional changes in CBF, CBV and deoxy-Hb. Furthermore, it was tested whether the post-stimulus response could be attributed to passive vascular mechanisms, rather than neurovascular interaction or neuronal $CMRO_2$.

3. Materials and Methods

All experiments were performed according to national and international animal care guidelines and were approved by the local official committee 'Landesamt für Gesundheit und Soziales', Berlin, Germany.
Supplementary details are described in the publications listed in the appendix.

Preparative Surgery

Anesthetized and artificially ventilated male Wistar rats (250 - 320 g) underwent surgical preparation of a closed (study 1) and superfused (study 2, 3) cranial window over the right somatosensory cortex.
The femoral artery was cannulated to monitor arterial blood pressure and to obtain serial arterial blood gases. The femoral vein was cannulated for infusion of anesthetics. Body temperature was kept at 37 ± 0.5 °C by a homeothermic blanket system.

Electrical forepaw stimulation

Two needle electrodes were inserted under the skin of the left forepaw for administering stimulus currents. Rectangle pulses with an intensity of 1.6 mA (study 1, 3) and a maximum of 2.0 mA (study 2) were applied with frequencies of 4 Hz (study 1) or 3 Hz (study 2, 3). Each stimulation train lasted 4 s (study 1), 16 s (study 2) or 30 s (study 3) with a minimum interval of 30 s (study 1), 75 s (study 2) and 2 min (study 3) between two successive stimulation trains.

EEG and SEP

To obtain a quantitative parameter of the underlying neuronal activity, a continuous EEG was recorded using a ball-tip silver electrode placed on the surface of the cortex**.** The reference electrode was inserted subcutaneously into the neck muscle. The EEG was digitized with a sampling rate of 10 kHz. For each stimulation train, the SEP was extracted post-hoc from the continuous data.

Simultaneous measurement of CBF and Hemoglobin Oxygenation

Combined measurement of CBF and hemoglobin changes in the somatosensory cortex was performed as described in Kohl-Bareis et al. (2005). In brief, relative CBF changes were measured using Laser Doppler Flowmetry (LDF) at 780 nm with a fiber distance of 350 µm. In an x-shaped arrangement, the two optical fibers for CBF measurement were combined with two optical fibers for measurement of hemoglobin

oxygenation (fiber distance 250 µm), resulting in a largely overlapping sample volume. Absolute concentration time courses of oxy-Hb and deoxy-Hb were determined from measured reflectance spectra in the wavelength range of 520 - 610 nm using a modified Lambert-Beer-algorithm. For relative CBV assessment, total hemoglobin was calculated (CBV = oxy-Hb + deoxy-Hb).

Relative change of $CMRO_2$ was calculated following Dunn et al. (2005) by

$$CMRO2(t) = CBF(t) \times \frac{deoxy - Hb(t)}{CBV(t)} \qquad \text{(Equation 1)}$$

assessing stoichiometrically the rate of deoxy-Hb production with CBF, deoxy-Hb and CBV in normalized values at time-point t as mentioned above. The equation was validated by induced hypothermia (study 1). In this regard, the Q_{10} value for $CMRO_2$, describing the quantitative relationship between $CMRO_2$ changes and temperature, was obtained by fitting the measured data for $CMRO_2$ to

$$\frac{CMRO_2(\Delta T)}{CMRO_2(T_0)} = Q_{10}^{\ \Delta T/10} \qquad \text{(Equation 2)}$$

with T_0 indicating the baseline temporalis muscle temperature, reflecting the brain temperature (Eshraghi et al., 2005). ΔT denotes the temporalis muscle temperature change in [°C] occuring during the experiment.

Experimental Protocols

After surgical preparation, the optical probe was placed closely over the cover glass of the cranial window and directed to the site of maximal functional CBF response upon forepaw stimulation with minimal contribution of superficial pial vessels. Data collection was started for CBF, oxy-Hb, deoxy-Hb and EEG while intermittently, forepaw stimulations were delivered.

