

Aus der Klinik für Neurologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Untersuchung neuronaler Inhibition bei der kortikalen Verarbeitung
somatosensorischer Stimulationen mittels EEG und fMRT

zur Erlangung des akademischen Grades
Doctor rerum medicinalium (Dr. rer. medic.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Till Moritz Hermann Nierhaus

aus Berlin

Datum der Promotion: 26.02.2016

Inhaltsverzeichnis

Vorwort	3
Abstract	5
Abstract (englisch)	6
Eidesstattliche Versicherung	7
Anteilerklärung	8
Auszug aus der Journal Summary List (ISI Web of KnowledgeSM)	9
Ausgewählte Publikation: <u>Nierhaus et al. 2015</u> : Imperceptible Somatosensory Stimulation Alters Sensori- motor Background Rhythm and Connectivity, The Journal of Neuroscience	11
Lebenslauf	20
Konferenzbeiträge	22
Publikationsliste	24
Danksagung	26

Vorwort

Die vorliegende Dissertation ist eingebettet in eine Serie von wissenschaftlichen Arbeiten zum somatosensorischen System des Menschen, an denen ich wesentlich beteiligt war. Das übergeordnete Ziel meiner wissenschaftlichen Arbeit in den vergangenen Jahren war es mit nicht-invasiven Neuroimaging-Verfahren (EEG/fMRT) neurophysiologische Mechanismen zu identifizieren, die der kortikalen Verarbeitung somatosensorischer Reize zugrundeliegen. Der Schwerpunkt lag dabei auf der funktionellen Bedeutung von neuraler Hintergrundaktivität, vor allem im Alpha Frequenzbereich und im niederfrequenten Bereich ($<0.1\text{Hz}$), sowie der Untersuchung von bei der Reizverarbeitung involvierten inhibitorischen Prozessen.

Nach einer Übersichtsarbeit zum Einfluss von Hintergrundaktivität auf evozierte Aktivität (Nierhaus et al. 2009) habe ich mich eingehend mit verschiedenen Formen der somatosensorischen Stimulation und Determinanten für deren Wahrnehmung beschäftigt. Speziell untersuchten wir, welchen Einfluss vorhergehende somatosensorische Stimulation auf nachfolgende perzeptuelle Wahrnehmungen ausübt (Thiel et al. 2014) und wir beschreiben den Effekt von somatosensorischem Rauschen (Iliopoulos et al. 2014) auf die Wahrnehmung sensorischer Stimuli („Stochastische Resonanz“). Um neurale Effekte der Stimulationsverfahren zu messen, bedienten wir uns des EEGs und der funktionellen Magnetresonanztomographie (fMRT). Die hohe zeitliche Auflösung des EEGs ermöglichte uns, anhand der Messung evozierter Potentiale in einem Doppelpuls-Paradigma, erstmals eine transkallosale Verbindung der beiden primären somatosensorischen Kortizes nachzuweisen, ebenso wie eine darüber vermittelte transkallosale Inhibition (Ragert*/Nierhaus* et al. 2011). Dagegen ermöglicht fMRT eine räumlich hochaufgelöste Abbildung von neuronalen Netzwerken funktioneller Konnektivität (für eine Übersicht Nierhaus et al. 2012), und wir konnten mittels fMRT-basierter Konnektivitäts-Analyse den sensomotorischen Kortex ganz ohne Stimulation in topische Unterareale gliedern (Long et al. 2014). Um die räumlich-zeitliche Dimension zerebraler Veränderungen gleichzeitig zu erfassen, werden beide Verfahren idealerweise gleichzeitig angewandt. Dem stehen allerdings – bei der verwendeten Feldstärke von 3 Tesla – erhebliche technische Schwierigkeiten durch Artefakte im EEG gegenüber. Wir konnten ein wesentliches Artefakt (Ventilations-

Artefakt) identifizieren und weitgehend eliminieren (Nierhaus et al. 2013), sowie darauf basierend erfolgreich eine simultane EEG-fMRI Studie bei somatosensorischer Stimulation durchführen (Goltz et al. J Neurosci, in revision). Außerdem konnten wir einen Ortspezifischen Effekt einer komplexen somatosensorischen Stimulation an einem Akupunkturpunkt in beiden Verfahren nachweisen (Nierhaus et al. 2015).

Die vorliegende Dissertationsschrift stützt sich auf zwei Studien zu den neuronalen Effekten subliminaler Stimulation (unterschwellige / nicht spürbare elektrische Pulse). Es ist bekannt, dass subliminale somatosensorische Stimulation zu einer präferentiellen thalamo-kortikalen Erregung inhibitorischer Interneurone führt. Mittels EEG konnten wir nun erstmals ein inhibitorisch evoziertes Potential (P60) nicht-invasiv identifizieren, sowie – als weiteres Korrelat vorwiegend inhibitorischer Prozesse – ein Anstieg des sogenannten Mu-Rhythmus (Alpha Rhythmus im somatosensorischen System) zeigen. Mittels fMRT konnten wir dann zum ersten Mal zeigen, dass diese vornehmlich inhibitorische Prozessierung der subliminalen Stimulation mit einer verringerten funktionellen Konnektivität des primären somatosensorischen Kortex' zu „höheren“ Arealen der bewussten somatosensorischen Informationsverarbeitung einhergeht.

Abstrakt

Experimentelle Untersuchungen mit invasiven Techniken haben gezeigt, dass die kortikale Verarbeitung sensorischer Reize durch eine Interaktion von exzitatorischen und inhibitorischen Prozessen gekennzeichnet ist. Die am Menschen eingesetzten nicht-invasiven Neuroimaging Techniken messen jedoch immer ein Mischsignal aus diesen beiden simultan ablaufenden Prozessen, deren Entflechtung nicht möglich ist. In der vorliegenden Arbeit wird daher eine Stimulation verwendet, von der schon gezeigt wurde, bevorzugt inhibitorische Interneurone im primären somatosensorischen Kortex (SI) anzuregen: nicht-spürbare (subliminale) somatosensorische Stimulation. Diese erlaubt eine gezielte nicht-invasive Untersuchung von vornehmlich inhibitorischen Prozessen.

Dazu wurden zwei Probandenstudien durchgeführt, in denen der Einfluss subliminaler Stimulation auf (i) evozierte und induzierte Aktivität im EEG und (ii) fMRT-basierte funktionelle Konnektivität untersucht wurde. Im EEG zeigt sich ein subliminal evoziertes Potential bei 60 ms, jedoch keine späteren evozierten Potentiale. Ferner führt subliminale Stimulation – im Gegensatz zu dem bekannten Phänomen der Desynchronisation nach spürbaren (supraliminalen) Stimuli – zu einer transienten Verstärkung (Synchronisation) des somatosensorischen Hintergrundrhythmus' im α -Frequenzband. Damit konnten zum ersten Mal nicht-invasive elektrophysiologische Korrelate von verstärkter inhibitorischer Aktivität beschrieben werden. Dasselbe (subliminale) Stimulationsparadigma während fMRT führt zu einer reduzierten Zentralität („Eigenvector Centrality“) des kontralateralen SI, welche sich hauptsächlich durch eine reduzierte funktionelle Konnektivität zu einem fronto-parietalen Netzwerk auszeichnet. Diese Ergebnisse zeigen zum ersten Mal eine Modulation der funktionellen Konnektivität durch nicht wahrgenommene sensorische Reize.

Wir schlussfolgern daraus, dass die exzitatorische vorwärts gerichtete („bottom-up“) Reizweiterleitung bei subliminaler Stimulation durch eine Dominanz inhibitorischer Aktivität in SI blockiert und somit eine bewusste Wahrnehmung verhindert wird. Die Erhöhte α -Aktivität sowie die reduzierte Konnektivität zwischen SI und fronto-parietalen Arealen können als Korrelate eines „Gating“-Mechanismus' interpretiert werden, welcher den Zugang zu bewusster Wahrnehmung reguliert.

Abstract

Invasive measurements have shown that cortical stimulus processing is reflected by the interplay of excitatory and inhibitory neuronal activity. A main challenge of non-invasive neuroimaging is to disentangle these simultaneously occurring processes. By employing imperceptible (subliminal) electrical finger nerve stimulation in humans – a paradigm previously shown to preferentially activate inhibitory interneurons in primary somatosensory cortex (SI) – we selectively investigate localized inhibitory cortical activity by means of non-invasive EEG and fMRI.

Two sets of experiments were performed to investigate the effect of subliminal stimulation on (i) evoked and induced activity in the EEG as well as (ii) fMRI based functional connectivity. Using EEG, we find a cortical evoked potential (P1) at 60 ms, but no further somatosensory evoked potential (SEP) components. Furthermore, in contrast to the well-studied effect of event-related desynchronization following perceivable (supraliminal) stimulation, subliminal stimulation transiently increase the somatosensory background rhythm in the α -frequency range. Using the same (subliminal) stimulation paradigm during fMRI, a reduced centrality of contralateral SI was found, which appeared to be mainly driven by reduced functional connectivity to fronto-parietal areas.

We conclude that after subliminal stimulation the (excitatory) feedforward sweep of bottom-up processing terminates in SI due to a predominance of inhibitory processing, thus preventing access to conscious experience. The increase in alpha activity and the disconnection of SI from fronto-parietal areas are likely correlates of a gating mechanism that serves as the access to conscious experience.

Eidesstattliche Versicherung

„Ich, Till Nierhaus, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Untersuchung neuronaler Inhibition bei der kortikalen Verarbeitung somatosensorischer Stimulationen mittels EEG und fMRT“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.

Mein Anteil an der ausgewählten Publikation entspricht dem, der in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben ist.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum

Unterschrift

Ausführliche Anteilserklärung an der erfolgten Publikation

Publikation:

Nierhaus T, Forschack N, Piper S, Holtze S, Krause T, Taskin B, Long X, Stelzer J, Margulies D, Steinbrink J, Villringer A. Imperceptible Somatosensory Stimulation Alters Sensorimotor Background Rhythm and Connectivity, The Journal of Neuroscience, 35(15):5917-5925, 2015

Beitrag im Einzelnen :

In dieser Arbeit wird die Verarbeitung subliminaler (nicht-spürbarer) somatosensorischer Reize mittels EEG und fMRT untersucht. Der Arbeitsanteil des Promovenden war die Konzeption der verschiedenen EEG und fMRT Experimente, die Entwicklung der experimentellen Aufbauten mit computerbasierter Ansteuerung der Elektrostimulatoren und gleichzeitiger EEG- bzw. fMRT-Triggerung, teilweise die Durchführung der EEG Messungen, die Durchführung der fMRT Messungen und die anschließenden Datenanalyse. Besonders die Matlab-basierte Datenanalyse erwies sich als sehr aufwendig, da einerseits die Programmierung von komplexen mathematischen Analyseverfahren notwendig war, um die sehr kleinen Effekte der subliminalen Stimulation zu veranschaulichen, und andererseits das Management von sehr großen Datenmengen erforderlich war. Ebenfalls Arbeitsanteil des Promovenden war das Zusammentragen und graphische Darstellen der Ergebnisse, Vorstellung und Diskussion der Ergebnisse auf internationalen Kongressen, der Entwurf des Manuskripts mit der erforderlichen Literaturrecherche, sowie die Bearbeitung des Review-Prozesses im Rahmen der Veröffentlichung beim Journal of Neuroscience.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

Unterschrift des Doktoranden/der Doktorandin

ISI Web of KnowledgeSM

Journal Citation Reports[®]

WELCOME ? HELP

2013 JCR Science Edition

Journal Summary List

[Journal Title Changes](#)

Journals from: **subject categories NEUROSCIENCES** [VIEW CATEGORY SUMMARY LIST](#)

Sorted by: **Impact Factor** SORT AGAIN

Journals 1 - 20 (of 252)

[1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10]

Page 1 of 13

MARK ALL UPDATE MARKED LIST

Ranking is based on your journal and sort selections.