Study 1: In the hypothermia group (n = 6) temperature was kept stable for ten minutes. The heating blanket was then turned off and hypothermia was induced by applying ice packs to the animal, leading to a cooling of the body and the head. The animals were cooled down by 10 °C and then rewarmed again by removing the ice packs and turning on the heating pad. For control animals (n = 4) body temperature was kept constant within physiological values.

Study 2: The cranial window was implanted and equipped with an inflow- / outflow system for superfusion of substances. During the first stimulation block aCSF was superfused. For the control group (n = 6) a vehicle was applied in the next block

(aCSF + 0.5 % ethanol). In the other groups different combinations of substances with a known inhibitory effect on functional hyperemia were superfused ($BaCl_2$ (n = 6); L-NNA, indomethacin, MS-PPOH, theophylline (n = 6); L-NNA, indomethacin, MS-PPOH, theophylline, $BaCl_2$ (n = 6) - each solved in vehicle). After 60 min, a second stimulation block was conducted analogous to the first one.

Study 3: The cranial window was prepared and the inflow tube was connected to a reservoir filled with aCSF for ICP modification. Counterpressure was applied through a cannula which was inserted into the cisterna magna and connected to a second reservoir with aCSF. The height of the reservoirs was adjusted to impose a hydrostatic pressure of 3.5 mmHg and the first stimulation block was conducted. Subsequently, ICP was increased (n = 9) by raising the aCSF reservoirs to 7 mmHg for the second stimulation block, then 14 mmHg and 28 mmHg for the third and fourth stimulation blocks, respectively. For control animals (n = 6) ICP was kept at 3.5 mmHg throughout the four stimulation blocks.

After the experiments, animals were sacrificed in deep anesthesia by i.v. administration of concentrated KCl.

Data analysis

Averaged functional activation time courses of CBF, CBV, deoxy-Hb and $CMRO_2$ were expressed as % changes from pre-stimulus baseline and compared with the respective control groups. Time courses were plotted as mean across animals ± standard error of mean or 95 % confidence intervals respectively.

SEP changes were calculated as per cent changes of the N1P1 amplitude of SEPs during control condition or as relative SEP amplitude normalised to baseline amplitude.

Further data processing and performed statistical analysis are described in more detail in the publications listed in the appendix.

4. Results

The results of this thesis have been included in the publications listed in the appendix. Here, the main findings are summarized, focussing either on baseline changes or stimulation induced changes or changes which occurred directly after stimulus cessation ('post-stimulus response').

Study 1: Hypothermia

Effects of hypothermia on neuronally coupled changes in CBF and $CMRO_2$

Lowering brain temperature decreased averaged functional changes of CBF and $CMRO_2$ as well as SEP amplitudes to approximately the same degree (~ -50 - -80 %). The responses continued to be clearly distinguishable, even after brain cooling by -8 to -10 °C. The correlation of CBF and $CMRO_2$ responses to the underlying neuronal activity was statistically significant during hypothermia ($r = 0.34$ and $r = 0.46$). In the control group stimulation induced vascular responses as well as neuronal activity (measured by SEPs) remained stable.

Calculation of Q_{10} for $CMRO_2$ based on vascular parameters

The $CMRO_2$ dependency on temperature was calculated for each animal from relative baseline changes in CBF, CBV and deoxy-Hb. The Q_{10} for $CMRO_2$ was estimated by fitting changes of relative $CMRO_2$ (Equation 2). The pooled data displayed a Q_{10} of 4.4 (95 % CI 3.7 - 5.1) obtained by linear regression analysis over all animals.

Study 2: Pharmacological intervention

Effects of inhibitors on CBF -, $CMRO_2$ - and deoxy-Hb responses

During superfusion of aCSF, stimulus induced CBF increased by ~ 50 %, $CMRO_2$ by ~ 10 % and deoxy-Hb level decreased by ~ 15 %. Combined inhibition of COX, NOS, adenosine receptors and CYP450 epoxygenase, led to a significant reduction of the averaged CBF response to functional activation by approximately two-thirds ($P < 0.01$). Moreover, CBF response inhibition by approximately two-thirds abolished the CBF response-related decrease of deoxy-Hb concentration: the deoxy-Hb concentration remained unchanged during the stimulation period, whereas activity-induced $CMRO_2$ responses as well as SEPs remained largely unaffected. In the control group vascular responses and SEPs remained stable throughout the experiment.

Study 3: Intracranial hypertension

Effects of elevated ICP on neurovascular coupling parameters

Stimulation induced amplitudes of CBF, CBV and $CMRO_2$ for all animals during non-elevated ICP increased by ~ 13 %, ~ 4 % and ~ 6 %, respectively while deoxy-Hb decreased by ~ 6 %. Upon ICP elevation responses of CBF and CBV appeared reduced but did not correlate with ICP. The accompanying amplitude of the deoxy-Hb decrease was reduced to ~ 2 % at ICP = 7 mmHg. At an ICP of 14 mmHg the deoxy-Hb response was close to zero and even reversed at an ICP of 28 mmHg. Deoxy-Hb amplitude and ICP were significantly correlated (r = 0.64). Time matched control animals without ICP elevation did not show relevant changes in stimulus-induced responses of CBF, CBV and deoxy-Hb. SEPs remained stable throughout the experiment in both groups.

Mean amplitude of baseline CBF significantly increased with ICP (median of ~ 19 %, ~ 24 % and ~ 76 % for ICP = 7 mmHg, 14 mmHg and 28 mmHg, relative to CBF at ICP = 3.5 mmHg; r = 0.74) with no concomitant rise in CBV: Mean baseline oxygen saturation of hemoglobin increased (r = 0.50) and was significantly correlated with baseline CBF (r = 0.59).

Post-stimulus response of deoxy-Hb during elevated ICP

The mean post-stimulus amplitude of deoxy-Hb for animals at ICP = 3.5 mmHg increased by ~ 2 % (post-stimulus overshoot). Quantification of the mean positive post-stimulus response for the ICP elevation group showed a significantly reduced post-stimulus area at the ICP of 28 mmHg compared to the response at the ICP of 3.5 mmHg. There was a significant correlation between ICP and the deoxy-Hb post-stimulus response (r = 0.49). In time control animals the overshoot response remained stable.

5. Discussion

The studies of this PhD-thesis use a well-established animal model of neurovascular coupling to demonstrate that

(1) activity-induced neurovascular coupling is preserved during hypothermia
(2) relative values of $CMRO_2$ can be quantified with optical methods
(3) combined inhibition of COX, NOS, adenosine receptors, and CYP450 epoxygenase reduces the CBF response to functional activation by approximately two-thirds while neuronal activity and $CMRO_2$ remain largely unaffected
(4) stimulation-induced deoxy-Hb decrease is abolished by pharmacologically blocking of the CBF response
(5) during ICP elevation, the stimulation-induced deoxy-Hb response decreases and eventually shows a reversal
(6) raising ICP suppresses the deoxy-Hb response in the post-stimulus period

In the following, issues relevant to these findings will be discussed.

Neurovascular coupling: useful when monitoring hypothermia?

Induced hypothermia is an established intervention in patients after cardiac arrest (Geocadin et al., 2006) and in unconscious patients, who are monitored through evoked potentials (Freye, 2005). In study 1 it was shown that despite cooling down the brain by as much as 10 °C, neurovascular coupling was preserved: Reduced changes in CBF, deoxy-Hb and $CMRO_2$ were accompanied by reduced neuronal activity emphasising the great potential of optical imaging (e.g. near infrared spectroscopy) or fMRI in monitoring brain function and the possible implication for clinical aspects of hypothermia as neuroprotective treatment. It is therefore promising to establish a multimodal approach that combines SEP and simultaneous optical measurement of the vascular response to monitor hypothermic patients, e.g. to judge both functional neuronal and vascular integrity in comatose survivors of cardiac arrest during hypothermic treatment.