Mark	Rank	Abbreviated Journal Title <i>(linked to journal information)</i>	ISSN	JCR Data						Eigenfactor [®] Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor [®] Score	Article Influence [®] Score
<input type="checkbox"/>	1	NAT REV NEUROSCI	1471-003X	30120	31.376	37.472	6.161	62	6.9	0.08887	16.773
<input type="checkbox"/>	2	ANNU REV NEUROSCI	0147-006X	13345	22.660	28.613	1.542	24	>10.0	0.02776	15.009
<input type="checkbox"/>	3	TRENDS COGN SCI	1364-6613	18076	21.147	18.920	2.983	60	7.9	0.04375	8.363
<input type="checkbox"/>	4	NEURON	0896-6273	71989	15.982	16.485	2.902	369	8.1	0.22596	8.682
<input type="checkbox"/>	5	MOL PSYCHIATR	1359-4184	13902	15.147	14.196	3.500	132	5.4	0.03924	4.672
<input type="checkbox"/>	6	NAT NEUROSCI	1097-6256	46095	14.976	16.273	3.725	236	7.4	0.15123	8.604
<input type="checkbox"/>	7	BEHAV BRAIN SCI	0140-525X	7017	14.962	22.821	4.476	21	>10.0	0.00965	10.342
<input type="checkbox"/>	8	TRENDS NEUROSCI	0166-2236	18523	12.902	14.345	2.534	73	9.9	0.03683	6.407
<input type="checkbox"/>	9	ANN NEUROL	0364-5134	33670	11.910	11.353	1.893	178	9.5	0.06302	4.184
<input type="checkbox"/>	10	PROG NEUROBIOL	0301-0082	11310	10.301	10.570	1.745	51	9.1	0.02116	3.480
<input type="checkbox"/>	11	NEUROSCI BIOBEHAV R	0149-7634	15111	10.284	11.075	1.401	207	6.7	0.03829	3.731
<input type="checkbox"/>	12	BRAIN	0006-8950	44457	10.226	10.846	2.125	272	8.2	0.08991	3.874
<input type="checkbox"/>	13	ACTA NEUROPATHOL	0001-6322	12284	9.777	8.854	2.717	120	6.5	0.03087	3.082
<input type="checkbox"/>	14	BIOL PSYCHIAT	0006-3223	40687	9.472	10.347	2.883	239	7.4	0.08145	3.332
<input type="checkbox"/>	15	SLEEP MED REV	1087-0792	3512	9.141	9.320	2.186	43	6.2	0.00917	3.201
<input type="checkbox"/>	16	CEREB CORTEX	1047-3211	24708	8.305	8.372	2.410	268	6.3	0.07654	3.462
<input type="checkbox"/>	17	NEUROPSYCHOPHARMACOL	0893-133X	21567	7.833	8.518	1.765	255	6.0	0.05741	2.820
<input type="checkbox"/>	18	J PINEAL RES	0742-3098	6136	7.812	5.961	2.011	88	5.9	0.00750	0.919
<input type="checkbox"/>	19	NEUROSCIENTIST	1073-8584	3594	7.618	6.491	1.702	47	6.6	0.00915	2.367
<input type="checkbox"/>	20	FRONT NEUROENDOCRIN	0091-3022	3070	7.581	10.579	1.160	25	5.4	0.00934	3.419

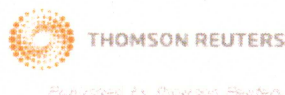
MARK ALL UPDATE MARKED LIST

Journals 1 - 20 (of 252)

[1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10]

Page 1 of 13

[Acceptable Use Policy](#)
Copyright © 2015 Thomson Reuters.



ISI Web of KnowledgeSM

Journal Citation Reports[®]

WELCOME ? HELP

2013 JCR Science Edition

Journal Summary List

[Journal Title Changes](#)

Journals from: **subject categories NEUROSCIENCES** [VIEW CATEGORY SUMMARY LIST](#)

Sorted by: **Impact Factor** [SORT AGAIN](#)

Journals 21 - 40 (of 252)

◀◀ [1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10] ▶▶▶

Page 2 of 13

[MARK ALL](#) [UPDATE MARKED LIST](#)

Ranking is based on your journal and sort selections.

Mark	Rank	Abbreviated Journal Title <i>(linked to journal information)</i>	ISSN	JCR Data						Eigenfactor [®] Metrics	
				Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor [®] Score	Article Influence [®] Score
<input type="checkbox"/>	21	J PSYCHIATR NEUROSCI	1180-4882	2519	7.492	7.234	1.105	38	5.5	0.00657	2.143
<input type="checkbox"/>	22	HUM BRAIN MAPP	1065-9471	14858	6.924	6.956	1.315	257	6.0	0.04166	2.440
<input type="checkbox"/>	23	CURR OPIN NEUROBIOL	0959-4388	12062	6.765	7.549	1.701	147	8.1	0.03586	4.031
<input type="checkbox"/>	24	J NEUROSCI	0270-6474	167915	6.747	7.648	1.232	1765	7.7	0.41315	3.058
<input type="checkbox"/>	25	NEURON GLIA BIOL	1740-925X	561	6.636	3.868		0	5.8	0.00161	1.269
<input type="checkbox"/>	26	NEUROIMAGE	1053-8119	69654	6.132	6.956	1.479	873	6.2	0.17268	2.214
<input type="checkbox"/>	27	BRAIN BEHAV IMMUN	0889-1591	7365	6.128	5.813	1.389	185	4.5	0.02120	1.657
<input type="checkbox"/>	28	CORTEX	0010-9452	5977	6.042	5.389	1.266	252	5.7	0.01474	1.685
<input type="checkbox"/>	29	BRAIN RES REV	0165-0173	8452	5.930	8.781		0	9.0	0.01313	2.975
<input type="checkbox"/>	30	SOC COGN AFFECT NEUR	1749-5016	2787	5.884	6.447	1.957	117	3.5	0.01209	2.403
<input type="checkbox"/>	31	PAIN	0304-3959	30877	5.836	6.341	1.084	323	9.2	0.04899	1.937
<input type="checkbox"/>	32	CURR OPIN NEUROL	1350-7540	5005	5.729	5.365	0.957	92	5.8	0.01477	1.902
<input type="checkbox"/>	33	PSYCHONEUROENDOCRINO	0306-4530	10669	5.591	6.090	0.893	318	5.8	0.02392	1.691
<input type="checkbox"/>	34	MOL AUTISM	2040-2392	335	5.486	6.080	0.644	45	2.4	0.00180	2.159
<input type="checkbox"/>	35	GLIA	0894-1491	10995	5.466	5.374	1.631	157	7.0	0.02247	1.675
<input type="checkbox"/>	36	BRAIN STIMUL	1935-861X	1502	5.432	6.950	0.822	129	3.0	0.00634	1.911
<input type="checkbox"/>	37	NEUROPSYCHOL REV	1040-7308	1914	5.400	7.672	0.700	20	5.6	0.00551	2.526
<input type="checkbox"/>	38	EUR NEUROPSYCHOPHARM	0924-977X	4652	5.395	4.736	0.773	185	5.5	0.01103	1.314
<input type="checkbox"/>	39	J CEREBR BLOOD F MET	0271-678X	14721	5.339	5.373	0.923	233	8.0	0.02875	1.755
<input type="checkbox"/>	40	MOL NEUROBIOL	0893-7648	3261	5.286	5.843	1.219	169	4.9	0.00838	1.716

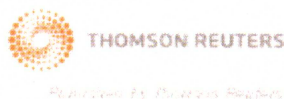
[MARK ALL](#) [UPDATE MARKED LIST](#)

Journals 21 - 40 (of 252)

◀◀ [1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10] ▶▶▶

Page 2 of 13

[Acceptable Use Policy](#)
Copyright © 2015 Thomson Reuters.



Imperceptible Somatosensory Stimulation Alters Sensorimotor Background Rhythm and Connectivity

Till Nierhaus,^{1,2,3} Norman Forschack,^{2,4} Sophie K. Piper,¹ Susanne Holtze,¹ Thomas Krause,^{1,5} Birol Taskin,^{1,5} Xiangyu Long,² Johannes Stelzer,² Daniel S. Margulies,^{2,3} Jens Steinbrink,^{1,5} and Arno Villringer^{1,2,3,5}

¹Berlin Neuroimaging Center and Department of Neurology, Charité Universitätsmedizin Berlin, 10117 Berlin, Germany, ²Max-Planck-Institute for Human Cognitive and Brain Sciences, Department of Neurology, 04303 Leipzig, Germany, ³Mind-Brain Institute and Berlin School of Mind and Brain, Charité and Humboldt-University, 10117 Berlin, Germany, ⁴Department of Psychology, University of Leipzig, 04109 Leipzig, Germany, and ⁵Center for Stroke Research Berlin, Charité Universitätsmedizin Berlin, 10117 Berlin, Germany

Most sensory input to our body is not consciously perceived. Nevertheless, it may reach the cortex and influence our behavior. In this study, we investigated noninvasive neural signatures of unconscious cortical stimulus processing to understand mechanisms, which (1) prevent low-intensity somatosensory stimuli from getting access to conscious experience and which (2) can explain the associated impediment of conscious perception for additional stimuli. Stimulation of digit 2 in humans far below the detection threshold elicited a cortical evoked potential (P1) at 60 ms, but no further somatosensory evoked potential components. No event-related desynchronization was detected; rather, there was a transient synchronization in the alpha frequency range. Using the same stimulation during fMRI, a reduced centrality of contralateral primary somatosensory cortex (SI) was found, which appeared to be mainly driven by reduced functional connectivity to frontoparietal areas. We conclude that after subthreshold stimulation the (excitatory) feedforward sweep of bottom-up processing terminates in SI preventing access to conscious experience. We speculate that this interruption is due to a predominance of inhibitory processing in SI. The increase in alpha activity and the disconnection of SI from frontoparietal areas are likely correlates of an elevated perception threshold and may thus serve as a gating mechanism for the access to conscious experience.

Key words: EEG background rhythms; fMRI; functional connectivity; somatosensory evoked potentials; subthreshold electrical stimulation; unconscious

Introduction

The human body is permanently exposed to sensory input, most of it, however, escapes conscious perception. Our nervous system seems to automatically categorize sensory input as either “relevant” or “irrelevant” for conscious experience. Based on detection curves for sensory stimuli at different intensities that typically have a sigmoid shape, one can define three categories of stimuli: (1) above a certain intensity, stimuli are (almost) always consciously perceived (suprathreshold); (2) stimuli at lower intensity (near-threshold) are perceived only in a certain percentage of trials; and, finally, (3) below a certain (“absolute”) detection threshold, stimuli are never perceived (more precisely: not more than null trials). Accordingly, we label these imperceptible stimuli as subthreshold. One might think that neural processing of such subthreshold stimuli should terminate very early

in the bottom-up chain of sensory processing. However, previous invasive recordings (Libet et al., 1967, Ray et al., 1999) showed at least one early SEP component, indicating that the information reaches the primary somatosensory cortex (SI).

Using analogous subthreshold stimulation as Libet et al. (1967), we have previously shown that trains of such stimuli induce a negative BOLD fMRI signal in contralateral SI, SII, and SMA, and impede stimulus processing in the somatosensory system (Blankenburg et al., 2003, Taskin et al., 2008). While this finding generally confirms the notion that subthreshold stimuli induce neural processing in the somatosensory cortex, it is still unknown which neural processes after subthreshold stimulation (1) prevent access to conscious experience and (2) underlie the impaired detection of (other) somatosensory stimuli.