Uncoupling of deoxy-Hb signaling from CBF by pharmacological intervention

$CBF/CMRO_2$ mismatch has been a matter of controversy since its first description by Fox and Raichle in 1986 (Fox and Raichle, 1986). Many explanations have been discussed (Buxton and Frank, 1997; Vafaee and Gjedde, 2000; Gjedde, 2002) and most of them emanate from the assumption that the increase in CBF serves the

delivery of oxygen to activated brain region. The findings of study 2 argue for a CBF response that is not closely matched to oxygen demands but rather overshoots with a safety margin. The safety factor of the CBF response with respect to relative hypoxia (as determined by microvascular deoxy-Hb concentration) is approximately three in this study and compatible with data on safety factors of other systems (Diamond, 2002). More importantly, reduction of the CBF response by two-thirds abolishes the stimulus-induced decrease in deoxy-Hb. This decrease however provides the basis for functional imaging using BOLD fMRI, a noninvasive technique which has become a standard tool for psychological and neurological research. The data provides evidence that under pathological conditions of impaired vascular reactivity (by the above mentioned drugs or due to aging or vascular dementia), neuronal activity might no longer be detectable by this technique.

Intracranial hypertension extinguishes or reverses deoxy-Hb signaling

The third study showed that stimulus-induced deoxy-signaling is again abrogated - under conditions of moderately increased ICP. At high ICP, an extinguished or even reversed deoxy-Hb response to functional stimulation was observed. The presumptive mechanism of this reversal involves an outwash of deoxy-Hb from the sample volume during compensatory CBF increase without concomitant CBV increase. Therefore, red blood cell velocity increased, resulting in a shortened capillary transit time, a drop in oxygen extraction fraction and a raised oxygen saturation of the sample volume. Under these circumstances, an unmasking of deoxy-Hb production as a result of increased $CMRO_2$ during stimulation takes place.

Negative functional BOLD-fMRI signals under pathophysiological conditions

The results contribute significantly to the ongoing debate on the physiological mechanisms underlying negative functional BOLD signals under pathophysiological conditions such as arterial hypotension or during seizures (Nagaoka et al., 2006; Wang et al., 2006; Schridde et al., 2008). BOLD fMRI has been introduced into presurgical assessment of brain tumor patients in order to map brain activity and identify so-called eloquent brain areas (Vlieger et al., 2004). The ICP of a patient with a brain tumor is often elevated and leads to typical symptoms of headache, nausea and vomiting (Forsyth and Posner, 1993). The presented findings suggest that BOLD fMRI may be unable to detect neuronal activity when ICP is increased only

moderately (~ 14 mmHg), therefore eloquent brain areas may not be identified, and thus damaged during surgery. When ICP increase is even more pronounced (~ 28 mmHg), BOLD fMRI signal characteristics would be reversed and suggest neuronal inhibition where activation is taking place.

The BOLD post-stimulus undershoot: a passive vascular phenomenon.

From a physiological perspective, study 3 gives answers regarding the BOLD post-stimulus undershoot (correlate of the deoxy-Hb overshoot) which is center stage in an ongoing debate since its first description by Kwong et al. (1992). Several explanations point in different directions concerning the underlying deoxy-Hb elevation after the end of the neuronal activation. Hypotheses reach from a CBV-CBF mismatch with vascular compliance (Buxton et al., 1998; Mandeville et al., 1999b) to an increased $CMRO_2$ after stimulus cessation (Frahm et al., 2008; Krüger et al., 1996; Lu et al., 2004) to a CBF undershoot (Chen and Pike, 2009; Hoge et al., 1999, Logothetis, 2003). Elevated ICP caused a significant diminution and levelling of the deoxy-Hb post-stimulus response while neurovascular coupling was kept intact. Therefore, the data is in line with Buxton et al. (1998) and Mandeville et al. (1999b) and suggests that passive vascular compliance is responsible for the post-stimulus deoxy-Hb elevation. It has been proposed that the BOLD post-stimulus undershoot is caused by increased $CMRO_2$ (Frahm et al., 2008; Krüger et al., 1996; Lu et al., 2004). This conclusion was drawn from indirect evidence since methodical assessment of the respective model and activation paradigm did not allow to directly calculate the post-stimulus $CMRO_2$. In agreement with Mandeville et al. (1999a), who did not find a post-stimulus $CMRO_2$ increase in a functional study on the somatosensory cortex, the present experiments demonstrate a deoxy-Hb elevation after stimulus cessation without concurrent increase in $CMRO_2$. Therefore, it seems unlikely that an increase in $CMRO_2$ can cause the BOLD post-stimulus undershoot.