To address these issues, we performed two series of experiments using EEG and fMRI, respectively, during subthreshold electrical stimulation of finger nerves. In both experiments, we compared effects of subthreshold stimulation to those elicited by suprathreshold stimulation. For our EEG experiments, we hypothesized (1) to find early SEP components corresponding to results of the previous invasive recordings (Libet et al., 1967, Ray et al., 1999), which so far have never been confirmed noninvasively. Given that later components correlate with conscious experience (Zhang and Ding, 2010, Aukstulewicz and Blankenburg, 2013), we expected an attenuation or lack of later components.

Received Sept. 11, 2014; revised Jan. 30, 2015; accepted Feb. 16, 2015.

Author contributions: T.N., J. Steinbrink, and A.V. designed research; T.N., N.F., S.P., S.H., T.K., and B.T. performed research; T.N. and D.M. contributed unpublished reagents/analytic tools; T.N., N.F., X.L., and J. Stelzer analyzed data; T.N., N.F., D.M., J. Steinbrink, and A.V. wrote the paper.

We thank Sylvia Stasch for technical support during EEG recordings as well as Annett Wiedemann and Sylvie Neubert for technical support during MRI measurements.

The authors declare no competing financial interests.

Correspondence should be addressed to Till Nierhaus, Berlin Neuroimaging Center and Department of Neurology, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail: till.nierhaus@charite.de.

DOI:10.1523/JNEUROSCI.3806-14.2015

Copyright © 2015 the authors 0270-6474/15/355917-09\$15.00/0

Regarding another key feature of the EEG response to (suprathreshold) somatosensory stimulation, the desynchronization of background alpha (μ) activity (event-related desynchronization, ERD), which is thought to reflect increased local neuronal processing, we suspected (2) that ERD would be attenuated or even absent after subthreshold stimulation.

Finally, given the lack of conscious experience and our previous findings that trains of subthreshold stimuli impede perception and locally decrease the BOLD signal in the sensorimotor system (Blankenburg et al., 2003), we hypothesized that (3) subthreshold stimulation may affect functional connectivity between somatosensory areas and regions involved in conscious perception. To test this hypothesis, the same stimulation paradigm as in the EEG experiment was applied during fMRI and compared with resting-state measurements in a functional connectivity analysis.

Materials and Methods

Subjects

In this study an EEG and an fMRI experiment were performed, both consisting of two sessions: 40 healthy volunteers participated in the first EEG session (age range 19–31 years, mean 25.3 ± 2.7 years SD; 21 females) and 41 healthy volunteers participated in the second EEG session (age range 20–33 years, mean 25.8 ± 2.9 years SD; 18 females); 16 subjects were measured in the first fMRI session (age range 20–32 years, mean 25.6 ± 3.3 years SD; 8 females) and another 16 subjects were measured in the second fMRI session (age range 22–34 years, mean 27.0 ± 3.3 years SD; 9 females). All subjects were right-handed [laterality score according to the Oldfield questionnaire: 89.0 ± 12.9 (SD) over a range of -100 (fully left-handed) to 100 (fully right-handed); Oldfield, 1971]. All experiments were performed in accordance with the principles laid down in the declaration of Helsinki. Before participation, all volunteers underwent a comprehensive neurological examination and had no history of neurological or psychiatric diseases or were on any medication. Due to defective or artificial EEG recording, one subject had to be excluded in the first EEG session (resulting in 39 datasets), and four subjects had to be excluded in the second EEG session (resulting in 37 datasets).

Experimental procedures

Electrical stimulation

Electrical finger nerve stimulation was performed with a constant-current stimulator (DS7; Digitimer) using single square wave pulses with a duration of $200 \mu\text{s}$, triggered with the stimulation software Presentation (Neurobehavioral Systems). In all experiments, steel wire ring electrodes were placed on the middle (anode) and the proximal (cathode) phalanx of the left index finger. For EEG session two, an additional pair of ring electrodes was placed on the right index finger. To ensure that subthreshold stimulations were always imperceptible, we determined the lowest intensity where subjects ever reported any sensation (“absolute perception threshold”). “Subthreshold” stimulation intensity was then set to 15% below this absolute perception threshold. In all experiments, subjects never reported any sensation due to the subthreshold stimulation intensity. Absolute perception thresholds were determined before and after each measurement block to control for potential drifts using the method of limits and a subsequent forced choice approach.

EEG acquisition

EEG session one. During stimulation blocks, EEG was recorded continuously from 32 scalp positions distributed over both hemispheres according to the international 10–20 system, using a commercial EEG acquisition system (BrainAmp; Brain Products). The mid-frontal electrode (FPz) was used as reference and an electrode at the sternum served as ground. Skin electrode impedance was $<5 \text{ k}\Omega$ for all channels. EEG was recorded with a bandpass filter between 0.1 Hz and 1 kHz and digitized with a sampling rate of 5 kHz.

To allow for proper detection of somatosensory evoked potentials (SEPs) and modulation of Rolandic rhythms, long interstimulus inter-

vals were chosen. Subthreshold electrical finger nerve stimulation with an intensity 15% below absolute perception threshold was presented at a mean interstimulus interval of 4 s with a jitter of ± 500 ms during three measurement blocks of 15 min each, resulting in 675 trials per subject. For the control condition, a fourth block (3 min duration) with a suprathreshold stimulation intensity (clearly perceivable for the subject but at least 15% above absolute perception threshold) was appended, where stimuli were applied every 1 ± 0.2 s, resulting in 180 trials.

EEG session two. As a confirmatory experiment, a second EEG study was performed in a slightly modified setup with shorter blocks and with intermingled suprathreshold stimuli to prevent subjects getting tired (“by nothing happening”). Subthreshold stimulation at an intensity 15% below absolute perception threshold was presented at a mean interstimulus interval of 2 s with a jitter of ± 300 ms during eight measurement blocks of 2 min each, resulting in 480 trials per subject. Additionally, in each block up to four suprathreshold stimuli (clearly perceivable for the subject but at least 50% above absolute perception threshold) were randomly presented to the left or the right hand. Due to the rare occurrence of the suprathreshold stimuli in this experiment we increased their intensity (50% above threshold vs 15% above threshold in EEG session one) to ensure their perception over the entire block. Subjects were instructed to relax and fixate a fixation cross.

An active electrode cap was used to record the EEG, sampling rate was 1 kHz; all other acquisition parameters were the same as in the first session.

fMRI acquisition

fMRI was measured using a 3 T Siemens Magnetom (Verio). BOLD-sensitive images were acquired using a T2*-weighted EPI sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90° , matrix 64×64 , FOV = 19.2 cm, in-plane resolution = $3 \text{ mm} \times 3 \text{ mm}$, slice thickness = 4 mm, interslice gap = 1 mm, 30 slices, interleaved). Measurement blocks of 180 volumes (6 min) were acquired. The first fMRI session consists of two blocks, one resting-baseline block followed by a second block during which subthreshold stimuli were applied every 4 ± 0.5 s with intensity 15% below absolute perception threshold. In the second fMRI session, in addition to resting-baseline and subthreshold stimulation, we acquired an additional block with suprathreshold stimulation (4 ± 0.5 s with intensity 50% above absolute perception threshold, i.e., clearly perceivable for the subject). The order of subthreshold and suprathreshold stimulation blocks was counterbalanced across subjects.

EEG data analysis

EEG data analysis was performed off-line using custom-built MATLAB scripts (The MathWorks). After downsampling to 500 Hz, the dataset of each subject (subthreshold and suprathreshold merged for EEG session one) underwent an independent component analysis (ICA) to remove sources of ocular artifacts (Li et al., 2006). After back projection, data were subdivided into epochs and digitally filtered using a standard third-order bandpass Butterworth filter (low cutoff frequency 1 Hz, high cutoff frequency 45 Hz).

SEPs. Epochs were defined ranging from -600 to 1100 ms relative to stimulus onset. For the control condition in session one (suprathreshold), however, epochs of -200 to 600 ms were defined since mere suprathreshold stimulation was presented at a shorter interstimulus interval. Finally, data were downsampled to 250 Hz and SEPs were obtained by averaging all trials.

Statistical analysis was performed on electrode C4 (i.e., over the right somatosensory cortex contralateral to the stimulation site). The SEP was analyzed in a 400 ms epoch post stimulus. A baseline was defined as a 200 ms prestimulus epoch (-200 to 0 ms). Each sample point of the post-stimulus epoch was successively compared with the mean prestimulus baseline value. For each comparison, a paired t test ($p < 0.05$) was performed and the Bonferroni correction method was used to correct for multiple comparisons (100 tests, $p_{BC} < 0.0005$).

Rolandic rhythms. Since Rolandic rhythms can be hidden under dominating occipital alpha activity, a preselection of “central” ICA components was performed before trial segmentation. For this purpose, all blocks were concatenated to run individual ICAs for EEG sessions one

and two, respectively. Rolandic background rhythms are characterized by a central localization and two peaks in the power spectrum, at alpha (8–15 Hz) and beta (16–30 Hz) frequency bands, respectively, which desynchronize after suprathreshold stimulation. Based on this “operational definition of Rolandic rhythms,” for each subject only those ICs were selected for which a central topography—the two respective peaks in the frequency spectrum and a desynchronization after suprathreshold stimulation—were identifiable. Using this procedure, 2–7 (mean 3 ± 1 SD) independent components were selected per subject for EEG session one, and 1–4 (mean 2 ± 1 SD) for EEG session two. The selected components were back projected and included in further analysis. After back projection of the “central” ICA components and segmentation according to subthreshold epochs defined above (–600 to 1100 ms relative to stimulus onset), a wavelet analysis was performed for the frequencies from 4 to 30 Hz in 1 Hz increments to allow for a time-resolved frequency analysis of ERD. The wavelet transformation was performed on each single trial using a five-cycle long wavelet and subsequent averaging of the respective results. A 200 ms prestimulus epoch (–200 to 0 ms) was used to define a baseline.

Statistical analysis for EEG session one was performed on electrode C4 (same electrode as for the SEP analysis). For EEG session two, however, CP4 showed the main effect of ERD after the selection of “central” ICA components and thus was used for statistical analysis. Individual data were permuted by generating 5000 sets of pseudotrials and wavelet transformation was performed for each permutation. Permutations were pooled across subjects and the change to mean baseline activity was compared with the original set of trials.

fMRI data analysis

The general approach was a functional connectivity analysis based on “eigenvector centrality mapping” (ECM) as it has been performed previously for “resting-state” data (Lohmann et al., 2010). After determining ECMs for each condition, in a second step, these maps were compared between the different conditions (“no stimulation,” “subthreshold stimulation,” and “suprathreshold stimulation”). Since in two of the three conditions stimulations were applied, we considered removing direct stimulation-induced effects in the frequency or time domain. However, to use a stimulation-associated regressor (of no interest) in the time domain would have meant using such a regressor only for the two “stimulation conditions.” To avoid this, we filtered out the main frequencies of the stimulation effect (0.25 Hz and higher harmonics) by applying a bandpass filter (0.01–0.2 Hz). Thus, the same preprocessing was applied to all three conditions (no stimulation, subthreshold stimulation, and suprathreshold stimulation).

In more detail preprocessing of the fMRI data was performed using LIPSIA-toolbox (Lohmann et al., 2001): head motion correction, slice time correction, bandpass filtering (0.01–0.2 Hz), spatial smoothing (7 mm kernel), and normalization to the MNI305 space. Networks of correlated brain activity can be identified from the temporal correlations of an ROI time series of spontaneous BOLD fMRI signal with all other brain regions (Cordes et al., 2001; Gusnard and Raichle, 2001; Fox and Raichle, 2007; Margulies et al., 2010; Nierhaus et al., 2012). Several studies have shown that brain regions, which show correlated activity during a task, also appear correlated at rest, resulting in similar “maps” of connected brain areas involved in certain brain functions (Biswal et al., 1995; Cordes et al., 2000; Fox et al., 2005, 2007). Here, we used ECM (similar to Google’s PageRank algorithm; Lohmann et al., 2010) as a data-driven analysis tool that characterizes each voxel’s connectivity within the whole-brain network. The ECM algorithm calculates linear correlations for each voxel to every other voxel (correlation matrix A). This matrix is then rescaled to positive values. The eigenvector centrality of the i th voxel is then defined as the i th entry of the (normalized) eigenvector of the largest eigenvalue of A . This procedure favors voxels that are strongly connected with many other voxels of high centrality. We computed a whole-brain ECM for each measurement block. The ECM results of session one (subthreshold stimulation compared with resting baseline) were then used to define an ROI for subsequent whole-brain, seed-based functional connectivity analysis. We used custom-built MATLAB scripts (The MathWorks) to calculate spatial correlation maps between the seed

region and all other voxels in the brain. The head motion, averaged signal from CSF, and white matter were regressed out of fMRI data in the spatial correlation analysis.

It should be noted that the ECM analysis is a whole-brain approach without any prior assumption. Only in those areas, which showed a statistically significant alteration in “overall connectivity,” did we subsequently perform a seed-based analysis. The question was as follows: Given that these areas show overall reduced connectivity compared with baseline, which are the most affected connections? In this step, no formal statistics was applied (double dipping); rather it was used to identify those areas that “contributed most” to the statistically significant effect of an overall reduced connectivity.

For the ECMs, voxelwise paired t test comparisons over all subjects were used to calculate statistical significant differences between the different measurement blocks. For the spatial correlation maps resulting from seed-based connectivity analysis, a voxelwise paired t test (contrasting the subthreshold stimulation block with the resting baseline of the first fMRI session) was used to calculate significant differences in functional connectivity. All resulting T -maps underwent a multiple-comparison procedure for significance thresholding based on Monte Carlo simulations with 1000 iterations (vmulticomp, LIPSIA toolbox; Lohmann et al., 2001). This method uses two features (cluster size and maximum z -value) to quantify a cluster as significant (Forman et al., 1995; Poline et al., 1997). We applied the cluster-size correction, using a voxelwise z -threshold of 2.57 and a significance level of $p < 0.01$ on cluster level.

Results

Noninvasive detection of SEP following subthreshold stimulation

While previous invasive studies (Libet et al., 1967; Ray et al., 1999) strongly suggested the existence of at least one early component of an SEP at ~ 50 – 60 ms following subthreshold stimulation, this component has not yet been demonstrated in noninvasive EEG recordings, probably due to its poor SNR. Therefore, in our EEG study we made sure that with a large number of trials and subjects, we would have enough SNR to identify even subtle evoked brain activity. Figure 1 (top) shows the grand average SEP following subthreshold stimulation (15% below absolute perception threshold). An early positive component at ~ 60 ms (P1, paired t test mean baseline value vs 55–65 ms time interval; $p = 0.0002$) can be clearly identified. This peak at 60 ms closely corresponds to the evoked activity measured invasively in previous studies (Libet et al., 1967; Ray et al., 1999). No later component was identified. The lower plot in Figure 1 shows the SEP following suprathreshold stimulation. The early positive component (P1) appears a bit earlier at ~ 50 ms and clearly has a larger amplitude compared with the P1 elicited by subthreshold stimulation. In addition, a late negative component ~ 170 ms (N1) is clearly seen.

The subthreshold and suprathreshold SEPs were lateralized to the right hemisphere, i.e., contralateral to the stimulation side (Fig. 2).

Subthreshold stimulation increases pericentral rhythmic EEG activity

Figure 3 shows the time-frequency plots for subthreshold (A, B) and suprathreshold (C) stimulation contralateral to the stimulation side. The wavelet analysis of the suprathreshold stimulation revealed the well studied effect of a stimulus-induced desynchronization in the alpha and beta range (Fig. 3C). For subthreshold stimulation, however, an increase of rhythmic activity was observed in both EEG studies. For the subthreshold stimulation in the first EEG session (Fig. 3A) a lower alpha-band activity (8–11 Hz) with a maximum ~ 80 ms post stimulus is followed by an

upper alpha-band activity (12–15 Hz) with a maximum ~ 200 ms post stimulus. In EEG session two, subthreshold stimulation induced alpha-band activity (8–12 Hz) from 50 to 450 ms. For visualization, the results of the statistical permutation testing is shown in Figure 3, bottom. The duration and precise frequencies were somewhat different between the two EEG experiments, which may be related to the slightly different stimulation protocols and to effects such as spatial attention and/or vigilance. Indeed, in a follow-up study, we are currently providing evidence that spatial attention modulates the effect of subthreshold stimulation (Forschack et al., 2014). The effect of desynchronization for subthreshold stimulation and the subthreshold stimulation-induced increase in Rolandic rhythmic activity were also lateralized to the right (contralateral) hemisphere (Fig. 2).

Subthreshold stimulation reduces eigenvector centrality of SI

ECM is a data-driven analysis tool based on BOLD signal changes in fMRI, which allows us to compare whole-brain functional connectivity at different states of the brain without prior spatial assumptions (Lohmann et al., 2010). In our fMRI study, we compared brain connectivity patterns for three different conditions: subthreshold stimulation versus suprathreshold stimulation versus no stimulation. In the first fMRI session we acquired a single resting-state (baseline) block and a single block with subthreshold stimulation in 16 subjects ($n = 16$). Thus EC maps with and without subthreshold stimulation can be compared with changes in whole-brain functional connectivity elicited by the continuous subthreshold input. The top row of maps in Figure 4 show the results of a paired t test contrasting the eigenvector centrality of the subthreshold stimulation block versus the baseline block. We found reduced eigenvector centrality in the contralateral hand area of SI during subthreshold stimulation, i.e., the BOLD activity in this area is less connected to whole-brain network during subthreshold stimulation (Fig. 4, top). In the second fMRI session a block with suprathreshold stimulation was added to the resting baseline and subthreshold stimulation block and again 16 subjects were acquired ($n = 16$). Suprathreshold stimulation did not significantly modulate eigenvector centrality in SI, showing only small changes (left inferior frontal and right posterior temporal) in areas unrelated to primary somatosensory processing (Fig. 4, middle). A direct comparison of subthreshold and suprathreshold stimulation blocks (independent of the resting-state baseline), however, reconfirms our result of the first fMRI session, additionally showing little modulation in ipsilateral SI (Fig. 4, bottom).

Subthreshold stimulation reduces functional connectivity from SI to frontoparietal areas

While the comparison of EC maps at different states (subthreshold stimulation, suprathreshold stimulation, and no stimulation; Fig. 4) identify brain regions with altered overall connectivity during electrical stimulation, they do not show the specific brain areas to which connectivity has changed. Seed-based functional connectivity, however, provides information about increased or

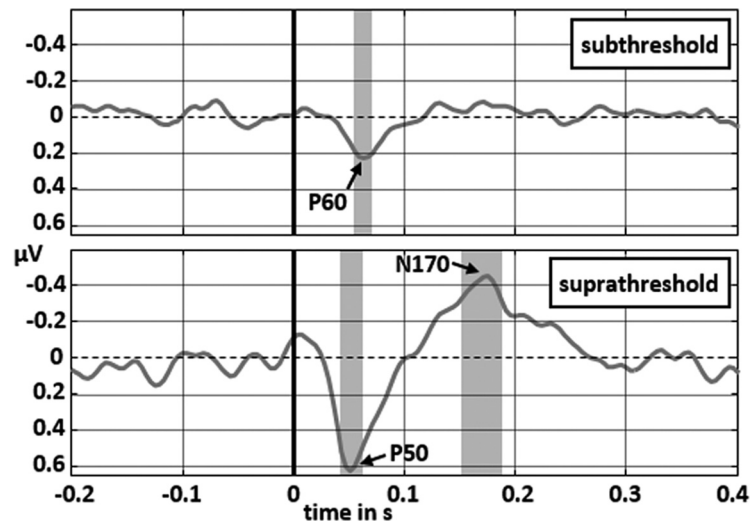


Figure 1. Comparison of subthreshold and suprathreshold SEP. Grand average SEPs ($n = 39$ subjects) resulting from subthreshold (top) and suprathreshold (bottom) stimulation in EEG session 1. Time is expressed relative to stimulus onset. Gray shaded areas indicate significant differences compared with mean baseline activity (paired t test, Bonferroni corrected $p_{BC} < 0.0005$, baseline: 200 ms segment prestimulus).

decreased connectivity of a predefined ROI (“seed”) to all other brain regions. Since ECM analysis of subthreshold electrical stimulation resulted in reduced overall connectivity of contralateral hand area (Fig. 4, top), in a second step, we used this region as ROI for a seed-based functional connectivity analysis. Please note that—though we had a strong a priori hypothesis of contralateral SI to be affected by our stimulation protocol (Blankenburg et al., 2003)—we first used ECM as a completely data-driven analysis tool to obtain a “whole-brain connectivity map” without prior assumptions. Only based on the results of ECM we used contralateral SI as ROI for the seed-based functional connectivity analysis.

A paired t test contrasting the resulting functional connectivity maps during the rest condition (no stimulation) with the subthreshold condition revealed the seed region to be significantly less correlated to medial parietal cortex (precuneus), posterior cingulate cortex, right inferior frontal gyrus, right operculum, left inferior parietal gyrus, and prefrontal cortex, as well as parts of cerebellum, during the subthreshold stimulation (Fig. 5).

Discussion

Using EEG and fMRI, we investigated neural signatures of unconscious cortical stimulus processing after subthreshold somatosensory stimulation. The goal was to identify mechanisms that (1) prevent access to conscious perception and (2) underlie behavioral consequences of subthreshold stimulation. The main findings are as follows. Subthreshold electrical single pulses generate an SEP peaking at 60 ms (P1), the amplitude of which is weaker than the P1 after suprathreshold stimulation and occurs ~ 10 ms later. No subsequent SEP components were detected. Subthreshold stimulation does not desynchronize Mu-rhythm; rather, there is a transient increase between 50 and 400 ms. Subthreshold stimulation decreases centrality of the contralateral SI hand area predominantly driven by reduced functional connectivity to frontoparietal areas.