In summary, different pathophysiological influences were studied on an animal model of neurovascular coupling. While preserved during hypothermia, neurovascular coupling was seriously disturbed by pharmacological intervention and intracranial hypertension. Future studies investigating these pathophysiological states in patients should be performed prior to an establishment of fMRI in the clinical setting.

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Appendix

Anteilserklärung

Martina Füchtemeier hatte folgenden Anteil an den vorgelegten Publikationen:

Publikation 1:	NeuroImage 2008; Vol. 40(4); 1523-1532.
Titel:	Hypothermia effects on neurovascular coupling and cerebral metabolic rate of oxygen.
Autoren:	Royl, G*., Füchtemeier, M.*, Leithner, C., Megow, D., Offenhauser, N., Steinbrink, J., Kohl-Bareis, M., Dirnagl, U., Lindauer, U. *equally contributed
Anteil:	50 Prozent
Beitrag im Einzelnen:	Planung und Etablierung des Protokolls, Durchführung sämtlicher Experimente, Beteiligung an der Datenauswertung und Schreiben des Manuskriptes.
Publikation 2:	J Cereb Blood Flow Metab. 2010; Vol. 30(2); 311-322.
Titel:	Pharmacological uncoupling of activation induced increases in CBF and CMRO(2).
Autoren:	Leithner, C., Royl, G., Offenhauser, N., Füchtemeier, M., Kohl-Bareis, M., Villringer, A., Dirnagl, U., Lindauer U.
Anteil:	30 Prozent
Beitrag im Einzelnen:	Unterstützung bei der Datenerhebung, Beitrag zum Manuskriptentwurf und Reviewprozess.
Publikation 3:	NeuroImage 2010; Vol. 52; 445-454.
Titel:	Elevating intracranial pressure reverses the decrease in deoxygenated hemoglobin and abolishes the post-stimulus overshoot upon somatosensory activation in rats.
Autoren:	Füchtemeier, M., Leithner, C., Offenhauser, N., Foddis, M., Kohl-Bareis, M., Dirnagl, U., Lindauer, U., Royl, G.
Anteil:	80 Prozent
Beitrag im Einzelnen:	Planung und Etablierung des Protokolls, Durchführung sämtlicher Experimente, Datenauswertung, Verfassen des Manuskriptes und Bearbeitung der Revisions.

Berlin, den 29.06.2010 Ute Lindauer Martina Füchtemeier

Publikation 1

Royl, G*., Füchtemeier, M.*, Leithner, C., Megow, D., Offenhauser, N., Steinbrink, J., Kohl-Bareis, M., Dirnagl, U., Lindauer, U.: Hypothermia effects on neurovascular coupling and cerebral metabolic rate of oxygen. NeuroImage 2008; Vol. 40(4); 1523-1532.

Publikation 2

Leithner, C., Royl, G., Offenhauser, N., Füchtemeier, M., Kohl-Bareis, M., Villringer, A., Dirnagl, U., Lindauer U.: Pharmacological uncoupling of activation induced increases in CBF and CMRO(2). J Cereb Blood Flow Metab. 2010; Vol. 30(2); 311-322.

Publikation 3

Füchtemeier, M., Leithner, C., Offenhauser, N., Foddis, M., Kohl-Bareis, M., Dirnagl, U., Lindauer, U., Royl, G.: Elevating intracranial pressure reverses the decrease in deoxygenated hemoglobin and abolishes the post-stimulus overshoot upon somatosensory activation in rats. NeuroImage 2010; Vol. 52; 445-454.

Curriculum vitae

Der Lebenslauf wird aus Datenschutzgründen in der elektronischen Version dieser Arbeit nicht veröffentlicht.

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Eidesstattliche Erklärung

„Ich, Martina Füchtemeier, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: „Neurovascular coupling studied in a rat model during pathophysiological states: implications for functional brain imaging in patients“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

Berlin, den 29.06.2010 Martina Füchtemeier

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