Previous studies on the detection of near-threshold (Zhang and Ding, 2010, Auzszulewicz and Blankenburg, 2013) and masked suprathreshold (Schubert et al., 2006) stimuli found an unchanged P1 and attenuated (if present at all) N1 component for undetected compared with consciously perceived trials. We

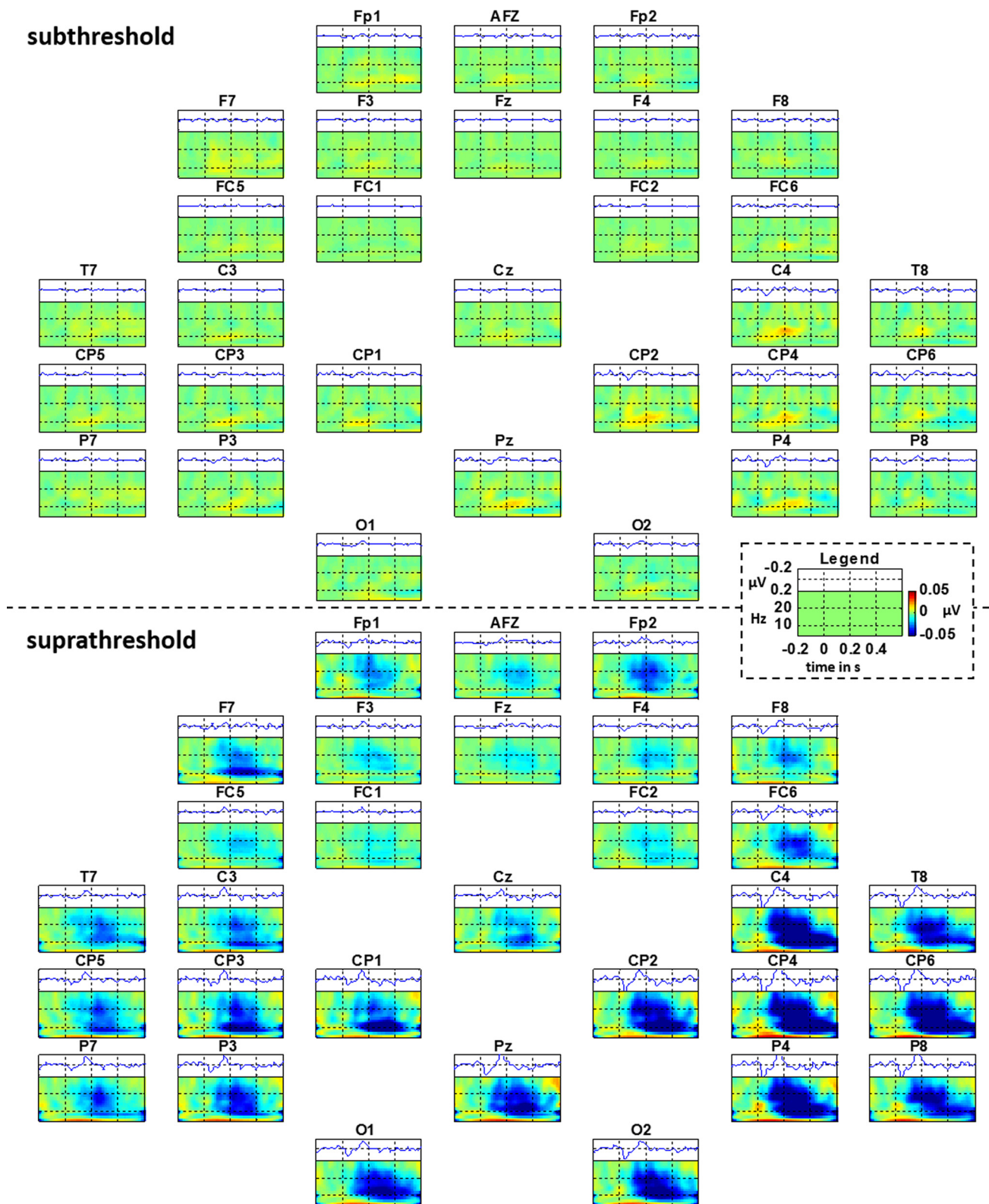


Figure 2. The oscillatory activity to subthreshold and suprathreshold stimulation is contralateralized. Grand average ($n = 39$) head plot of the SEP (blue curve) and the oscillatory activity (color-coded time-frequency plots) for subthreshold (top) and suprathreshold stimulation (bottom) in EEG session 1, after selection of central ICA components. Time is expressed relative to stimulation onset, and oscillatory activity is expressed relative to mean baseline power (baseline: 200 ms segment prestimulus).

extended these studies to (always imperceptible) subthreshold stimuli, for which we find a reduced and delayed P1 and absence of later components. Since our recordings show a similar shape and temporal kinetics as previous invasive studies (Libet et al.,

1967; Ray et al., 1999), we regard our findings as the first noninvasive demonstration of “subthreshold SEPs.” P1 is a well known SEP component, which has been suggested to reflect an IPSP (Wikström et al., 1996), originating in BA1 within SI (Allison et

al., 1992; Srisa-an et al., 1996). The relatively slow kinetics of the observed P1 following subthreshold stimulation is compatible with the temporal shape of cortical IPSPs, which are less sharp and have a smaller amplitude than EPSPs, due to substantially different synaptic driving forces (Whitehorn and Towe, 1968; Swadlow, 2003). However, given that excitatory and inhibitory processing in SI are always tightly coupled (Miller et al., 2001), it seems rather unlikely that at any given processing step there is just one type of synaptic activity (i.e., inhibitory) involved. Thus, a more appropriate view is that of a balance between excitatory and inhibitory activity (Isaacson and Scanziani, 2011). Given a lower stimulation threshold of inhibitory interneurons (as opposed to excitatory principal neurons), one can infer a preferential activation of inhibitory interneurons at low amplitude stimulation (Gil and Amitai, 1996; Swadlow, 2003). Thus, it seems plausible that the shift in peak timing as well as the lower amplitude of P1 reflect a modulation of the local excitation/inhibition ratio toward a dominance of inhibitory processing. No subsequent ERP component was detected suggesting that this predominant inhibition leads to a termination of the (mainly excitatory) bottom-up sweep at this time point. Specifically, there is no N1 component, which has been suggested to partly represent the neural correlates of conscious perception (Cauller, 1995), and to reflect activity in SI after feedback input from higher order cortices such as SII, PFC, and posterior parietal cortex (Cauller and Kulics, 1991; Knight et al., 1999; Staines et al., 2002; Golmayo et al., 2003). We think that subthreshold stimulation failed to trigger these feedback loops. Together, a plausible explanation of our results seems that the bottom-up sweep after subthreshold stimulation is terminated after ~ 60 ms due to a predominance of feedforward inhibition in BA1 preventing access to conscious experience.

The notion of predominant inhibition after subthreshold stimulation is further supported by alterations in Mu-rhythm and functional connectivity as outlined subsequently. After suprathreshold somatosensory stimulation, between 100 and 600 ms, we confirm the well described ERD (Neuper and Pfurtscheller, 2001; Ploner et al., 2006; Stancák, 2006) in the alpha and beta frequency bands. An ERD is usually regarded as a sign of local ongoing stimulus processing. In contrast to this, for subthreshold stimulation, we find

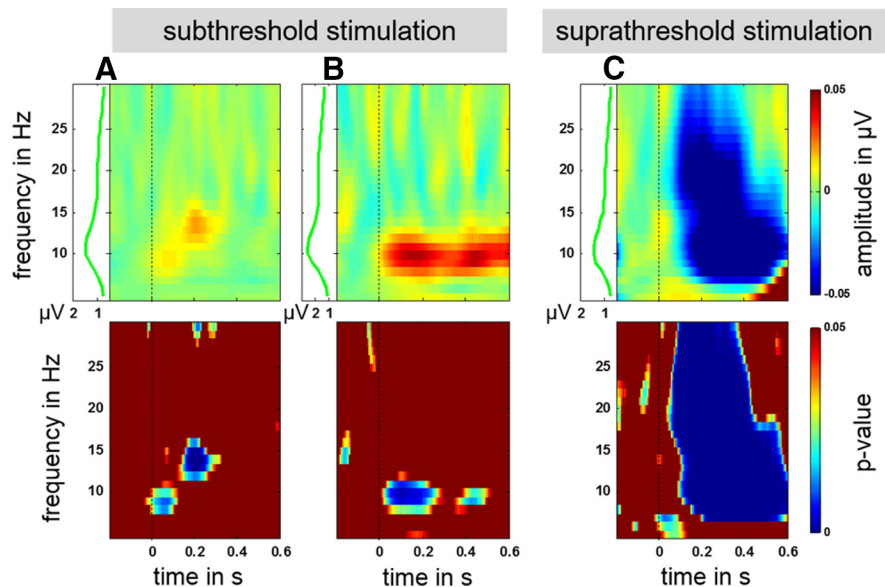


Figure 3. Subthreshold stimulation increases Rolandic rhythms. Grand average time-frequency plots (contralateral to stimulation side) for subthreshold (**A**, EEG session 1, electrode C4, $n = 39$; **B**, EEG session 2, electrode CP4, $n = 37$) and suprathreshold (**C**, EEG session 1, electrode C4, $n = 39$) stimulation after selection of central ICA components. Time is expressed relative to stimulation onset, and oscillatory activity is expressed relative to baseline power (baseline: 200 ms prestimulus). The green line on the left of the time-frequency plots indicates mean baseline power. Bottom plots indicate p values derived from the permutation statistics.

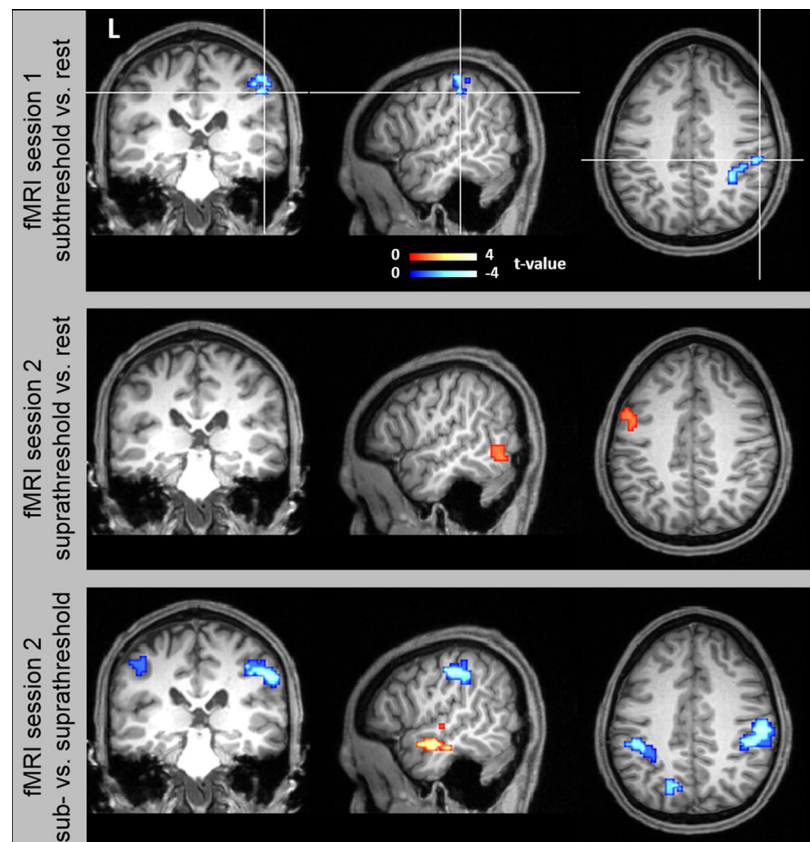


Figure 4. Reduced connectivity of SI during subthreshold stimulation revealed by ECM. Results of a paired t test are shown for contrasting the conditions subthreshold versus rest (top), suprathreshold versus rest (middle), and subthreshold versus suprathreshold (bottom). Warm colors indicate an increase, and cold colors indicate a decrease in centrality (slice coordinates $x = 143, y = 121, z = 67$).

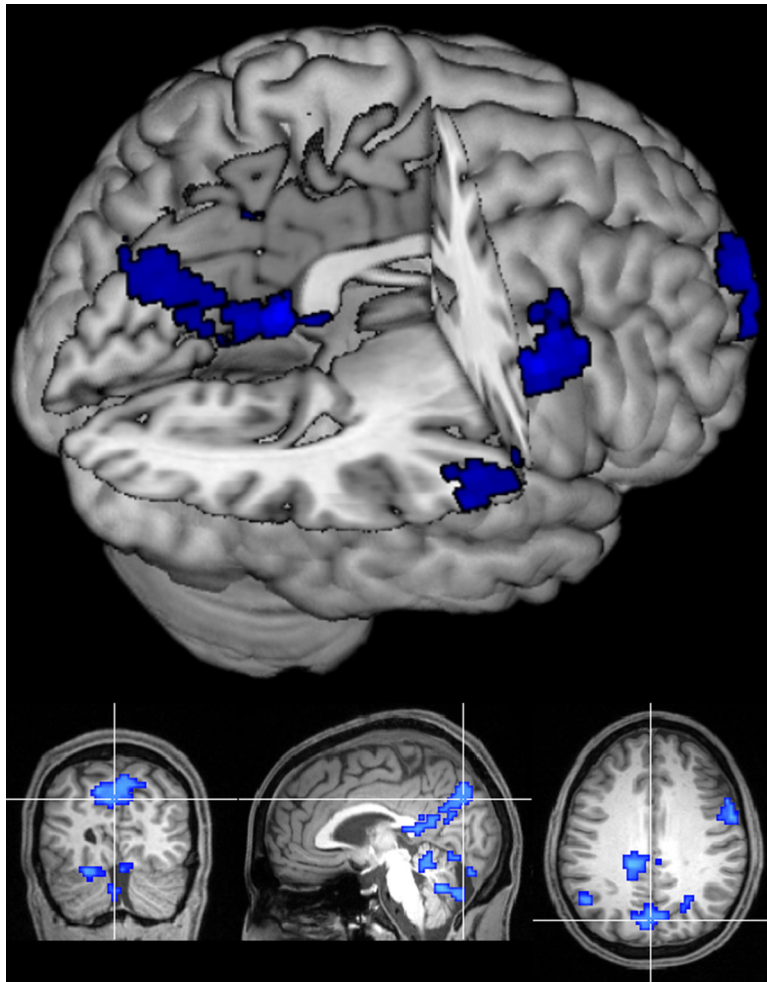


Figure 5. Reduced connectivity of SI to frontoparietal areas revealed by seed-based functional connectivity. The area described by the ECM result (Fig. 4 top, reduced eigenvector centrality during subthreshold stimulation) was used as seed. Blue areas indicate decreased correlation to the seed region, resulting from a paired *t* test contrasting functional connectivity maps of the subthreshold stimulation block versus rest block (fMRI session 1). Dark blue to light blue means $-$ min to $-$ max (slice coordinates $x = 87, y = 166, z = 76$).

the opposite, a transient increase in Mu-rhythm strength. Several authors suggested that increases in alpha rhythm indicate a “deactivated” state of the respective cortical area, reflecting predominant inhibitory synaptic processing (Lopes da Silva, 1991; Pfurtscheller et al., 1996; Klimesch et al., 2007; Bollimunta et al., 2008; Jensen et al., 2010, 2012; Buzsáki, 2006). Along with behavioral data supporting this view (Linkenkaer-Hansen et al., 2004; van Dijk et al., 2008; Weisz et al., 2014), the deactivated state is also indexed by the inverse relationship between alpha strength and cortical BOLD signal (Goldman et al., 2002; Laufs et al., 2003; Moosmann et al., 2003; de Munck et al., 2009; Ritter et al., 2009). Also, when inhibiting a response in a motor task, synchronized Mu-rhythm activity and, in a follow-up study, BOLD signal decreases have been observed (Hummel et al., 2002, 2004). The fact that diazepam (a benzodiazepine receptor agonist of the GABA_A receptor) has been shown to facilitate MEG background rhythms in healthy subjects (Jensen et al., 2005; Hall et al., 2010) also supports a relationship between local alpha activity and inhibitory processing. Thus, the transient Mu-rhythm increase after subthreshold stimulation may result from a stimulation-induced increase in the magnitude of inhibitory bouts produced by GABAergic interneuronal activity, as proposed previously (Jensen and Mazaheri, 2010).

It seems that after suprathreshold stimulation, a predominant excitatory processing in SI (indexed by an early and strong P1) is followed by local stimulus processing as indexed by the ERD and further ERP components such as the N1, whereas after subthreshold stimulation, a predominant inhibitory processing in SI (indexed by a delayed and weaker P1) prevents further stimulus-specific processing, but triggers a transient elevation of Mu-rhythm as an indicator of a transient downregulation of the system. The latter is consistent with our previous findings in humans that trains of subthreshold stimulation impede the perception of near-threshold stimuli on the same as well as adjacent fingers, accompanied by a focal fMRI deactivation (Blankenburg et al., 2003; Taskin et al., 2008).

Interestingly, an ERD has been described after unperceived near-threshold stimuli (Palva et al., 2005). While we did not investigate the effect of near-threshold stimuli, it seems an intriguing possibility that the bottom-up sweeps of subthreshold and near-threshold stimulation, respectively, are prevented from reaching consciousness at different steps of neural processing. Subthreshold stimuli might be stopped already at the first cortical processing stage in SI, as inhibitory processing outweighs excitatory processing, whereas near-threshold stimuli might be stopped only following more widespread cortical activation but short of conscious perception. Within the nomenclature of Dehaene’s global workspace model (Dehaene et al., 2006), near-threshold stimuli might reach a preconscious state, i.e., the necessary conditions for subsequent conscious detection, whereas subthreshold stimuli remain subliminal due to early termination of bottom-up processing.

In general, from our experimental design we cannot differentiate whether the observed effects for subthreshold stimulation are caused by different stimulation strengths or by the absence of perception. As subthreshold stimuli are never consciously detected, a design that contrasts perceived versus unperceived stimuli with the same stimulation strength was not possible. While we speculate that the reduced amplitude of P1 (clearly before any conscious experience) corresponds to the weak stimulation strength, the lack of later ERP components as well as the alpha synchronization may be related to either the difference in stimulation strength and/or the lack of conscious processing. In fact, here we speculate that it is both, i.e., along with the reduced stimulation strength, no further local and widespread processing occurs and hence there is no neural correlate related to conscious processing.

The interpretation of an inhibited access to conscious processing after subthreshold stimulation is further supported by our fMRI findings of reduced connectivity of SI, mainly to areas associated with conscious and higher somatosensory processing. Precuneus and posterior cingulate cortex have not only been de-

scribed as “higher order motor areas” within a sensorimotor network (Vogt and Vogt, 2003; Margulies et al., 2009; Morecraft et al., 2012), they also seem to be involved in conscious signal processing (Vogt and Laureys, 2005; Cavanna, 2007). Inferior frontal gyrus, operculum, and inferior parietal cortex have been shown to be part of a higher order somatosensory network involved in the processing of tactile stimulation (Dijkerman and de Haan, 2007; Kostopoulos et al., 2007; Spitzer et al., 2014; Weisz et al., 2014). Furthermore, the precuneus–prefrontal connection is associated with conscious perception (Kjaer et al., 2001; Dehaene et al., 2006) and task performance (Utevsy et al., 2014). The decrease in S1 connectivity observed in fMRI after subthreshold stimulation may be closely related to the increased Mu-rhythm, in analogy to the findings of a recent simultaneous EEG fMRI study, which showed that high alpha power in the visual system was associated with decreased local and long-range connectivity of the visual cortex (Scheeringa et al., 2012). A direct link of the two effects is not possible in our data since we did not investigate the same subjects in the EEG and fMRI experiments. However, based on our results it seems reasonable to plan future experiments using simultaneous EEG/fMRI.

In summary, this study provides evidence that for subthreshold stimuli access to conscious perception is prevented as bottom-up processing is terminated at an early stage in SI, likely due to dominant inhibitory processing. A transient predominance of local inhibitory processing would furthermore be consistent with the transient Mu-rhythm increase and the reduced SI connectivity to areas relevant for conscious perception, which can explain the (inhibitory) behavioral effects of trains of subthreshold stimulation on somatosensory perception. We suggest that these processes may serve the suppression of noise and overall the sharpening of somatosensory perception. Notably, this mechanism seems to be generalizable to other sensory systems, as analogous evidence—behaviorally and on alpha rhythm increase (Bareither et al., 2014a, 2014b)—has recently been provided for subliminal visual stimuli.

References

- Allison T, McCarthy G, Wood CC (1992) The relationship between human longlatency somatosensory evoked potentials recorded from the cortical surface and from the scalp. *Electroencephalogr Clin Neurophysiol* 84:301–314. [CrossRef Medline](#)
- Auksztulewicz R, Blankenburg F (2013) Subjective rating of weak tactile stimuli is parametrically encoded in event-related potentials. *J Neurosci* 33:11878–11887. [CrossRef Medline](#)
- Bareither I, Villringer A, Busch N (2014a) Decreased visual detection during subliminal stimulation. *J Vis* 14(12):20. [CrossRef Medline](#)
- Bareither I, Chaumon M, Bernasconi F, Villringer A, Busch NA (2014b) Invisible visual stimuli elicit increases in alpha-band power. *J Neurophysiol* 112:1082–1090. [CrossRef Medline](#)
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 34:537–541. [CrossRef Medline](#)
- Blankenburg F, Taskin B, Ruben J, Moosmann M, Ritter P, Curio G, Villringer A (2003) Imperceptible stimuli and sensory processing impediment. *Science* 299:1864. [CrossRef Medline](#)
- Bollimunta A, Chen Y, Schroeder CE, Ding M (2008) Neuronal mechanisms of cortical alpha oscillations in awake-behaving macaques. *J Neurosci* 28:9976–9988. [CrossRef Medline](#)
- Buzsáki G (2006) *Rhythms of the brain*. New York: Oxford UP.
- Caulier L (1995) Layer I of primary sensory neocortex: where top-down converges upon bottom-up. *Behav Brain Res* 71:163–170. [CrossRef Medline](#)
- Caulier LJ, Kulics AT (1991) The neural basis of the behaviorally relevant N1 component of the somatosensory-evoked potential in SI cortex of awake monkeys: evidence that backward cortical projections signal conscious touch sensation. *Exp Brain Res* 84:607–619. [CrossRef Medline](#)
- Cavanna AE (2007) The precuneus and consciousness. *CNS Spectr* 12:545–552. [Medline](#)
- Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, Quigley MA, Meyerand ME (2000) Mapping functionally related regions of brain with functional connectivity MR imaging. *Am J Neuroradiol* 21:1636–1644. [Medline](#)
- Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, Quigley MA, Meyerand ME (2001) Frequencies contributing to functional connectivity in the cerebral cortex in “resting-state” data. *Am J Neuroradiol* 22:1326–1333. [Medline](#)
- Dehaene S, Changeux JP, Naccache L, Sackur J, Sergent C (2006) Conscious, preconscious, and subliminal processing: a testable taxonomy. *Trends Cogn Sci* 10:204–211. [CrossRef Medline](#)
- de Munck JC, Gonçalves SI, Mammoliti R, Heethaar RM, Lopes da Silva FH (2009) Interactions between different EEG frequency bands and their effect on alpha-fMRI correlations. *Neuroimage* 47:69–76. [CrossRef Medline](#)
- Dijkerman HC, de Haan EH (2007) Somatosensory processes subserving perception and action. *Behav Brain Sci* 30:189–201; discussion 201–239. [CrossRef Medline](#)
- Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995) Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 33:636–647. [CrossRef Medline](#)
- Forschack N, Nierhaus T, Müller MM, Villringer A (2014) Attention modulates cerebral responses to conscious and unconscious tactile events. Poster, OHBM, 20th Annual Meeting, Hamburg.
- Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8:700–711. [CrossRef Medline](#)
- Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 102:9673–9678. [CrossRef Medline](#)
- Fox MD, Snyder AZ, Vincent JL, Raichle ME (2007) Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron* 56:171–184. [CrossRef Medline](#)
- Gil Z, Amitai Y (1996) Properties of convergent thalamocortical and intracortical synaptic potentials in single neurons of neocortex. *J Neurosci* 16:6567–6578. [Medline](#)
- Goldman RI, Stern JM, Engel J Jr, Cohen MS (2002) Simultaneous EEG and fMRI of the alpha rhythm. *Neuroreport* 13:2487–2492. [CrossRef Medline](#)
- Golmays L, Nuñez A, Zaborszky L (2003) Electrophysiological evidence for the existence of a posterior cortical-prefrontal-basal forebrain circuitry in modulating sensory responses in visual and somatosensory rat cortical areas. *Neuroscience* 119:597–609. [CrossRef Medline](#)
- Gusnard DA, Raichle ME (2001) Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci* 2:685–694. [CrossRef Medline](#)
- Hall SD, Barnes GR, Furlong PL, Seri S, Hillebrand A (2010) Neuronal network pharmacodynamics of GABAergic modulation in the human cortex determined using pharmacological-magnetoencephalography. *Hum Brain Mapp* 31:581–594. [CrossRef Medline](#)
- Hummel F, Andres F, Altenmüller E, Dichgans J, Gerloff C (2002) Inhibitory control of acquired motor programmes in the human brain. *Brain* 125:404–420. [CrossRef Medline](#)
- Hummel F, Saur R, Lasogga S, Plewnia C, Erb M, Wildgruber D, Grodd W, Gerloff C (2004) To act or not to act. Neural correlates of executive control of learned motor behavior. *Neuroimage* 23:1391–1401. [CrossRef Medline](#)
- Isaacson JS, Scanziani M (2011) How inhibition shapes cortical activity. *Neuron* 72:231–243. [CrossRef Medline](#)
- Jensen O, Mazaheri A (2010) Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci* 4:186. [CrossRef Medline](#)
- Jensen O, Goel P, Kopell N, Pohja M, Hari R, Ermentrout B (2005) On the human sensorimotor-cortex beta rhythm: sources and modeling. *Neuroimage* 26:347–355. [CrossRef Medline](#)
- Jensen O, Bonnefond M, VanRullen R (2012) An oscillatory mechanism for prioritizing salient unattended stimuli. *Trends Cogn Sci* 16:200–206. [CrossRef Medline](#)
- Kjaer TW, Nowak M, Kjaer KW, Lou AR, Lou HC (2001) Precuneus-

- prefrontal activity during awareness of visual verbal stimuli. *Conscious Cogn* 10:356–365. [CrossRef Medline](#)
- Klimesch W, Sauseng P, Hanslmayr S (2007) EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev* 53:63–88. [CrossRef Medline](#)
- Knight RT, Staines WR, Swick D, Chao LL (1999) Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta Psychol* 101:159–178. [CrossRef Medline](#)
- Kostopoulos P, Albanese MC, Petrides M (2007) Ventrolateral prefrontal cortex and tactile memory disambiguation in the human brain. *Proc Natl Acad Sci U S A* 104:10223–10228. [CrossRef Medline](#)
- Laufs H, Kleinschmidt A, Beyerle A, Eger E, Salek-Haddadi A, Preibisch C, Krakow K (2003) EEG-correlated fMRI of human alpha activity. *Neuroimage* 19:1463–1476. [CrossRef Medline](#)
- Li Y, Ma Z, Lu W, Li Y (2006) Automatic removal of the eye blink artifact from EEG using an ICA-based template matching approach. *Physiol Meas* 27:425–436. [CrossRef Medline](#)
- Libet B, Alberts WW, Wright EW Jr, Feinstein B (1967) Responses of human somatosensory cortex to stimuli below threshold for conscious sensation. *Science* 158:1597–1600. [CrossRef Medline](#)
- Linkenkaer-Hansen K, Nikulin VV, Palva S, Ilmoniemi RJ, Palva JM (2004) Prestimulus oscillations enhance psychophysical performance in humans. *J Neurosci* 24:10186–10190. [CrossRef Medline](#)
- Lohmann G, Müller K, Bosch V, Mentzel H, Hessler S, Chen L, Zysset S, von Cramon DY (2001) LIPSIA—a new software system for the evaluation of functional magnetic resonance images of the human brain. *Comput Med Imaging Graph* 25:449–457. [CrossRef Medline](#)
- Lohmann G, Margulies DS, Horstmann A, Pleger B, Lepsien J, Goldhahn D, Schloegl H, Stumvoll M, Villringer A, Turner R (2010) Eigenvector centrality mapping for analyzing connectivity patterns in fMRI data of the human brain. *PLoS One* 5:e10232. [CrossRef Medline](#)
- Lopes da Silva F (1991) Neural mechanisms underlying brain waves: from neural membranes to networks. *Electroencephalogr Clin Neurophysiol* 79:81–93. [CrossRef Medline](#)
- Margulies DS, Vincent JL, Kelly C, Lohmann G, Uddin LQ, Biswal BB, Villringer A, Castellanos FX, Milham MP, Petrides M (2009) Precuneus shares intrinsic functional architecture in humans and monkeys. *Proc Natl Acad Sci U S A* 106:20069–20074. [CrossRef Medline](#)
- Margulies DS, Böttger J, Long X, Lv Y, Kelly C, Schäfer A, Goldhahn D, Abbushi A, Milham MP, Lohmann G, Villringer A (2010) Resting developments: a review of fMRI post-processing methodologies for spontaneous brain activity. *MAGMA* 23:289–307. [CrossRef Medline](#)
- Miller KD, Pinto DJ, Simons DJ (2001) Processing in layer 4 of the neocortical circuit: new insights from visual and somatosensory cortex. *Curr Opin Neurobiol* 11:488–497. [CrossRef Medline](#)
- Moosmann M, Ritter P, Krastel I, Brink A, Thees S, Blankenburg F, Taskin B, Obrig H, Villringer A (2003) Correlates of alpha rhythm in functional magnetic resonance imaging and near infrared spectroscopy. *Neuroimage* 20:145–158. [CrossRef Medline](#)
- Morecraft RJ, Stilwell-Morecraft KS, Cipolloni PB, Ge J, McNeal DW, Pandya DN (2012) Cytoarchitecture and cortical connections of the anterior cingulate and adjacent somatomotor fields in the rhesus monkey. *Brain Res Bull* 87:457–497. [CrossRef Medline](#)
- Neuper C, Pfurtscheller G (2001) Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. *Int J Psychophysiol* 43:41–58. [CrossRef Medline](#)
- Nierhaus T, Margulies DS, Long X, Villringer A (2012) fMRI for the assessment of functional connectivity. In: *Neuroimaging methods* (Bright P, ed). Rijeka: In Tech.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97–113. [CrossRef Medline](#)
- Palva S, Linkenkaer-Hansen K, Näätänen R, Palva JM (2005) Early neural correlates of conscious somatosensory perception. *J Neurosci* 25:5248–5258. [CrossRef Medline](#)
- Pfurtscheller G, Stancák A Jr, Neuper C (1996) Event-related synchronization (ERS) in the alpha band - an electrophysiological correlate of cortical idling: a review. *Int J Psychophysiol* 24:39–46. [CrossRef Medline](#)
- Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A (2006) Pain suppresses spontaneous brain rhythms. *Cereb Cortex* 16:537–540. [CrossRef Medline](#)
- Poline JB, Worsley KJ, Evans AC, Friston KJ (1997) Combining spatial extent and peak intensity to test for activations in functional imaging. *Neuroimage* 5:83–96. [CrossRef Medline](#)
- Ray PG, Meador KJ, Smith JR, Wheless JW, Sittenfeld M, Clifton GL (1999) Physiology of perception: cortical stimulation and recording in humans. *Neurology* 52:1044–1049. [CrossRef Medline](#)
- Ritter P, Moosmann M, Villringer A (2009) Rolandic alpha and beta EEG rhythms' strengths are inversely related to fMRI-BOLD signal in primary somatosensory and motor cortex. *Hum Brain Mapp* 30:1168–1187. [CrossRef Medline](#)
- Scheeringa R, Petersson KM, Kleinschmidt A, Jensen O, Bastiaansen MC (2012) EEG alpha power modulation of fMRI resting-state connectivity. *Brain Connect* 2:254–264. [CrossRef Medline](#)
- Schubert R, Blankenburg F, Lemm S, Villringer A, Curio G (2006) Now you feel it—now you don't: ERP correlates of somatosensory awareness. *Psychophysiology* 43:31–40. [CrossRef Medline](#)
- Spitzer B, Goltz D, Wacker E, Aukstulewicz R, Blankenburg F (2014) Maintenance and manipulation of somatosensory information in ventrolateral prefrontal cortex. *Hum Brain Mapp* 35:2412–2423. [CrossRef Medline](#)
- Srisa-an P, Lei L, Tarkka IM (1996) Middle latency somatosensory evoked potentials: noninvasive source analysis. *J Clin Neurophysiol* 13:156–163. [CrossRef Medline](#)
- Staines WR, Graham SJ, Black SE, McLroy WE (2002) Task-relevant modulation of contralateral and ipsilateral primary somatosensory cortex and the role of a prefrontal-cortical sensory gating system. *Neuroimage* 15:190–199. [CrossRef Medline](#)
- Stancák A (2006) Cortical oscillatory changes occurring during somatosensory and thermal stimulation. *Prog Brain Res* 159:237–252. [CrossRef Medline](#)
- Swadlow HA (2003) Fast-spike interneurons and feedforward inhibition in awake sensory neocortex. *Cereb Cortex* 13:25–32. [CrossRef Medline](#)
- Taskin B, Holtz S, Krause T, Villringer A (2008) Inhibitory impact of subliminal electrical finger stimulation on SI representation and perceptual sensitivity of an adjacent finger. *Neuroimage* 39:1307–1313. [CrossRef Medline](#)
- Utevsky AV, Smith DV, Huettel SA (2014) Precuneus is a functional core of the default-mode network. *J Neurosci* 34:932–940. [CrossRef Medline](#)
- van Dijk H, Schoffelen JM, Oostenveld R, Jensen O (2008) Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. *J Neurosci* 28:1816–1823. [CrossRef Medline](#)
- Vogt BA, Laureys S (2005) Posterior cingulate, precuneus and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Prog Brain Res* 150:205–217. [CrossRef Medline](#)
- Vogt BA, Vogt L (2003) Cytology of human dorsal midcingulate and supplementary motor cortices. *J Chem Neuroanat* 26:301–309. [CrossRef Medline](#)
- Weisz N, Wühle A, Monittola G, Demarchi G, Frey J, Popov T, Braun C (2014) Prestimulus oscillatory power and connectivity patterns predispose conscious somatosensory perception. *Proc Natl Acad Sci U S A* 111:E417–E425. [CrossRef Medline](#)
- Whitehorn D, Towe AL (1968) Postsynaptic potential patterns evoked upon cells in sensorimotor cortex of cat by stimulation at the periphery. *Exp Neurol* 22:222–224. [CrossRef Medline](#)
- Wikström H, Huttunen J, Korvenoja A, Virtanen J, Salonen O, Aronen H, Ilmoniemi RJ (1996) Effects of interstimulus interval on somatosensory evoked magnetic fields (SEFs): a hypothesis concerning SEF generation at the primary sensorimotor cortex. *Electroencephalogr Clin Neurophysiol* 100:479–487. [CrossRef Medline](#)
- Zhang Y, Ding M (2010) Detection of a weak somatosensory stimulus: role of the prestimulus mu rhythm and its top-down modulation. *J Cogn Neurosci* 22:307–322. [CrossRef Medline](#)

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Konferenzbeiträge

Forschack N, Nierhaus T, Müller MM, Villringer A (2015) Prestimulus oscillatory state differentially influences cerebral processing of attended versus unattended somatosensory stimuli. **SfN** Conference, Chicago

Khalil A, Oswaldt AC, Nierhaus T, Audebert HJ, Villringer K, Villringer A, Fiebach JB (2015) Diagnostic and volumetric agreement between BOLD signal delay and bolus-tracking MRI on perfusion deficits in acute ischaemic stroke. **ESO** Conference, Glasgow

Till Nierhaus, Arno Villringer (2014) Unconscious Pattern Recognition: Cortical Processing of Imperceptible Somatosensory Stimulation Pattern. **OHBM**, 20th Annual Meeting, Hamburg

Till Nierhaus, Arno Villringer (2014) Differential effects of subliminal single pulse vs. train (7 Hz) stimulation. **OHBM**, 20th Annual Meeting, Hamburg

Sabrina D. Thiel, Sebastian Bitzer, Till Nierhaus, Christian Kalberlah, Sven Preusser, Jane Neumann, Vadim V Nikulin, Elke van der Meer, Arno Villringer, Burkhard Pleger (2014) Hysteresis as an implicit prior in tactile spatial decision making. **OHBM**, 20th Annual Meeting, Hamburg

Xiangyu Long, Dominique Goltz, Daniel S. Margulies, Till Nierhaus, Arno Villringer (2014) Influence of prior task performance on functional connectivity-based parcellation of brain regions. **OHBM**, 20th Annual Meeting, Hamburg

Dominique Goltz, Christopher Gundlach, Till Nierhaus, Arno Villringer, Matthias Müller (2014) Somatosensory steady state signal negatively correlates with BOLD activity in primary somatosensory cortex during vibrotactile stimulation. **OHBM**, 20th Annual Meeting, Hamburg

Norman Forschack, Till Nierhaus, Matthias M. Müller, Arno Villringer (2014) Attention modulates cerebral responses to conscious and unconscious tactile events. **OHBM**, 20th Annual Meeting, Hamburg

Hove, M. J., Stelzer, J., Nierhaus, T., Thiel, S., Gundlach, C., Margulies, D. S., Van Dijk, K.R.A., Turner, R., Keller, P.E., & Merker, B. (2014). Brain-Network Reconfiguration and Perceptual Decoupling during Trance. Poster presented at the Cognitive Neuroscience Society **CNS**. April. Boston, MA

Till Nierhaus, Johannes Stelzer, Xiangyu Long, Jens Steinbrink, Daniel Margulies, Arno Villringer (2013) Imperceptible Somatosensory Stimulation Functionally Disconnects Primary Somatosensory Cortex. **OHBM**, 19th Annual Meeting, Seattle

Till Nierhaus, Daniel Pach, Wenjing Huang, Xiangyu Long, Claudia Witt, Arno Villringer (2012) Acupuncture Point Specific Brain Activity Changes in EEG and fMRI. **OHBM**, 18th Annual Meeting, Beijing

Johannes Stelzer, Michael Hove, Till Nierhaus, Sabrina Thiel, Christopher Gundlach, Daniel Margulies, Robert Turner, Peter Keller, Björn Merker (2012) Rhythm-induced shamanic trance: A simultaneous fMRI & EEG study of altered states of consciousness. **OHBM**, 18th Annual Meeting, Beijing

Till Nierhaus, Jens Steinbrink, Arno Villringer (2011) Power and phase of ongoing mu-oscillation at stimulus onset differentially influence the SEP. **OHBM**, 17th Annual Meeting, Quebec

Sabrina Thiel, Till Nierhaus, Arno Villringer, Burkhard Pleger (2011) The neurophysiology of tactile decision making. **OHBM**, 17th Annual Meeting, Quebec

Xiangyu Long, Till Nierhaus, Daniel Margulies, Birol Taskin, Arno Villringer (2011) Detection of functional organization within primary somatosensory cortex by resting-state fMRI. **OHBM**, 17th Annual Meeting, Quebec

Till Nierhaus, Sophie Piper, Susanne Holtze, Birol Taskin, Jens Steinbrink, Arno Villringer (2010) Subliminal Somatosensory Stimulation And Cortical Inhibitory Processes. **OHBM**, 16th Annual Meeting, Barcelona

Patrick Ragert, Till Nierhaus, Arno Villringer (2010) Interhemispheric interactions of the human primary somatosensory cortex. **OHBM**, 16th Annual Meeting, Barcelona

Till Nierhaus, Sophie Piper, Susanne Holtze, Birol Taskin, Jens Steinbrink, Arno Villringer (2009) Subliminal Somatosensory Stimulation Increases Rolandic (Mu) Rhythm. **SfN**, 39th Annual Meeting, Chicago

Sophie Piper, Till Nierhaus, Susanne Holtze, Thomas Krause, Oliver Berthold, Birol Taskin, Jens Steinbrink, Arno Villringer (2009) Brain Responses to Subliminal Somatosensory Stimulation in the EEG. **OHBM**, 15th Annual Meeting , San Francisco

Publikationsliste

(jeweiliger Impact Factor und Eigenfactor Score nach ISI Web of KnowledgeSM 2013)

Hove MJ, Stelzer J, Nierhaus T, Thiel SD, Gundlach C, Margulies DS, Van Dijk KR, Turner R, Keller PE, Merker B (2015) Brain Network Reconfiguration and Perceptual Decoupling During an Absorptive State of Consciousness. *Cereb Cortex*. 2015 Jun 23. pii: bhv137. [Epub ahead of print]
Impact Factor 8.31; Eigenfactor Score 0.08

Goltz D, Gundlach C, Nierhaus T, Villringer A, Müller M, Pleger B (2015) Connections between Intraparietal Sulcus and a Sensorimotor Network Underpin Sustained Tactile Attention. *The Journal of Neuroscience*, 35(20), 7938-7949.
Impact Factor 6.75; Eigenfactor Score 0.41

Nierhaus T, Forschack N, Piper S, Holtze S, Krause T, Taskin B, Long X, Stelzer J, Margulies D, Steinbrink J, Villringer A (2015) Imperceptible Somatosensory Stimulation Alters Sensorimotor Background Rhythm and Connectivity, *The Journal of Neuroscience*, 35(15): 5917-5925.
Impact Factor 6.75; Eigenfactor Score 0.41

Nierhaus T, Pach D, Huang W, Long X, Napadow V, Roll S, Liang F, Pleger B, Villringer A and Witt CM (2015) Differential cerebral response to somatosensory stimulation of an acupuncture point vs. two non-acupuncture points measured with EEG and fMRI. *Front. Hum. Neurosci.* 9:74. doi: 10.3389/fnhum.2015.00074.
Impact Factor 2.89; Eigenfactor Score 0.01

Scharinger M, Herrmann B, Nierhaus T, Obleser J (2014) Simultaneous EEG-fMRI brain signatures of auditory cue utilization. *Front Neurosci.* 8:137. doi: 10.3389/fnins.2014.00137.

Thiel SD, Bitzer S, Nierhaus T, Kalberlah C, Preusser S, Neumann J, Nikulin VV, van der Meer E, Villringer A, Pleger B (2014) Hysteresis as an implicit prior in tactile spatial decision making. *PLoS One*. 9(2):e89802. doi: 10.1371/journal.pone.0089802.
Impact Factor 3.53; Eigenfactor Score 1.17

Long X, Goltz D, Margulies DS, Nierhaus T, Villringer A (2014) Functional connectivity-based parcellation of the human sensorimotor cortex. *Eur J Neurosci.* 39(8):1332-42. doi: 10.1111/ejn.12473.
Impact Factor 3.67; Eigenfactor Score 0.05

Iliopoulos F, Nierhaus T, Villringer A (2013) Electrical Noise Modulates Perception of Electrical Pulses in Humans: Sensation Enhancement via Stochastic Resonance. *J Neurophysiol.* 111(6):1238-48. doi: 10.1152/jn.00392.2013.
Impact Factor 3.04; Eigenfactor Score 0.06

Nierhaus T, Gundlach C, Goltz D, Thiel SD, Pleger B, Villringer A (2013) Internal ventilation system of MR scanners induces specific EEG artifact during simultaneous EEG-fMRI. *Neuroimage* 74:70-6.
Impact Factor 6.13; Eigenfactor Score 0.17

Nierhaus T, Margulies DS, Long X, Villringer A (2012). fMRI for the Assessment of Functional Connectivity. *Neuroimaging - Methods*, Prof. Peter Bright (Ed.), ISBN: 978-953-51-0097-3, InTech – open access publisher.
Available from: <http://www.intechopen.com/books/neuroimaging-methods/fmri-for-the-assessment-offunctional-connectivity>.

Huang W, Pach D, Napadow V, Park K, Long X, Neumann J, Maeda Y, Nierhaus T, Liang F, Witt CM (2012) Characterizing acupuncture stimuli using brain imaging with fMRI--a systematic review and meta-analysis of the literature. PLoS ONE 7(4):e32960. Impact Factor 3.53; Eigenfactor Score 1.17

Ragert P*, Nierhaus T*, Cohen LG, Villringer A (2011) Interhemispheric Interactions between the Human Primary Somatosensory Cortices. PLoS ONE 6(2): e16150. (*equal contribution) Impact Factor 3.53; Eigenfactor Score 1.17

Telkemeyer S, Rossi S, Nierhaus T, Steinbrink J, Obrig H and Wartenburger I (2011) Acoustic processing of temporally modulated sounds in infants: evidence from a combined near-infrared spectroscopy and EEG study. Front. Psychology, 2:62. doi: 10.3389. Impact Factor 2.80

Nierhaus T*, Schön T*, Becker R, Ritter P, Villringer A (2009) Background and evoked activity and their interaction in the human brain. Magnetic Resonance Imaging, Oct 27(8):1140-50. (*equal contribution) Impact Factor 2.02; Eigenfactor Score 0.01

Telkemeyer S, Rossi S, Koch SP, Nierhaus T, Steinbrink J, Poeppel D, Obrig H, Wartenburger I (2009) Sensitivity of Newborn Auditory Cortex to the Temporal Structure of Sounds. The Journal of Neuroscience, Nov 25;29(47):14726-14733. Impact Factor 6.75; Eigenfactor Score 0.41

Bourayou R, Boeth H, Benav H, Betz T, Lindauer U, Nierhaus T, Klohs J, Wunder A, Dirnagl U, Steinbrink J (2008) Fluorescence tomography technique optimized for noninvasive imaging of the mouse brain. J Biomed Opt, Jul-Aug;13(4):041311. Impact Factor 2.75; Eigenfactor Score 0.02

Klohs J, Steinbrink J, Nierhaus T, Bourayou R, Lindauer U, Bahmani P, Dirnagl U, Wunder A (2006) Noninvasive near-infrared imaging of fluorochromes within the brain of live mice: an in vivo phantom study. Mol Imaging, Jul;5(3):180-7. Impact Factor 2.19; Eigenfactor Score 0.003

Danksagung

Diese Arbeit ist in Kooperation von der Charité Universitätsmedizin Berlin und dem Max-Planck-Institut für Kognitions- und Neurowissenschaften Leipzig entstanden. Mein besonderer Dank gilt Prof. Arno Villringer und Dr. Jens Steinbrink, die mich während der Dissertation stets unterstützt haben und mir dabei genügend Freiheiten zur Verwirklichung meiner Projekte gelassen haben. Meinen zahlreichen Kollegen in Berlin und Leipzig danke ich für die vielen hilfreichen Gespräche und Diskussionen, die im Rahmen unserer wissenschaftlichen Tätigkeit unabdingbar sind. Bedanken möchte ich mich auch bei allen technischen und organisatorischen Mitarbeitern, die durch ihr Engagement ein großartiges Umfeld für wissenschaftliches Arbeiten schaffen.

Schließlich danke ich ganz herzlich meiner Familie und Freunden für den ständigen Rückhalt und die erforderliche Geduld.